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The effects of different VOCs on blood cells and biochemical parameters

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Abstract. Volatile organic compounds (VOCs) poses serious hazards to the human body. Since 2010, the World Health Organization has been aware of the hazards of VOCs and has established quantitative standards for indoor air toxic substances that have an impact on physical health in the Indoor Air Quality Guidelines released that year. In animal model experiments, studies have shown that VOC leads to increased liver weight, liver damage, endocrine disorders, and blood related diseases. The relationship between human related blood and liver indicators and VOCs has thus received attention. Also due to the different types of VOCs, the mechanisms of their impact on the human body may vary, depending on the type of compound and the level of exposure to pollutants over time. This study comprehensively considered the possible effects of different types of VOCs on biochemical indicators and blood cells, then identified the various effects of different types of VOCs on biochemical indicators, aiming to explore the responding mechanisms of toxicity caused by different VOCs.

Keywords: volatile organic compounds (VOC), biochemical indicators, blood cells.

1. Introduction

Volatile organic compounds (VOCs) poses serious hazards to the human body. Since 2010, the World Health Organization has been aware of the hazards of VOCs and has established quantitative standards for indoor air toxic substances that have an impact on physical health in the Indoor Air Quality Guidelines released that year. The report also mentioned that there is sufficient evidence to suggest a causal relationship between benzene in the air and lung cancer [1]. VOCs poses a serious threat to the human body and has a wide range of impacts. The main way VOCs harms the human body is inhalation through respiration tract. Accidental exposure to VOCs can cause irritation to the eyes, nose, lungs, etc. Short term continuous exposure may cause harm to the liver, kidneys, and central nervous system. Long term exposure to low concentrations of substances can also lead to decreased lung function or cardiovascular disease [2]. In animal model experiments, studies have shown that VOCs leads to increased liver weight, liver damage, endocrine disorders, and blood related diseases [3]. The relationship between human related blood and liver indicators and VOCs has thus received attention.

In addition to benzene, VOCs contains many types of organic compounds, such as toluene, methanol, cyclohexanone, etc. The spread of VOCs pollution is very widespread, and traces of VOCs have been found in many places. The main sources are the use of natural gas, the volatilization of solvents used in paint, and the catalytic generation of high temperature during the process of automobile exhaust

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emissions. Trajectory analysis shows that the spread of VOCs pollution is mainly through short distance transportation, which is greatly affected by local levels [4].

Also due to the different types of VOCs, the mechanisms of their impact on the human body may vary, depending on the type of compound and the level of exposure to pollutants over time [2]. This study comprehensively considered the possible effects of different types of VOCs on biochemical indicators and blood cells, then identified the various effects of different types of VOCs on biochemical indicators, aiming to explore the responding mechanisms of toxicity caused by different VOCs.

The data were obtained from the National Health and Nutrition Examination Survey (NHANES) database in the United States, and the linear fitting and machine learning methods were used to analyse the relationship between VOCs and blood cell parameters and biochemical indicators. The corresponding toxicity and its mechanisms were predicted to the human body caused by different VOCs through comparing VOCs concentration levels.

2. Methods

2.1. Source of data

The VOCs exposure pollution data, blood cells and biochemical indicators are accessed from NHANES. To study impact of VOCs, the data set for this study was 2017-2018 Laboratory Data, which included the data of blood VOCs and trihalomethanes content. The data used has 2608 observations and for VOCs, the dataset gave a large range of 40 different VOCs detection values, and for the affected objects of complete blood count (CBC) with 5-part differential and standard biochemistry profile, including 12 blood cell related indicators and 22 biochemical indicators.

2.2. VOCs detection

The sample was kept in 2-8℃ and sent to Laboratory Sciences, National Center for Environmental Health, Centers for Disease Control and Prevention, Atlanta, GA for analysis. The laboratory established an automated analytical system of comprehensive use of capillary gas chromatography (GC) and mass spectrometry (MS) with selected-ion monitoring (SIM) detection and isotope-dilution. The system were sensitive measurement of low VOCs values for non-occupationally exposed individuals to monitor the sustained or recent low-level exposure.

2.3. Laboratory methodology for CBC and standard biochemistry profile

The principle of the experimental method for obtaining parameters of CBC dataset was the Beckman Coulter methodology of counting and sizing. The measurement of biochemical indicators, named BIOPRO dataset, was carried out by first conducting biological or chemical reaction colorimetry. Absorbance measured on the Roche Cobas 6000 (c501 module) analyzer to reflect concentration.

2.4. Data selection and processing

Due to the limitations of the spectrophotometry method and the instruments used for detection, each substance has a lower detection limit. The accuracy of the value below the lower detection limit were not guaranteed because of them less than minimum precision of the instrument. Considering the accuracy of the fitting, a 95% confidence intervals was selected, and the VOC types that have less than 5% data which above detection limit were rounded out. In addition, a test positive below 5% were excluded since the small degree of pollution could not reflect the degree of pollution harm. Finally, among 2608 populations, the numbers of whose detection value equal or above the detection limit accounted for more than 5%, and this kind of VOC were analysed subsequently (Table1).

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Table 1. The detection limit of different VOCs and numbers of data.

VOC type	Detection limit (ng/mL)	NO. ⩾ detection limit	NO. < detection limit	Missing
Blood m-/p-Xylene	0.034	1940	916	316
Blood Chloroform	0.008	1420	1438	314
Blood 1,4-Dichlorobenzene	0.04	1119	1736	317
Blood Benzene	0.024	914	1926	332
Blood Ethylbenzene	0.024	793	2073	306
Blood o-Xylene	0.024	782	2084	306
Blood Bromodichloromethane	0.006	484	2380	308
Blood 2,5-Dimethylfuran	0.011	467	467	306
Blood Furan	0.025	446	2395	331
Blood Dibromochloromethane	0.005	381	2484	307
Blood Bromoform	0.008	227	2630	315
Blood Isobutyronitrile	0.04	224	2611	337
Blood Benzonitrile	0.15	179	2687	306
Blood Tetrachloroethene	0.048	168	2556	448

The next step is to select the indicators of blood cell and biochemistry for calculation of their correlation with VOC. Here, this experiment selected the variables with a correlation greater than 0.08 for further research.

2.5. Statistical analysis

First, in order to compare the correlation between different VOCs with CBC or BIOPRO, linear fitting was used to fit the model and get the P-value. Subsequently, this study also tried to use random forest of machine learning to provide a possible fitting model for the impact of VOCs on CBC and BIOPRO using computer algorithms. In order to find the best efficiency, the random forest, preliminary experiments were conducted to find lest tree number (Figure 1). The plot showed that error numbers tend to stabilize after 60 trees for conducting in subsequent fit models. When performing random forest calculations, the calculated increase in node purity (IncNodePurity) represents the impact of each variable on the heterogeneity of observations at each node of the classification tree. Data analysis was completed by using R 4.1.3 and EXCEL.

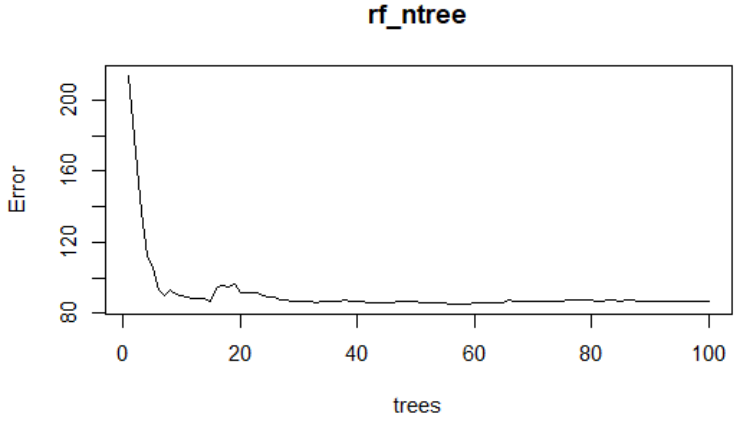

Figure 1. The erros and trees in random forest model.

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3. Results and discussion

3.1. Demographic analysis

A total of 2608 subjects were included in this study, including 1270 males (48.7%) and 1338 females (51.3%) with an average age of 45.84 years old. Most participants were non-Hispanic white (35.2%), followed by Non-Hispanic black (22.1%) and then Mexican American (13.9%). The place of residence, education level, and income level of the respondents may be related to the degree of VOC pollution for conducting statistics analysis (Table 2, next page).

3.2. Comparative analysis of pollution levels among VOC types

By analyzing the VOCs content in blood samples, it can reflect the absorbed amount in human body and the degree of pollution. As showed in Figure 2, take the average level of contamination in the blood into account, the contents of LBXV4C ,LBXVBZN, LBXVDB, LBXVIBN, LBXVXY are relatively high, which is blood 1,1,1,2-tetrachloroethane, blood benzonitrile, blood 1,4-dichlorobenzene, blood isobutyronitrile, blood m-/p-Xylene. 1,4-Dichlorobenzene is often used in moth repellents and deodorants. 1,1,1,2-tetrachloroethane is used as a solvent, organic synthesis raw material, and extractant in the production of common adhesives. Benzonitrile is mainly used as an intermediate or solvent in advanced coatings. Heterodyne is often used as an intermediate in the synthesis of insecticides. Xylene is a common intermediate in chemical synthesis and also appears in PET plastics and gasoline. And it has been classified as a Class 3 carcinogen by the World Health Organization in 2017 [2].

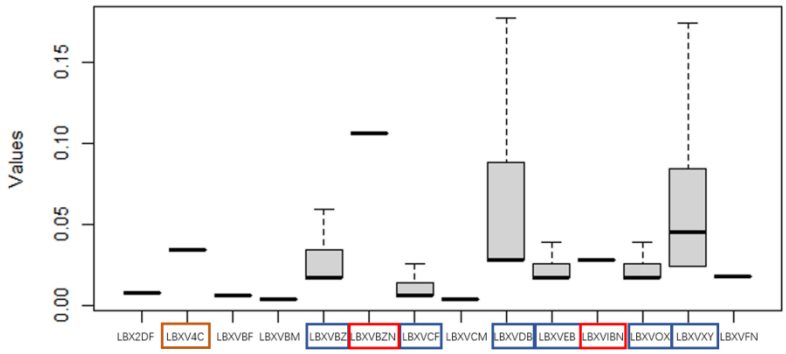

Figure 2. The VOC contents in blood.

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Table 2. Demographic analysis of the populations.

Variables		Count	Proportion (%)
Gender	Male	1270	48.73
	Female	1338	51.34
Race	Mexican American	363	13.93
	Other Hispanic	244	9.36
	Non-Hispanic White	917	35.19
	Non-Hispanic Black	577	22.14
	Non-Hispanic Asian	361	13.85
	Other Race - Including Multi-Racial	146	5.60
Income level	$0 to $34,999	877	33.65
	$35,000 to $74,999	688	26.40
	$75,000 and over	701	26.90
Education level	Less than 11th grade or no diploma	412	15.81
	High school graduate/GED or equivalent	540	20.72
	College/AA or above degree	1223	46.93
Length of time in US	Less than 1 year	17	0.65
	Years [1 -10)	148	5.68
	Years [10 -30)	282	10.82
	Years [30 -50)	179	6.87
	Years [50 -)	45	1.73
	Refused or don't know	27	1.04

These VOCs that can enter the human bloodstream are quite common in daily life [5]. Even if occupational hazards are avoided, they can still enter the human body through pathways such as insecticides, coatings, and gasoline. However, it is difficult for the human body to metabolize VOCs, so that they may accumulate in the bloodstream, which is quite dangerous.

3.3. P-value analysis of linear fitting model

Considering that the variables involved in the study are all continuous numerical variables, the author first adopt multivariate regression to obtain the linear relationship between VOC concentration and physical indicators. The fitted P-value, of linear regression can reflect the degree of linearity. In statistics, it is generally believed that data with a P-value greater than 0.6 have a better linear correlation [6]. In here, counting results showed that significant linear correlation obtained between LBXVBM, LBXVCF, LBXVCM, and body indicators, with half of the fitted models observing a P-value greater than 0.6 between the VOC and the indicator from 14 fitting models, which is blood bromodichloromethane, blood chloroform and blood dibromochloromethane. The possible reason for the good linear correlation is that these pollutants have a significant impact on biochemical indicators and are relatively toxic, or it may just be a coincidence of the linear fitting model, as most of the other VOCs have P-values between 0.4 and 0.9 without significant differences among VOCs.

3.4. Weight Analysis of Random Forest

Subsequently, in order to compare the importance of variables, random forest analysis was used for the selected VOC types and high correlation CBC and BIOPRO indicators with VOCs. Coincidentally, in the prediction of VOCs and CBC, first 6 of the IncNodePurity are LBXVXY, LBXVDB, LBXVCF, LBXVBZ, LBXVEB, LBXVOX, which are much larger than the remaining 8, although their specific ranking may fluctuate by one to two places (Figure 3).

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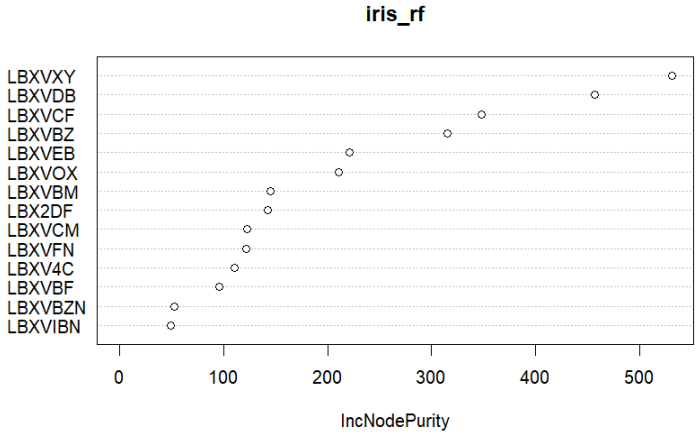

Figure 3. Radom forest increases in node purity of VOCs and CBC .

In Figure 3, the author took the random forest fitting with VOC and hemoglobin content (g/dL) as an example, and the data showed that the importance of the six VOCs mentioned before was much higher than the remaining VOCs. The remaining fitted graphs were not shown due to space limitations.

The random forest analysis of VOCs and BIOPRO showed similar and different parts. Similar to the analysis results of VOCs and CBC, the same 6 VOCs were also high in the result of IncNodePurity VOCs and BIOPRO. These 14 random forest models were similar rankings, suggesting that LBXVXY, LBXVDB, LBXVCF, LBXVBZ, LBXVEB, LBXVOX, respectively blood m-/p-Xylene, blood 1,4-Dichlorobenzene, blood Chloroform, blood Benzene, blood Ethylbenzene, blood o-Xylene has a significant impact on human body indicators.

In addition, the results of VOCs and CBC or BIOPRO had some differences, as shown in Figure 4. In the random forest model of alanine amino transfer (ALT) and Gamma glutamyl transferase (GGT), blood bromoform has high IncNodePurity. Aspartate aminotransferase (AST) fitting showed blood tetrachloroethene has high IncNodePurity. Triglycerides showed blood 2,5-dimethylfuran has high IncNodePurity. Previous studies have shown that different VOCs have different levels of toxicity. If the toxicity of volatile compounds is small, the harm caused by emitting more VOCs is not as great as that of emitting high toxic VOCs. It has been found that the carcinogenic equivalent CEQ may vary with the type of VOC [7]. This indicates that different VOCs influenced on different biochemical parameters. Special type of VOC has its own reaction mechanism for a certain biochemical indicator with high IncNodePurity.

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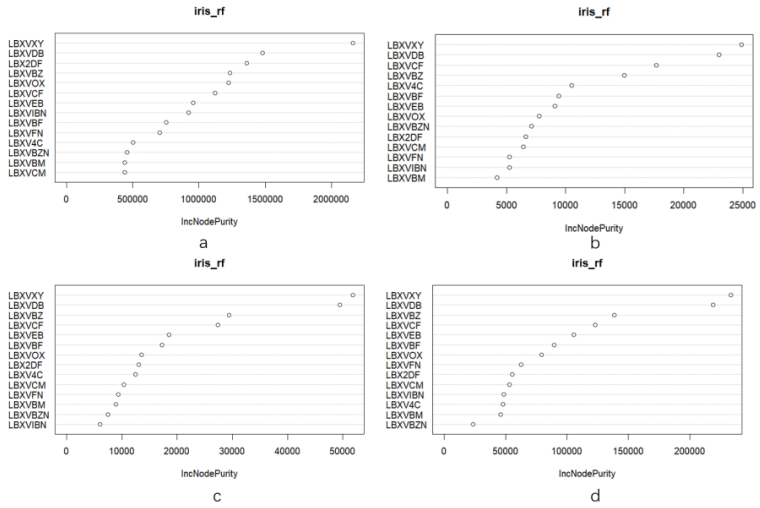

Figure 4. Special case of increase in node purity of VOCs and BIOPRO.

And blood cells are regulated by biochemical indicators with a comparable low IncNodePurity, suggesting the importance of low frequency VOCs is weakened. Nevertheless, the six indicators with a larger impact still are highlighted.

3.5. The dose of pollution and its harmful degree

Combine the six VOCs obtained in part of 3.4 that have a general impact on physiological indicators with the VOC content in the blood obtained in part of 3.2 for simultaneous analysis, and visually frame them in box plot, as shown in the blue frame of Figure 2. It can be clearly seen from the graph that the VOC content, which has a wide impact on human indicators, is not low. VOC needs to have a certain concentration in the body to have an impact on physical indicators. In other words, VOC with lower concentrations is considered to have very low harm to the human body and can be ignored.

From another perspective, it can be observed from the graph that there are other VOCs with high concentrations but low impact on physical indicators, which shown in the red and orange frame of Figure 2. The concentration of these VOCs may even be higher than the VOCs in the blue box, but their impact is not the most common or severe. The LBXV4C with orange frame, which is blood tetrachloroethene shows high IncNodePurity with the fitting of Aspartate aminotransferase (AST). This suggests that the influence of VOC on blood and biochemical parameters is targeted. Sabit Cakmak et al. used data from Canada as a sample and found that VOC does indeed affect some physiological indicators, including hematological parameters, liver and kidney function markers, etc. This in turn affects liver and kidney function [8]. There have also been studies exploring the relationship between VOC and indicators of liver lipid metabolism and liver injury, indicating that exposure to VOC can lead to disturbances in liver lipid metabolism [9].

High concentrations of the same VOC may have significant or minor effects on different biochemical indicators simultaneously. Noticeably, the LBXVBZN and LBXVIBN, which are blood Benzonitrile and blood Isobutyronitrile, do not show any significant impact on biochemical indicators anywhere. Therefore, it is believed that the impact of these two types of VOCs on the human body is relatively small. Two hypotheses are proposed here, one is that the toxicity of these two types of VOCs is low, and the other is that they may not participate in biochemical reactions very much, thus they cannot be metabolized, and eventually they do not affect biochemical reactions although their content in the body is high [10].

4. Conclusion

In conclusion, this author used linear fitting models and machine learning random forest models to analyze the relationship between VOC and some biochemical indicators and blood cell parameters. From

the perspective of the differences in toxicity between different VOCs and the mechanisms of their impact on biochemical indicators, LBXVXY, LBXVDB, LBXVCF, LBXVBZ, LBXVEB, LBXVOX have a significant impact on the human body and may have significant toxicity. Moreover, different VOCs have different effects on different indicators, indicating that the mechanisms of their impact are different. Then, analyzing the relationship between the impact of VOC and its content, it was found that the concentrations of several VOCs with significant impact were not low. It is possible that VOCs require a certain concentration to exhibit toxicity. In addition, based on the affected blood cell and biochemical indicators, it can be inferred that VOC poisoning may lead to erythrocytosis or agranulocytosis, damage liver function, and further reduce the processing capacity of blood cells.

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