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Chemical Exposures and Risk of Acute Myeloid Leukemia and Myelodysplastic Syndromes in a Population-Based Study

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Abstract

Benzene exposure is one of the few well-established risk factors for myeloid malignancy. Exposure to other chemicals has been inconsistently associated with hematologic malignancies. We evaluated occupational and residential chemical exposures as risk factors for AML and MDS using population-based data. AML and MDS cases were identified by the Minnesota Cancer Surveillance System. Controls were identified through the Minnesota driver's license/identification card list. Chemical exposures were measured by self-report. Unconditional logistic regression was used to calculate odds ratios (ORs) and 95% confidence intervals (CI). We included 265 MDS cases, 420 AML cases, and 1388 controls. We observed significant associations between both MDS and AML and benzene (OR=1.77, 95% CI 1.19, 2.63 and OR=2.10, 95% CI 1.35, 3.28, respectively) and vinyl chlorides (OR=2.05, 95% CI 1.15, 3.63 and OR=2.81, 95% CI 1.14, 6.92). Exposure to soot, creosote, inks, dyes and tanning solutions, and coal dust were associated with AML (range ORs=2.68–4.03), while no association was seen between these exposures and MDS (range ORs=0.57–1.68). Pesticides and agricultural chemicals were not significantly associated with AML or MDS. Similar results were observed in analyses stratified by sex. In addition to providing risk estimates for benzene from a population-based sample, we also identified a number of other occupational and residential chemicals that were significantly associated with AML; however, all exposures were reported by only a small percentage of cases (10%). While chemical

exposures play a clear role in the etiology of myeloid malignancy, these exposures do not account for the majority of cases.

Introduction

Myelodysplastic Syndrome (MDS) is a heterogeneous disruption of the hematopoietic stem cell system that can progress to acute myeloid leukemia (AML) in about one third of cases. Little is known about the etiology of either malignancy; however, the large percentage of cases that progress from MDS to AML supports an overlapping etiology. Chemotherapy (particularly alkylating agents) or radiation therapy from a previous cancer can cause MDS and AML^{1, 2}. In the SEER database, these therapy-related cases account for a small percentage of MDS (1.5%)³ and AML (<1%)³, while the majority of cases are *de novo*.

Known risk factors for AML include increasing age, male sex, prior chemotherapy, cigarette smoking, obesity, exposure to benzene and other chemicals including formaldehyde^{4, 5}. Of these, age, obesity, smoking, and chemical exposures have been evaluated in MDS^{6–10}. The majority of evidence comes from case-control studies and occupational studies with a relatively small number of cases^{11–16}. While the results of these studies in MDS have not been entirely consistent, the majority support an association with benzene and other industrial chemicals^{6, 8, 11–14}.

In this analysis, we used data from population-based case-control studies of AML and MDS conducted in Minnesota to evaluate associations between both diseases and exposure to a wide range of occupational and recreational chemicals.

Materials and Methods

Case Ascertainment

Cases for both studies were identified by the Minnesota Cancer Surveillance System (MCSS), which is a population-based registry that collects information on all cancers diagnosed in Minnesota, using a rapid case ascertainment system. Pathology logs were typically received and reviewed by MCSS staff within 1–2 months of diagnosis. Cases were eligible for the study if they were a Minnesota resident, diagnosed between the ages of 20 and 79 years (up to 85 years for MDS), and could understand English or Spanish. Proxy interviews were not conducted.

AML Study

Detailed information regarding case and control recruitment and response rates has been described¹⁷. In this analysis, we included eligible cases who were diagnosed with AML (ICD-O-3 codes: 9840, 9861, 9866–9867, 9871–9874, 9891–9897, 9910, 9920) between June 1, 2005 and November 30, 2009. Centralized pathology and cytogenetics review were conducted to confirm the classification as AML as previously described¹⁷. AML cases were subclassified by the World Health Organization (WHO) subtypes¹⁸. Of the 907 patients (all subtypes of myeloid leukemia) referred to the study, 58% completed the study. This analysis

includes 420 cases with AML. Case recruitment was conducted from 6/2005—3/2010. The median time from diagnosis to questionnaire completion was 70 days (range 2—1307 days).

MDS Study

Methods for recruitment have been previously described⁹. Cases were eligible for the study if they had a diagnosis of MDS (ICD-O-3 codes: 9980, 9982–9987, 9989) between April 1, 2010 and October 31, 2014. Centralized pathology and cytogenetics review were conducted to confirm diagnosis and classify by subtypes. Only cases with confirmed MDS following independent reviews by two board-certified hematopathologists, a cytogeneticist and a medical oncologist were included in the analysis. MDS subtype was categorized based on WHO classification using the 2008 revised criteria¹⁸. Fifty-nine percent of patients referred to the study completed the interview. This analysis is based on an interim dataset of 265 cases deemed to have confirmed MDS following centralized pathology review. Recruitment of cases was conducted from 4/2010—3/2015. The median time from diagnosis to questionnaire completion was 140 days (range 7—1333).

Control Recruitment

For both studies, controls were identified through the Minnesota State driver's license/identification card list and were eligible if they were alive at the time of contact, resided in Minnesota, were between the ages of 20 and 80 years (up to 85 years for MDS controls), could understand English or Spanish, and had no prior diagnosis of myeloid leukemia. Controls were frequency matched to cases on decile of age. For the leukemia study, 701 controls were recruited (response rate 64%). For the MDS study, a total of 698 controls were recruited (interim response rate 49%). Since the same recruitment protocol and risk factor questionnaire were used, the control groups from both studies were combined to improve precision of the estimates. Control recruitment for the AML cases was conducted from 10/2005—3/2010 while controls for the MDS study were recruited from 7/2010—7/2014. The median time from first contact to questionnaire completion date was 34 days (range 2—1328 days) for AML controls and 39 days (2—1130 days) for MDS controls.

This study was approved by the Institutional Review Boards of the University of Minnesota, the Mayo Clinic, the Minnesota Department of Health and participating area hospitals.

Exposure Assessment

Exposure data were collected by a self-administered questionnaire that included demographics, anthropometrics, lifestyle factors, physical activity, medication use, medical history, reproductive history, family cancer history, farm/rural living, pesticide exposure, occupational exposures, and residential chemical exposures. Occupational pesticide exposure assessment included exposure to pesticides overall including duration of use. Respondents were also provided with a list of specific insecticides, herbicides, fungicides and fumigants and asked to report any they had mixed or applied as part of their job. In addition to the section specific to occupational pesticide exposure, we also collected information on both occupational and/or residential exposure to a variety of chemicals, including benzene, asphalt/tar/pitch, motor vehicle oils, gasoline, fertilizers, arsenic, mineral oils, soot, creosote, inks/dyes/tanning solutions, dry cleaning agents, rubber and rubber

products, vinyl chloride/plastics, acrylic and oil-based paints, varnish/lacquers/glues, paraffin waxes, coal dust, metals, if participants were exposed for at least 8 hours per week for 1 year or more. Duration of use was also recorded for each chemical on the list. We also asked the participants to report the occupation they held for the longest duration during adult life.

Statistical Analysis

Crude and adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were computed to evaluate associations between myeloid leukemia or MDS and categorical variables. Analyses were adjusted for age and sex. Other potential confounders included race/ethnicity (non-Hispanic white, other), education (high school, some post high school training, college graduate), household income (< \$40,000, ≥ \$40,000 – \$80,000, > \$80,000), smoking status (never, former, current), occupational and recreational physical activity, NSAID use (yes, no), personal and family history of cancer (yes, no), and prior cancer treatment (yes, no). Potential confounders were included in the final models if they changed the parameter estimate for the association between chemical exposures and myeloid neoplasms more than 10%. All analyses were performed using SAS (Version 9.4, SAS Institute Inc., Cary, NC, USA) and all reported p-values were two-sided. Odds ratios were not calculated when there were fewer than five exposed cases in a category.

Results

Table 1 includes selected characteristics of the MDS and AML cases and the combined control group. As expected given the higher incidence rates, there were more male cases than female cases for both AML and MDS. The majority of the cases and controls were non-Hispanic white. The MDS cases were older compared with the AML cases. There were no significant differences in education or household income in either group. Being a former smoker and having a personal history of cancer were positively associated with both AML and MDS while being a current smoker was associated only with AML.

In our analysis of occupational pesticide exposure, we did not observe any significant associations with either MDS or AML with overall pesticide exposure or by duration of use (Table 2). Due to small numbers, individual pesticides were grouped by category for analysis. We did not observe significant associations between classes of pesticide and either MDS or AML. Similar results were seen in analyses stratified by sex (data not shown).

Benzene exposure for ≥ 5 years was significantly associated with AML (OR=1.77, 95% CI 1.19, 2.63) and MDS (OR=2.10, 95% CI 1.35, 3.28; Table 3). Benzene exposure for < 5 years was also associated with AML. The association between benzene exposure for five or more years and AML was similar in males (OR=1.60, 95% CI 1.04–2.45) and females (OR=2.84, 95% CI 0.96–8.39) in a stratified analysis (Supplementary Table). Due to the limited number of exposed cases, we were unable to evaluate the association between benzene and MDS in women. We compared benzene exposed and unexposed cases to identify any differences in clinical and demographic characteristics (Table 4). As expected, exposed cases were more likely to be male (Table 4; OR=4.30, 95% CI 1.62–11.4 for MDS and OR=3.00, 95% CI 1.64–5.49 for AML). Benzene exposed cases were less likely to have

graduated from college (MDS: OR=0.30, 95% CI 0.12–0.73; AML: OR=0.56, 95% CI 0.28–1.14). Benzene exposed cases with MDS were more likely to report working on a farm (OR=2.11, 95% CI 1.08–4.51) while benzene exposed AML cases were more likely to be smokers ($p=0.02$). For MDS, exposed cases were less likely to have abnormal cytogenetics and more likely to be categorized as MDS-Unclassifiable. For AML, we did not observe cytogenetic differences but exposed cases were more likely to be therapy related and have recurrent genetic abnormalities.

Vinyl chloride was also associated with both diseases (Table 3), although the association with AML was observed only for exposures < 5 years. Soot (OR=2.68, 95% CI 1.57, 4.57), creosote (OR=2.83, 95% CI 1.46, 5.47), and coal dust (OR=4.03, 95% CI 1.79, 9.06) were associated with AML. We also observed an association of inks/dyes/tanning solutions and fertilizers with AML, although these associations were seen only in cases with short term exposure (Table 3). The association between soot and fertilizers and AML were similar in males and females (Supplementary Table). Due to the limited number of cases, we were unable to evaluate associations between AML and creosote, coal dust, and inks/dyes/tanning solutions in females.

We compared the reported chemical exposures with occupation to determine plausibility of exposures. Sixty five percent of the individuals who reported benzene exposure had an occupation in the following job categories: mechanics/repairers, construction/extractive, precision/production working, transportation/material moving, handlers/equipment cleaners/laborers, or military. The majority of the individuals who reported agriculture/forestry/fishing as their main occupation reported pesticide exposure (81%); however, of those who reported pesticide exposure, only 29% were in this job category. Since we did not collect a complete occupational history, it is possible that participants were exposed to these chemicals in a job other than their longest held occupation.

Discussion

In this comprehensive analysis of chemical exposures in myeloid malignancy, we provide additional support for the association between benzene and risk of AML and MDS in a population-based dataset. We also observed associations for vinyl chloride and both MDS and AML. Further, additional chemical exposures including soot, creosote, coal dust, fertilizers and inks/dyes/tanning solutions were associated only with AML. While we observed moderate to strong associations for these chemicals, reported exposure was uncommon in both cases and controls. Surprisingly, we did not observe associations with an extensive list of agricultural chemical exposures.

Exposure to a variety of agricultural chemicals has been evaluated as a risk factor for MDS and AML incidence and/or mortality^{6, 8, 11, 16, 19–21}. A recent meta-analysis reported a modest but statistically significant association between pesticide exposure and MDS (OR = 1.95, 95% CI 1.23, 3.09)²². For myeloid leukemia, a weak, borderline significant association was reported in a meta-analysis of studies evaluating pesticide exposure (OR=1.21, 95% CI 0.99, 1.48), with evidence that this association was significant for pesticide manufacturers or pesticide applicators but not for agricultural/farm workers¹⁹. A previous case control study

of leukemia in men in Minnesota and Iowa reported an association between leukemia overall and animal insecticides while no association was observed for fungicides, herbicides, or crop insecticides²¹. Data from the Agricultural Health Study suggest that risk of leukemia overall may differ for individual agricultural chemicals, with significant associations detected between leukemia and organochlorine insecticides, fonofos, diazinon, and EPTC^{23–26} while no associations were detected for other chemicals^{27–29}. When we evaluated questions specifically on occupational exposure to a variety of agricultural chemicals, we did not observe any significant associations. When we evaluated combined occupational and recreational exposure, we did observe an association between exposure to fertilizers and AML, although this association was restricted to individuals exposed for less than five years.

Possible reasons for the lack of association in our study include differences in the level of exposure in our study compared to previous studies (e.g. farming/agricultural exposure rather than pesticide manufacturing/application), inaccurate reporting of exposure, differences in the type of pesticide exposure and limited power. Previous studies have reported only weak associations with pesticides overall^{19, 22} while stronger associations have been observed for specific types of pesticides and leukemia. While we were able to evaluate associations for classes of pesticides, we did not have sufficient power to conduct analyses for specific pesticides in our study. A previous study in Chinese leukemia patients and controls found that self-report of most chemical exposures was comparable to using a job exposure matrix (JEM), although the correlation was lower for assessment of pesticide exposure³⁰. We did not collect a complete occupational history so we were unable to utilize a JEM; however, we did not observe an increased risk of MDS or AML in participants who reported agriculture as their longest held occupation in adulthood. While the majority of individuals who reported agriculture as their primary occupation also reported exposure to pesticides, the majority of individuals who reported occupational pesticide exposure reported other occupations.

Occupational exposure to benzene and other solvents is one of the most consistently observed risk factors for myeloid malignancy^{6, 8, 12, 13, 15, 31–37}. The International Agency for Research on Cancer (IARC) has determined that benzene exposure is carcinogenic to the bone marrow and causes both AML and MDS, with several potential mechanistic explanations for this association⁵. Currently, the major occupational uses of benzene are in the manufacture of organic chemicals and chemical intermediates⁵. Benzene also occurs naturally in petroleum products and is added to unleaded gasoline⁵. Non-occupational sources of exposure also exist, with the majority of exposure due to cigarette smoking and emissions from automobiles and industry⁵.

Most of the evidence for a role of benzene in leukemia comes from occupational studies³⁷, primarily including studies of shoe manufacturers³¹ and petroleum industry workers³². Numerous cohort studies of workers in the petrochemical industry have been conducted, with the majority supporting an association with benzene exposure for workers employed in a variety of job classifications^{12, 34–36}. Interestingly, a recent update from petroleum industry workers in Australia, Canada, and the United Kingdom reported a significant association between benzene and MDS but not AML in workers exposed to lower doses of benzene, suggesting the MDS may be the more relevant outcome for current

employees^{12, 35}. A long-standing cohort study of occupational benzene exposure in China has also documented increased risks of MDS/AML in benzene exposed workers³³, with the most recent report showing similar elevated risks in males and females and across different occupations after 28 years of follow-up³⁸. Several studies in the general population have also shown associations between benzene and MDS and AML^{6, 8, 13, 15, 16, 39}. The odds ratios we observed in our study were consistent with previously reported associations, including results from a meta-analysis of AML and benzene that reported RRs of 1.94 (95 % CI = 0.95–3.95), 2.32 (95 % CI = 0.90–5.94), and 3.20 (95 % CI = 1.09–9.45) for low, medium, and high benzene exposure, respectively⁴⁰. Similar to a previous study in China⁴¹, MDS exposed cases in our study were more likely to be classified as MDS-Unclassified and were less likely to have abnormal cytogenetics compared with MDS cases not exposed to benzene, although the numbers were very small. We did not observe any consistent differences in AML subtypes by benzene exposure.

Vinyl chloride is classified by IARC as a Group 1 carcinogen for risk of liver cancer; however, available data at the time of review did not support classification as a carcinogen for hematopoietic malignancy⁵. While a few studies have reported increased leukemia mortality following exposure to vinyl chloride^{42, 43}, the majority of studies have not reported an association⁴⁴. In our analysis, we observed significant associations between vinyl chloride and both MDS and AML, although the association with AML was observed only among individuals who reported short term exposure. In vitro data exist to suggest that a reactive metabolite of vinyl chloride, 2-chloroacetaldehyde, increases cellular levels of DNA cleavage by topoisomerase II α ⁴⁵. Given the well-documented risk of therapy related MDS and AML in individuals treated with topoisomerase II inhibitors⁴⁶, a relationship between vinyl chloride and myeloid malignancy is plausible. Further studies will be required to clarify the role of vinyl chloride in myeloid malignancy.

We also observed statistically significant associations between four additional chemicals (soot, creosote, coal dust, and inks/dyes/tanning solutions) and risk of AML, but not MDS. Little evidence exists for a role of any of these chemicals in lymphohematopoietic cancer. Creosote is a heterogeneous group of chemicals that includes wood creosote, coal tar creosote, coal tar, coal tar pitch, and coal tar pitch volatiles, and the major source of exposure is occupational⁴⁷. A number of studies have demonstrated carcinogenicity of various coal tar products⁴⁷, although results have not been entirely consistent and interpretation of results is often limited by exposure to multiple potential carcinogens in the same workers. Workers exposed to creosote at wood-treating plants in the United States did not have elevated cancer mortality⁴⁸ while an excess of lymphohematopoietic cancers was observed among aluminum reduction plant workers⁴⁹. The majority of studies that have evaluated the carcinogenicity of coal dust have been conducted in coal mine workers and have demonstrated increased risk of lung and stomach cancers⁵⁰. Soot is also a well-established carcinogen, with increased risks for scrotal and skin cancers⁵. In summary, these exposures are all known carcinogens that could plausibly increase risk of AML and MDS; however, the available evidence to date is not sufficient to determine what role these exposures play in the etiology of myeloid malignancy.

There are a number of strengths associated with our study, including rapid case ascertainment for these rapidly fatal diseases and absence of proxy interviews. The rigorous and standardized pathology review is also a strength, as this process ensures that only confirmed cases of AML and MDS were included in the analysis. However, there are also a number of limitations including the potential for recall and survival bias and the reliance on self-reported exposures. The majority of individuals who reported benzene exposure held an occupation where benzene exposure was plausible. For pesticide exposures, the majority of those with reported exposure were not employed in agriculture. We did not collect a complete occupational history so it is possible that this exposure occurred as part of a previous job. Misreporting of household pesticide exposure as occupational exposure is also possible. Inaccurate reporting of exposures in both cases and controls would produce non-differential misclassification bias and would attenuate results to the null. Given the poor outcomes associated with both AML and MDS, there is a potential for survival bias. While rapid case ascertainment was used to reduce this possibility, there is a possibility of bias if the cases who died soon after diagnosis differed with respect to their exposure history. Similarly, the absence of proxy interviews could introduce bias if cases who were unable to complete the interview due to severe illness or rapid death were more likely to be exposed to occupational chemicals; however, the validity of proxy interview data for the exposures of interest in this analysis is likely to be unreliable. Selection bias is also possible given the response rates, although we observed no difference between cases and controls with respect to education or income.

In conclusion, we confirmed the well-established risk of MDS and AML associated with benzene exposure and provide risk estimates in a population-based study. While benzene is clearly carcinogenic to the bone marrow, the majority of cases do not report exposure. Using the prevalence of the exposure from our controls (9%) as an estimate of the population exposure prevalence and the risk estimates from a meta-analysis of AML and benzene as an approximation of the relative risk⁴⁰, we estimate that the population attributable fraction for benzene exposure ranges from 8% to 16%. We also identified additional chemical exposures that have a plausible association with myeloid malignancy that should be confirmed in additional studies. While these associations have relatively strong risk estimates, the majority of cases in our study and others have not reported exposure to these chemicals^{6, 8, 11, 16}, suggesting that these exposures are not responsible for the majority of cases.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

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Novelty and Impact

The population-based design and the availability of data for both AML and MDS cases drawn from the same source population are unique features of our study. While the associations observed in our study have relatively strong risk estimates, the majority of cases have not reported exposure to these chemicals, suggesting that these exposures are not responsible for the majority of cases.

Table 1

Selected Characteristics of the Study Population (controls, MDS and AML cases)

Characteristic	MDS			AML	
	Controls	Cases	OR ³ (95% CI)	Cases	OR ³ (95% CI)
N¹	1388	265		420	
Sex²					
Male	773 (56)	180 (68)		249 (59)	
Female	615 (44)	85 (32)		171 (41)	
Age² (years)					
< 50	222 (16)	7 (3)		124 (30)	
50 – 59	250 (18)	27 (10)		90 (21)	
60 – 69	401 (29)	77 (29)		131 (31)	
70 – 79	412 (30)	98 (37)		75 (18)	
80	103 (7)	56 (21)		0	
Hispanic/Latino²					
No	1370 (99)	264 (99)		413 (98)	
Yes	17 (1)	1 (0.4)		7 (2)	
Race²					
White	1350 (97)	260 (98)		401 (95)	
Other	38 (3)	5 (2)		19 (5)	
Education					
HS grad	433 (31)	97 (37)	<i>Ref</i>	122 (29)	<i>Ref</i>
Some post HS	460 (33)	69 (26)	0.86 (0.61–1.22)	161 (39)	1.08 (0.82–1.43)
College grad	489 (35)	97 (37)	1.14 (0.83–1.58)	134 (32)	0.83 (0.62–1.10)
p-trend			0.27		0.13
Household Income					
\$40,000	496 (37)	112 (43)	<i>Ref</i>	149 (36)	<i>Ref</i>
\$40,000–\$80,000	526 (39)	92 (36)	0.98 (0.71–1.34)	165 (40)	0.99 (0.76–1.28)
> \$80,000	336 (25)	54 (21)	1.05 (0.72–1.52)	95 (23)	0.87 (0.64–1.17)
p-trend			0.94		

Characteristic	MDS			AML		
	Controls	Cases	OR ³ (95% CI)	Cases	OR ³ (95% CI)	
Smoking Status⁴						
Never smoker	694 (50)	110 (42)	<i>Ref</i>	179 (43)	<i>Ref</i>	
Former smoker	521 (38)	137 (52)	1.48 (1.12–1.97)	161 (39)	1.43 (1.11–1.84)	
Current smoker	162 (12)	17 (6)	0.88 (0.51–1.53)	74 (18)	1.56 (1.12–2.16)	
p-trend			0.01		0.004	
Lived on farm/rural area 1 year						
No	547 (39)	114 (43)	<i>Ref</i>	182 (43)	<i>Ref</i>	
Yes	841 (61)	151 (57)	0.70 (0.53–0.92)	238 (57)	0.99 (0.79–1.24)	
Lived or worked on farm 1 year						
No	780 (56)	147 (56)	<i>Ref</i>	262 (63)	<i>Ref</i>	
Yes	607 (44)	117 (44)	0.83 (0.63–1.09)	157 (37)	0.90 (0.72–1.14)	
Personal History of cancer						
No	1215 (88)	187 (71)	<i>Ref</i>	353 (84)	<i>Ref</i>	
Yes	173 (12)	78 (29)	2.10 (1.53–2.90)	67 (16)	1.91 (1.38–2.64)	

OR: Odds Ratio; CI: Confidence Interval

¹Numbers may not sum to total due to missing values

²Odds ratios not computed for sex, age (matching variables), race and ethnicity.

³ORs adjusted for age as a continuous variable

⁴Smoking status includes cigarette smoking only

Table 2

Association between occupational agricultural chemicals and MDS/AML

Characteristic	MDS				AML			
	Controls ² N ^I = 1388	Cases N ^I = 265	OR ³	95% CI	Controls ² N ^I = 1348	Cases N ^I = 405	OR ⁴	95% CI
Occupational pesticide exposure (years)								
None	1146 (83)	220 (83)	<i>Ref</i>		1114 (83)	342 (84)	<i>Ref</i>	
Any	242 (17)	45 (17)	0.89	0.60–1.32	234 (17)	63 (16)	0.89	0.64–1.24
None	1146 (83)	220 (83)	<i>Ref</i>		1114 (83)	342 (84)	<i>Ref</i>	
< 1 year – 10 years	151 (11)	27 (10)	0.96	0.60–1.55	145 (11)	43 (11)	0.90	0.61–1.32
> 10 years	91 (7)	18 (7)	0.80	0.45–1.41	89 (7)	20 (5)	0.87	0.51–1.47
p-trend				0.74				0.78
Pesticide Classes⁵								
Any pesticide, crop, livestock, or structural insecticides, herbicides, fungicides, or fumigants	223 (16)	41 (15)	0.85	0.57–1.28	215 (16)	58 (14)	0.93	0.66–1.31
None	1165 (94)	224 (85)			1133 (84)	347 (86)		
Any Crop, Nursery, Lawn & Garden Insecticides	62 (4)	13 (5)	1.16	0.60–2.22	61 (5)	11 (3)	0.57	0.29–1.12
None	1326 (96)	252 (95)			1287 (95)	394 (97)		
Any Crop, Poultry, Livestock, Animal Confinement Area Insecticides	170 (12)	33 (12)	0.96	0.62–1.50	162 (12)	34 (8)	0.74	0.49–1.11
None	1218 (88)	232 (88)			1186 (88)	371 (92)		
Any herbicide	199 (14)	35 (13)	0.82	0.53–1.26	194 (14)	52 (13)	0.91	0.63–1.29
None	1189 (86)	230 (87)			1154 (86)	353 (87)		
Any fungicide	20 (1)	7 (3)	1.74	0.70–4.34	20 (1)	7 (2)	1.36	0.56–3.31
None	1368 (99)	258 (97)			1328 (99)	398 (98)		
Any fumigant	29 (2)	4 (2)	-	-	29 (2)	11 (3)	1.44	0.70–2.99
None	1359 (98)	261 (98)			1319 (98)	394 (97)		

OR: Odds Ratio; CI: Confidence Interval

¹Numbers may not sum to total number of cases/controls due to missing values.²Controls are different for MDS and AML due to missing values for different covariates in the analyses³MDS ORs adjusted for age (continuous), sex, exposure to chemotherapy, and having lived on a farm or in a rural area 1 year

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4 AML ORs adjusted for age (continuous), sex, household income (< \$40,000, \$40,000–\$80,000, > \$80,000), smoking (ever, never), exposure to radiation, and having lived on a farm or in a rural area 1 year

5 Report of specific pesticides in each category were combined for analysis. Numbers may not sum to total if respondents reported using pesticides overall but didn't specify the name of the pesticide used. Participants could report exposure in more than one category.

Table 3
Association between occupational or recreational exposure to other chemicals and MDS/AML

Characteristic	MDS				AML			
	Controls ² N ^I = 1388	Cases N ^I = 265	OR ³	95% CI	Controls ² N ^I = 1348	Cases N ^I = 405	OR ⁴	95% CI
Benzene or other solvents								
None	1260 (91)	221 (84)	<i>Ref</i>		1223 (91)	332 (82)	<i>Ref</i>	
< 5 years	32 (2)	5 (2)	0.79	0.29–2.17	30 (2)	26 (6)	2.74	1.57–4.80
5 years	92 (7)	36 (14)	2.10	1.35–3.28	91 (7)	45 (11)	1.77	1.19–2.63
p-trend				0.004				<.0001
Cutting oils, motor vehicle oils								
None	1181 (85)	212 (81)	<i>Ref</i>		1144 (85)	336 (83)	<i>Ref</i>	
< 5 years	39 (3)	5 (2)	0.72	0.27–1.92	38 (3)	11 (3)	0.75	0.37–1.53
5 years	167 (12)	46 (17)	1.38	0.92–2.05	165 (12)	58 (14)	1.10	0.78–1.56
p-trend				0.21				0.61
Asphalt, tar or pitch								
None	1328 (96)	247 (94)	<i>Ref</i>		1290 (96)	384 (95)	<i>Ref</i>	
< 5 years	19 (1)	8 (3)	1.89	0.78–4.60	19 (1)	12 (3)	1.95	0.91–4.18
5 years	38 (3)	7 (3)	0.79	0.33–1.89	36 (3)	8 (2)	0.77	0.35–1.71
p-trend				0.31				0.18
Gasoline								
None	1223 (88)	225 (86)	<i>Ref</i>		1185 (88)	343 (85)	<i>Ref</i>	
< 5 years	40 (3)	4 (2)	-	-	40 (3)	14 (3)	0.96	0.50–1.83
5 years	124 (9)	33 (13)	1.11	0.71–1.74	122 (9)	46 (11)	1.40	0.95–2.06
p-trend								0.22
Fertilizers								
None	1300 (94)	246 (93)	<i>Ref</i>		1262 (94)	365 (90)	<i>Ref</i>	
< 5 years	15 (1)	6 (2)	2.04	0.73–5.76	15 (1)	15 (4)	2.77	1.30–5.93
5 years	71 (5)	13 (5)	0.74	0.39–1.41	69 (5)	24 (6)	1.40	0.85–2.31
p-trend				0.25				0.02
Mineral Oils								

Characteristic	MDS					AML				
	Controls ²		Cases		OR ³	95% CI		Controls ²		OR ⁴
	N ¹ = 1388	N ¹ = 1388	N ¹ = 265	N ¹ = 265				N ¹ = 1348	N ¹ = 405	
None	1344 (97)	1344 (97)	257 (97)	257 (97)	Ref			1305 (97)	392 (97)	
< 5 years	7 (1)	7 (1)	3 (1)	3 (1)	-	-	-	7 (1)	4 (1)	-
5 years	35 (3)	35 (3)	5 (2)	5 (2)	0.72	0.27-1.94	0.72	34 (3)	8 (2)	0.72
p-trend										0.32-1.60
Soot										
None	1344 (97)	1344 (97)	256 (97)	256 (97)	Ref			1305 (97)	375 (93)	Ref
< 5 years	4 (0.3)	4 (0.3)	-	-	-	-	-	4 (0.3)	3 (1)	-
5 years	37 (3)	37 (3)	9 (3)	9 (3)	1.04	0.47-2.31	1.04	36 (3)	27 (7)	2.68
p-trend										1.57-4.57
Creosote										
None	1344 (97)	1344 (97)	254 (96)	254 (96)	Ref			1307 (97)	385 (95)	Ref
< 5 years	13 (1)	13 (1)	1 (0.4)	1 (0.4)	-	-	-	13 (1)	2 (1)	-
5 years	26 (2)	26 (2)	9 (3)	9 (3)	1.31	0.56-3.05	1.31	23 (2)	17 (4)	2.83
p-trend										1.46-5.47
Inks, dyes, tanning solutions										
None	1326 (96)	1326 (96)	256 (97)	256 (97)	Ref			1286 (96)	374 (93)	Ref
< 5 years	13 (1)	13 (1)	3 (1)	3 (1)	-	-	-	13 (1)	14 (3)	3.14
5 years	46 (3)	46 (3)	5 (2)	5 (2)	0.57	0.22-1.51	0.57	46 (3)	16 (4)	1.17
p-trend										0.64-2.12
Dry cleaning agents										0.02
None	1367 (99)	1367 (99)	259 (98)	259 (98)	Ref			1327 (99)	394 (97)	Ref
< 5 years	7 (1)	7 (1)	3 (1)	3 (1)	-	-	-	7 (1)	6 (1)	2.85
5 years	11 (1)	11 (1)	2 (1)	2 (1)	-	-	-	11 (1)	5 (1)	1.56
p-trend										0.52-4.62
Rubber and rubber products										
None	1303 (94)	1303 (94)	253 (95)	253 (95)	Ref			1264 (94)	383 (95)	Ref
< 5 years	12 (1)	12 (1)	1 (0.4)	1 (0.4)	-	-	-	12 (1)	8 (2)	1.90
5 years	71 (5)	71 (5)	11 (4)	11 (4)	0.91	0.46-1.79	0.91	70 (5)	14 (3)	0.57
p-trend										0.31-1.04

Characteristic	MDS				AML			
	Controls ² N ^I = 1388	Cases N ^I = 265	OR ³	95% CI	Controls ² N ^I = 1348	Cases N ^I = 405	OR ⁴	95% CI
Vinyl chloride, plastics								
None	1325 (96)	241 (91)	<i>Ref</i>		1287 (96)	378 (93)	<i>Ref</i>	
< 5 years	10 (1)	4 (2)	-	-	10 (1)	11 (3)	2.81	1.14-6.92
5 years	50 (4)	20 (8)	2.05	1.15-3.63	49 (4)	16 (4)	1.03	0.57-1.86
p-trend								0.08
Acrylic and oil-based paints								
None	1265 (91)	239 (90)	<i>Ref</i>		1229 (91)	359 (89)	<i>Ref</i>	
< 5 years	37 (3)	7 (3)	0.91	0.39-2.12	37 (3)	18 (4)	1.74	0.96-3.15
5 years	83 (6)	19 (7)	1.05	0.60-1.81	79 (6)	27 (7)	1.16	0.73-1.85
p-trend				0.96				0.17
Varnish, lacquers, or glues								
None	1275 (92)	240 (91)	<i>Ref</i>		1239 (92)	365 (90)	<i>Ref</i>	
< 5 years	33 (2)	5 (2)	0.68	0.25-1.83	32 (2)	10 (2)	1.01	0.48-2.11
5 years	78 (6)	20 (8)	1.12	0.65-1.92	75 (6)	29 (7)	1.29	0.82-2.05
p-trend				0.68				0.55
Coal Dust								
None	1359 (98)	257 (97)			1322 (98)	392 (97)	<i>Ref</i>	
< 5 years	10 (1)	2 (1)	-	-	9 (1)	1 (0.3)	-	-
5 years	15 (1)	6 (2)	1.68	0.63-4.50	13 (1)	12 (3)	4.03	1.79-9.06
p-trend								
Metals (lead, nickel, zinc)								
None	1309 (94)	242 (91)	<i>Ref</i>		1272 (95)	368 (91)	<i>Ref</i>	
< 5 years	16 (1)	5 (2)	1.90	0.64-5.61	16 (1)	10 (2)	1.72	0.75-3.97
5 years	61 (4)	18 (7)	1.24	0.69-2.21	58 (4)	27 (7)	1.44	0.88-2.35
p-trend				0.41				0.17
Radioactive materials								
None	1372 (99)	261 (98)	<i>Ref</i>		1332 (99)	400 (99)	<i>Ref</i>	
< 5 years	5 (0.4)	1 (0.4)	-	-	5 (0.4)	4 (1)	2.70	0.70-10.4
5 years	8 (0.6)	3 (1)	-	-	8 (0.6)	1 (0.3)	0.54	0.07-4.48

Characteristic	MDS				AML			
	Controls ² N ¹ = 1388	Cases N ¹ = 265	OR ³	95% CI	Controls ² N ¹ = 1348	Cases N ¹ = 405	OR ⁴	95% CI
p-trend								0.30
X-ray machines								
None	1360 (98)	261 (98)	Ref		1321 (98)	395 (98)	Ref	
< 5 years	9 (0.7)	-	-	-	9 (0.7)	5 (1)	1.66	0.53–5.22
5 years	17 (1)	4 (2)	-	-	16 (1)	5 (1)	1.19	0.42–3.23
p-trend								0.65

OR: Odds Ratio; CI: Confidence Interval

¹Numbers may not sum to total number of cases/controls due to missing values

²Controls are different for MDS and AML due to missing values for different covariates in the analyses

³ORs adjusted for age (continuous), sex, exposure to chemotherapy, and having lived on a farm or in a rural area 1 year

⁴ORs adjusted for age (continuous), sex, household income (< \$40,000, \$40,000–\$80,000, > \$80,000), smoking (ever, never), exposure to radiation, and having lived on a farm or in a rural area 1 year

Table 4
Comparison of demographic and disease characteristics in benzene exposed and unexposed cases

Characteristic	MDS			AML		
	Benzene Exposure N ^I = 43	No Benzene Exposure N ^I = 220	OR (95% CI)	Benzene Exposure N ^I = 74	No Benzene Exposure N ^I = 337	OR (95% CI)
Sex N (%)						
Female	5 (12)	79 (36)	Ref.	16 (22)	152 (45)	Ref.
Male	38 (88)	141 (64)	4.30 (1.62–11.39)	58 (78)	185 (55)	3.00 (1.64–5.49)
Age at diagnosis N (%)						
50	1 (2)	6 (3)	-	18 (24)	101 (30)	0.69 (0.17–2.83)
50 – 59	5 (12)	21 (10)	1.13 (0.24–5.36)	17 (23)	72 (21)	0.92 (0.40–2.10)
60 – 69	14 (33)	62 (28)	Ref.	28 (38)	102 (30)	Ref.
70 – 79	18 (42)	80 (36)	0.93 (0.24–3.57)	11 (15)	62 (18)	0.63 (0.26–1.54)
80	5 (12)	51 (23)	0.38 (0.04–3.80)	-	-	-
Education N (%)						
≤ HS	21 (49)	75 (34)	Ref.	23 (32)	98 (29)	Ref.
Post-HS	13 (30)	56 (26)	0.68 (0.30–1.54)	35 (48)	121 (36)	1.24 (0.69–2.25)
College graduate	9 (21)	87 (40)	0.30 (0.12–0.73)	15 (21)	116 (35)	0.56 (0.28–1.14)
Smoking Status ² N (%)						
Never	16 (37)	93 (42)	Ref.	20 (28)	154 (46)	Ref.
Former	24 (56)	112 (51)	1.24 (0.62–2.47)	37 (52)	122 (37)	2.35 (1.27–4.34)
Current	3 (7)	14 (6)	1.15 (0.29–4.51)	15 (21)	57 (17)	2.02 (0.97–4.23)
Lived or worked on a farm 1 year N (%)	25 (58)	90 (41)	2.11 (1.08–4.51)	29 (39)	125 (37)	1.05 (0.62–1.78)
No	18 (42)	129 (59)	Ref.	45 (61)	211 (63)	Ref.
Personal History of cancer N (%)	13 (30)	63 (29)	1.08 (0.53–2.21)	17 (23)	50 (15)	1.68 (0.89–3.17)
No	30 (70)	157 (71)	Ref.	57 (77)	287 (85)	Ref.
Cytogenetics						
Abnormal	14 (39)	101 (54)	0.54 (0.26–1.14)	44 (63)	176 (58)	1.27 (0.73–2.21)
Normal	22 (61)	84 (45)	Ref.	26 (37)	127 (42)	Ref.
WHO Disease Subtype (MDS)						
RARS	7 (16)	39 (18)	1.43 (0.50–4.08)			
RCMD	14 (33)	49 (22)	1.86 (0.77–4.48)			

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Characteristic	MDS			AML		
	Benzene Exposure N _I = 43	No Benzene Exposure N _I = 220	OR (95% CI)	Benzene Exposure N _I = 74	No Benzene Exposure N _I = 337	OR (95% CI)
RAEB 1/2	12 (28)	80 (36)	Ref.			
Therapy related	5 (12)	33 (15)	1.05 (0.33–3.31)			
MDS with del 5q	0	11 (5)	-			
MDS-U	5 (12)	8 (4)	4.52 (1.20–17.0)			
WHO Disease Subtype (AML)						
With recurrent genetic abnormalities (A,B,C,D)				20 (29)	70 (22)	1.79 (0.88–3.62)
With multilineage dysplasia (E)				6 (9)	33 (10)	0.88 (0.33–2.36)
Therapy related (F)				5 (7)	8 (3)	4.82 (1.36–17.1)
Without specific lineage of differentiation (G1/G2/G3/G10)				26 (37)	136 (43)	Ref.
With a specific differentiation pattern (G4/G5/G6)				13 (19)	73 (23)	0.88 (0.42–1.83)

OR: odds ratio; CI: confidence interval

¹Numbers may not sum to total due to missing values

²Smoking status includes cigarette smoking only