The Correlation between the Indoor Polluted Gases and Leukemia

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Abstract: With the developing of the society, the standards of human's life are growing up. It is reasonable for people to pursue a better living environment, which means they want to live in a clean, tidy and warm working place to work and live. So plenty of people spent much money to decorate their homes. However, they were not realized perhaps it is this kind of behavior that makes indoor air pollution more pollution sources and factors affecting air quality which is harmful to their health. For example a large amount of formaldehyde, benzene and other volatile organic compounds in the materials used for interior decoration will cause various health hazards to the exposed population, including cancer. Besides, as the research at home and abroad, urban residents spend about 80 to 90 percent of their time in the indoor environment everyday. So diseases caused by harmful indoor gases arouse attention from the public and the government. More specifically, in 1990, the US Environmental Protection Agency published a list of chemical substances that have bad effects to the human body. The list of chemical substances covered four categories: particular matter, inorganic gases, volatile organic compounds, and polycyclic aromatic hydrocarbons. Hind two kinds of material are indoor harmful gas main component. So the research on the effect of harmful gases on human body is urgently needed. However, China's scientific research in this area is not sufficient, unable to adapt to the needs of government management decisions and public health requirements. Therefore, the composition of various chemicals indoor air and their effects on health are still very important topics at present. In this article we will discuss the correlation between the harmful chemical gases, more specifically are formaldehyde and benzene, and leukemia.

1 INTRODUCTION

The incidence of leukemia in China is (1-4) 100,000. Among the death rates caused by malignant tumors, leukemia ranks 6th (male) and 7th (female). Children and adults under the age of 35 ranked first. The incidence was slightly higher in males than in females (1.81:1). The most common acute leukemia is acute myeloid leukemia in adults and acute lymphoblastic leukemia in children. The incidence of chronic myeloid leukemia increases with age. The incidence of chronic lymphocytic leukemia increases significantly after the age of 50. Our country leukaemia incidence of a disease and Asian other country close, under euramerican country. In particular, chronic lymphocytic leukemia is less than 5% of the total incidence of leukemia, while in European and American countries, it accounts for 25%~30%.

In a 2021 study funded by the Natural Science Foundation of Inner Mongolia Autonomous Region, the relationship between toxic gases and blood diseases was revealed through an analysis of blood diseases induced by benzene exposure. Researchers for patients admitted to hospital inspection, treatment process and working condition of research for many times, finally found benzene metabolites have toxicity to hematopoietic stem/progenitor cells, not only affect the bone marrow hematopoietic cell

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proliferation, still can cause blood cells differentiation and maturation of disorder, can lead to uniparental cells, whole blood reduced, and even induce aplastic anemia. Years of exposure to benzene and organic solvents containing benzene are associated with leukemia.Long-term exposure to benzene and other harmful substances, considering the incidence of leukemia is closelyrelated to benzene exposure. Chemically-induced leukemia is more common in AML.

In this paper, on the basis of the existing research, the relationship between toxic gas and leukemia was further explored. In addition, the researchers found that toxic gases such as formaldehyde, benzene and other chemical gases can also be released through household furniture, carpets and wallpaper. Therefore, this paper analyzes the relationship between household air pollution and blood diseases. Through the analysis of various types of blood diseases and chemical substances, in-depth understanding of the impact of toxic gases on human body, and finally found that household pollution gases such as formaldehyde, benzene and leukemia have a high correlation.

2 BACKGROUND OF HARMFUL GASES EMITTED BY BUILDING MATERIALS

2.1 The Source of the Chemical Gases

The source of indoor polluted gases are mainly from the fuel burning, smoking, daily using, building materials and decoration materials. Burning material are natural gases, coal and plant leaves. When burned, these substances produce carbon oxides, nitrogen oxides, sulfur oxides, and polycyclic aromatic hydrocarbons. The indoor harmful gases produced by smoking are nicotine, nitrogen dioxide, carbon dioxide. Besides, chemical gases are mainly from the building and decoration materials, for example, decorate plank, coating, cementing compound. Which is worth mentioning, furniture, carpets and wallpaper also emit chemical gases.

2.2 The Types of the Indoor Chemical Pollution and the Diseases May Bring

Table 1: Classification of indoor hazardous gases and possible diseases.

Pollutant	Critical outcome(s) for guideline definition
Benzene	Acute myeloid leukaemia (sufficient evidence on causality)
Formaldehyde	Sensory irritation
Naphthalene	Respiratory tract lesions leading to inflammation and malignancy in animal studies.
Radon	Lung cancer
Trichloroethylene	Carcinogenicity with the assumption of genotoxicuty
Tetrachloroethylene	Effect in the kidney indicative of early renal disease and impaired performance
Polycyclic aromatic hydrocarbons	Lung cancer

The table1 is from an article which is published by WTO (OMS 2000), which discuss about the main types of the pollution gases and the disease they may cause. Atpresent,the international classification standards for carcinogens are formulated by the International Institute under the jurisdiction of the United States. It mainly covered four stages: A, B, C and D, among them A represented that a well-documented carcinogenicity in humans. According to the report published by IARC in 2008,which showed that formaldehyde and benzene were belonging to the class A carcinogen .So in this article we will discuss the correlation between the formaldehyde ,benzene and leukemia.

2.3 The Introduction about the Formaldehyde and Benzene

2.3.1 General Description of the Benzene

Benzene is an aromatic compound with a single six-member unsaturated carbon ring. This is a colorless transparent liquid with a special aroma, which is able to rapid evaporation at room temperature. Inhalation of high concentration of benzene vapor in a very short period of time can caused acute benzene poisoning, excitement or intoxication, accompanied by symptoms of mucosa irritation (OMS 2000).

2.3.2 Indoor Sources of the Benzene

Indoor benzene often from decoration materials, furniture, garbage, storage appliances and human activities. At the same time, indoor concentration also affected by the frequency and area of indoor and outdoor air circulation. In the United States, everybody absorbs indoor benzene each day on average was between 180 and 1300μg (WHO 2000). In general, the amount of benzene emitted from food is very tiny. In addition to normal source of benzene, such as decoration materials, cigarette smoke is also a vital source of benzene in indoor air, which is harmful to the human's lung.

2.3.3 Hazards of Benzene to Human Body

To the mechanism of action of benzene toxicity, it always has two types. At the high level benzene concentration, it just like a narcotic that depress the central nervous system and causes cardiac sensitization and finally lead to the leukemia. More specifically, benzene is genetically toxic, leading to the missing of the chromosomes long arms. This change may bring to myelodysplastic syndrome, which is the start of the leukemia. Benzene can also causes mutations in alleles, in this situation, bone marrow cells will experience mutations and then becomes to leukemia (Wang et al 1998). The bad effects of the benzene under low-level is lack of the suitable animal model, so we will not discuss it.

There are plenty of reports of people deaths from inhaling high concentrations of benzene. Human may die immediately or die several hours later in this situation. When concentration between the 300 and 3000ppm (CRONIN, and Herbert 1924), Flury,1928, Midzenski, et al, 2010),the symptoms are always shown as the speaking problems, headaches, dizziness, insomnia (OMS 2000).

Benzene metabolites also trigger chromosomal aberrations. The carcinogenic of action of benzene has relationship with its genotoxic effects and the critical health outcomes are bloody dyscrasias and leukemia, especially becomes to the acute myeloid leukemia (OMS 2000).

2.4 The Introduction of the Formaldehyde

2.4.1 General Description of the Formaldehyde

Formaldehyde is a naturally occurring compound with the formula CH2O.The pure compound is colorless, flammable gas at room temperature and has a pungent odor. Which is worth mentioning, formaldehyde is a versatile, reactive substance, in common use to the industry because of its low prize and ease of production. So it is familiar and can be easily found in our daily-used products.

2.4.2 The Source of the Indoor Formaldehyde

Major source of formaldehyde is the building materials and consumer products (Salthammer, Mentese and Marutzky 2010, Kelly, Smith, Satola 1999). It is always found in the composite wood products, furniture and so on.

The possible routes of exposure to formaldehyde are inhalation, ingestion and dermal absorption. Human can be exposed to formaldehyde by breathing air containing off gassed formaldehyde.

2.4.3 The Health Effect of the Formaldehyde

In recent years, formaldehyde has come under increased scrutiny of its potential negative health effects. After acute and short-term exposure to formaldehyde at indoor levels, people may have sensory irritation to the eyes and upper airways, lung discomfort and finally eczema (OMS 2000).

The meta-analysis on account of the highest exposure levels reported that formaldehyde can cause especially myeloid leukemia **(**Salthammer, Mentese and Marutzky 2010**)**. Firstly, blood will deliver the formaldehyde to the bone marrow, and in bone marrow would lead to origination in a stem. Secondly, as a portion of the bone marrow stem and progenitor cells circulate in the peripheral blood, they may be started by formaldehyde which was absorbed into the blood.

Lastly, the starts of the initial multifunctional stem cells provided within the nasal mucosa could occur, followed with transport to the bone marrow.

3 THE INTRODUCTION OF LEUKEMIA AND ITS PATHOGENESIS

Nowadays, leukemia is separated into 4 main types based on acute or chronic diseases and myeloid or lymphocytic diseases.

3.1 Acute Myeloid (or Myelogenous) Leukaemia (AML)

Acute myeloid leukemia is a disease caused by an increasing number of myeloid cells in the marrows and their maturation is repressed, which caused hematopoietic insufficiency, such as granulocytopenia, thrombocytopenia, or anemia, with or without the leukocytosis.

Through molecular pathogenesis, Acute myeloid leukemia is related to specific cytogenetic lesions.

Through the research, the alteration of AML1-CBFb is one of the major reasons which caused the AML. The DNA-binding subunit of AML1-CBFb, a transcription factor that is the essential for normal development of the hematopoietic system. Through the AML associated chromosomal rearrangement inv(16) or its variant t(16;16) targets CBFb, AML1-CBFb is the target of the t(12;21) translocation in several rare translocations in AML, making it become the most common target of chromosomal rearrangements in human leukemia.

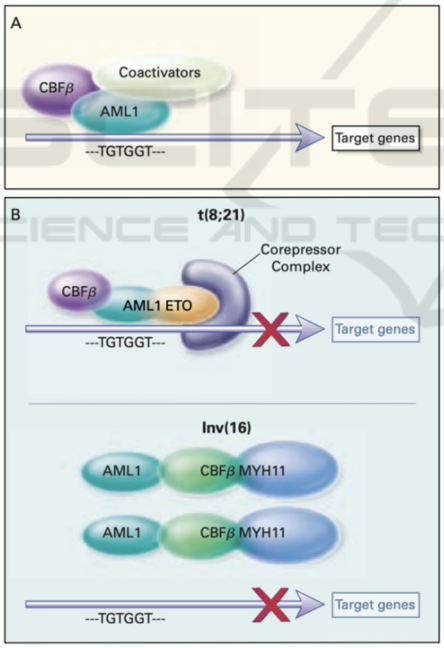

Figure 1: The AML1-CBFb Transcription Factor.

Through figure 1, the CBFb and the AML1 and Coactivators can be normally pass through to the target gene. However, the DNA-binding and CBFb-interaction domains, form the C-terminal portion of the 821 genes (ETO) on chromosome 8 and the corepressor complex caused the failure to activate transcription. In the inv(16) (p13;q22) and the t(16;16)(p13;q22), mutations caused the CBFb subunit of the core binding-factor complex on chromosome 16q22 to be fused to the smooth-muscle myosin heavy-chain gene MYH11 on chromosome 16p13.32 and make a product of CBFb-MYH11 chimeric, which caused the inactivation of AML1 and fail to be a transcript. meric, which caused the inactivation of AML1 and fail to be transcript(Appelbaum, et al 1999).

3.2 Acute Lymphocytic (or Lymphoblastic) Leukaemia (ALL)

Acute lymphocytic leukemia (ALL) is a lymph cancer, and its characters can be seen as the development of large numbers of immature lymphocytes. The ALL influences the bone marrow and the blood. The ALL can be developed very fast and it can be easy to cause death without appropriate treatment.

Acute lymphocytic leukemia (ALL) is caused by several reasons.

1) Idiopathic (most of ALL)
2) Haematological disorders (Underlying)
3) Chemicals and Drugs
4) Ionization radiation
5) Viruses (HTLV-I)
6) Hereditary/ Genetic conditons

Most of the ALL is Idiopathic which means there are not any distinct causes and there is still no clear answer as to what causes ALL. Chemicals and Drugs and Ionization radiation can be also defined as environmental factors.

Through the viruses (HTLV I) can also be caused the ALL, the pathological mechanism of transforming retroviruses HTLV-I is unclear, but there are only 2 ways to caused the disease of ALL, which is encoding oncogenes that mediate viral transformation or disrupt cellular gene expression as a byproduct of proviral integration.

The last reason is the hereditary/genetic conditions, this reason is also complex without any clear evidence that can be used to prove how it caused acute lymphocytic leukemia (Gatza, Watt and Marriott 2003).

3.3 Chronic Myeloid (or Myelogenous) Leukaemia (CML)

Chronic myeloid leukemia (CML) is caused by the bone marrow hematopoietic stem cells growing in the form of clonal proliferation and became a malignant tumor. Chronic myeloid leukemia is asymptomatic in the early stages, CML does not become apparent until

the middle and even ultimately leads to death in the late stage.

The pathological mechanism can be attributed to the altered function of the 2 genes in the Ph transcription. The genes are ABL and BCR genes are changed and caused the CML. The BCR gene is on chromosome number 22. The ABL gene is on chromosome number 9. The ABL part in the chimeric protein is invariably constant, but the BCR gene varies greatly. The ABL gene has the transforming principle and the size of the BCR sequence can determine the phenotype of the disease.

Through the research, the BCR-ABL is the combination of genes ABL and BCR which are the gene sequence and found in the abnormal chromosome 22 of people with chronic myeloid leukemia. The mutation in the BCR-ABL can affect the organization of cell membrane and cytoskeleton and also it can be caused the communication between cells and the environment and disturb the response by the cells. Therefore, the mutated BCR-ABL protein caused not just a change in a single path, it can also change in multiple paths (shown in figure 2). As a result, it caused chronic myeloid leukemia (Melo 2001)

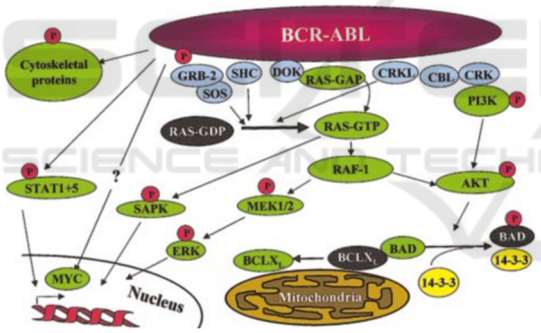

Figure 2: The signaling pathways shown in the activated BCR-ABL.

3.4 Chronic Lymphocytic Leukaemia (CLL)

Chronic lymphocytic leukemia (CLL) is most common in B-cell, the feature is the accumulation of CD5 + B cells in the blood, bone marrow, lymph nodes, and spleen. The early stage of chronic lymphocytic leukemia (CLL) does not have any symptoms but may show symptoms in the middle and later stages.

The mechanism of chronic lymphocytic leukemia (CLL) is unclear, but it can be identified by the accumulation of B-cell, and the trend of B-cell caused the lymphadenopathy, liver and spleen enlargement, anemia and bleeding, and complication (Olsson, et al 2007).

4 BENZENE AND FORMALDEHYDE HARMFUL TO HUMAN BODY

4.1 Metabolism of Formaldehyde and Benzenes

4.1.1 Metabolic Process and Products of Formaldehyd

Formaldehyde (chemical formula HCHO) is the simplest aldehyde molecule and is toxic. It has been listed as a Class I carcinogen by the International Agency for Research on Cancer of the World Health Organization on October 27, 2017.The metabolism of formaldehyde in the human body mainly depends on the catalysis of enzymes. The enzymes that degrade formaldehyde are mainly ethanol dehydrogenase I distributed in pyramidal and granulocytes of hippocampal formation, cerebral cortex and vascular epithelial tissue of brain; ethanol dehydrogenase III existing in various tissues and organs; and dehydrogenase II, the most active of aldehyde dehydrogenase which is mainly distributed in cell mitochondria. Formaldehyde is degraded to formic acid, which is directly discharged from the kidney or exhaled out of the body through oxidation to CO2 (Tulpule, Hohnholt, and Dringen 2013). This was confirmed in experiments: Zhang Ruiwen et al. (Zhang and Wang 1990) studied the metabolic process of formaldehyde in red blood cells based on the ability of separation of formaldehyde dehydrogenase in human red blood cells and liver and found that formaldehyde metabolizes into formic acid in red blood cells, and the higher the initial formaldehyde concentration, the slower the metabolic process and the lower the metabolic rate.

4.1.2 Metabolic Process and Products of Benzenes

Benzene, toluene and xylene (collectively referred to as the three benzenes) are the most representative benzenes. They are gaseous at room temperature and can enter the human body through multiple channels such as respiratory tract, gastrointestinal tract, skin and mucous membrane, thus affecting human health. Among them, benzene was listed as a Class I carcinogen by the International Agency for Research

on Cancer of the World Health Organization on October 27, 2017, and toluene and xylene were listed as Class III carcinogens.

Some benzene substances in the human body can be directly discharged through urine, while the benzene substances that are not discharged are first oxidized to epoxy benzene under the action of cytochrome P450 monooxygenase in the liver, and the epoxy benzene continues to combine with glutathione to form S-phenylmercapturic acid (SPMA); or continue to be metabolized into phenol, catechol and others, which are discharged in the form of glucosidic acid or sulfate conjugates; or are oxidized to adipic acid. This has also been confirmed by experiments: the study of Wan Lingli et al. (Wan, Zheng, pan, Ke 2021) found that six metabolites such as S-phenylmercaptouric acid (SPMA) and hippuric acid (HA) were much higher in people chronically exposed to benzenes than those not exposed.

4.2 Effects of Formaldehyde and Benzenes on Humanbody

4.2.1 Liver

Formaldehyde and benzenes can affect the expression level of metabolism related genes in the liver (Chen, et al 2009), reduce the ability of liver tissue to scavenge oxygen free radicals and antioxidants, decrease trace elements in liver tissue, cause liver injury, and cause inflammatory changes and even tumor in the liver.

4.2.2 Skin

Formaldehyde and benzenes can affect the content of ceramide in basic lipid components of skin (Nardo, Di, et al 2007), causing contact dermatitis and mucosal irritation. Irritation of human skin by formaldehyde and benzenes produces discoloration, redness, hardening and skin scaling. The lesions usually appear first on the hand and forearm as papules; rashes may appear on other parts of the body as fused papules, with erythema in some areas, followed by desquamation, and exfoliative dermatitis on hands and feet in severe cases.

4.2.3 Respiratory Tract

Formaldehyde and benzenes inhibit the formation of nasal cilia, especially the front end of nasal cilium, which has a mutagenic and damaging effect on DNA of human bronchial cells, and cause irritation of the human nose and upper respiratory tract (Ballenger 2010), thus increase the incidence of respiratory symptoms, chronic rhinitis, bronchitis, pneumonia and abnormal pulmonary function.

4.3 The Correlation between Toxic Gases and Leukemia

Leukemia is a type of malignant tumor of the vascular system, and although its pathology is still not fully understood, the current understanding is that the mechanism of its occurrence has some correlation with the environment, genetic factors, and other elements. Currently, the relationship between toxic gases and leukemia is receiving increasing interest from the scientific community, with critical research needed to confirm this theory and determine methods of decreasing people's exposure to toxic gases and thereby reducing the rate of disease occurrence. Research clearly shows leukemia occurrence rates to be related to benzene, formaldehyde, chlorine, and over 100 other kinds of volatile, toxic gases and pollutants. Benzene and its metabolites, along with other toxic gases, damage the bone marrow through the body's immune response, resulting in leukemia (Jiang, Gao 2014).

Through related studies, it has been found that people with a history of smoking have an elevated occurrence rate of leukemia, because burning tobacco releases large amounts of toxic gases, including benzene as well as radioactive chemical compounds and nitrosamine, of which benzene and the BTEX family of compounds make up a very large proportion. Benzene can increase the occurrence of leukemia by any of the following methods: 1) Benzene and its metabolites, including hydroquinone and benzoquinone, produce oxygen free radicals as a product of their metabolism, which can harm the DNA of bone marrow cells; 2) It can induce changes in chromosomal structure, such as chromosome deletion or translocation; 3) Benzene exposure can lead to IL6 and cytochrome P450 2E1 methylation, causing cells to show genetic changes. As for smokers, over 80% of benzene exposures are due to tobacco smoke, and the daily benzene intake of smokers is 6-10 times that of non-smokers. The dosage of benzene in every pack of cigarettes smoked can reach 1.5mg, raising the benzene intake, and the occurrence of leukemia, in smokers far above that of non-smokers (Gross and Paustenbach 2017).

In the building renovation process, paints, composite materials, furniture, and other materials can release benzene, formaldehyde, chlorine, and over 100 other kinds of volatile, toxic gases. Among these, formaldehyde, a colorless, highly oxidizing irritant with a strong odor, is most prevalent.

Formaldehyde has a multitude of pathogenic mechanisms, including its tendency to break apart the DNA of bone marrow cells and form DNA-protein cross-links, thereby producing severe genotoxicity. After a person comes into contact with formaldehyde-containing air, their microRNA expression may be lowered, leading to cancer. Related studies show that formaldehyde concentration and whole blood viscosity have a positive correlation, and that higher formaldehyde concentrations cause more oxidative damage to the membrane of red blood cells. The correlation between formaldehyde concentration and whole blood viscosity is lower in females than in males of the same age group. Overall, formaldehyde exposure is related to increased occurrence of leukemia in adults (Wei, et al 2017).

Vehicle exhaust emissions release many types of toxic gases, including cancer-causing PM2.5, benzene, and many other polycyclic aromatic hydrocarbons (PAH), and may also lead to the occurrence of leukemia. Among these, PM2.5 has a small particle size with relatively large surface area, and remains in the air for long periods of time, adsorbing large quantities of free radicals and heavy metal ions. It also has an effect on bronchial epithelial cells, stimulating inflammation in the respiratory system due to the release of oxygen free radicals, and subsequently inducing an oxidative stress reaction. Under the effects of oxidative damage, the lipid layer of the cell membrane undergoes oxidation, leading to calcium overload in the cell, and thereby destroying the functionality of the mitochondria. This forms a vicious cycle wherein free radicals induce calcium overload in the cell, and ultimately leads to the death of the cell. Therefore, PM2.5 also has a very high correlation with the occurrence of leukemia (Teras, et al 2019).

5 CONCLUSIONS

Through the study of multiple papers, we find that about three directions reasons may cause leukemia:1) a history of smoking is associated with a higher incidence of leukemia, mainly through benzene and nitrous acid to change the body to increase the risk of leukemia. 2) In the building construction, such as oil paint and composite materials, they emit formaldehyde is the most common toxic gas which lead the whole blood viscosity rise up, finally cause leukemia. 3)Car exhaust emissions are mainly PM2.5, which can absorb and carry a large number of free radicals, induce stress response, and ultimate destroy mitochondrial function, leading to bronchial epithelial cells, it is the primary pathogenesis of leukemia.

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