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Leukemia and Pesticides

RESEARCH ARTICLE

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The Determining of Pesticide Residue Levels in Children Diagnosed with Acute Leukemia in Cukurova Region, Turkiye

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Abstract

Background: Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. in children. Children can be exposed to pesticides during pregnancy or by their parent carried out pesticides to home. The objective of this study was to study pesticide residues in both acute leukemia patients and healthy children. **Methods:** Twenty nine patients with acute leukemia [22 boys (76%) and 7 girls (24%)] and 33 healthy children [(19 boys (57%), 14 girls (43%)] were included in the study. We analyzed eight PCB (PCB 28, PCB 52, PCB 101, PCB 118, PCB 138, PCB 153, PCB 180 and PCB 202), HCB, three HCH isomers, 4,4′-DDT, 4,4′-DDD and 4,4′-DDE were investigated in bone marrow of newly diagnosed acute leukemia patients and peripheral blood samples of healthy children. **Results:** The most detectable OCPs were β-HCH, δ-HCH and PCB28, triflumizole and thiometon were commonly found as OPPs. The significant difference was found statistically between ALL cases and control group according to the residues of PCB28 (74,06±85,29), β-HCH (72,06±89,07) and δ-HCH (23,35±42,93) (p=0.001). Additionally, OPPs consisted triflumizole (7,23±9,17), thiometon (3,37±4,30) and halfenprox (1,90±3,22) showed distinctive difference statistically (p=0.001). **Conclusion:** Pesticide residues were estimated significantly in bone marrow of leukemia patients should be considered an important for public health with the decreasing or preventing of pesticide exposure which have a role in leukemia ethiology.

Keywords: Leukemia- pesticide- organophosphorus- organochlorine- children

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Introduction

Acute lymphoblastic leukemia (ALL) is the most common childhood malignancy. in children under the age of 15 years, comprises over a quarter of all malignancies diagnosed in children ages 19 or younger, and the incidence continues to rise [1]. Studies showed that environmental factors can cause to genetic damage and various cancers can occur. Pesticides (agriculture chemicals), solvents and radiation are the most common factors among environmental factors. Children can be exposed to pesticides during pregnancy or by their parent carried out pesticides to home. The relationship between pesticides and leukemia was pointed in various studies. Environmental exposure to pesticides generates oxidative stress, which results in abnormal chromosomal translocation, increased proliferation, and ultimately result in leukaemia [2].

There are some pesticides (insecticides, herbicides and fungicides) currently used in some regions. Hexachlorobenzene (HCB), hexachlorocyclohexane isomer (γ-HCH consists of α-HCH and β-HCH) and dichlorodiphenyltrichloroethane (DDT) are organochlorine pesticides (OCPs) and have been used for many years [3]. The agriculture, forestry and wood preservation in indoor and outdoor applications are the areas of DDT using. HCB is an insecticide and mainly for the treatment of seeds [4]. PCB (PCB 28, PCB 52, PCB 101, PCB138, PCB 153 and PCB 180) were applied as plasticizers, additives in paints, sealants, paper industry and in several technical applications in closed systems such as transformers and hydraulic systems [5]. The International Agency for Research on Cancer (IARC) classified PCB, DDT and HCB carcinogenic to humans. For DDE sufficient evidence exists that it is carcinogenic in experimental animal studies [6]. Higher levels of organophosphates metabolites have been reported in children compared to adult populations. Pyrethroid (cis-permethrin and trans-

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permethrin) or organophosphate (OPPs) pesticides, as their most common indoor-use pesticides [7].

In Turkiye, Cukurova has big agricultural areas. Therefore pesticides mostly have been using in this region. In our present study, we wanted to investigate whether pesticides residues can be found in patients with acute leukemia and healthy children.

Materials and Methods

Study design

Total of 29 children diagnosed with acute leukemia and control group, 33 of healthy children were included in this study in between January 2018 and July 2022 in Cukurova University Faculty of Medicine, and City Hospital, Adana, Turkiye. Age, gender, leukemia types, risk classification, the situation of relapsed and last status of patients were recorded. The ethical approval was obtained from "The Local Scientific Research Permission Commission" and conducted with the ethical principles of the Helsinki Declaration. Parental written informed consent was obtained for all children.

Sample Preparation and chemicals

The bone marrow and peripheral blood sampling of both study and control groups, respectively were collected from each participant in a 5 mL EDTA tube (K2EDTA 5.4 mg, BD Vacutainer, Plymouth, UK) and stored at -20°C until the analyzing of pesticide residues was started. All reference standards of pesticide analysis were received from Dr Ehrenstorfer (Augsburg, Germany) and certified as being of greater than 98% purity. Methanol (MeOH) and LC grade ultrapure water from Merck (99.8-100%, Darmstadt, Germany); Oasis HLB cartridges (3cc, 60 mg) for solid phase extraction (SPE) from Waters Corporation (Milford, MA, USA) were purchased.

One mL of bone marrow and peripheral blood samples was taken into a glass tube and 3 mL of 0.1 M pH: 7.4 phosphate buffer solution with internal standard (10 ng/mL dimethoate-d6 and α-HCH)) was added. The samples were centrifuged at 3000 rpm, 10 min. The Oasis HLB cartridge (3cc, 60 mg) was conditioned with 2 mL methanol and 2 mL distilled water, respectively. Then the cartridges were washed (5% methanol) and the eluents removed with 2 mL of methanol. The eluents were evaporated to dryness under a gentle nitrogen stream and reconstituted with 150 µL MeOH. The residues of organochlorine pesticides (OCPs) consisted of hexachlorobenzene (HCB), hexachlorocyclohexane (HCH), polychlorinated biphenyls (PCBs), dichloro-diphenyl-dichloroethylene (DDE), 1,1-dichloro-2,2,-bischlorophenylethane (DDD) and dichlorodiphenyltrichloroethane (DDT) and organophosphorus pesticides (OPPs) included triflumizole, propamocarb hydrocloride, pyridate, clothianidine, imidachloropid, acetamiprid, thiometon, ethiofencarb, halfenprox, pyriproxypen, myclobutanil were investigated in both bone marrow in children diagnosed with acute leukemia and in healthy children's peripheral blood. The extracts were analyzed by an optimized Liquid Chromatography Tandem Mass Spectrometry (LC-MS/MS) and Gas Chromatographic (GC) methods.

Chemical analysis

OCPs and OPPs concentrations were calculated using an internal standard approach by the measurement of 12 calibration solutions with concentrations between 0.01 and 5.0 µg/L and with linear correlation coefficients $r > 0.998$. The correlation between concentration and peak area ratio (analytical/surrogate) were examined using leastsquared quadratic regression. Weighting factors of calibration curve was selected to 1/x. Limits of quantification (LoQ) in plasma were verified prior to the analysis by multiple measurement of spiked matrix samples at the concentration levels of LoQ according to ISO/TS 13530 Annex A.

Statistical Analysis

IBM SPSS Statistics Version v25.0 (Armonk, NY: IBM Corp) was used for all statistical analyses. Normality of the data was determined by One-Sample Kolmogorov-Smirnov test. Wilcoxon signed-rank test or T-test was applied depending on the normal distribution to examine the differences between two study groups. Multigroup comparisons among independent or dependent groups were performed by Friedman test, One-way ANOVA or Kruskal-Wallis test. Statistical significance was defined as a p-value < 0.05.

Results

Twenty nine patients with acute leukemia [22 boys (76%) and 7 girls (24%)] and 33 healthy children [(19 boys (57%), 14 girls (43%)] were included in the study. Of 18 boys were diagnosed with ALL and 4 was AML. The mean age in acute leukemia and control group were (ALL 5,84±3,58; AML 6,88±6,09 year) and 5,67±3,02 year, respectively. Most of patients with ALL (20 patients, %68,96) were alive and non-relapsed. Two of them were non-follow up patients. The mean of overall survival (OS) and event free survival (EFS) were little decreased in children with ALL than that of AML cases such as 11,36±7,47 and 10,48±6,93 months, respectively. The significant difference was not found according to gender (wilcoxon signed-rank test or T-test), leukemia type (kruskal-wallis test) and risk stratification (friedman test) ($p>0.05$). The demographics of children are shown in Table 1.

We analyzed eight PCB (PCB 28, PCB 52, PCB 101, PCB 118, PCB 138, PCB 153, PCB 180 and PCB 202), HCB, three HCH isomers, 4,4′-DDT, 4,4′-DDD and 4,4′-DDE in 29 bone marrow and peripheral blood samples (Table 2). PCB 28 is exhibited distinctive and meaningful conclusion as the highest mean concentrations. β-HCH and δ-HCH are the only two rised organochlorine pesticides in ALL cases. OCPs concentrations were at below LoQ in nearly all AML bone marrow samples, except PCB28 and p,p′-DDD. Otherwise, two pesticide residues of PCB153 and p,p′-DDE were detected as below LoQ in both leukemia patients.

The residue levels of OCPs and OPPs were presented in Table 2. Compared with those with below limit of quantitation of pesticide residues, the detectable results were mostly received in ALL patients than that of AML

Table 1. The Demographics of Children

		Leukemia			
		ALL n=25 Mean± SD	AML n=4 Mean± SD	Control n=33 Mean± SD	P-value
Gender	Boy	18	4	19	0,185
	Girl	7	0	14	
Age		5.84±3.58	6.88±6.09	5.67±3.02	0.940
Risk	SRG	8	0	*	*
	MRG	11	0	*	
	HRG	6	0	*	
Relaps	Relapsed	3	0	*	0.464
	Non-relapsed	22	4	*	
OS		11.36±7.47	14.25±9.74		0.409
EFS		10.48±6.93	13.50±9.88		0.409
Last status	Exitus	3	1	*	0.627
	Alive	20	3	*	
	Non-follow	2	0	*	

ALL, Acute Lymphoblastic Leukemia; AML, Acute Myeloblastic Leukemia; HRG, High Risk Group; SRG, Standart Risk Group; MRG, Intermediate Risk Group; OS, Overall Survival; EFS, Event Free Survival

cases. Both PCB153 and p,p′-DDE were at below limit of quantitation in ALL and AML cases. While the most detectable OCPs were β-HCH, δ-HCH and PCB28, triflumizole and thiometon were commonly found as OPPs. Patients with ALL had much more HCH and PCB residues than that of AML cases. The significant difference was found statistically between ALL cases and control group according to the residues of PCB28 (74,06±85,29), β-HCH (72,06±89,07) and δ-HCH (23,35±42,93) ($p<0.001$). There was little difference between cases and controls in relation to PCB101 level ($p=0.045$). There were no association among other PCB residues. Additionally, OPPs consisted triflumizole (7,23±9,17), thiometon (3,37±4,30) and halfenprox (1,90±3,22) showed distinctive difference statistically ($p=0,00001$) (Table 2).

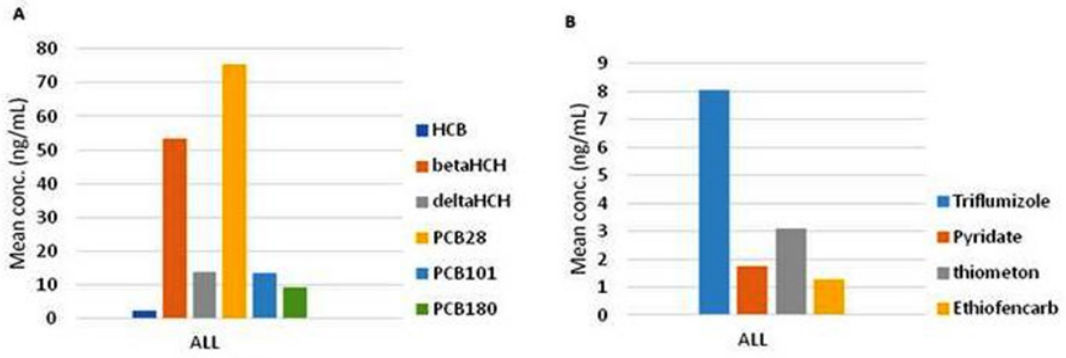

Figure 1. A. Organochlorine pesticides (OCPs) residues B. Organophosphorus pesticides (OPPs) residues in patients with ALL

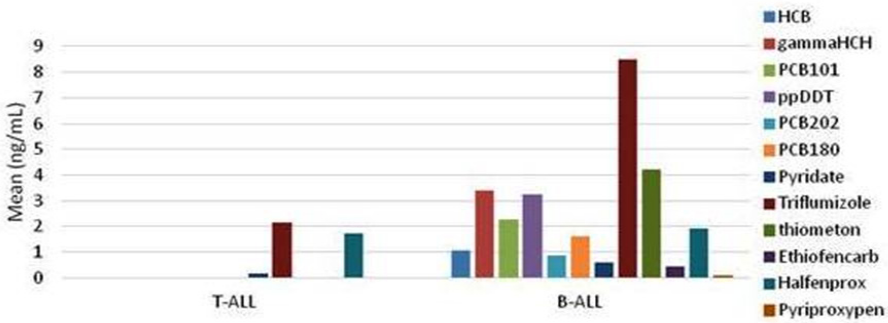

Figure 2. Pesticide Concentrations between T and B-ALL Patients

Table 2. The Pesticide Residue Concentrations in Children

	ALL (Mean± SD) (ng/mL)	AML Mean± SD (ng/mL)	Control (Mean± SD) (ng/mL)	P-value
Organochlorine pesticides (OCPs)				
HCB	0.84±1.02	<LOQ	0.11±0.61	0.001
β-HCH	72.06±89.07	<LOQ	<LOQ	0.00001
δ-HCH	23.35±42.93	<LOQ	<LOQ	0.00001
γ--HCH	2.71±7.54	<LOQ	<LOQ	0.101
PCB28	74.06±85.29	35.27±70.54	2.32±8.33	0.00001
PCB52	2.15±9.54	<LOQ	<LOQ	0.222
PCB101	1.81±4.50	<LOQ	<LOQ	0.045
PCB118	2.02±7.35	<LOQ	<LOQ	0.612
PCB138	0.29±1.46	<LOQ	<LOQ	0.477
PCB153	<LOQ	<LOQ	<LOQ	1.000
PCB180	1.30±3.10	<LOQ	<LOQ	0.045
PCB202	0.69±1.88	<LOQ	<LOQ	0.019
opDDD	0.23±1.13	<LOQ	<LOQ	0.477
ppDDD	1.28±5.06	1.29±2.58	<LOQ	0.066
opDDE	0.70±3.49	<LOQ	<LOQ	0.477
ppDDE	<LOQ	<LOQ	<LOQ	1.000
opDDT	0.59±2.97	<LOQ	<LOQ	0.477
ppDDT	2.58±9.94	<LOQ	<LOQ	0.101
Organophosphorus pesticides (OPPs)				
Triflumizole	7.23±9.17	2.77±3.20	<LOQ	0.00001
Propamocarb hydrocloride	0.75±3.15	0.50±0.99	<LOQ	0.066
Pyridate	0.51±0.80	0.30±0.59	<LOQ	0.003
Clothianidine	0.04±0.15	<LOQ	<LOQ	0.222
Imidachloropid	0.24±0.93	0.14±0.29	<LOQ	0.063
Acetamiprid	0.08±0.31	0.24±0.47	<LOQ	0.059
Thiometon	3.37±4.30	0.79±1.57	<LOQ	0.00001
Ethiofencarb	0.35±0.65	0.35±0.71	<LOQ	0.012
Halfenprox	1.90±3.22	0.74±1.49	<LOQ	0.00001
Pyriproxypen	0.07±0.19	<LOQ	<LOQ	0.101
Myclobutanil	<LOQ	<LOQ	1.06±6.06	0.644

< LOQ, below limit of quantitation; SD, standard deviation; HCB, Hexachlorobenzene; HCH, Hexachlorocyclohexane; PCB, Polychlorinated biphenyls; DDE, Dichloro-diphenyl-dichloroethylene; DDD, 1,1-dichloro-2,2,-bischlorophenylethane; DDT, Dichlorodiphenyltrichloroethane

Children diagnosed with ALL had high level of OCPs included PCB28 and betaHCH (Figure 1A). OPPs involved triflumizole was determined as the highest level of pesticide residue in ALL patients. Thiometon was another rised range of OPPs residue that following up triflumizole (Figure 1B). The OPPs residues involved triflumizole and thiometon were estimated as increased quantity for B-ALL patients in all of pesticides (Figure 2).

Discussion

Pesticide usage and cancer development have been researched in many studies. Pesticides can show their carcinogenic effects with mechanisms such as genotoxicity, hormonal effects and immunotoxicity. Genotoxic effects of some pesticide types on hemopoietic cells were demonstrated [8]. While studies noted the increasing of cancer in agricultural workers who were exposed to pesticides, other studies presented that they had no exposure. Although we performed our study in Cukurova region where the biggest agriculture area of Turkiye, there wasn't any relationship determined between leukemia and pesticides used in children. In another study done in Antalya, the Southwest of Turkiye where intense agricultural soils are present, the author stated that no correlation was recorded with pesticide usage and esophageal and gastric cancer [9].

Pesticides using and childhood leukemia risk have been investigating in many studies. It was reported that the exposuring of pesticide in houses during childhood could cause to leukemia [10-12]. Childhood Leukemia International Consortium (CLIC) informed about the risk

of leukemia in children who were sustained pesticides in periods included before conception, pregnancy and after birth [13]. The food chain is the main source of exposure to organochlorine residues in human body and food samples including dairy products, livestock meat and water [14]. In our study, even though the exposuring style of pesticide could not be determined, higher PCB28 and betaHCH pesticide residues as OCPs in leukemia patients were noted than that of healthy controls. Since PCB and HCB had been known as carcinogenic to humans, our results should be worth mentioning.

Children may be exposed to PCBs and persistent organochlorine pesticides in utero, through breast-feeding and other dietary sources, through inhalation, and through ingestion of house dust [15]. Sources of PCBs in carpet dust, particularly in older homes, include paints, sealants, caulking, floor finishing products, and older light fixtures [16]. In summary, we observed an increasing risk of ALL associated with increasing residential concentrations of PCBs. Since our study consisting of small samples compared bone marrow concentrations of PCBs in 29 children with ALL and peripheral blood in 33 healthy children, additional studies are needed to further evaluation for distinctive findings.

Residential exposure to PCBs and child¬hood leukemia risk has not been evaluated previously in a population-based study. A small study comparing bone marrow concen-trations of PCBs in 29 children with ALL and peripheral blood in 33 healthy children selected from the same hospital found no significant differences in mean concentrations across the two sample pools. That study was limited by a small size, measurement of PCBs in samples collected postdiagnosis, and use of a comparison group that may not have been representative of the general population. PCBs are thought to exert their carcinogenic effect through several possible mechanisms, depending on the specific congener and tumor site. All of the PCB congeners that measured have demonstrated immunotoxic effects and, except for PCB 105, were individually associated with elevated risk of ALL [17-19]. We found that PCB28 was increased compared to other OCPs.

Little is known about the ability of insecticide active ingredients to act as leukemogens in children. The International Agency for Research on Cancer (IARC) classifies the organophosphate insecticides diazinon and malathion as probably carcinogenic to humans based on mechanistic studies, animal studies, and limited evidence from epidemiologic studies of non-Hodgkin lymphoma, leukemia, prostate, and lung cancer and occupational exposures in adults [6] Increased OPPs level included triflumizole and thiometon were estimated in bone marrow and peripheral blood in leukemia and healthy chidren, respectively in the present study. Ding et al. reported that children diagnosed with leukemia had organophosphate metabolites in their urine [20]. Although our samples were few, the measurement of organophosphate residues were much more in B-ALL patients' bone marrow than that of T-ALL. When patients and healthy controls were matched on OCPs and OPPs, it was not clear that how insecticides were receiving during childhood.

Our study has several limitations that should be considered when interpreting our findings. First, the sample size is relatively small; secondly, the absence of detailed environmental and behavioral exposure assessments are as a limitation. While our study focused on direct residue detection in biological samples, incorporating contextual exposure information (such as parental occupation, household pesticide use, dietary habits, or residential proximity to agricultural areas) would indeed enhance the interpretation of our findings and the identification of possible exposure pathways. Additionally, the organic versus non-organic diet habits were not questioned in terms of contaminating with pesticides. Our measurements may be most reflective of recent exposures, and since the sample was taken after diagnosis it may not reflect the most etiologically relevant period for childhood ALL, particularly if case households changed their insecticide use after diagnosis. This may explain, in part, why we did not observe increased odds of ALL with any insecticide concentrations. Given the limitations to our study, our results should be interpreted within the context of the study design.

In conclusion, although we did not observe distinctive association with OCPs and OPPs that we measured in children with leukemia, pesticide residues were found in patients significantly. The duration and pattern of pesticide exposuring should be emphasized as etiologic risk factors for leukemia. Even though pesticides are beneficial for agriculture, undergo a strict procedures should be applied such as devices and education in terms of reducing their harmful effect on health.

Author Contribution Statement

Yilmaz S. organized and designed the study. Bayram I., Kupeli S, Sezgin G., Ozkan A., Leblebisatan G., Kupeli Yagci B. Boz N and Barutcu A. contributed to the collection of leukemia cases. Daglioglu N., Inandiklioglu N. and Atasoy Aydin A. were involved in the laboratory organization work. Daglioglu N. and Atasoy Aydin A. analysed blood materials. İsmail Ethem Goren performed statistical analysis. Yilmaz S., and Inandiklioglu N. prepared and reviewed the manuscript. All authors have read and approved the content of the manuscript.

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Conflicts of interest

All authors declared no conflict of interest.

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