Environment International 125 (2019) 229–235

Contents lists available at ScienceDirect

Environment International

journal homepage: www.elsevier.com/locate/envint

Pre-diagnostic serum concentrations of organochlorines and risk of acute myeloid leukemia: A nested case-control study in the Norwegian Janus Serum Bank Cohort

Bryan A. Bassig[a,*], Lawrence S. Engel[b], Hilde Langseth[c], Tom K. Grimsrud[c], Kenneth P. Cantor[a], Roel Vermeulen[d], Mark P. Purdue[a], Dana Boyd Barr[e], Jason Y.Y. Wong[a], Aaron Blair[a], Nathaniel Rothman[a,1], Qing Lan[a,1]

[a] Occupational and Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA
[b] Department of Epidemiology, University of North Carolina Gillings School of Global Public Health, Chapel Hill, NC, USA
[c] Department of Research, Cancer Registry of Norway, Institute of Population-Based Cancer Research, Oslo, Norway
[d] Institute for Risk Assessment Sciences, Division of Environmental Epidemiology, Utrecht University, Utrecht, the Netherlands
[e] Department of Environmental Health, Rollins School of Public Health, Emory University, Atlanta, GA, USA

ARTICLE INFO

Handling Editor: Heather Stapleton

Keywords:
Acute myeloid leukemia
Organochlorines
Pesticides
Polychlorinated biphenyls

ABSTRACT

Background: Epidemiologic studies suggest an increased risk of leukemia among individuals occupationally exposed to some organochlorine (OC) compounds. Associations between serum OC pesticide and polychlorinated biphenyl (PCB) levels and risk of acute myeloid leukemia (AML), the most common subtype of acute leukemia in adult populations, have not been evaluated prospectively in the general population.

Objective: We evaluated the risk of AML in relation to pre-diagnostic serum levels of OC pesticides and PCBs in a case-control study nested within the Janus Serum Bank Cohort.

Methods: Janus is a large population-based cohort containing biologic samples collected beginning in the early 1970s from ~318,000 individuals in Norway. Serum levels of 11 OC pesticides or their metabolites and 34 PCB congeners were measured in 56 AML cases and 288 controls. Conditional logistic regression was conducted to evaluate associations between lipid-adjusted serum OC levels and risk of AML.

Results: Higher serum levels of total chlordane/heptachlor metabolites were associated with AML risk (3rd vs. 1st tertile odds ratio (OR) = 2.26, 95% confidence interval (CI) = 0.91–5.63; p_{trend} = 0.11). Significant exposure-response associations were observed for levels of heptachlor epoxide (3rd vs. 1st tertile OR = 2.85, 95% CI = 1.05–7.73; p_{trend} = 0.02) and dieldrin (3rd vs. 1st tertile OR = 2.71, 95% CI = 1.07–6.83; p_{trend} = 0.03). No significant exposure-response associations with AML risk were observed for total DDT or individual isomers and derivatives. Higher serum levels of p,p′-DDT showed a non-significant increase in risk, but the exposure-response became attenuated when co-adjusting for heptachlor epoxide or dieldrin levels. Serum PCB levels were not significantly associated with AML risk.

Conclusions: Our data suggest that higher serum levels of dieldrin and metabolites derived from chlordane/heptachlor are associated with risk of AML in the general Norwegian population, based on samples collected on average ~17 years before diagnosis. Further research in populations with historically high or recent exposure to DDT is warranted to assess the association with AML risk with body burden of specific DDT isomers and derivatives.

1. Introduction

Organochlorine compounds (OC) are a class of structurally diverse chemicals that are widespread environmental contaminants resulting from their use as pesticides and for other industrial applications. OCs include chemicals that have been manufactured and applied as

* Corresponding author at: Occupational & Environmental Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, 9609 Medical Center Drive, Rm. 6E132, Rockville, MD 20850, USA.
E-mail address: bryan.bassig@nih.gov (B.A. Bassig).
[1] Co-senior authors.

https://doi.org/10.1016/j.envint.2019.01.066
Received 6 August 2018; Received in revised form 22 January 2019; Accepted 24 January 2019
Available online 02 February 2019

pesticides, including dichlorodiphenyltrichloroethane (DDT) and chlorinated alicyclics (e.g. chlordane), as well as polychlorinated biphenyls (PCBs), which are persistent organic pollutants consisting of 209 chemical congeners that were produced and used for a variety of industrial processes and products beginning in the 1930s (Ross, 2004). Commercial products that have contained PCBs include transformers and capacitors, as well as oil-based paints and other building materials.

Commercial uses of OCs have been phased out in most developed countries because of concerns about their environmental persistence, biomagnification, and adverse environmental and health effects (Ross, 2004). However, DDT continues to be used in several countries for vector control (van den Berg et al., 2017), and PCBs are still found in older products such as electrical transformers and building materials and may consequently leach from waste disposal sites if improperly disposed of. Shared chemical properties of OC pesticides and PCBs, specifically their environmental persistence and ability to bioaccumulate in adipose tissue, result in continued exposure from dietary sources and environmental contamination. Occupational sources of exposure are also still possible particularly in countries where DDT is still used and in farming populations who may have continued contact with OC residues. The widespread environmental exposure to OCs has been well-documented in population-based biomonitoring studies (Sjodin et al., 2014). For instance, data from the National Health and Nutrition Examination Survey (NHANES) show that a relatively large proportion (i.e., > 50%) of the general population in the United States continues to have detectable serum levels of OCs, with levels generally higher among older individuals (Sjodin et al., 2014; Xue et al., 2014). Levels of PCBs and OC pesticides also continue to be detectable among Norwegians and the consumption of fatty fish and gull eggs has been suggested as important sources of OC exposure in this population (Polder et al., 2009). PCBs were used for industrial purposes in Norway until 1980. DDT specifically was used in Norway until 1970 as an insecticide including in orchards and to treat conifer seedlings, and high concentrations continue to be measured in mussels and fish since the early 1990s (Ruus et al., 2010; Bakke, 1970).

Specific OCs have been associated with human cancer risk with varying degrees of evidence. The International Agency for Research on Cancer (IARC) concluded in 2013 that there is sufficient evidence to classify PCBs as a human carcinogen (Group 1) based on their association with malignant melanoma and additional evidence for positive associations with non-Hodgkin lymphoma (NHL) and breast cancer (International Agency for Research on Cancer, 2015). The insecticides lindane and pentachlorophenol are classified as Group 1 carcinogens based on sufficient evidence in humans for an association with NHL (Guyton et al., 2016; Loomis et al., 2015). DDT and dieldrin are classified as probable human carcinogens (Group 2A) (Guyton et al., 2016; Loomis et al., 2015), whereas chlordane, heptachlor, and hexachlorobenzene (HCB) were evaluated by IARC in 2001 and classified as possible human carcinogens (Group 2B) (International Agency for Research on Cancer, 2001).

Findings from pesticide-exposed occupational cohorts suggest an increased risk of myeloid leukemia (ML), or specifically the acute myeloid leukemia (AML) subtype, although the extent to which OCs specifically contribute to this risk is unclear given the likely exposure to multiple classes of pesticides among these workers (Van Maele-Fabry et al., 2007). In the prospective Agricultural Health Study (AHS), ever-exposure to OC pesticides among applicators was associated with a statistically significant two-fold increased risk of overall leukemia, an effect driven by chlordane/heptachlor exposure (Purdue et al., 2007). An analysis of female spouses of pesticide applicators exposed to chlordane in the AHS showed a non-significantly elevated risk of myeloid leukemia, although the number of exposed cases was small (Louis et al., 2017). A higher risk of AML among farmers who used DDT at least 20 years prior to being interviewed has also been reported in a population-based case-control study in Iowa and Minnesota (Brown et al., 1990). There are currently no prospective data on serum levels of OC compounds and risk of AML, the most common subtype of acute leukemia in adult populations.

Experimental studies and case-reports, as well as some epidemiological evidence, suggest immunotoxicity and/or development of blood dyscrasias, including aplastic anemia, among individuals exposed to certain OC compounds (Rugman and Cosstick, 1990; Serdar et al., 2014; Tryphonas et al., 2003). Chlordane and heptachlor, which have been used as insecticides in the residential setting, have long been suspected to be myelotoxic based on reports of anemias, thrombocytopenia, and leukemias in humans exposed in both residential and occupational settings (Epstein and Ozonoff, 1987). These hematologic effects resemble those resulting from occupational exposure to benzene, a known cause of AML (Lan et al., 2004). Further, higher serum levels of PCBs have been associated with reduced red and white blood cell counts in an analysis of NHANES data (Serdar et al., 2014), and some PCB congeners share similar toxicological properties as dioxins (Giesy and Kannan, 1998), which were associated with myeloid leukemia risk in subjects residing around the site of a large industrial accident in Seveso, Italy (Bertazzi et al., 2001; Pesatori et al., 2009). These findings support the biologic plausibility that at least some OC pesticides may be associated with AML risk, given the observed relationship between immunosuppression and development of this hematologic malignancy in humans (Gale and Opelz, 2012; Isidori et al., 2014).

While these observations are suggestive of a potential role of OCs in the development of myeloid leukemogenesis, epidemiologic investigations are needed to determine if serum OC levels are associated with AML in the general population. To evaluate this hypothesis, we conducted a case-control study nested within the prospective Janus Serum Bank Cohort in Norway, which has stored pre-diagnostic blood samples collected beginning in the early 1970s.

2. Methods

2.1. Study population

The study population in the Janus Serum Bank Cohort has been described in detail elsewhere (Koutros et al., 2015; Langseth et al., 2017; Purdue et al., 2009). Briefly, the cohort is based on a large population-based research biobank that includes serum samples from ~318,000 Norwegians who were recruited from one of two sources. Approximately 90% of cohort participants were recruited from cardiovascular health surveys (age range 20–49 years) conducted in selected counties (Finnmark, Oslo, Sogn og Fjordane, and Oppland) in Norway during the 1970s and 1980s. The participation rates for the cohort ranged from 65 to 87% across these counties. Another approximately 10% of the cohort were recruited from Red Cross blood donors, who were not included in the present study. Serum was collected from all participants and stored at −25 degrees Celsius (Langseth et al., 2017). At the time of blood collection, information on smoking habits for each participant was collected and was provided to the study team by the Norwegian Institute of Public Health (Hjerkind et al., 2017). The study was approved by the regional committees for medical and health research ethics, Oslo, Norway (REC no. 2010/3054) and is based on a broad consent from the Janus participants.

2.2. Case and control identification

This nested case-control study of AML is part of a larger study within the Janus Serum Bank Cohort designed to evaluate associations between OC compounds and nine different cancer types. To identify incident cancer cases, participants in the Janus Serum Bank Cohort were linked to the Cancer Registry of Norway using their national personal identification number. Controls were randomly selected members of the cohort who were cancer-free (except for nonmelanoma skin cancer if present) at the time of their matched case's diagnosis. Initially, at least 1 control was matched to each AML case by sex,

county of residence, age at blood draw (2-year strata), and date of blood draw (1-year strata) ($n = 75$ controls). To increase statistical power, additional controls ($n = 213$) that were initially matched to other cancer types but analyzed in the same laboratory batch as an AML case were also included in the statistical analyses. The current study includes 56 cases of AML (range in time between blood collection and diagnosis = 3.9 to 27.6 years) who were diagnosed between 1978 and 2002 and 288 total controls. All subjects in this nested case-control study provided blood samples between the years 1972 and 1978.

2.3. Laboratory analyses

Laboratory methods and procedures for the overall Janus OC project, which also apply to the current study of AML, have been previously described in detail (Koutros et al., 2015). Briefly, serum concentrations of 11 OC pesticides or their metabolites (o,p′-DDT, p,p′-DDE, p,p′-DDT, β-hexachlorocyclohexane (β-HCH), γ-hexachlorocyclohexane (γ-HCH), dieldrin, HCB, mirex, heptachlor epoxide, oxychlordane, and trans-nonachlor), 34 PCB congeners (International Union of Pure and Applied Chemistry (IUPAC) congeners 18, 28, 44, 49, 52, 66, 74, 87, 99, 101, 118, 128, 138, 146, 149, 151, 153, 156, 157, 167, 170, 172, 177, 178, 180, 183, 187, 189, 194, 195, 196, 201, 206, 209), and lipid levels were measured at the United States Centers for Disease Control and Prevention (CDC), National Center for Environmental Health. These analytes represent the major classes of OC pesticides and PCB congeners that have been observed to be detectable in human populations and are measured as part of a standard panel at the CDC. Each serum sample was spiked with isotopically labeled internal standards and then purified by automated accelerated solvent extraction and high-resolution gel permeation chromatography on a high-performance liquid chromatograph. Concentrated extracts were analyzed by gas chromatography/high-resolution mass spectrometry (Barr et al., 2006; Barr et al., 2003). A parametric model-based estimation procedure was used to impute values that were below the instrumental limits of detection (LOD) (Lubin et al., 2004), with a total of five separate imputed datasets constructed. As a QC check for possible errors in measurement due to interfering compounds, the ratio of ^{35}Cl to ^{37}Cl was calculated for each analyte and compared with the expected ratio for that analyte. Analyte measurements with observed isotope ratios (IRs) greater than ± 20% of the expected IR were flagged as being out of tolerance (OFT) and were treated as imputed measurements. Analytes with measurements either < LOD or flagged as OFT in at least 50% of subjects were excluded from the statistical analyses.

Measurements of total cholesterol and triglycerides were used to calculate total lipid concentrations, which were then used for the lipid-adjustment of OC measurement values (Phillips et al., 1989). Masked QC samples, which consisted of pairs of replicate samples and single QC samples from a pool, were randomly included in the laboratory batches. The median intra- and interbatch coefficients of variation (CV) across analytes was 6 and 37, respectively. For the pesticides, the median intraclass correlation coefficient (ICC) was 0.86 and was > 0.8 for 10 of 11 compounds measured (an outlier was mirex with an ICC of 0.15). For the PCBs, the median ICC was 0.94 and was > 0.8 for 32 of the 34 measured compounds (ICCs for congeners 167 and 189 were both 0.77). All matched sets of AML cases and controls in the current study were analyzed in the same laboratory batches.

2.4. Statistical analyses

Concentrations of lipid-adjusted OCs were initially compared between AML cases and all controls using Wilcoxon rank sum tests. OC concentrations were then categorized into tertiles according to the distribution of each analyte among all 288 study controls. Conditional logistic regression models stratified on laboratory batch were used to calculate odds ratios (ORs) and 95% confidence intervals (95% CIs) for the associations between OC compounds and risk of AML, with adjustment for sex, county of residence, continuous age at blood draw, continuous date of blood collection, and smoking status (ever, former, never). Further adjustment for body mass index (BMI) resulted in similar results and this variable was not retained in the final analyses. The MIANALYZE procedure in SAS was used to combine the parameter estimates and standard errors to obtain the appropriate variance, given the imputed data. The laboratory batch was used as the matching variable in the models to account for interbatch laboratory variation in the OC measurements, as well as to include additional controls in the analysis that were originally matched to other case types in order to maximize statistical power. To evaluate exposure-response relationships, OC compounds were modeled using the median values of the exposure tertiles as a continuous variable.

We also conducted several sensitivity analyses. Associations between lipid-adjusted OCs and AML risk were evaluated using conditional logistic regression models including all AML cases, but with only controls who were directly matched to those cases on the aforementioned matching variables ($n = 75$). These models were stratified on the matched strata and were further adjusted for smoking status. In addition, we conducted sensitivity analyses excluding samples flagged as OFT that were > 10 times larger than the instrumental LOD for the specific analytes (corresponding on average to < 1% of the samples across all analytes). These analyses showed similar results to models including all samples, and therefore all samples were retained in the results presented here. Third, we conducted analyses of AML risk using the sample weight adjusted OC levels (spearman r between the sample weight and lipid adjusted measurements ranged from +0.86 to +0.99 across all compounds) with models further adjusted for BMI.

Associations with OCs were evaluated using several exposure metrics. Each OC was evaluated individually, as well as total concentrations of pesticide metabolites and a priori groupings of PCBs based on degree of chlorination or biologic activity. Specifically, we evaluated associations for total chlordane/heptachlor-related compounds (sum of heptachlor epoxide, oxychlordane, and *trans*-nonachlor), total DDT (sum of *o,p′*-DDT, *p,p′*-DDT, and *p,p′*-DDE), total PCBs (sum of all PCB congeners), and PCBs based on the levels of chlorination (low chlorinated: PCB congeners 18, 28, 44, 49, 52, 66, and 74; moderately chlorinated: PCB congeners 99, 118, 128, 138, 146, 153, 156, 157, 167, 170, 172, 177, 178, and 189; and highly chlorinated: PCB congeners 194, 195, 196, 201, 206, and 209). PCBs were additionally categorized according to groupings proposed by Wolff et al. (Wolff et al., 1997), which are based on the functional characteristics of the congeners (Wolff 1A: PCB congeners 44, 49, and 52; Wolff 1B: PCB congeners 101, 177, 187, and 201; Wolff 2A: PCB congeners 66, 74, 118, 156, and 167; Wolff 2B: PCB congeners 128, 138, and 170; Wolff 3: PCB congeners 99, 153, 180, 183, and 196). Finally, analyses were conducted for the sum of dioxin-like PCBs (PCB congeners 118, 156, 157, 167, and 189). All tests were two-sided and conducted at the $\alpha = 0.05$ level, and all analyses were conducted using SAS v. 9.3 (Cary, NC).

3. Results

Selected characteristics of the AML cases and controls included in the analysis are shown in Table 1. The average age at blood collection was 44 years (± 6) in AML cases and 43 years (± 6) in controls, with the majority of participants providing blood samples between 1975 and 1978 (55% of AML cases and 59% of controls). A majority of participants in the analysis were male (68% of AML cases and 62% of controls). Compared to controls, AML cases had a slightly higher proportion of current smokers (55% vs. 48%). A similar proportion had a BMI < 25 kg/m^2 (57% vs. 56%). Among cases, the average age at AML diagnosis was 61 ± 9 years and the average number of years from blood draw to diagnosis was 17 ± 6 years. Nearly all of the evaluated OC pesticides or their metabolites and PCB congeners were detectable or within tolerance in > 50% of the measured samples (Table 2), with the exception of PCB congeners 87 (67% < LOD or flagged as out of

Table 1
Selected characteristics of acute myeloid leukemia cases and controls from the Janus Serum Bank Cohort included in the organochlorine analysis.

Characteristic	AML Cases (n = 56)	Controls (*n* = 288)	*P*[a]
Age at blood collection (mean ± SD)	44 ± 6	43 ± 6	0.96
Sex (n, %)			0.39
Male	38 (68)	178 (62)	
Female	18 (32)	110 (38)	
Year of blood collection (n, %)			0.64
1972–1974	25 (45)	119 (41)	
1975–1978	31 (55)	169 (59)	
Cigarette smoking status at enrollment (n, %)			0.59
Never	18 (32)	102 (35)	
Former	7 (13)	47 (16)	
Current	31 (55)	139 (48)	
Body Mass Index at enrollment (n, %)			0.81
< 25 kg/m^2	32 (57)	161 (56)	
25–29 kg/m^2	19 (34)	108 (38)	
≥30 kg/m^2	3 (5)	14 (5)	
Missing	2 (4)	5 (2)	
Age at AML diagnosis (mean ± SD)	61 ± 9	–	
Years from blood draw to AML diagnosis (mean ± SD)	17 ± 6	–	

[a] *P*-value for difference between cases and controls using a *t*-test for age at blood collection and chi-square test for sex, year of blood collection categories, cigarette smoking status, and body mass index.

tolerance), 128 (52% < LOD or flagged as out of tolerance), 149 (57% < LOD or flagged as out of tolerance), and 151 (53% < LOD or flagged as out of tolerance). Lipid-adjusted concentrations of p,p′-DDT and heptachlor epoxide were significantly higher in AML cases compared to controls (Table 2).

Associations between OC pesticide levels and AML risk are shown in Table 3. Higher serum levels of total chlordane/heptachlor compounds were associated with risk of AML (2nd vs. 1st tertile OR = 1.84, 95% CI = 0.77–4.37; 3rd vs. 1st tertile OR = 2.26, 95% CI = 0.91–5.63; p_{trend} = 0.11). The largest risk was for heptachlor epoxide, which showed a significant exposure-response relationship (2nd vs. 1st tertile OR = 1.26, 95% CI = 0.46–3.51; 3rd vs. 1st tertile OR = 2.85, 95% CI = 1.05–7.73; p_{trend} = 0.02). An increased risk of AML was also observed for higher levels of oxychlordane (2nd vs. 1st tertile OR = 1.65, 95% CI =0.71–3.80; 3rd vs. 1st tertile OR = 2.14, 95% CI = 0.89–5.13; p_{trend} = 0.10). When these analyses were conducted using log-transformed continuous levels, results were stronger for oxychlordane (OR = 1.80, 95% CI = 1.11–2.95 per unit increase in log-transformed ng/g lipid) than for heptachlor epoxide (OR = 1.09, 95% CI = 0.75–1.59 per unit increase in log-transformed ng/g lipid). The three chlordane/heptachlor compounds were moderately to strongly correlated, particularly oxychlordane and *trans*-nonachlor (r_{sp} = + 0.75) (Supplemental Table 1). In addition, a higher risk of AML was observed among those with the highest serum levels of dieldrin and a significant exposure-response relationship was observed (2nd tertile vs. 1st tertile OR = 1.47, 95% CI = 0.59–3.64; 3rd vs. 1st tertile OR = 2.71, 95% CI = 1.07–6.83; p_{trend} = 0.03).

Although the OR for AML risk was elevated for the highest tertile levels of p,p′-DDE, it was not statistically significant and no significant

Table 2
Lipid-adjusted serum concentrations of organochlorine pesticides and polychlorinated biphenyls in acute myeloid leukemia cases and controls from the Janus Serum Bank Cohort.

OC Compound	Cases (n = 56)	Controls (n = 288)	% Samples imputed (Ca/Co)[b]	PCB congener	Cases (*n* = 56)	Controls (n = 288)	% Samples imputed (Ca/Co)[b]
	Median (25th, 75th) ng/g lipid[a]	Median (25th, 75th) ng/g lipid[a]			Median (25th, 75th) ng/g lipid[a]	Median (25th, 75th) ng/g lipid[a]	
Organochlorine pesticides				128	3.1 (0.5, 5.5)	1.0 (0.4, 6.3)	46/53
Oxychlordane	18.5 (13.0, 27.2)	16.5 (10.9, 25.5)	5/14	138	178.0 (136.8, 217.3)	167.5 (126.6, 217.8)	2/2
Trans-nonachlor	26.4 (20.6, 42.4)	24.7 (17.6, 34.7)	2/0	146	44.6 (35.1, 57.9)	43.4 (33.0, 61.1)	4/4
Heptachlor epoxide	14.0 (9.2, 21.0)[c]	11.9 (8.1, 16.0)	16/14	149	0.9 (0.3, 6.7)	1.0 (0.3, 6.9)	55/57
p,p′-DDT	339.7 (209.0, 513.8)[c]	278.1 (173.9, 402.4)	0/0	151	1.3 (0.3, 8.3)	1.0 (0.3, 6.8)	52/54
p,p′-DDE	2319.6 (1588.6, 4274.7)	2105.9 (1434.3, 3493.2)	0/0	153	390.1 (294.0, 476.6)	353.0 (276.6, 468.8)	2/0
o,p′-DDT	26.0 (14.7, 37.6)	21.4 (12.8, 33.7)	2/1	156	31.5 (22.4, 37.7)	28.0 (21.3, 38.2)	2/3
Mirex	1.6 (1.2, 2.1)	1.4 (0.9, 2.5)	7/11	157	4.7 (0.8, 6.3)	4.6 (0.8, 7.3)	34/34
Hexachlorobenzene	567.9 (336.2, 959.0)	583.7 (323.3, 912.6)	0/0	167	7.9 (3.2, 11.9)	8.8 (3.2, 12.8)	30/27
Dieldrin	60.9 (34.1, 110.0)	50.9 (23.3, 81.4)	21/20	170	84.0 (69.4, 102.1)	78.1 (60.1, 106.7)	2/2
γ-Hexachlorocyclohexane	7.9 (4.7, 12.6)	7.5 (4.4, 12.6)	13/11	172	11.0 (5.8, 15.1)	10.4 (6.5, 15.8)	23/19
β-Hexachlorocyclohexane	164.0 (113.4, 242.7)	148.0 (107.4, 200.2)	0/0.3	177	16.6 (11.0, 20.7)	16.0 (11.7, 20.7)	7/6
PCB congener				178	10.8 (4.4, 13.9)	10.9 (4.5, 16.2)	25/25
18	40.7 (21.1, 82.1)	40.1 (20.9, 71.3)	0/0.3	180	188.4 (155.8, 250.8)	181.3 (136.0, 247.7)	4/6
28	84.8 (41.6, 149.2)	64.6 (41.2, 130.2)	0/0	183	26.3 (21.0, 31.8)	24.5 (18.2, 34.4)	4/7
44	10.2 (6.2, 19.8)	10.7 (5.6, 18.6)	9/12	187	64.7 (48.3, 74.2)	60.9 (47.4, 84.7)	2/3
49	6.1 (2.8, 13.7)	5.9 (3.1, 10.8)	16/14	189	2.3 (0.4, 3.5)	2.0 (0.4, 3.4)	41/45
52	21.1 (12.5, 36.1)	18.6 (10.8, 30.1)	2/1	194	25.4 (19.5, 30.8)	23.4 (17.8, 32.3)	5/1
66	19.7 (12.1, 30.6)	17.9 (12.8, 26.9)	0/0.3	195	6.7 (5.1, 8.0)	6.1 (4.3, 8.4)	9/12
74	49.8 (33.3, 67.7)	47.9 (35.6, 66.4)	0/0.3	196	13.0 (9.8, 15.4)	12.4 (9.5, 16.3)	2/0.7
87	0.7 (0.2, 5.6)	0.8 (0.2, 6.0)	66/67	201	21.6 (16.4, 27.5)	19.7 (14.8, 28.3)	2/2
99	65.5 (47.2, 90.3)	61.0 (45.5, 84.5)	0/0	206	9.4 (7.8, 13.4)	9.1 (6.9, 12.0)	2/1
101	14.8 (9.1, 18.6)	13.2 (9.1, 20.1)	13/8	209	7.5 (5.4, 10.7)	6.8 (5.5, 9.8)	4/1
118	105.1 (85.7, 146.4)	102.4 (81.8, 134.3)	0/0.3				

[a] Organochlorine concentrations from a single imputation presented.
[b] Percentage of total measurements imputed due to being below the limit of detection or flagged as out of tolerance.
[c] P-value < 0.05 from Wilcoxon rank sum test comparing concentrations between cases and controls.

Table 3
Associations between lipid-adjusted serum organochlorine pesticide levels and risk of acute myeloid leukemia in the Janus Serum Bank Cohort.

Pesticide/metabolite	Tertile 1[a]	Tertile 2	OR (95% CI)[b]	Tertile 3	OR (95% CI)[b]	p-trend[c]
	Ca/Co	Ca/Co		Ca/Co		
Chlordane/heptachlor	11/96	21/97	1.84 (0.77–4.37)	24/95	2.26 (0.91–5.63)	0.11
Oxychlordane	13/95	19/97	1.65 (0.71–3.80)	24/96	2.14 (0.89–5.13)	0.10
trans-Nonachlor	12/95	22/98	1.68 (0.75–3.76)	22/95	1.63 (0.68–3.91)	0.39
Heptachlor epoxide	15/95	14/97	1.26 (0.46–3.51)	27/96	2.85 (1.05–7.73)	0.02
DDT	16/95	16/97	0.87 (0.39–1.97)	24/96	1.37 (0.59–3.17)	0.31
p,p′-DDT	12/95	19/97	1.48 (0.62–3.53)	25/96	2.09 (0.83–5.26)	0.12
p,p′-DDE	15/95	17/98	1.08 (0.48–2.43)	24/95	1.55 (0.68–3.55)	0.25
o,p′-DDT	17/95	16/98	0.86 (0.39–1.90)	23/95	1.23 (0.53–2.85)	0.51
Other OC pesticides						
Mirex	13/96	29/97	2.28 (1.05–4.92)	14/95	1.22 (0.50–2.97)	0.86
Hexachlorobenzene	20/96	15/96	0.63 (0.24–1.66)	21/96	1.00 (0.38–2.67)	0.65
Dieldrin	12/95	17/97	1.47 (0.59–3.64)	27/96	2.71 (1.07–6.83)	0.03
γ-Hexachlorocyclohexane	17/96	23/97	1.35 (0.60–3.04)	16/95	0.77 (0.29–2.04)	0.40
β-Hexachlorocyclohexane	16/96	15/96	0.90 (0.38–2.13)	25/96	1.35 (0.56–3.25)	0.39

[a] Number of cases and controls based on tertile distributions of a single imputation (5 total imputations conducted).
[b] Calculated using conditional logistic regression stratified on laboratory batch and adjusted for sex, county of residence, age at blood collection, blood collection date, and smoking, comparing 2nd and 3rd tertiles to the 1st tertile.
[c] p-trends calculated using median values of tertiles modeled as a continuous variable.

exposure-response relationship was observed (Table 3). The sum of DDT derivatives was also not significantly associated with AML risk. Higher serum levels of p,p′-DDT were associated with AML risk (2nd vs 1st tertile OR = 1.48, 95% CI = 0.62–3.53; 3rd vs. 1st tertile OR = 2.09, 95% CI = 0.83–5.26; p_{trend} = 0.12). Levels of p,p′-DDT and heptachlor epoxide, the chlordane/heptachlor metabolite most strongly associated with AML in tertile analyses, were moderately correlated (r_{sp} = +0.48; Supplemental Table 1). In models that included both p,p′-DDT and heptachlor epoxide serum levels, the exposure-response association with AML risk remained significant for heptachlor epoxide (3rd vs. 1st tertile OR = 2.49, 95% CI = 0.87–7.10; p_{trend} = 0.046) but became weaker for p,p′-DDT (3rd vs. 1st tertile OR = 1.62, 95% CI = 0.60–4.36; p_{trend} = 0.36). Similarly, the exposure-response with AML risk became weaker for p,p′-DDT in models mutually adjusted for dieldrin, whereas for dieldrin the trend remained borderline significant (p,p′-DDT 3rd vs. 1st tertile OR = 1.71, 95% CI = 0.66–4.45; p_{trend} = 0.31; dieldrin 3rd vs. 1st tertile OR = 2.43, 95% CI = 0.93–6.37; p_{trend} = 0.07).

Serum levels of other evaluated OC pesticides (mirex, HCB, HCH) showed no consistent association with risk of AML (Table 3). Similarly, evaluation of total PCBs, groupings of PCBs according to the degree of chlorination, dioxin-like properties, or Wolff classification, and individual PCB congeners suggested no significant exposure-response associations with risk of AML (Supplemental Tables 2 and 3).

In sensitivity analyses that retained AML cases and only controls directly matched to those cases (Supplemental Table 4), similar patterns in the ORs for associations with AML were observed for p,p′-DDT (3rd vs. 1st tertile OR = 1.83, 95% CI = 0.64–5.22; p_{trend} = 0.18), heptachlor epoxide (3rd vs. 1st tertile OR = 3.28, 95% CI = 0.90–11.99; p_{trend} = 0.06), and dieldrin (3rd vs. 1st tertile OR = 2.40, 95% CI = 0.77–7.46; p_{trend} = 0.13) as in the analyses including all controls. Results from analyses using the sample weight adjusted OC levels were also generally consistent with those using the lipid-adjusted levels, with ORs > 2 for AML risk for the highest tertile levels of oxychlordane, heptachlor epoxide, p,p′-DDT, and dieldrin (Supplemental Table 5).

4. Discussion

We conducted a case-control study of the associations between serum OC levels and risk of AML nested in the Janus Serum Bank Cohort in Norway, using blood specimens collected during the 1970s. To our knowledge, this is the first study to prospectively evaluate associations between serum levels of OC compounds and risk of AML. We observed evidence for an association between higher serum levels of some OC pesticides and risk of AML, including for dieldrin and metabolites derived from chlordane/heptachlor. These findings, which were observed in cases with an average of about 17 years of follow-up between blood collection and AML diagnosis, suggest that serum levels of these pesticides or their metabolites may be associated with AML risk in general, non-occupationally exposed populations.

Higher levels of chlordane/heptachlor compounds, which included oxychlordane, *trans*-nonachlor, and heptachlor epoxide, were associated with risk of AML in our study, with the strongest association and evidence of an exposure-response relationship observed for the heptachlor epoxide metabolite. Chlordane and heptachlor are structurally related cyclodiene insecticides, with the technical grade of each chemical containing about 10%–20% of the other (International Agency for Research on Cancer, 2001). Like other OC compounds, metabolites of chlordane/heptachlor can persist in the environment for decades as they bioaccumulate in adipose tissue and undergo biomagnification in the food chain (International Agency for Research on Cancer, 2001).

Epidemiologic data on chlordane/heptachlor exposures and risk of leukemia are limited, particularly for the myeloid subtype, as available cohort studies have primarily reported associations with lymphatic/hematopoietic cancers combined due to small numbers. Overall leukemia risk was evaluated in the prospective AHS (Purdue et al., 2007), which found elevated associations for ever-use of chlordane (RR = 1.5, 95% CI = 0.8–2.6) and heptachlor (RR = 2.1, 95% CI = 1.1–3.9), and for greater number of lifetime exposure days to chlordane/heptachlor combined (RR = 2.6, 95% CI = 1.2–6.0). A non-significantly elevated risk of myeloid leukemia (RR = 1.8, 95% CI 0.6–6.1), based on 3 cases exposed to chlordane, was reported among female spouses of pesticide applicators in the AHS (Louis et al., 2017). A case-control study conducted in Iowa and Minnesota found a non-significantly higher risk of overall leukemia among farmers reporting ≥10 days of chlordane use (Brown et al., 1990). Our results suggest that serum levels of one or more chlordane/heptachlor metabolites are associated with AML risk, which to our knowledge is the first report of an association with this specific subtype. Although our tertile analyses suggested that these associations were strongest for heptachlor epoxide, we were unable to clearly disentangle effects of the three chlordane/heptachlor metabolites given the correlations among them.

The mechanism by which chlordane/heptachlor exposure may contribute to AML may be related to reported effects of these chemicals on the hematopoietic system. Experimental studies in rats demonstrate

that exposure to chlordane compounds causes increased numbers of white blood cells and lymphocyte subsets (Tryphonas et al., 2003) and significant dose-related increases in circulating erythrocytes and total blood hemoglobin (Bondy et al., 2004). In humans, various blood dyscrasias including anemias have been reported following residential use of chlordane or heptachlor (Epstein and Ozonoff, 1987). A cross-sectional analysis using data from NHANES suggested increased WBC levels in individuals with the highest blood levels of oxychlordane and *trans*-nonachlor (Serdar et al., 2014). Our findings of an association with AML suggest that additional molecular epidemiology studies that evaluate the hematologic effects of these exposures in humans may be useful to provide insight into the underlying mechanisms of action for this observed association.

While a non-significant association was observed between higher levels of p,p′-DDT and AML risk in our study, the exposure-response became weaker when co-adjusting for levels of heptachlor epoxide or dieldrin and no significant association was observed for levels of total DDT or for p,p′-DDE, the major DDT isomer that had the highest concentration of any OC compound measured in both AML cases and controls. P,p′-DDE is the most persistent derivative of DDT and serum levels reflect cumulative DDT exposure that may be most relevant in studies of cancer etiology, whereas levels of p,p′-DDT may reflect more recent exposure. Studies of DDT and myeloid leukemia have been limited. A non-significantly increased risk of myeloid leukemia mortality was observed in relation to increasing number of days of occupational exposure to DDT among sprayers in Sardinia, Italy, but this was based on only two deaths (Cocco et al., 1997). A follow-up of this cohort reported no excess of total leukemia mortality based on 24 deaths, among whom 18 were exposed to DDT (Cocco et al., 2005). Another occupational cohort, in Australia, observed marginally elevated SIRs for myeloid leukemia in workers likely exposed to DDT; however, these associations were not statistically significant with no increasing trend and were based on only a few cases (Beard et al., 2003). In the AHS, DDT use was not associated with risk of overall leukemia among applicators (RR = 1.1, 95% CI = 0.6–1.9) (Purdue et al., 2007) and risk of myeloid leukemia was non-significantly elevated among the female spouses of pesticide applicators who reported ever use of DDT, based on a small number of cases (n = 3; RR = 1.66, 95% CI = 0.49–5.56) (Louis et al., 2017). Overall, results from the existing limited number of studies combined with our data do not suggest a consistent or convincing association between DDT exposure and AML risk. However, further research in populations with historically high or recent exposure to DDT is warranted to assess the association with AML risk with body burden of specific DDT isomers and derivatives given some mechanistic evidence in rats suggesting that this exposure may cause immunotoxicity (Banerjee et al., 1996).

Of the other OC pesticides evaluated, a significant exposure-response association with AML risk was observed for dieldrin, a highly persistent pesticide used in the United States through the early 1970s. In contrast, we found no consistent evidence of an association with AML risk for serum levels of mirex, HCB, and γ- and β-HCH, which have not previously been evaluated prospectively in relation to risk of AML. While dieldrin has been designated a probable carcinogen by IARC, based on limited evidence for an association with breast cancer in humans (Guyton et al., 2016), to our knowledge this is the first evaluation of AML risk in relation to this exposure and therefore replication is needed. A non-significantly elevated risk of overall leukemia, based on 10 cases exposed to dieldrin (RR = 1.7, 95% CI = 0.8–3.6), was previously reported in the AHS (Purdue et al., 2007), but no cases exposed to dieldrin were available for analysis in the spouses of pesticide applicators enrolled in the AHS (Louis et al., 2017).

Some PCB congeners are immunotoxicants, particularly those that are highly chlorinated as these have strong affinity for the aryl hydrocarbon receptor that modulates immune responses (Lauby-Secretan et al., 2016). Our data did not support an etiologic association between exposure to PCBs, either for individual congeners or when categorized in groups according to degree of chlorination or biologic activity, and risk of AML in this cohort. This is the first population-based cohort study to our knowledge to evaluate the relationship between serum levels of PCBs and risk of AML. Occupational cohort studies of PCBs have reported associations primarily for overall leukemia or combined lymphohematopoietic cancers (both of which may include subtypes of non-Hodgkin lymphoma) (International Agency for Research on Cancer, 2015), hampering direct comparisons with our study that evaluated a specific subtype of myeloid leukemia.

An advantageous feature of our cohort is that all biologic samples were collected during the 1970s when we would expect peak or near-peak body burdens of these chemicals in the Norwegian general population because of usage patterns. This also mitigates the potential influence of disease bias given that all samples were collected before AML diagnosis (mean = 17 years). The primary limitation of our study was the relatively small number of AML cases in the cohort. We did not have available data on more traditional indicators of socioeconomic status (SES) such as education or income of the participants, and instead adjusted all models for county of residence at the time of blood collection as a general proxy for SES. This is an imperfect surrogate for SES but may control for broad differences in the participants who were enrolled from multiple counties in Norway. It is conceivable that SES could be a proxy for other factors that may affect serum OC levels, but in terms of demographic characteristics age and sex are much stronger risk factors for AML (Deschler and Lübbert, 2006). We also did not have data on other established or suspected risk factors for AML such as occupational exposure to benzene or formaldehyde or exposure to ionizing radiation, but we do not have evidence from the literature to suggest that these exposures would be strongly correlated with serum levels of organochlorines. The participation rates for the cohort (65–87% across counties) were relatively high for a population-based study, but it is possible that the cohort participants could have differed with respect to some characteristics relative to the total eligible population. For example, individuals willing to participate in the cohort may be more health conscious than the general Norwegian population (Hjerkind et al., 2017; Jenum et al., 2007). The AML cases and controls in this study were all drawn from the same base cohort population (i.e. the 90% completing the health surveys) and key demographic variables were considered in the statistical analysis, which should limit any major selection bias. It is also possible that time since blood draw in relation to the sample analysis could have contributed to some decay of blood lipid levels (Jansen et al., 2014). However, the total mean lipid concentrations and cholesterol levels were very similar in the AML cases (total lipids: 699.2 mg/dl; cholesterol: 204.9 mg/dl) and controls (total lipids: 676.2 mg/dl; cholesterol: 206.3 mg/dl) in this analysis suggesting that any bias would likely be non-differential. Similar results were also obtained using the sample weight adjusted OC levels.

The OC pesticide metabolites measured in our study were generally moderately correlated. As such, we were unable to completely disentangle which specific compound is driving the increased AML risk. We also cannot rule out the possibility of false-positive findings given the relatively large number of compounds measured, but as described we note that the plausibility of our findings for the OC pesticides is supported by previous mechanistic data and observed associations from some epidemiologic studies.

In summary, we conducted the first population-based prospective study evaluating pre-diagnostic serum levels of OC pesticides and PCBs in relation to AML risk, using samples collected during the 1970s in a large population-based cohort in Norway. Our results suggested that higher levels of chlordane/heptachlor metabolites and dieldrin may be associated with risk of AML in the Norwegian general population. Replication of these findings would be informative in other study populations, including in prospective cohorts that collected biospecimens during time periods when OC concentrations were expectedly high.

Funding

This work was supported by the Intramural Research Program of the Division of Cancer Epidemiology and Genetics, National Cancer Institute, National Institutes of Health. The Norwegian Cancer Society provided funding for the Janus Serum Bank management through the years of cohort recruitment. The authors declare they have no competing financial interests.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2019.01.066.

References

Bakke, A., 1970. The use of DDT in Norwegian forestry. Review and present situation. Tidsskr Slogbr 78, 304–309.
Banerjee, B.D., Ray, A., Pasha, S.T., 1996. A comparative evaluation of immunotoxicity of DDT and its metabolites in rats. Indian J. Exp. Biol. 34, 517–522.
Barr, J.R., Maggio, V.L., Barr, D.B., Turner, W.E., Sjodin, A., Sandau, C.D., et al., 2003. New high-resolution mass spectrometric approach for the measurement of polychlorinated biphenyls and organochlorine pesticides in human serum. J. Chromatogr. B Anal. Technol. Biomed. Life Sci. 794, 137–148.
Barr, D.B., Weihe, P., Davis, M.D., Needham, L.L., Grandjean, P., 2006. Serum polychlorinated biphenyl and organochlorine insecticide concentrations in a Faroese birth cohort. Chemosphere 62, 1167–1182.
Beard, J., Sladden, T., Morgan, G., Berry, G., Brooks, L., McMichael, A., 2003. Health impacts of pesticide exposure in a cohort of outdoor workers. Environ. Health Perspect. 111, 724–730.
Bertazzi, P.A., Consonni, D., Bachetti, S., Rubagotti, M., Baccarelli, A., Zocchetti, C., et al., 2001. Health effects of dioxin exposure: a 20-year mortality study. Am. J. Epidemiol. 153, 1031–1044.
Bondy, G., Curran, I., Doucet, J., Armstrong, C., Coady, L., Hierlihy, L., et al., 2004. Toxicity of trans-nonachlor to Sprague-dawley rats in a 90-day feeding study. Food Chem. Toxicol. 42, 1015–1027.
Brown, L.M., Blair, A., Gibson, R., Everett, G.D., Cantor, K.P., Schuman, L.M., et al., 1990. Pesticide exposures and other agricultural risk factors for leukemia among men in Iowa and Minnesota. Cancer Res. 50, 6585–6591.
Cocco, P., Blair, A., Congia, P., Saba, G., Ecca, A.R., Palmas, C., 1997. Long-term health effects of the occupational exposure to DDT. A preliminary report. Ann. N. Y. Acad. Sci. 837, 246–256.
Cocco, P., Fadda, D., Billai, B., D'Atri, M., Melis, M., Blair, A., 2005. Cancer mortality among men occupationally exposed to dichlorodiphenyltrichloroethane. Cancer Res. 65, 9588–9594.
Deschler, B., Lübbert, M., 2006. Acute myeloid leukemia: epidemiology and etiology. Cancer 107, 2099–2107.
Epstein, S.S., Ozonoff, D., 1987. Leukemias and blood dyscrasias following exposure to chlordane and heptachlor. Teratog. Carcinog. Mutagen. 7, 527–540.
Gale, R.P., Opelz, G., 2012. Commentary: does immune suppression increase risk of developing acute myeloid leukemia? Leukemia 26, 422–433.
Giesy, J.P., Kannan, K., 1998. Dioxin-like and non-dioxin-like toxic effects of polychlorinated biphenyls (pcbs): implications for risk assessment. Crit. Rev. Toxicol. 28, 511–569.
Guyton, K.Z., Loomis, D., Grosse, Y., El Ghissassi, F., Bouvard, V., Benbrahim-Tallaa, L., et al., 2016. Carcinogenicity of pentachlorophenol and some related compounds. Lancet Oncol. 17, 1637–1638.
Hjerkind, K.V., Gislefoss, R.E., Tretli, S., Nystad, W., Bjorge, T., Engeland, A., et al., 2017. Cohort profile update: the Janus Serum Bank Cohort in Norway. Int. J. Epidemiol. 46, 1101–1102f.
International Agency for Research on Cancer, 2001. IARC monographs. In: Some Thyrotropic Agents. vol 79. https://monographs.iarc.fr/wp-content/uploads/2018/06/mono79.pdf, Accessed date: 1 March 2018.
International Agency for Research on Cancer, 2015. IARC monographs. In: Polychlorinated Biphenyls and Polybrominated Biphenyls. vol 107. http://monographs.iarc.fr/ENG/Monographs/vol107/mono107.pdf Accessed 3/1/2018.
Isidori, A., Salvestrini, V., Ciciarello, M., Loscocco, F., Visani, G., Parisi, S., et al., 2014. The role of the immunosuppressive microenvironment in acute myeloid leukemia development and treatment. Expert. Rev. Hematol. 7, 807–818.
Jansen, E.H.J.M., Beekhof, P.K., Schenk, E., 2014. Long term stability of parameters of lipid metabolism in frozen human serum: triglycerides, free fatty acids, Total-, HDL- and LDL-cholesterol, apolipoprotein-A1 and B. J. Mol. Biomark. Diagn. 5, 182.
Jenum, A.K., Graff-Iverson, S., Selmer, R., Søgaard, A.J., 2007. Risk factors for cardiovascular disease and diabetes through three decades. Tidsskr. Nor. Laegeforen. 127, 2532–2536.
Koutros, S., Langseth, H., Grimsrud, T.K., Barr, D.B., Vermeulen, R., Portengen, L., et al., 2015. Prediagnostic serum organochlorine concentrations and metastatic prostate cancer: a nested case-control study in the Norwegian Janus Serum Bank Cohort. Environ. Health Perspect. 123, 867–872.
Lan, Q., Zhang, L., Li, G., Vermeulen, R., Weinberg, R.S., Dosemeci, M., et al., 2004. Hematotoxicity in workers exposed to low levels of benzene. Science 306, 1774–1776.
Langseth, H., Gislefoss, R.E., Martinsen, J.I., Dillner, J., Ursin, G., 2017. Cohort profile: The Janus Serum Bank Cohort in Norway. Int. J. Epidemiol. 46, 403–404g.
Lauby-Secretan, B., Loomis, D., Baan, R., El Ghissassi, F., Bouvard, V., Benbrahim-Tallaa, L., et al., 2016. Use of mechanistic data in the IARC evaluations of the carcinogenicity of polychlorinated biphenyls and related compounds. Environ. Sci. Pollut. Res. Int. 23, 2220–2229.
Loomis, D., Guyton, K., Grosse, Y., El Ghissasi, F., Bouvard, V., Benbrahim-Tallaa, L., et al., 2015. Carcinogenicity of lindane, DDT, and 2,4-dichlorophenoxyacetic acid. Lancet Oncol. 16, 891–892.
Louis, L.M., Lerro, C.C., Friesen, M.C., Andreotti, G., Koutros, S., Sandler, D.P., et al., 2017. A prospective study of cancer risk among Agricultural Health Study farm spouses associated with personal use of organochlorine insecticides. Environ. Health 16, 95.
Lubin, J.H., Colt, J.S., Camann, D., Davis, S., Cerhan, J.R., Severson, R.K., et al., 2004. Epidemiologic evaluation of measurement data in the presence of detection limits. Environ. Health Perspect. 112, 1691–1696.
Pesatori, A.C., Consonni, D., Rubagotti, M., Grillo, P., Bertazzi, P.A., 2009. Cancer incidence in the population exposed to dioxin after the "Seveso accident": twenty years of follow-up. Environ. Health 8, 39.
Phillips, D.L., Pirkle, J.L., Burse, V.W., Bernert Jr., J.T., Henderson, L.O., Needham, L.L., 1989. Chlorinated hydrocarbon levels in human serum: effects of fasting and feeding. Arch. Environ. Contam. Toxicol. 18, 495–500.
Polder, A., Skaare, J.U., Skjerve, E., Løken, K.B., Eggesbø, M., 2009. Levels of chlorinated pesticides and polychlorinated biphenyls in Norwegian breast milk (2002–2006), and factors that may predict the level of contamination. Sci. Total Environ. 407, 4584–4590.
Purdue, M.P., Hoppin, J.A., Blair, A., Dosemeci, M., Alavanja, M.C., 2007. Occupational exposure to organochlorine insecticides and cancer incidence in the Agricultural Health Study. Int. J. Cancer 120, 642–649.
Purdue, M.P., Engel, L.S., Langseth, H., Needham, L.L., Andersen, A., Barr, D.B., et al., 2009. Prediagnostic serum concentrations of organochlorine compounds and risk of testicular germ cell tumors. Environ. Health Perspect. 117, 1514–1519.
Ross, G., 2004. The public health implications of polychlorinated biphenyls (pcbs) in the environment. Ecotoxicol. Environ. Saf. 59, 275–291.
Rugman, F.P., Cosstick, R., 1990. Aplastic anaemia associated with organochlorine pesticide: case reports and review of evidence. J. Clin. Pathol. 43, 98–101.
Ruus, A., Green, N.W., Maage, A., Amundsen, C.E., Schøyen, M., Skei, J., 2010. Post World War II orcharding creates present day DDT-problems in the Sørfjord (Western Norway)–a case study. Mar. Pollut. Bull. 60, 1856–1861.
Serdar, B., LeBlanc, W.G., Norris, J.M., Dickinson, L.M., 2014. Potential effects of polychlorinated biphenyls (pcbs) and selected organochlorine pesticides (ocps) on immune cells and blood biochemistry measures: a cross-sectional assessment of the nhanes 2003–2004 data. Environ. Health 13, 114.
Sjodin, A., Jones, R.S., Caudill, S.P., Wong, L.Y., Turner, W.E., Calafat, A.M., 2014. Polybrominated diphenyl ethers, polychlorinated biphenyls, and persistent pesticides in serum from the national health and nutrition examination survey: 2003–2008. Environ. Sci. Technol. 48, 753–760.
Tryphonas, H., Bondy, G., Hodgen, M., Coady, L., Parenteau, M., Armstrong, C., et al., 2003. Effects of cis-nonachlor, trans-nonachlor and chlordane on the immune system of Sprague-Dawley rats following a 28-day oral (gavage) treatment. Food Chem. Toxicol. 41, 107–118.
van den Berg, H., Manuweera, G., Konradsen, H., 2017. Global trends in the production and use of DDT for control of malaria and other vector-borne diseases. Malar. J. 16, 401.
Van Maele-Fabry, G., Duhayon, S., Lison, D., 2007. A systematic review of myeloid leukemias and occupational pesticide exposure. Cancer Causes Control 18, 457–478.
Wolff, M.S., Camann, D., Gammon, M., Stellman, S.D., 1997. Proposed pcb congener groupings for epidemiological studies. Environ. Health Perspect. 105, 13–14.
Xue, J., Liu, S.V., Zartarian, V.G., Geller, A.M., Schultz, B.D., 2014. Analysis of NHANES measured blood pcbs in the general US population and application of SHEDS model to identify key exposure factors. J. Expo. Sci. Environ. Epidemiol. 24, 615–621.