International Journal of Epidemiology, 2020, 1326–1337
doi: 10.1093/ije/dyaa066
Advance Access Publication Date: 1 May 2020
Original article

Miscellaneous

Dicamba use and cancer incidence in the agricultural health study: an updated analysis

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Editorial decision 17 March 2020; Accepted 26 March 2020

Abstract

Background: The herbicide dicamba has been commonly used agriculturally and residentially. Recent approval of genetically engineered dicamba-resistant crops is expected to lead to increased dicamba use, and there has been growing interest in potential human health effects. A prior analysis in the Agricultural Health Study (AHS) suggested associations between dicamba and colon and lung cancer. We re-evaluated dicamba use in the AHS, including an additional 12 years and 2702 exposed cancers.

Methods: The AHS is a prospective cohort of pesticide applicators in Iowa and North Carolina. At enrollment (1993–1997) and follow-up (1999–2005), participants reported dicamba use. Exposure was characterized by cumulative intensity-weighted lifetime days, including exposure lags of up to 20 years. We estimated relative risks (RR) and 95% confidence intervals (CI) using multivariable Poisson regression for incident cancers diagnosed from enrollment through 2014/2015.

Results: Among 49 922 applicators, 26 412 (52.9%) used dicamba. Compared with applicators reporting no dicamba use, those in the highest quartile of exposure had elevated risk of liver and intrahepatic bile duct cancer ($n_{exposed} = 28$, $RR_{Q4} = 1.80$, CI: 1.26–2.56, $P_{trend} < 0.001$) and chronic lymphocytic leukaemia (CLL, $n_{exposed} = 93$, $RR_{Q4} = 1.20$, CI: 0.96–1.50, $P_{trend} = 0.01$) and decreased risk of myeloid leukaemia ($n_{exposed} = 55$, $RR_{Q4} = 0.73$, CI: 0.51–1.03, $P_{trend} = 0.01$). The associations for liver cancer and myeloid leukaemia remained after lagging exposure of up to 20 years.

Conclusions: With additional follow-up and exposure information, associations with lung and colon cancer were no longer apparent. In this first evaluation of liver and intrahepatic bile duct cancer, there was an association with increasing use of dicamba that persisted across lags of up to 20 years.

Key words: Dicamba, cancer, pesticides, agriculture, agricultural health study

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ED_005172C_00001666-00001

Key Messages

- Dicamba is an herbicide that has been commonly used in agricultural and residential settings.
- The recent approval of genetically engineered dicamba-resistant cotton and soybean crops is expected to lead to increased agricultural use of dicamba in the years to come, and there has been growing interest in the potential human health effects of this chemical.
- In a large (n = 49 922) prospective US cohort of pesticide applicators, dicamba was associated with increased risk of liver and intrahepatic bile duct cancer.
- This association was robust to exposure lags of up to 20 years.

Introduction

Dicamba is a selective benzoic acid herbicide that has been used in agricultural, industrial, and residential settings since the 1960s for post-emergent control of broadleaf weeds and woody plants. Historically, dicamba has been widely used in US agriculture on corn, soybeans, cotton and wheat.[1] Though use has waned over the last two decades, as recently as 2012 dicamba was ranked among the top 20 most commonly used agricultural pesticides and the top ten most commonly used residential pesticides.[2] Dicamba is water soluble and mobile in the environment.[1] It can volatilize following application, in certain conditions migrating as far as 200 feet from the site of initial application.[3]

In a 2006 review, the US Environmental Protection Agency (EPA) did not find evidence that dicamba is carcinogenic to humans, based on feeding studies in rats, mice, dogs and rabbits.[1] A dietary risk assessment of dicamba conducted jointly by the World Health Organization (WHO) and the Food and Agriculture Organization of the United Nations found limited evidence of carcinogenicity in rats, specifically lymphoma and thyroid C-cell carcinoma.[4] A previous analysis in the Agricultural Health Study (AHS) cohort found suggestive associations for lung and colon cancer, though the lung cancer finding was not robust across different exposure metrics.[5] A recent pooled analysis utilizing data from three cohorts in the AGRICOH consortium, which includes the AHS cohort,[6] found that dicamba use was associated with a suggestive elevated risk of multiple myeloma.[7] A Canadian case-control study of lymphoid malignancies found that dicamba use was associated with non-Hodgkin lymphoma (NHL);[8] no associations were observed for multiple myeloma or Hodgkin lymphoma.[9–11] A US case-control study found a positive association between dicamba and NHL among farmers who reported at least 15 years since last exposure, but no association with leukaemia.[12,13] Another case-control study in Canada using a job-exposure matrix to determine pesticide exposure found a positive association between dicamba use and prostate cancer.[14] The AHS reported no association between dicamba and risk of NHL or prostate cancer,[5,15] whereas the relationship between dicamba use and leukaemia has not been evaluated in the cohort.

With the recent approval of genetically engineered dicamba-resistant cotton and soybean crops,[16] and the potential for increased use, there has been growing interest in the potential human health effects of this pesticide. Although there is no clear consensus in the epidemiologic literature regarding the potential for carcinogenic effects of dicamba, with case-control studies suggesting an association with NHL and prospective studies suggesting associations with multiple myeloma, lung cancer and colon cancer, further information is needed. In this study, we conducted an updated evaluation of the association between dicamba use and cancer incidence in the prospective AHS cohort. This analysis included a total of 3770 incident dicamba-exposed cancer cases, with an additional 2702 incident exposed cases and more than 12 additional years of follow-up compared with the previous evaluation.[5]

Methods

Study population

The AHS is described elsewhere.[17] Briefly, the AHS is a prospective cohort that includes 57 310 licensed private and commercial pesticide applicators enrolled during 1993–1997 in Iowa (IA) and North Carolina (NC). Applicators were recruited when they applied for or renewed their restricted-use pesticide license. They completed a self-administered questionnaire providing detailed information about lifetime pesticide use, agricultural practices, demographic characteristics, behavioural factors, and personal and family medical history. We conducted follow-up via computer-assisted telephone interview ~5 years after enrollment during 1999–2005. AHS

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questionnaires are available at https://aghealth.nih.gov/collaboration/questionnaires.html. The study protocol, including implied consent for completion of questionnaires, was approved by all relevant institutional review boards.

Case ascertainment and classification

We obtained incident cancer information via linkage with IA and NC state cancer registries. We analysed first primary cancers diagnosed from enrollment through date of death, movement out of state or last study follow-up (31 December 2015 for IA, 31 December 2014 for NC), whichever was earliest. Cancer site was classified according to the International Classification of Diseases for Oncology, 3rd revision (ICD-O-3).[18] Solid tumours were grouped according to the Surveillance, Epidemiology, and End Results (SEER) Site Recode ICD-O-3/WHO 2008 Definition. Lymphoma subtypes were grouped per the 2008 SEER Lymphoma Subtype Recode.[19] Lung cancer subtypes were grouped using ICD-O-3 histology based on the International Agency for Research on Cancer classifications: small cell carcinoma, squamous cell carcinoma, adenocarcinoma.[20] We defined aggressive prostate cancer as meeting one or more of the following conditions: distant stage, poorly differentiated, Gleason score ≥ 7 or fatal.[15]

Exposure assessment

On the enrollment questionnaire, applicators provided information on duration (years) and frequency (average days/year) of dicamba use in categories. The midpoints of the categories were multiplied to obtain an estimate of cumulative days of exposure at enrollment. At the follow-up interview, applicators provided updated information regarding dicamba days/year applied in the last year they farmed. If the last year the applicator farmed was after study enrollment, we assumed that he/she applied dicamba for the number of days/year reported at follow-up interview for each year from enrollment through the last year farmed. We used multiple imputation to estimate pesticide exposures at follow-up for individuals who did not complete the interview ($n = 20\,968$, 37%); these methods have been described.[21] To address issues related to latency, we lagged dicamba use by 10 and 20 years, and for lymphohaematopoietic cancers we additionally evaluated 5-year exposure lags. To determine exposure lags, we calculated cumulative exposure for each year of follow-up until cancer diagnosis, death, movement out of state or end of cohort cancer incidence follow-up; we then subtracted the lag interval of 5, 10 or 20 years.

We evaluated cumulative intensity-weighted days of dicamba use through AHS follow-up interview. Intensity-weighted days is cumulative lifetime days multiplied by an intensity-weighting factor, which incorporates information on factors that influence pesticide exposure, including repair and cleaning of equipment, application method, whether the applicator mixed pesticides and personal protective equipment use.[22] Lifetime intensity-weighted days were categorized as no exposure or quartiles of exposure among all incident cancer cases for sites with 20 or more exposed. For analyses of rarer cancer sites and subtypes with 10–20 exposed cases, intensity-weighted days were categorized as no, low or high exposure based on the median.

Statistical analysis

We excluded applicators enrolled out of state ($n = 341$), diagnosed with cancer prior to enrollment ($n = 1096$) and those with missing dicamba intensity-weighted days at enrollment and follow-up ($n = 5951$), leaving 49 922 applicators.

Relative risks (RR) and 95% confidence intervals (CIs) were estimated using Poisson regression for each category of dicamba use compared with no use, with follow-up time considered prospectively in 2-year intervals. All models were adjusted for attained age (continuous, time-varying in 2-year increments), state (IA, NC), applicator type (private, commercial), race (White, other/missing), sex (male, female), cigarette smoking history at enrollment [never, former smoker ($\geq$100 lifetime cigarettes), current smoker, missing], family history of cancer (yes, no, missing; specific site where available), education (high school or less, more than high school, missing) and use of imazethapyr, the pesticide ingredient most correlated with dicamba (Spearman $P = 0.49$), classified as no, low, high or missing based on median intensity-weighted days of use (10–708.8, >708.8, missing). We further adjusted cancer-specific models for known risk factors including detailed 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, 11.5–28.5, >28.5, missing), smokeless tobacco use (ever, never), frequency of alcohol consumption (never, up to four times/week, every day or almost every day, missing) and body mass index (BMI; <25, 25–29.9, 30+ kg/m^2, missing). We considered adjustment for additional correlated pesticides including 2,4-D ($P = 0.45$), trifluralin ($P = 0.40$), atrazine ($P = 0.39$) and cyanazine ($P = 0.38$); the results were similar and only imazethapyr was included in the final models to avoid overstratification. We also conducted a sensitivity analysis including only intensity-weighted days of dicamba exposure reported at enrollment (no imputed data). To evaluate the robustness of our findings, we compared selected results

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from Poisson models to those fitting Cox proportional hazard models; results were nearly identical.

Analyses were performed using SAS version 9.4 (SAS Institute, Inc., Cary, NC). All statistical tests were two-sided with $\alpha = 0.05$.

Results

Table 1 displays selected characteristics of 49 922 AHS applicators stratified by dicamba never use and intensity-weighted days of dicamba use in quartiles. Applicators reporting dicamba use were more likely to be younger, from IA, commercial applicators, male, White and more highly educated compared with non-users. Dicamba users were less likely to report current smoking and more likely to report occasional and frequent alcohol consumption. BMI did not differ substantially based on dicamba use. Dicamba use was associated with higher self-reported ever use of imazethapyr, 2,4-D, trifluralin, atrazine and cyanazine. Dicamba users were more likely to report beef, hogs, field corn and soybeans as a major source of income. Among applicators who reported using dicamba at enrollment, 80% first used dicamba in the 1970s or 1980s. 31% continued to use dicamba at study follow-up, whereas among never users at enrollment, only about 7% reported use at study follow-up (results not shown).

There was no association between intensity-weighted days of dicamba use and all cancer sites combined ($P_{trend} = 0.57$); however, we did note some site-specific associations. Results for cancers with at least 20 dicamba-exposed cases (quartiles of intensity-weighted days) are presented in Table 2; results for cancers with 10–19 exposed cases (≤median, >median intensity-weighted days) are presented in Table 3. Tonsil cancer was positively associated with low use of dicamba and inversely associated with high use of dicamba compared with unexposed ($n = 16$, $RR_{low} = 1.86$, CI: 1.19–2.88, $RR_{high} = 0.64$, CI: 0.39–1.04, $P_{trend} < 0.001$). Increasing intensity-weighted days of dicamba use was associated with cancers of the liver and intrahepatic bile duct (C22.0–C22.1; $RR_{Q4} = 1.80$, CI: 1.26–2.56, $P_{trend} < 0.001$). This association was driven by a relatively small number ($n = 10$ of 28 total exposed cases) of intrahepatic bile duct cancers ($RR_{high} = 2.92$, CI: 1.71–5.01, $P_{trend} < 0.001$). Dicamba use was inversely associated with lung cancer among low-exposed applicators ($RR_{Q1} = 0.67$, CI: 0.47–0.94, $RR_{Q2} = 0.74$, CI: 0.55–1.01) compared with unexposed; however, there was no evidence of an exposure–response trend for all lung cancers ($P_{trend} = 0.22$) or any subtype. Dicamba use was associated with lower risk of myeloid leukaemia ($RR_{Q4} = 0.73$, CI: 0.51–1.03, $P_{trend} = 0.01$). High dicamba use was positively associated with acute/other lymphocytic leukaemia ($n = 13$, $RR_{high} = 4.59$, CI: 2.11–19.98, $P_{trend} < 0.001$). Chronic lymphocytic leukaemia (CLL), a common lymphoid malignancy, was associated with increasing dicamba use ($RR_{Q4} = 1.20$, CI: 0.96–1.50, $P_{trend} = 0.01$). Dicamba use was also associated with mantle cell lymphoma (MCL, $RR_{high} = 3.47$, CI: 2.06–5.85) with 18 exposed cases, although there was no evidence of a monotonic trend. Risk was weakly elevated in the fourth quartile of dicamba exposure for all lymphoid malignancies combined, as well as for diffuse large B-cell lymphoma (DLBCL), follicular lymphoma and multiple myeloma. Results evaluating cumulative days of dicamba use were similar to intensity-weighted days (Supplementary Table 1, available as Supplementary data at *IJE* online). Modelling results including only pesticide exposure information reported at enrollment (no imputed data) were generally similar in magnitude and direction to imputed results (Supplementary Table 2, available as Supplementary data at *IJE* online).

To address issues related to latency, we lagged dicamba exposure by 5-, 10- and 20-year increments. The results for lymphohaematopoietic cancers lagging dicamba exposure 5 years were similar in magnitude and direction to the unlagged analyses (Supplementary Table 3, available as Supplementary data at *IJE* online). Associations with tonsil cancer, liver and intrahepatic bile duct cancer, myeloid leukaemia and MCL remained after lagging dicamba exposure up to 20 years (Table 4). We also noted elevated risk of kidney cancer lagging exposure by 20-years ($RR_{Q4} = 1.61$, CI: 1.04–2.50, $P_{trend} = 0.04$). The association between dicamba and CLL in unlagged analyses was not apparent after lagging exposure 10 ($RR_{Q4} = 0.95$, CI: 0.77–1.17, $P_{trend} = 0.98$) and 20 ($RR_{Q4} = 0.89$, CI: 0.71–1.12, $P_{trend} = 0.27$) years.

Discussion

This updated analysis of dicamba use and cancer incidence in the AHS cohort adds 2702 incident dicamba-exposed cancer cases and >12 additional years of follow-up. We observed elevated risk of liver and intrahepatic bile duct cancers, acute/other lymphocytic leukaemia, CLL and MCL. Conversely, we observed a decreased risk of tonsil cancer and myeloid leukaemia among applicators exposed to high levels of dicamba. None of these associations has been previously reported in the epidemiologic literature.

We observed increased risk of liver and bile duct cancer with increasing dicamba use among relatively few exposed cases ($n = 28$). Looking separately at liver cancer and intrahepatic bile duct cancer, only intrahepatic bile duct cancer ($n = 10$) demonstrated elevated risk with dicamba use, although there was a positive trend for liver cancer after a 20-year exposure lag. These findings were robust to

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Table 1. Selected characteristics of Agricultural Health Study pesticide applicators ($n = 49\,922$), stratified by lifetime intensity-weighted days of dicamba use

Participant characteristics	Intensity-weighted days of dicamba use				
	No use $n = 23510$ n (%)[a]	≤449.5 $n = 6292$ n (%)[a]	449.6–1260 $n = 6522$ n (%)[a]	1260.1–3689 $n = 6896$ n (%)[a]	>3689 $n = 6702$ n (%)[a]
Attained age, years					
<50	3336 (14.2)	713 (11.3)	683 (10.5)	673 (9.8)	611 (9.1)
50–59	5924 (25.2)	1725 (27.4)	1888 (28.9)	2053 (29.8)	2105 (31.4)
60–69	6645 (28.3)	1982 (31.5)	2076 (31.8)	2265 (32.8)	2298 (34.3)
70+	7605 (32.3)	1872 (29.8)	1875 (28.7)	1905 (27.6)	1688 (25.2)
State					
Iowa	10 193 (43.4)	5537 (88)	5918 (90.7)	6341 (92)	5979 (89.2)
North Carolina	13 317 (56.6)	755 (12)	604 (9.3)	555 (8)	723 (10.8)
Applicator type					
Private	21 847 (92.9)	5861 (93.2)	6108 (93.7)	6219 (90.2)	5357 (79.9)
Commercial	1663 (7.1)	431 (6.8)	414 (6.3)	677 (9.8)	1345 (20.1)
Gender					
Male	22 434 (95.4)	6222 (98.9)	6465 (99.1)	6852 (99.4)	6657 (99.3)
Female	1076 (4.6)	70 (1.1)	57 (0.9)	44 (0.6)	45 (0.7)
Race					
White	22 545 (95.9)	6222 (98.9)	6450 (98.9)	6841 (99.2)	6636 (99)
Other	965 (4.1)	70 (1.1)	72 (1.1)	55 (0.8)	66 (1)
Education					
High school or less	13 501 (57.4)	3257 (51.8)	3341 (51.2)	3551 (51.5)	3483 (52)
At least some college	9336 (39.7)	2885 (45.9)	3044 (46.7)	3223 (46.7)	3101 (46.3)
Missing/other	673 (2.9)	150 (2.4)	137 (2.1)	122 (1.8)	118 (1.8)
Smoking status at enrolment					
Never	11 344 (48.3)	3657 (58.1)	3828 (58.7)	3937 (57.1)	3594 (53.6)
Former	7250 (30.8)	1745 (27.7)	1840 (28.2)	1992 (28.9)	1957 (29.2)
Current	4627 (19.7)	829 (13.2)	804 (12.3)	920 (13.3)	1111 (16.6)
Missing	289 (1.2)	61 (1)	50 (0.8)	47 (0.7)	40 (0.6)
Alcohol consumption frequency at enrolment					
Never	9567 (40.7)	1555 (24.7)	1434 (22)	1374 (19.9)	1270 (18.9)
Occasional (<1 day/month to 4 days/week)	12 169 (51.8)	4247 (67.5)	4542 (69.6)	4924 (71.4)	4689 (70)
Every day or almost every day	1276 (5.4)	353 (5.6)	433 (6.6)	513 (7.4)	671 (10)
Missing	498 (2.1)	137 (2.2)	113 (1.7)	85 (1.2)	72 (1.1)
Body mass index (kg/m^2)					
<25	4679 (19.9)	1253 (19.9)	1231 (18.9)	1278 (18.5)	1058 (15.8)
25–29.9	8005 (34.0)	2378 (37.8)	2670 (40.9)	2753 (39.9)	2547 (38.0)
30+	3787 (16.1)	1044 (16.6)	1102 (16.9)	1262 (18.3)	1284 (19.2)
Missing	7039 (29.9)	1617 (25.7)	1519 (23.3)	1603 (23.2)	1813 (27.1)
Ever use of correlated pesticides					
Imazethapyr	4655 (19.8)	3455 (54.9)	3964 (60.8)	4742 (68.8)	4685 (69.9)
2,4-D	14 318 (60.9)	5526 (87.8)	5912 (90.6)	6393 (92.7)	6299 (94)
Trifluralin	7692 (32.7)	3756 (59.7)	4234 (64.9)	4797 (69.6)	4820 (71.9)
Atrazine	12 801 (54.4)	5181 (82.3)	5579 (85.5)	6102 (88.5)	5992 (89.4)
Cyanazine	5139 (21.9)	3214 (51.1)	3427 (52.5)	3917 (56.8)	4105 (61.3)
Major income-producing crops and animals at enrolment[b]					
Beef cattle	7222 (30.7)	2569 (40.8)	2758 (42.3)	2877 (41.7)	2706 (40.4)
Hogs	5061 (21.5)	2469 (39.2)	2766 (42.4)	3013 (43.7)	2589 (38.6)
Poultry	988 (4.2)	202 (3.2)	186 (2.9)	189 (2.7)	205 (3.1)
Field corn	12 874 (54.8)	5326 (84.6)	5673 (87)	5967 (86.5)	5280 (78.8)
Cotton	1779 (7.6)	119 (1.9)	74 (1.1)	83 (1.2)	101 (1.5)
Soybeans	12 589 (53.5)	4863 (77.3)	5191 (79.6)	5559 (80.6)	4964 (74.1)
Wheat	3643 (15.5)	423 (6.7)	379 (5.8)	377 (5.5)	477 (7.1)

[a]Percentages may not sum to 100 due to rounding.
[b]Categories are not mutually exclusive.

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Table 2. Multivariable Poisson regression models estimating adjusted[a] rate ratios (RR) and 95% confidence intervals (CI) for each category of cumulative dicamba intensity-weighted days of use compared with no use

Cancer site	No use	5.0–449.5		449.6–1260.0		1260.1–3689.0		>3689.0		P_{trend}[b]
	n	*n*	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)	*n*	RR (95% CI)	
All sites[c]	3721	943	0.97 (0.89–1.05)	944	0.95 (0.87–1.03)	941	0.93 (0.86–1.01)	942	1.01 (0.93–1.10)	0.57
Lip[c,d]	24	9	0.83 (0.34–1.99)	10	1.07 (0.48–2.35)	5	0.50 (0.17–1.47)	6	0.70 (0.26–1.86)	0.44
Oesophagus[c,e,f]	44	14	0.99 (0.45–2.20)	10	0.96 (0.44–2.06)	23	1.99 (1.10–3.59)	11	0.96 (0.46–2.03)	1.00
Stomach[e,f]	60	15	0.95 (0.50–1.81)	8	0.56 (0.26–1.22)	14	0.83 (0.42–1.62)	10	0.67 (0.32–1.41)	0.37
Small intestine	20	8	1.17 (0.48–2.81)	5	0.76 (0.27–2.14)	5	0.71 (0.24–2.08)	5	0.85 (0.29–2.50)	0.72
Colon[f]	263	64	0.91 (0.67–1.23)	59	0.78 (0.56–1.09)	59	0.80 (0.58–1.09)	68	1.01 (0.74–1.37)	0.71
Rectum[f]	127	31	0.91 (0.58–1.42)	28	0.81 (0.51–1.26)	22	0.65 (0.40–1.07)	24	0.71 (0.44–1.16)	0.19
Liver and intrahepatic bile duct[e,f]	43	4	0.32 (0.18–0.57)	6	1.38 (0.98–1.96)	8	1.15 (0.80–1.67)	10	1.80 (1.26–2.56)	<0.001
Pancreas[c,f]	86	18	0.96 (0.53–1.74)	25	1.33 (0.79–2.24)	16	0.88 (0.48–1.60)	18	1.08 (0.60–1.93)	0.92
Larynx[c]	37	5	0.68 (0.24–1.91)	5	0.43 (0.14–1.37)	5	0.53 (0.19–1.47)	8	0.80 (0.33–1.92)	0.88
Lung[c]	449	52	0.67 (0.47–0.94)	58	0.74 (0.55–1.01)	65	0.76 (0.57–1.02)	65	0.76 (0.56–1.02)	0.22
Small cell lung	81	8	0.52 (0.24–1.13)	9	0.56 (0.27–1.19)	3	0.18 (0.05–0.63)	18	0.82 (0.44–1.53)	1.00
Squamous cell lung	113	12	0.72 (0.38–1.38)	18	0.90 (0.50–1.63)	13	0.69 (0.37–1.29)	20	0.98 (0.56–1.71)	0.90
Adenocarcinoma	130	18	0.60 (0.32–1.12)	20	0.80 (0.48–1.35)	31	1.14 (0.72–1.79)	17	0.65 (0.37–1.13)	0.28
Melanoma	167	51	1.07 (0.74–1.54)	49	1.05 (0.73–1.50)	49	0.94 (0.64–1.37)	48	1.00 (0.69–1.45)	0.91
Prostate	1334	396	1.03 (0.91–1.17)	386	1.00 (0.88–1.13)	406	1.03 (0.90–1.18)	372	1.07 (0.93–1.22)	0.36
Aggressive prostate	706	212	0.95 (0.80–1.13)	241	1.07 (0.91–1.26)	222	0.97 (0.82–1.16)	223	1.11 (0.93–1.32)	0.22
Testis	26	5	0.69 (0.24–1.95)	6	0.75 (0.27–2.14)	7	1.00 (0.40–2.50)	5	0.73 (0.25–2.14)	0.71
Bladder[c]	183	54	1.16 (0.83–1.62)	40	0.77 (0.52–1.16)	52	1.00 (0.70–1.42)	45	0.86 (0.58–1.27)	0.43
Kidney[c,f]	128	28	0.91 (0.58–1.41)	32	0.97 (0.61–1.55)	35	1.05 (0.68–1.63)	38	1.28 (0.85–1.94)	0.17
Brain	37	10	0.88 (0.40–1.93)	15	1.23 (0.62–2.44)	11	0.90 (0.43–1.90)	12	1.10 (0.52–2.32)	0.81
Thyroid[c,f]	41	10	0.84 (0.40–1.76)	11	0.70 (0.33–1.51)	9	0.65 (0.30–1.43)	11	0.76 (0.36–1.61)	0.60
Leukaemia	60	18	1.18 (0.88–1.60)	21	1.29 (0.98–1.69)	20	1.15 (0.89–1.50)	17	0.80 (0.61–1.06)	0.02
Myeloid leukaemia	49	14	1.16 (0.81–1.66)	17	1.31 (0.97–1.78)	13	0.94 (0.69–1.29)	11	0.73 (0.51–1.03)	0.01
Acute myeloid leukaemia	37	9	1.17 (0.81–1.70)	15	1.5 (1.04–2.17)	11	0.99 (0.70–1.38)	9	0.84 (0.61–1.17)	0.06
Non-Hodgkin lymphoid malignancies	268	78	0.99 (0.75–1.31)	96	1.23 (0.94–1.60)	86	1.11 (0.84–1.47)	92	1.25 (0.94–1.64)	0.15
Chronic/small lymphocytic leukaemia	62	17	0.74 (0.59–0.92)	22	0.90 (0.73–1.12)	27	0.95 (0.76–1.20)	27	1.20 (0.96–1.50)	0.01
Diffuse large B-cell lymphoma	64	15	0.82 (0.43–1.56)	20	1.31 (0.75–2.29)	11	0.65 (0.32–1.33)	17	1.20 (0.65–2.19)	0.60
Follicular lymphoma	31	12	1.16 (0.56–2.42)	13	1.22 (0.58–2.53)	7	0.73 (0.29–1.81)	13	1.32 (0.63–2.75)	0.56
Multiple myeloma	64	20	1.42 (0.81–2.48)	19	1.38 (0.77–2.44)	18	1.40 (0.78–2.51)	15	1.24 (0.65–2.36)	0.74

[a]Adjusted for age, race, sex, state, applicator type, education, imazethapyr, smoking (current, former, never), family history of cancer.
[b]*P*-value for trend using a Wald test.
[c]Additionally adjusted for pack-years smoked (tertiles by smoking status).
[d]Additionally adjusted for non-combustible tobacco use.
[e]Additionally adjusted for alcohol consumption.
[f]Additionally adjusted for body mass index.

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Table 3. Multivariable Poisson regression models estimating adjusted[a] rate ratios (RR) and 95% confidence intervals (CI) for low (≤median) and high dicamba intensity-weighted days of use compared with no use. Results for cancer sites with 10–19 exposed cases

Cancer site	No use	5.0–1260.0		>1260.0		P_{trend}[b]
	n	*n*	RR (95% CI)	*n*	RR (95% CI)	
Tongue[c,d]	18	10	0.93 (0.36–2.38)	6	0.50 (0.17–1.45)	0.17
Tonsil[c]	9	11	1.86 (1.19–2.88)	5	0.64 (0.39–1.04)	<0.001
Liver and intrahepatic bile duct						
Liver[e,f]	37	5	0.53 (0.19–1.48)	13	1.04 (0.46–2.34)	0.64
Intrahepatic bile duct[e,f]	6	5	1.74 (0.99–3.08)	5	2.92 (1.71–5.01)	<0.001
Leukaemia						
Chronic myeloid leukaemia	12	7	0.97 (0.24–3.94)	3	0.81 (0.20–3.31)	0.76
Acute/other lymphocytic leukaemia	3	3	2.60 (1.13–5.96)	10	4.59 (2.11–9.98)	<0.001
Hodgkin lymphoma	14	9	1.06 (0.40–2.82)	4	0.50 (0.12–2.07)	0.29
Non-Hodgkin lymphoid malignancies						
Marginal zone lymphoma	6	6	2.07 (0.54–7.96)	4	1.28 (0.27–5.97)	0.90
Mantle cell lymphoma	7	10	5.29 (3.41–8.18)	8	3.47 (2.06–5.85)	0.12

[a]Adjusted for age, race, sex, state, applicator type, education, imazethapyr, smoking (current, former, never), family history of cancer.
[b]*P*-value for trend using a Wald test.
[c]Additionally adjusted for pack-years smoked (tertiles by smoking status).
[d]Additionally adjusted for non-combustible tobacco use.
[e]Additionally adjusted for alcohol consumption.
[f]Additionally adjusted for body mass index.

sensitivity analyses and exposure lags of up to 20 years. The association between dicamba and liver and/or intrahepatic bile duct cancer has not been reported in the epidemiologic literature. In the AHS, the herbicide metolachlor has been associated with liver cancer risk;[23] the association with dicamba remained unchanged after adjustment for metolachlor use in our analysis. Liver cancer is rare, and incidence is lower than expected in farming populations including the AHS,[24,25] possibly due to the healthy worker effect and/or behavioural factors, such as lower alcohol consumption. Where appropriate, we controlled for known risk factors that may confound the relationship between dicamba and liver cancer, including gender, tobacco use, alcohol consumption and body size. We did not have data on certain medical risk factors, including chronic hepatitis infection and cirrhosis, but have no reason to assume these conditions would be associated with dicamba use. Experimental studies have demonstrated a potential link between dicamba and liver cancer. Dicamba is considered a peroxisome proliferator *in vivo*,[26] with the potential to increase peroxisomal enzyme activity in the liver and eventually cause liver tumours.[27] Additionally, in a study of female rats dicamba was associated with increased risk of liver tumours when administered in combination with other carcinogens.[28]

Dicamba has previously been associated with NHL overall[8,12] and suggestively associated with multiple myeloma,[29] a non-Hodgkin lymphoid malignancy.[30] Our study was the first to evaluate aetiologically distinct NHL subtypes while also using detailed exposure assessment that utilized time-varying and intensity-weighted metrics. Our analysis is the first prospective study to demonstrate increased risk of CLL among pesticide applicators reporting use of dicamba. We did not observe strong associations with any category of exposure for multiple myeloma or evidence of an exposure–response trend. The positive association with CLL in unlagged and 5-year lagged analyses, and the absence of an association with longer exposure lags may suggest a relatively short latency or a promoting effect. Dicamba may potentially influence progression from monoclonal B-cell lymphocytosis, a CLL precursor, to clinical CLL.[31] CLL has been associated with living or working on a farm and occupation as a crop farmer in a large pooled study,[32] but the lack of information on specific pesticides did not allow risk to be directly linked to dicamba. Though there is limited experimental evidence for the carcinogenicity of dicamba *in vivo*, a single study found increased lymphoma risk among rats fed dicamba over a 2 year period.[33] We observed a positive association with dicamba use and another lymphoid malignancy, MCL. However, this association was based on relatively few exposed cases ($n = 18$) and there was limited evidence of a monotonic exposure–response trend in all but the 20-year lagged analysis. MCL is rare, with only 0.8 cases diagnosed

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Table 4. Multivariable Poisson regression models estimating adjusted[a] rate ratios (RR) and 95% confidence intervals (CI) for each category of cumulative dicamba intensity-weighted days of use lagged 10 and 20 years, compared with no exposure, for selected cancer sites

Cancer site	10-Year exposure lag			20-Year exposure lag		
		n	RR (95% CI)		*n*	RR (95% CI)
All sites[b]						
	0	3945	1.00 (ref)	0	4848	1.00 (ref)
	5.0–396.0	882	0.99 (0.91–1.07)	5.0–315.0	668	1.04 (0.96–1.14)
	396.1–1120.0	884	0.98 (0.90–1.07)	315.1–937.5	627	0.97 (0.89–1.06)
	1120.1–3315.0	880	0.97 (0.89–1.05)	937.6–2800.0	646	0.99 (0.91–1.08)
	>3315.0	881	1.04 (0.96–1.13)	>2800.0	644	1.09 (1.00–1.19)
	P_{trend}[c]		0.28	P_{trend}		0.08
Tonsil[b]						
	0	11	1.00 (ref)	0	14	1.00 (ref)
	5.0–1120.0	7	1.17 (0.79–1.73)	5.0–937.5	6	1.09 (0.71–1.67)
	>1120.0	5	0.60 (0.38–0.96)	>937.5	3	0.49 (0.28–0.87)
	P_{trend}		0.01	P_{trend}		0.01
Colon[d]						
	0	275	1.00 (ref)	0	335	1.00 (ref)
	5.0–396.0	56	0.90 (0.66–1.23)	5.0–315.0	53	1.21 (0.89–1.65)
	396.1–1120.0	56	0.87 (0.63–1.21)	315.1–937.5	41	0.93 (0.67–1.31)
	1120.1–3315.0	64	1.01 (0.75–1.36)	937.6–2800.0	39	0.88 (0.62–1.24)
	>3315.0	60	1.04 (0.76–1.42)	>2800.0	41	1.01 (0.71–1.42)
	P_{trend}		0.59	P_{trend}		0.84
Liver and bile duct[d,e]						
	0	45	1.00 (ref)	0	46	1.00 (ref)
	5.0–396.0	2	0.45 (0.27–0.75)	5.0–315.0	2	0.65 (0.39–1.09)
	396.1–1120.0	6	1.23 (0.87–1.75)	315.1–937.5	8	1.31 (0.89–1.92)
	1120.1–3315.0	6	1.34 (0.96–1.86)	937.6–2800.0	4	1.76 (1.26–2.45)
	>3315.0	12	1.80 (1.32–2.43)	>2800.0	11	1.91 (1.39–2.63)
	P_{trend}		<0.001	P_{trend}		<0.001
Liver[d,e]						
	0	38	1.00 (ref)	0	39	1.00 (ref)
	5.0–1120.0	4	0.52 (0.17–1.57)	5.0–937.5	4	0.82 (0.28–2.44)
	>1120.0	13	1.18 (0.54–2.58)	>937.5	12	1.88 (0.89–3.99)
	P_{trend}		0.44	P_{trend}		0.08
Bile duct[d,e]						
	0	7	1.00 (ref)	0	7	1.00 (ref)
	5.0–1120.0	4	1.49 (0.88–2.53)	5.0–937.5	6	1.13 (0.65–1.96)
	>1120.0	5	2.49 (1.49–4.15)	>937.5	3	2.71 (1.66–4.42)
	P_{trend}		<0.001	P_{trend}		<0.001
Lung[b]						
	0	464		0	517	1.00 (ref)
	5.0–396.0	47	0.65 (0.47–0.92)	5.0–315.0	35	0.77 (0.54–1.10)
	396.1–1120.0	57	0.79 (0.58–1.07)	315.1–937.5	41	0.84 (0.60–1.17)
	1120.1–3315.0	60	0.79 (0.59–1.05)	937.6–2800.0	47	0.88 (0.64–1.21)
	>3315.0	61	0.75 (0.56–1.02)	>2800.0	43	0.79 (0.57–1.10)
	P_{trend}		0.17	P_{trend}		0.21
Kidney[b,d]						
	0	136	1.00 (ref)	0	157	1.00 (ref)
	5.0–396.0	21	0.76 (0.47–1.22)	5.0–315.0	19	0.99 (0.60–1.61)
	396.1–1120.0	34	1.09 (0.71–1.68)	315.1–937.5	33	1.76 (1.18–2.62)
	1120.1–3315.0	33	1.12 (0.74–1.71)	937.6–2800.0	24	1.27 (0.81–2.00)
	>3315.0	36	1.37 (0.91–2.06)	>2800.0	27	1.61 (1.04–2.50)
	P_{trend}		0.08	P_{trend}		0.04

(Continued)

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Table 4. Continued

Cancer site	10-Year exposure lag			20-Year exposure lag		
		n	RR (95% CI)		*n*	RR (95% CI)
Myeloid leukaemia						
	0	53	1.00 (ref)	0	67	
	5.0–396.0	12	1.04 (0.81–1.34)	5.0–315.0	10	0.54 (0.39–0.77)
	396.1–1120.0	14	0.70 (0.51–0.96)	315.1–937.5	10	0.65 (0.48–0.89)
	1120.1–3315.0	14	0.67 (0.51–0.89)	937.6–2800.0	9	0.43 (0.30–0.62)
	>3315.0	9	0.53 (0.39–0.73)	>2800.0	6	0.50 (0.35–0.71)
	P_{trend}		<0.001	P_{trend}		<0.001
Acute/other lymphocytic leukaemia						
	0	6	1.00 (ref)	0	8	1.00 (ref)
	5.0–1120.0	3	0.64 (0.32–1.27)	5.0–937.5	2	0.22 (0.08–0.62)
	>1120.0	7	1.25 (0.72–2.16)	>937.5	6	0.97 (0.58–1.65)
	P_{trend}		0.12	P_{trend}		0.50
Non-Hodgkin lymphoid malignancies						
	0	291	1.00 (ref)	0	369	1.00 (ref)
	5.0–396.0	81	1.10 (0.85–1.44)	5.0–315.0	62	1.14 (0.86–1.51)
	396.1–1120.0	84	1.15 (0.87–1.50)	315.1–937.5	63	1.16 (0.88–1.54)
	1120.1–3315.0	81	1.13 (0.86–1.48)	937.6–2800.0	61	1.13 (0.85–1.50)
	>3315.0	83	1.21 (0.92–1.60)	>2800.0	60	1.25 (0.94–1.68)
	P_{trend}		0.24	P_{trend}		0.16
Chronic/small lymphocytic leukaemia						
	0	65	1.00 (ref)	0	78	1.00 (ref)
	5.0–396.0	16	0.81 (0.66–1.00)	5.0–315.0	17	0.86 (0.69–1.07)
	396.1–1120.0	25	0.87 (0.72–1.06)	315.1–937.5	22	0.84 (0.68–1.04)
	1120.1–3315.0	24	0.80 (0.66–0.99)	937.6–2800.0	18	0.70 (0.55–0.88)
	>3315.0	25	0.95 (0.77–1.17)	>2800.0	18	0.89 (0.71–1.12)
	P_{trend}		0.98	P_{trend}		0.27
Mantle cell lymphoma						
	0	7	1.00 (ref)	0	13	1.00 (ref)
	5.0–1120.0	12	3.12 (2.07–4.68)	5.0–937.5	4	0.94 (0.57–1.54)
	>1120.0	6	1.75 (1.06–2.89)	>937.5	7	1.65 (1.06–2.58)
	P_{trend}		0.63	P_{trend}		0.02

[a]Adjusted for age, race, sex, state, applicator type, education, imazethapyr, smoking (current, former, never), family history of cancer.
[b]Additionally adjusted for pack-years smoked (tertiles by smoking status).
[c]*P*-value for trend using a Wald test.
[d]Additionally adjusted for body mass index.
[e]Additionally adjusted for alcohol consumption.

per 100 000 US adults, though it has been reported that incidence is increasing.[34] Pesticide exposure has been implicated as a potential risk factor for MCL,[35] but this is the first study to evaluate MCL risk in relation to dicamba use.

We noted an inverse association for increasing dicamba use and myeloid leukaemia. In the AHS, the herbicides glyphosate and alachlor have been associated with elevated risks of AML,[36,37] though adjusting for these herbicides did not substantially alter the inverse association for dicamba. A case-control study conducted in IA and Minnesota in the early 1980s found that dicamba use was associated with decreased risk of leukaemia.[13] However, caution should be taken comparing these results, as this earlier study included CLL in the definition of leukaemia. For lymphocytic leukaemias in our analysis [mostly acute lymphocytic leukaemias (ALL)], dicamba use was associated with elevated risk of disease; however, there were few exposed cases ($n = 13$) and these findings did not remain after lagging exposure more than 5 years. This may indicate a short latency of effect, or this may be a spurious finding based on few cases. ALL is rare (1.7 cases per 100 000) especially in adults, as about 55% of cases are diagnosed in children.[34,38] As such, certain environmental risk factors for ALL are well characterized in children,[39] but less so in adults.[40]

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In laboratory animals there is limited evidence that dicamba may be carcinogenic to rats, based on weakly elevated risks for certain tumours (lymphomas and thyroid parafollicular cell carcinomas).[33] However, a number of studies suggest that dicamba may be genotoxic. *In vitro*, dicamba increases the frequency of sister chromatid exchanges, alterations in cell cycle progression and decreases in cell proliferation in human lymphocytes.[41–43] Oxidative stress has been suggested as a mechanism by which dicamba causes DNA damage.[44] Furthermore, a single study found that inert ingredients in commercial product formulations containing dicamba, which due to the proprietary nature of commercial formulations were not known, may influence genotoxicity as well through an entirely separate mechanism.[44]

An earlier analysis in the cohort noted associations with lung and colon cancer,[5] which we did not observe in this updated analysis. Samanic *et al.*[5] found that compared with unexposed applicators, individuals in the highest tertile of dicamba exposure had ~50% greater risk of colon and lung cancer. Our study added more than 12 years of follow-up and included 250 dicamba-exposed colon cancer cases and 240 exposed lung cancer cases, compared with 59 and 52, respectively. For lung cancer, an important strength of our analysis is the evaluation of histopathologic subtypes that may have distinct aetiologies and risk factors.[45] Bonner *et al.* recently evaluated several pesticides and risk of incident lung cancer in the AHS with follow-up through 2011, and similarly did not observe an association with dicamba.[46] The slight inverse association with lung adenocarcinoma could potentially be due to residual confounding of tobacco use, as dicamba users were less likely to report being current smokers at study enrollment. Outside the AHS, no other study has evaluated dicamba exposure with these cancer sites.

One factor that makes interpretation of our results complicated in the context of historical studies of dicamba and lymphohaematopoietic cancers is the evolution of how these tumours are classified. Prior to the use of current standardized classifications of lymphoid malignancies in epidemiologic studies,[19] CLL was often classified as a leukaemia, which makes comparison of historical studies to our work challenging. In our analysis, we evaluated the finest subtype classification possible in order to avoid grouping tumours with distinct aetiologies, with all historic cases coded according to the SEER/World Health Organization Lymphoma Subtype Recode (2008).[19]

We were not able to account for spatial autocorrelation between farmer residences in our statistical analysis. This could theoretically lead to residual confounding if an unmeasured spatial covariate is related to the observed associations between dicamba use and cancer; however, we believe it is unlikely that such an unmeasured confounder exists that would meaningfully impact our risk estimates. Spatial autocorrelation could also result in issues with estimating variance if farmers in our population are not truly independent. To account for this, in our interpretation of results we evaluated not only CIs but also tests for linear trend, effect size, and existing laboratory and epidemiologic literature.

Our exposure assessment extends through the first follow-up of the AHS cohort (1999–2005), with 19.6% of the cohort continuing to use dicamba at follow-up questionnaire. However, this assessment does not include the period following approval of genetically engineered dicamba-resistant crops in the USA in 2016,[16] after which use is expected to increase. Although it is unlikely that these most recent exposures would be relevant with respect to cancer outcomes, it would be of interest to know how approval of these crops may change patterns of dicamba use and exposure. For example, the newest dicamba products on the market have been formulated to be less volatile than formulations applied historically.[47]

Conclusions

In a large prospective cohort, use of the herbicide dicamba was associated with increased risk of liver and intrahepatic bile duct cancers. Dicamba use was also inversely associated with myeloid leukaemia. Elevated risk of CLL was associated with high dicamba exposure, but this association was only observed in unlagged analyses. We additionally observed associations with tonsil cancer, lymphocytic leukaemia and MCL, though these analyses were based on fewer than 20 dicamba-exposed cases. With additional follow-up, we did not see evidence for elevated risks for lung and colon cancer that have been previously reported in the cohort. Future work should focus on replication of these findings and understanding whether the mechanisms for carcinogenicity reported in animal models, such as oxidative stress and DNA damage, are relevant in humans. Rigorous epidemiologic studies of dicamba are necessary given the potential for widespread agricultural exposures with the introduction of dicamba-resistant crops.

Supplementary data

Supplementary data are available at *IJE* online.

Acknowledgements

This work was supported by the intramural research program of the National Institutes of Health, the National Cancer Institute at the National Institutes of Health (Z01-CP010119), and the National Institute of Environmental Health Sciences at the National Institutes

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of Health (Z01-ES049030). Data in this analysis are based on Agricultural Health Study releases *P1REL201701* and *P2REL201701*.

Conflict of interest

None declared.

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