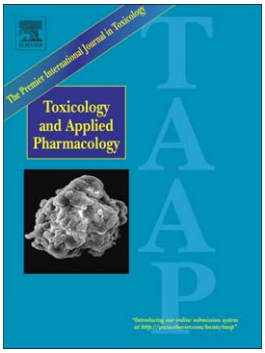

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Current Understandings and Perspectives on Non-Cancer Health Effects of Benzene: A Global Concern

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Abbreviations

- AChE. Acetyl cholinesterase
- ADA: Adenosine deaminase
- ALP: Alkaline phosphatase
- ALT: Alanine aminotransferase
- AST: Aspartate transaminase
- BUN: Blood urea nitrogen
- DNA: DeoxyRibo Nucleic Acid
- DOPA: Dopamine
- EDCs: Endocrine disrupting chemicals
- ERK1/2: Extracellular signal- regulated kinases 1and 2
- Hb: Hemoglobin
- IL-2: Interleukin 2
- Kg: kilogram
- LDH: Lactate dehydrogenase
- LINE-1: Long interspersed nuclear element-1
- MCHC: Mean Corpuscular Hemoglobin Concentration
- MPV: Mean platelet volume
- Mg: Milligram
- OSHA: Occupational Safety and Health Administration
- ROS: Reactive oxygen species
- VOCs: Volatile Organic Compounds
- WBCs: White blood cells

Abstract

Objective: Benzene, as a volatile organic compound, is known as one of the main air pollutant in the environment. The aim of this review is to summarize all available evidences on non-cancerous health effects of benzene providing an overview of possible association of exposure to benzene with human chronic diseases, specially, in those regions of the world where benzene concentration is being poorly monitored.

Methodology: A bibliographic search of scientific databases including PubMed, Google Scholar, and Scirus was conducted with key words of "benzene toxic health effects", "environmental volatile organic compounds", "diabetes mellitus and environmental pollutants", "breast cancer and environmental pollution", "prevalence of lung cancer", and "diabetes prevalence". More than 300 peer reviewed papers were examined. Experimental and epidemiologic studies reporting health effects of benzene and volatile organic compounds were included in the study.

Results: Epidemiologic and experimental studies suggest that benzene exposure can lead to numerous non-cancerous health effects associated with functional aberration of vital systems in the body like reproductive, immune, nervous, endocrine, cardiovascular, and respiratory.

Conclusion: Chronic diseases have become a health burden of global dimension with special emphasis in regions with poor monitoring over contents of benzene in petrochemicals. Benzene is a well known carcinogen of blood and its components, but the concern of benzene exposure is more than carcinogenicity of blood components and should be evaluated in both epidemiologic and experimental studies. Aspect of interactions and mechanism of toxicity in relation to human general health problems especially endocrine disturbances with particular reference to diabetes, breast and lung cancers should be followed up.

Keywords

Benzene, Disease, Glucose homeostasis, Hepatotoxicity, Hematotoxicity, Immunotoxicity, Nephrotoxicity, Neurotoxicity

Introduction

Benzene (C_6H_6) is an organic hydrocarbon commonly used as a solvent in industries. Benzene is one of the most widely used chemical in the synthesis of various polymers, resins, and synthetic fibers (Velasco Lezama et al., 2001).

Human exposure to benzene: Human life is surrounded by a wide range of environmental volatile organic compounds (VOCs) among which benzene has been known to have deleterious health effects (Karakitsios et al., 2007). Benzene is released to our environment from industries effluents, combustion of gasoline and other petrochemicals used in our cars and industries. Cigarettes smoke is the main source for indoor benzene exposure (Wallace, 1996b, Wallace, 1996a). Being extensively used chemical in petroleum industries, and subsequent presence in the environment from other sources, human exposure to benzene is unavoidable and the possible adverse health effects associated with benzene chronic or acute exposure remains a matter of great concern for public (Snyder, 2012). Humans are exposed to benzene most frequently through inhalation of vapors in the workplace, environment and by eating processed foods such as smoked and canned fish (Medeiros Vinci et al., 2012). Apart from above-mentioned sources, an additional quantity of approximately 10 kg/ton of benzene is released to our environment during manufacturing, transferring and storage (Etzel and Ashley, 1994).

Occupations associated with prominent benzene exposure: Occupations dealing with leather, petrochemicals (refining, service station operators), scientific laboratories, rubber industries, coal based coke production, steel manufacturing, printing and plastic manufacturing industries, have possibility of their personnel to be highly exposed to benzene (Galbraith et al., 2010).

Benzene as human carcinogen: Benzene has long been known to act as carcinogen of human blood components. A first case of "benzene associated lymphoma" was reported by French researchers in 1947. According to recent studies, benzene at 3.19 mg/m^3 exposure in air has been accounted to induce hematological effects in humans (Lan et al., 2004, Qu et al., 2002). It has been reported from China, Italy, and Turkey that occupational benzene exposure in the range of 638.8 to 5110.8 mg/m^3 has caused acute myeloid leukemia, myelodysplastic syndrome, non-Hodgen lymphoma and possibly childhood leukemia (Eden, 2010, McHale et al., 2012, Brandt, 1992).

Current global regulations on benzene gasoline ratio:

Aromatic hydrocarbons are added to gasoline for maintaining high octane number and for best anti knock properties. Refined petroleum products generally contain 2-3% benzene by volume (Wong and Fu, 2005). Due to hazardous effects of lead (Pb) on human health, the content of its additives in gasoline has been reduced and almost eliminated since the last decade, but for anti knocking purposes, benzene is mixed with gasoline, so that the contents of benzene in gasoline have reached to more than 5% in some countries (Verma and des Tombe, 2002, Karakitsios et al., 2007). In the USA, Australia, and Europe the concentration of benzene in gasoline has been reduced to 1% by volume (Verma and des Tombe, 2002), but in other regions like Russia, India, Malaysia, UAE, Bangladesh, Saudi Arabia, Egypt, Libya and some African countries, concentration of benzene in gasoline is estimated to be in the range of 3-7% volume. Pakistan, Iran, Iraq, Turkmenistan, Uzbekistan, Syria, and Sudan are the countries where no monitoring is exercised over benzene contents and any standard for benzene concentration in gasoline has not been yet set (Figure 1). Information regarding benzene gasoline ration in different parts of the world taken from "International fuel quality center, August 2013 and Hart Energy Research and Consulting" have been brought in Table 1.

As recommended by the U.S. Environmental Protection Agency, current threshold limit for benzene is 1.59 mg/m^3 at workplace and 0.01597 mg/m^3 for drinking water (Galbraith et al., 2010). In the Western and European countries, the concentration of benzene in the ambient air has fallen since 1990. As reported, the annual atmospheric concentration of benzene in European cities is in the range of few $\mu g/m^3$ to 0.050 mg/m^3 in busy streets and areas with high traffic density (Skov et al., 2001).

However, this concern regarding other countries particularly developing ones is increasing, so that health hazards of exposure to benzene need more attentions for management from side of environmental health scientists and agencies.

Table 1: Benzene gasoline ratio in different countries of the world

Countries	**Concentration of benzene in gasoline**
USA, China, European Countries, Australia	Less than 2 volume%
Russia, India, Malaysia, UAE, Bangladesh, Saudi Arabia, Egypt, Libya and South Africa	Benzene in gasoline (3-7 volume %)

Pakistan, Iran, Iraq, Turkmenistan, Uzbekistan, Syria, Sudan	No standard yet defined

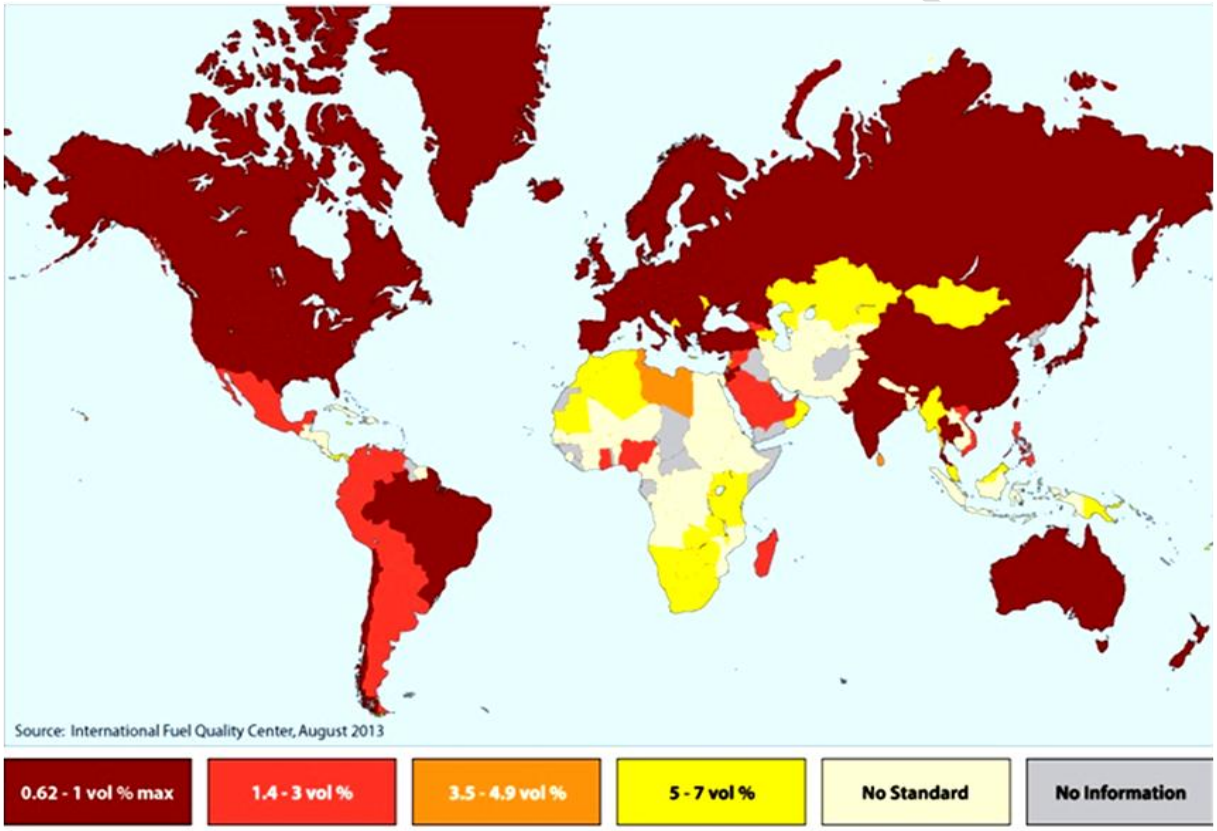

Figure 1: International limits on benzene contents in gasoline. Adopted from international fuel quality center (http://www.ifqc.org/Spotlight.aspx?Id=130), August 2013; Hart Energy Research and Consulting with permission.

Evidences for non- cancerous health effects of benzene

Hematological Effects

Chronic exposure

The toxic effects of benzene exposure on blood components have been studies in detail. Both in experimental and epidemiologic studies, it has been reported that chronic exposure to benzene is associated with decrease in hemoglobin (Hb), platelets count, and white blood cells (WBCs) count (Travis et al., 1994, Hsieh et al., 1990). Neutrophils and mean platelet volume (MPV) in the blood have been reported as the most affected parameters by benzene exposure in workers

exposed to benzene in a factory in China, where the recorded weekly average benzene concentration was 7.4 mg/m^3 (Robert Schnatter et al., 2010). Bogadi-Sare et al. (1995) have reported a significant decrease in Hb and mean corpuscular hemoglobin concentration (MCH) in workers exposed via inhalation in a shoe making factory to vapors of benzene in the range of 6.0 to 47.2 mg/m^3. However, no effect on hematological parameters was observed in a subgroup of workers exposed to benzene less than 15.9 mg/m^3 (Bogadi-Sare et al., 1995) but another study suggests that long-time exposure to benzene at concentration below 15.9 mg/m^3 may cause suppression of hematological parameters (Ward et al., 1996, Baak et al., 1999). And this was supported by Lan et al. (2004) who reported a decrease in WBCs and platelets in workers exposed to benzene at 3.19 mg/m^3 concentration for a long time (Lan et al., 2004). And there are reports that chronic benzene exposure might be a risk factor in the incidence of other blood disorders like aplastic anemia and leukemia in human (Smith, 1996b, Travis et al., 1994).

Since the last two decades, much stress has been laid on personal protection and good industrial hygiene practices having appreciably reduced the risk to employees. It is evidenced that chronic exposure to benzene at very low concentration poses health complications by affecting the components of blood**.** However, no reports have been traced about acute toxicity of benzene or at higher exposure on blood parameters, which suggest that exposure period might play an important role in the incidence of hematological effects.

Immunological Effects

Chronic exposure

Benzene chronic exposure has been reported, both in experimental and epidemiologic studies, to suppress the components and functions of immune system including serum immunoglobulins and the immune cells. Farris et al. (1997) in their experimental study observed benzene induced reduction in B and T lymphocytes in mice exposed via inhalation to benzene at 319 mg/m^3 or 638 mg/m^3 concentrations for a period of 8 weeks (Farris et al., 1997). Hsieh et al. (1990) reported a decrease in lymphocytes count (lymphopenia) and suppression of B-and T-cells mitogenesis in male mice exposed to benzene in drinking water at concentration of 166 mg/m^3 for 4 weeks (Hsieh et al., 1990). Another study carried out by Fans et al. (1992) showed an imbalance in the immune system of mice exposed to benzene at dose of 27 to 154 mg/kg/day orally for 28 days. The interleukin 2 (IL-2) cells have been found sensitive while the natural

killer cells are resistant to the action of benzene (Fan, 1992). Reduction in mice femoral B, splenic T and B, and thymic T-lymphocytes have been observed after inhalation of benzene (319 or 638.9 mg/m^3) for 8 weeks (Farris et al., 1997). Epidemiologic studies regarding benzene effects on immune system function are few. A decrease in some components of immune system like immunoglobulins, CD4T cells, and CD4/CD8 ratio has been reported in gasoline filling workers exposed to benzene via inhalation. The limitation of this study is not mentioning the concentration of benzene and duration of exposure at workplace (Uzma et al., 2010). Bogadi-Sare et al. (2000) have reported immunotoxicity in the form decline in B-lymphocytes in female factory workers due to benzene exposure. These workers had been exposed to vaposrs of benzene upto 47.8 mg/m^3, however the period of exposure of workers was not mentioned in that study (Bogadi-Sare et al., 2000). Similarly another epidemiological case control study conducted by kirkeleit et al. (2006) evaluated the components of immune system in cargo tanks workers exposed to 0.479 mg/m^3 of benzene at 12 hours/day work for three days. They reported a decrease in IgM, IgA and CD4 T cells in the exposed group comparing to non-exposed workers (Kirkeleit et al., 2006).

The mechanism by which benzene produces its immunotoxic effects may be related to chromosomal damage, oxidative stress and DNA strands break (Smith, 2010).

The immunotoxic effects of benzene exposure in both acute and chronic cases have been reported in both experimental and epidemiologic studies. The epidemiologic studies, regarding the toxic effects of benzene on immune functions, published so far are related to occupational exposure. It is still unclear whether benzene existing in our environment play any role in the incidence of immunological problems.

Reproductive and Developmental Effects

Chronic exposure

Since long there has been a growing concern about the potential harmful effect of environmental pollutants and industrial solvents on reproductive health of both male and female (Lemasters et al., 1999, Katukam et al., 2012). A vital factor in male fertility is normal morphology of sperms on which benzene at concentration below U.S. Occupational Safety and Health Administration (OSHA) permissible limits has been reported to possess toxic effects (Xing et al., 2010). Katukam et al. (2012) have published a prospective cohort study of 160 workers exposed to

benzene via inhalation. They have reported a decrease in total sperm count and sperm motility along with a significant increase in Comet tail length in the exposed group in comparison to controls. No significant macroscopic changes were observed in the semen. The concentration of benzene in the workplace which might have affected the reproductive health of theses workers has not been moniotred in that study (Katukam et al., 2012). Another epidemiological case control study published by Song et al (2005b) have reported spermatic DNA damage in 27 workers exposed to benzene (86.49 ± 2.83 mg/m^3) for two years (Song et al., 2005b). Similarly low sperm motility has been noted in 50 aircraft maintenance workers exposed to jet fuel containing benzene (Lemasters et al., 1999). Besides affecting the reproductive health of male, benzene has been reported to affect the reproductive health of female by disturbing the menstrual cycle and various hormones of reproductive system (Reutman et al., 2002). A study published from china by Huang (1991) has shown reproductive dysfunction in female workers exposed to benzene and toluene in shoe making industry. Menstrual disorder in the exposed group (223 workers) was significantly high as compared to control group (327 unexposed workers). The rate of miscarriage and toxemia were 5.7% and 22.6%, respectively, higher in the exposed group than the control, 2.4% and 10.5%, respectively (Huang, 1991). Another study published by Yin et al. (1987) showed hypermenorrhea (prolonged menstruation) in 174 female workers exposed to benzene via inhalation at 188.4 mg/m^3 for 65 months (Yin et al., 1987).

The molecular mechanism of benzene in reproductive toxicity seems mediated through its metabolites. Benzene metabolites cause DNA damage and this could be the possible mechanism by which benzene acts as a toxicant for spermatogenesis (Song et al., 2005a, Song et al., 2005b). Benzene exposure may also cause increase in aneuploidy of sperm sex chromosomes and producing chromosomally defective sperms (Liu et al., 2000, Marchetti et al., 2012).

Apart from having toxic effects on reproductive health, chronic benzene exposure has been shown to associate with birth defects in the offspring (Lupo et al., 2011). Risks of low birth weights and fetal malformations have been reported to increase with work-related contact of pregnant women to benzene and other organic solvents (Khattak et al., 1999, Chen et al., 2000). Traffic-related air contains benzene fumes which may increase the risk of adverse effect on the intrauterine fetal growth (Crebelli et al., 2001, Parker et al., 2005). An epidemiologic case control study published by Lupo et al. (2011) from Texas 1999-2004 have reported high incidence of birth defects in the offspring's of mothers previously exposed to benzene (Lupo et

al., 2011). Elevated rate of low birth weights have been reported by Slama et al. (2009) in a cohort study of 271 non-smoking pregnant women exposed to benzene via inhalation at median concentration of 0.0018 mg/m^3 (Slama et al., 2009). Chen et al. (2000) also reported low birth weights of fetuses born to women exposed to benzene at 0.0543 to 0.61mg/m^3 in a petrochemical industry (Chen et al., 2000). In an experimental study, low birth weights were also seen in rats exposed to benzene via inhalation (7 to 14 day of gestation) at concentration of 150 mg/m^3 (Tatrai et al., 1980). Another experimental study published by Kuna and Kapp (1981) studied the effect of benzene on pregnant rats (day 6th to 15th of gestation). Fetotoxic effects of benzene were observed at concentration of 159.7 or 1597.3 mg/m^3 for 7 hours/day inhalation as compared to control group (Kuna and Kapp, 1981). Based on the evidences brought together about the reproductive health of human, the role of benzene in causing fertility related problems cannot be overlooked. There is a need to further evaluate the effect of benzene on targeted population in respect of reproductive health effects by considering the concentration and duration of exposure.

Central nervous system effects

Chronic exposure

Neurological effects: Long-term exposure to benzene may cause neurological abnormalities. Baslo and Aksoy (1982) published a cohort study of eight patients previously exposed to solutions containing benzene (9-88%). Six patients showed neurological abnormalities in the form of atrophy of lower extremities and neuropathy of upper extremities (Baslo and Aksoy, 1982). That study suggested that benzene may produce some toxic effects on the peripheral nerves. The limitation of this study was the possibility of patients' exposure to other organic solvents along with benzene. Experimental data regarding the benzene exposure and its possible effects on nerves could not be traced.

Alzheimer's disease: Alzheimer disease is an irreversible neurodegenerative disorder characterized by dementia. Beside other factors, environmental toxins have been recognized as a risk factor for causing Alzheimer disease (Moulton and Yang, 2012). Animal studies show that benzene causes inhibition of brain acetylcholinesterase (AChE). Sun et al. (1992) observed a decrease in brain AChE in mice after exposing the animals to various concentrations of benzene 39.9, 9.9, and 2.49 mg/m^3 for 2 hours/day for 30 days. Animals exposed to 39.9 mg/m^3 and 9.9 mg/m^3 of benzene showed a decrease in brain AChE activity as compared to control group (Sun

et al., 1992). Benzene has been reported to decrease acetylcholine level in rat hippocampus (Kanada et al., 1994).

Based on insufficient studies, it is premature to say that benzene might contribute to the incidence of Alzheimer diseases. It would be really helpful to carry out research activities with specific biomarkers in epidemiological studies on target population.

Cognitive effects: Benzene has been implicated in animal studies to cause long-lasting cognitive effects, motor and behavioral changes. Lo Pumo et al.(2006) reported behavioral, motor and cognitive changes in the neonates of pregnant animals acutely exposed to benzene by subcutaneous injection of 0.1 mg/kg at day 15 of gestation (Lo Pumo et al., 2006). The results of another experimental study published by Kanada et al.(1994) showed that benzene given orally (950 mg/kg) causes a decrease in acetylcholine level in the rat hippocampus, dopamine and norepinephrine in the rat midbrain (Kanada et al., 1994).

ROS formation and oxidative stress may be the possible involved mechanisms in causing CNS related toxicities induced by benzene (Saeidnia and Abdollahi, 2013).

Respiratory Effects

Acute exposure

Acute exposure to benzene has been shown to possess toxic effects on respiratory system in humans. Avis and Hutton (1993) have published a case report of accidental exposure to benzene vapors at high concentration which caused three fatalities. Hemorrhagic and edematous lungs were reported by autopsy of the victims (Avis and Hutton, 1993). Wink and Collom (1971) have published a report of benzene poisoning of 18 years old male. On autopsy they found bronchitis and massive hemorrhages of the lungs (Winek and Collom, 1971).

Chronic exposure

Apart from acute effects, benzene chronic exposure may also cause toxic effects on the respiratory system. In experimental studies benzene has been reported to have toxic effects on respiratory organs. Weaver et al. (2007) reported that inhalation of benzene (958.4mg/m^3) by rats for 7 days caused apoptotic changes in the parenchymal components of the lungs (Weaver et al., 2007). Further epidemiologic studies are necessary to find the role of benzene and other hydrocarbons in non-infectious respiratory diseases while available data are not sufficient to correlate the prevalence of respiratory diseases with benzene exposure.

Endocrine effects

Chronic exposure

Many synthetic and natural compounds exist in the environment affecting the much sensibly-regulated hormonal messenger system of the body. In this way, they have been categorized as endocrine disrupting chemicals (EDCs) which has been a major topic of debate for environmental scientists since long (Verma and Rana, 2009, Uzma et al., 2008). Many organic compounds and industrial solvents have been shown to act as endocrine disruptors for humans and wildlife (Colborn et al., 1993). Benzene is an organic volatile compound and known to have endocrine disrupting properties (Verma and Rana, 2009). In one epidemiologic case control study of petroleum filling station workers, benzene exposure for 2-15 years via inhalation caused an increase in tetra iodothyronine (T4) and free thyroxine (T4F) and decreased thyroid stimulating hormone (TSH) and tri-iodothyronine (T3) (Uzma et al., 2008). Disturbed pituitary hypothalamic adrenocortical activity has been reported by Hsieh et al (1991) in experimental animals by orally feeding benzene at 31 to 790 mg/m^3 (Hsieh et al., 1991). Furthermore, there are reports that benzene containing gasoline had increased the risk of pancreatic cancer in the workers engaged in refinery (Mehlman, 1990).

Effect on glucose homeostasis

Acute exposure

Liver and pancreas are the two principal organs responsible for glucose homeostasis. In animal studies, a single dose of 800 mg/kg orally, has altered the activity of the main enzyme of glycolytic pathway. Acute benzene exposure is suspected to have caused increase in hexokinase level of intestine and liver, and decrease in hexokinase amount of brain, renal cortex and medulla (Khan and Yusufi, 2009). Decreased activity of glucose 6-phosphatase and fructose-1,6-biphosphatase, main enzymes responsible for gluconeogenesis, has also been evident in experimental animals exposed to benzene (Khan and Yusufi, 2009). Neither in experimental nor in epidemiologic studies the role of benzene in the incidence of diabetes has been evaluated in detail. So more experimental studies are required to objectively asses the toxicity of chronic benzene exposure on pancreas with special reference to synthesis, secretion, and release of insulin.

Cardiovascular effects

Chronic exposure

Environmental pollutants such as benzene are of primary concern in causing chronic diseases; however limited epidemiologic data are available to describe benzene as one of the causative agents of hypertension. An epidemiologic study published by Wiwanitkit (2007) indicated that hypertension is more prevalent in benzene-exposed group as compared to control. However, this study failed to monitor the concentration and duration of benzene exposure (Wiwanitkit, 2007). Another epidemiologic study published by Kotseva and Popov (1998) supported the possible role of benzene and other organic solvents in causing hypertension. They found an increased arterial hypertension and pathologic changes on ECG of the benzene-exposed subjects in a petrochemical factory (Kotseva and Popov, 1998). The suggested mechanism for benzene to causes hypertension is through disturbing the nitric oxide pathway, however the exact mechanism is still unknown (Wiwanitkit, 2007, Mohammadi et al., 2012).

The possible role of benzene in the incidence of hypertension and other cardiovascular diseases is an under studied subject in experimental studies. The available epidemiologic data suggesting benzene as a contributing factor to the cause of hypertension have the limitations of monitoring the concentration of benzene contents in the workplace. So more experimental data would be of great help to further evaluate the status of benzene in causing cardiovascular problems.

Effects on Liver

Acute exposure

Liver is more vulnerable organ to the toxic effects of hydrocarbons. Chronic exposure to hydrocarbons including benzene has been reported to produce adverse effects on liver enzymes (Perez et al., 2006). The metabolites of benzene, in addition to adduct formation with DNA and RNA also attach to the proteins of liver, kidney, bone marrow and stomach (Lindstrom et al., 1997; Snyder and Hedli, 1996). Dere and Ari (2009) reported that acutely exposed rats at dose 100 mg/kg benzene orally show an increase in the acitivity of hepatic enzymes lactate dehydrogenase (LDH), alkaline phosphatase (ALP), aspartate transaminase (AST) and alanine aminotransferase (ALT). Another animal study indicated a decrease in P450-2E1 by 34% and induction of glutathione activity by 30% in female CD-1 mice treated with 50 mg/kg benzene for

three weeks (Daiker et al., 1996). Turhan and Dere (2007) have also reported inhibition of hepatic adenosine deaminase (ADA) in rats by injecting benzene 100 mg/kg. Benzene has also been shown to cause an increase in liver weight, a decrease in protein content and change in hepatic drug metabolism in animals (Pawar and Mungikar, 1975; Yamamura et al., 1999).

Chronic exposure

To observe the effect of chronic benzene exposure and other hydrocarbons on liver functions, there is one published case control study of 92 workers by Perez et al. (2006). They have observed hypertransaminasemia in workers exposed to hydrocarbons including benzene. All these workers, in addition to other hydrocarbons, were exposed to benzene at 4.798 mg/m^3 via inhalation. The mechanism for change in the activity of liver enzymes may be related to celluer degenaration, down regulation of gene expression, oxidative stress and related pathways stimulated in hepatocellular cytosols (Dere and Ari, 2009; Davis H. Daiker, 1996).

The effect of benzene on liver functions is suggested more by experimental studies. Epidemiologic data in this regard are limited, and one case control mentioned has not accounted the presence of other hydrocarbons which might have altered the activity of certain liver enzyme.

Renal Effects

Chronic exposure

Exposure to halogenated hydrocarbons, petroleum distillates, ethylene glycol, and dioxane may cause oliguria and azotemia (Lauwerys et al., 1985, Roy et al., 2008). Khan and Yusufi (2009) reported the nephrotoxic effects of benzene by examining 33% increase in blood urea nitrogen (BUN) and 30% increase in serum creatinine in rats exposed to benzene at dose 800 mg/kg for 30 days (Khan and Yusufi, 2009). Viau et al (1987) published a cross sectional study of 53 male oil refinery workers exposed to hydrocarbons including benzene and 61 non-exposed workers. The result of this study showed that chronic low level of hydrocarbons exposure does not pose any risk for renal diseases (Viau et al., 1987) (Figure 2).

Very limited data is available suggesting the toxic effects of benzene on renal functions. So in order to determine the long-term effects of benzene on renal functions more in depth studies are still needed.

Table 2: List of studies whose results show the association of benzene exposure and incidence of health effects

Reference	Model	Route of exposure	Benzene concentration	Duration of exposure	Targets system/ organ studied	Results
Aksoy et al. 1971)	Epidemiologic	Inhalation	95.7 to 669.9 mg/m^3	Chronic 3 months to 17 years	Hematological	Thrombocytopenia, leucopenia, pancytopenia and Hb↓
Lan et al. (2004)	Epidemiologic	inhalation	Less than 3.19 mg/m^3	Chronic 6.1 years	Hematological	White blood cells and platelets↓
Hsieh et al. (1990)	Experimental	Oral	166 mg/m^3	Chronic 4 weeks	Hematological	Leucopenia and lymphopenia
Robert Schnatter et al. (2010)	Epidemiologic	Inhalation	More than 7.4mg/m^3	Chronic	Hematological	Total WBCs, Hb, MCV↓
Bogadi-Sare et al. (1995)	Epidemiologic	Inhalation	6.0 to 47.2 mg/m^3	Chronic	Hematological	Hb and MCHC↓
Perez et al. (2006)	Epidemiologic	Inhalation	4.7 mg/m^3	Chronic 9 months	Liver	Hypertransaminasemia
Dere and Ari. (2009)	Experimental	injection	100 mg/kg	Acute 16 hours	Liver	LDH, ALP activity↓, ALT level↑
Daiker et al. (1996)	Experimental	Oral	50 mg/kg/d	Chronic 3 weeks	Liver metabolizing enzymes	Cytochrome p-450-2E1 activity↓ Glutathione transferase activity↑
Turhan and Dere. (2007)	Experimental	Oral	100 mg/kg	Acute 64 hours	Liver	Hepatic ADA activity↓
Yamamura et al. (1999)	Experimental	Oral	260 mg/kg	Chronic 3 weeks	Liver	P450 activity↑, Glutathione S-transferase activity↑
Khan and yusufi. (2009)	Experimental	Oral	800 mg/kg	Chronic 30 days	Kidney	Blood urea nitrogen and serum creatinine↑
Bogadi-sare et al. (2000)	Epidemiologic	Inhalation	47.8 mg/m^3	Chronic	Immunological	Circulating B-lymphocytes↓
Uzma et al. (2010)	Epidemiologic	Inhalation	--	Chronic	Immunological	Immunoglobulin levels, CD4T cells and CD4/CD8 ratio↓
Farris et al. (1997)	Experimental	Inhalation	3.19 to 638 mg/m^3	Chronic 8 weeks	Immunological	Femoral B-splenic T- and B- and thymic T-Lymphocytes↓
Kirkeleit et	Epidemiologic	Inhalation	0.319 mg/m^3	Chronic	Immunological	IgM, IgA and CD4 T

al. (2006)						cells↓
Hsieh et al. (1990)	Experimental	Oral	166 mg/L	Chronic 4 weeks	Immunological	T cells↓
Fan. (1992)	Experimental	Oral	27 mg/kg/day	Chronic 28 days	Immunological	IL-2 production↓, imbalance between natural killer cells and IL-2
Slama et al. (2009)	Epidemiologic (Pregnant women)	Inhalation	0.0018 mg/m^3	Chronic 9 months	Developmental	Birth weight and head circumference↓
Chen et al. (2000)	Epidemiologic (Pregnant women)	Inhalation	0.0542 to 0.609 mg/m^3	Chronic 9 months	Developmental	Birth weight↓
Tatrai et al. (1980)	Experimental (Pregnant rats)	Inhalation	450 mg/m^3	7-14 days	Developmental	Body weight of fetuses↓, mortality↑
Kuna and kapp. (1981)	Experimental (Pregnant rats	Inhalation	159 to 1595 mg/m^3 for 7 hours/day	6-15 days	Developmental	Mean weight↓
Lemasters et al. (1999)	Epidemiologic (Male)	Inhalation	1.8 mg/m^3	Chronic 30 weeks	Reproductive	Sperm motility (19.5%) ↓
Katukam et al. (2012)	Epidemiologic (Male)	Inhalation	--	Chronic 5-15 years	Reproductive	Total sperm count↓ Sperm motility↓ Abnormal sperm morphology Sperm DNA damage
Song et al. (2005b)	Epidemiologic (Male)	Inhalation	86.49 mg/m^3	Chronic 2 years	Reproductive	Sperm DNA damage
Huang (1991)	Epidemiologic (Female)	Inhalation	--	Chronic	Reproductive	Dysmenorrhea, Gestosis, Menstrual disorders
Yin et al. (1987)	Epidemiologic (Female)	Inhalation	188 mg/m^3	Chronic	Reproductive	Hypermenorrhea
Reutman et al. (2002)	Epidemiologic (Female)	Inhalation	Benzene breath level 0.311 mg/m^3	Chronic	Reproductive / endocrine	LH↓
Sun et al. (1992)	Experimental	Inhalation	9.9 and 39.9 mg/m^3 2 hours/day	Chronic 30 days	Neurobehavioral	Acetyl cholinesteraselevel in brain↓, CNS functions inhibited
Lo Pumo et al. (2006)	Experimental	Sub cutaneous	0.1 mg/kg	Acute at day 15 of gestation	Neurobehavioral	Behavioral, motor and cognitive changes
Kanada et al. (1994)	Experimental	Oral	950 mg/kg	Acute2 hours	Neurobehavioral	Acetylcholine, norepinephrine and

						DOPA level↓
Weaver et al. (2007)	Experimental	Inhalation	957 mg/m^3	Acute 1weeks	Respiratory	Apoptotic changes in the lung parenchyma
Hsieh et al. (1991)	Experimental	Oral	0.31, 166 and 790 mg/L	Chronic 28 days	Hypothalamic pituitary – adrenocortical axis	Hypothalamic-pituitary-adrenocortical activity stimulated, cortisone level↑
Uzma et al. (2008)	Epidemiologic	Inhalation	---	Chronic	Thyroid	T4 and T4F↑, TSH and T3↓
Khan and yusufi. (2009)	Experimental	Oral	800 mg/kg	Chronic 30days	Enzymes of carbohydrates metabolism	Hexokinase activity in intestine and liver↑ but in brain, renal, cortex and medulla↓, G6Pase and FBPase activity↓
Wiwanitkit (2007)	Epidemiologic	Inhalation	--	Chronic	Cardiovascular	Hypertension in the exposed group
Kotseva and Popov. (1998)	Epidemiologic	Inhalation	--	Chronic	Cardiovascular	Arterial hypertension and pathologic changes on ECG

ADA: Adenosine deaminase; ALP: Alkaline phosphatase; G6Pase: glucose -6- phosphatase; AST: Aspartate transaminase; DOPA: Dopamine; FBPases: Fructose-1, 6-biphosphatase; Hb: Hemoglobin; IL-2: Interleukin 2; LDH: Lactate dehydrogenase; LH: luteinizing hormone; MCHC: Mean Corpuscular Hemoglobin Concentration; MPV: Mean platelet volume; TSH: Thyroid stimulating hormone; WBCs: White blood cells; ↓: Reduction; ↑: (Increase)

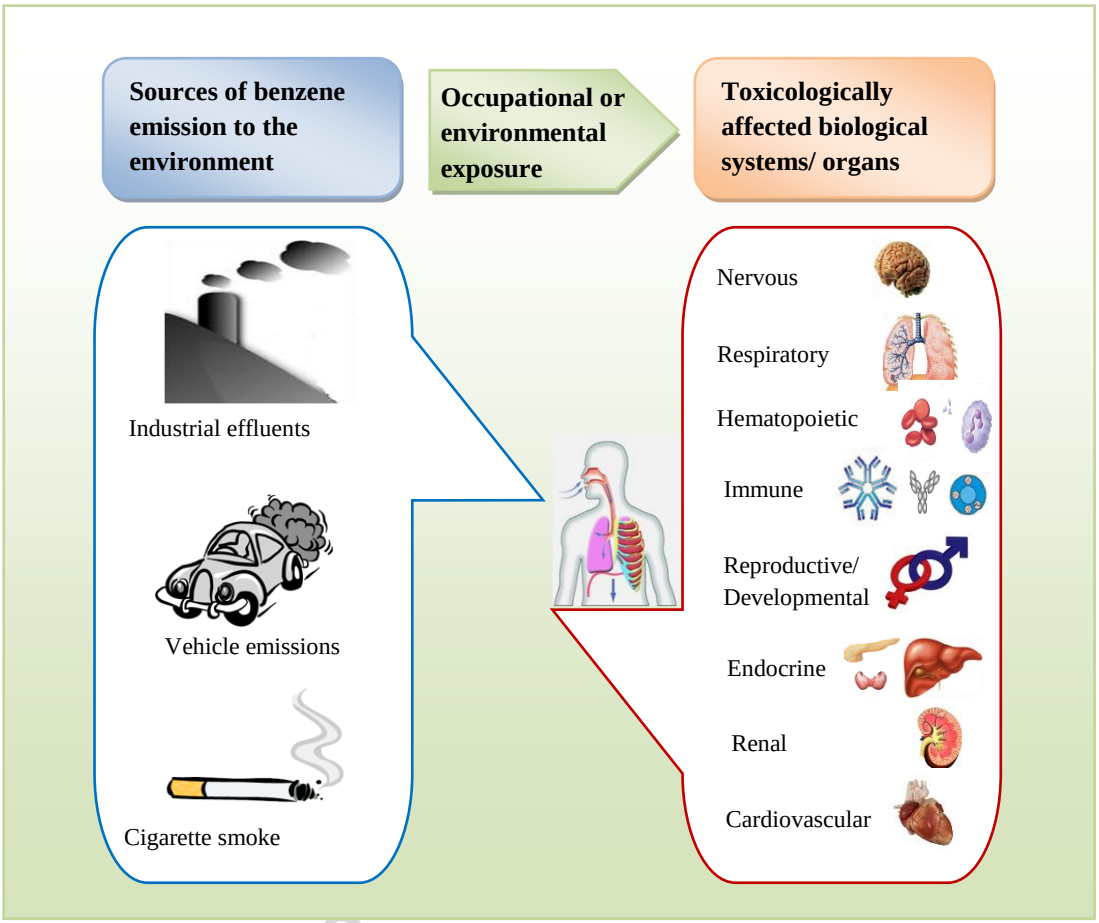

Figure 2: Routes of benzene release to the environment and its toxic effects on human health from the viewpoint of biological systems

Mechanisms of Benzene Toxicity

Formation of reactive oxygen species (ROS) and oxidative stress

After being metabolized in the liver and bone marrow by CYP4502E1 oxidation pathways, benzene produces free radicals and quinone metabolites like phenol, hydroquinone, benzoquinone, and 1,2,4-benzenetriol. Studies suggest that benzene exerts its cytotoxicity via these critically toxic metabolites and free radicals (Smith, 1996a, Atkinson, 2009, Kolachana et al., 1993). In the course of an experimental study on HL60 human leukemia cells, Shen et al. (1996) have found benzoquinone and 1,2,4-benzenetriol as the most potent inducers of ROS among benzene metabolites. They further demonstrated that benzene metabolites and free radicals cause lipid peroxidation and subsequent cell toxicity (Shen et al., 1996). Observations from liver, plasma, and bone marrow studies indicate that benzene exposure is associated with increased lipid peroxidation which in turn augments further production of free radicals (Atkinson, 2009). Benzene and its phenolic metabolites have been shown to exert their toxic effect via oxidative damage to DNA (Kolachana et al., 1993). Lewis et al. (1988) have reported that oxygen radicals produced by benzene metabolite; 1,2,4-benzenetriol and hydroquinone can lead to a significant damage to DNA (Lewis et al., 1988). Wan et al.(2005) have hypothesized that interfering cell signaling pathways by disregulated level of reactive oxygen species (ROS) can be a main mechanism by which benzene exerts its toxicities (Wan et al., 2005). An experimental study conducted by Ruiz-Ramos et al. (2005) on HL-60 cells treated with 1,4-benzoquinone, has indicated rapid and prolonged phosphorylation of extracellular signal-regulated kinases 1and 2 (ERK1/2) proteins of cell signaling cascade in addition to an increase in ROS formation (Ruiz-Ramos et al., 2005).

Genetic damages

Benzene has adverse effects on the genome of living cells and has been shown to be genotoxic in human at relatively low exposure levels of 0.3 mg/m^3 (Nilsson et al., 1996, Holeckova et al., 2004). Among various forms of benzene-induced genetic alterations, the aneuploidy and chromosomal breakage are the early genotoxic events caused by benzene metabolites (Holeckova et al., 2004, Chen et al., 1994, Zhang et al., 2011). Chromosomal aberration in the

peripheral blood lymphocytes, bone marrow and sperms of people chronically exposed to benzene has become evident through different studies (Zhang et al., 2011, Andreoli et al., 1997, Bogadi-Sare et al., 1997, Kasuba et al., 2000, Zhang et al., 2002, Morimoto, 1983). Zhang et al. (2011) has reported dose-dependent chromosomal aneuploidies (monosomy & trisomy) in the peripheral blood lymphocytes of 47 workers exposed to benzene (Zhang et al., 2011). In another study published by Zhang et al. (2012) an increased monosomy 7 and 8 level was found in 28 benzene-exposed workers in comparison to control subjects (Zhang et al., 2012). Macron et al. (1999) has also reported an increase in breakage frequencies in the chromosomes 1 and 9 of cultured lymphocytes isolated from workers exposed to benzene (Marcon et al., 1999). Eastmond et al. (2001) and Chen et al. (1994) presented occurrence of chromosomal breakage and subsequent micronuclei formation in erythrocytes of mouse bone marrow (Eastmond et al., 2001, Chen et al., 1994).

Sister chromatid exchange was also shown to happen in human lymphocytes cell culture treated with benzene (Morimoto, 1983). The results of three other studies showed that metabolites of benzene can cause DNA adduct formation in rat liver mitoplasts, rabbit bone marrow mitoplasts and mitochondrial RNA inhibition (Kalf et al., 1982, Rushmore et al., 1984, Kalf et al., 1985). Bodell et al. (1993) has also noted the DNA adducts formation in human bone marrow and HL-60 cells (Bodell et al., 1993). 1,2,4-Benezene triol as one of the benzene metabolites has been shown to cause DNA strands breaks via formation of ROS (Lewis et al., 1988, Li et al., 1995).

Chromosomal aberration is a deleterious event whose induction in sperm cells can lead to infertility (Marchetti et al., 2012) and to some extent, carcinogenic effect of benzene has been thought to be mediated by its metabolite quinone; a potent inducer of sister chromatid exchange (Eastmond, 1993, Zhang et al., 2002). However, carcinogenicity of benzene involves a complex of mechanisms including DNA mutation, chromosomal damage, oncogene activation, inhibition of gap-junction intercellular communication and down-regulation of host tumor control mechanism by benzene metabolites and free radicals (Atkinson, 2009, Rivedal and Witz, 2005, Uzma et al., 2010).

Epigenetic modifications

Benzene is one of the main pollutants firstly used as a model for new omics technology in the environmental health research. In this respect, one new opening area is epigenomics which encompasses studies on heritable changes in cellular gene expression profile without altered DNA sequence and consists of three main marks of DNA methylation, histone modifications, and non-coding RNAs. The first human study exploring the epigenetic mechanism of low-dose benzene exposure was conducted by Bollati et al. (2007). They have reported a decrease in genome-wide methylation of long interspersed nuclear element-1 (LINE-1) and AluI repetitive elements, gene-specific hypermethylation in p15 and hypomethylation in MAGE-1 (Bollati et al., 2007). There are also two recent reports on altered global DNA and repetitive element methylation in low-level exposure to benzene in gasoline station attendants (Fustinoni et al., 2012) and petrochemical workers (Seow et al., 2012). In another study carried out on normal hepatic cells, benzene and its metabolites have been shown to change global DNA methylation probably through altered activity of DNA methyltransferase (Hu et al., 2011). However, such studies are on their way to offer bioinformatics more knowledge regarding the mechanisms and interactions implicated in benzene induced health hazards (Figure 3).

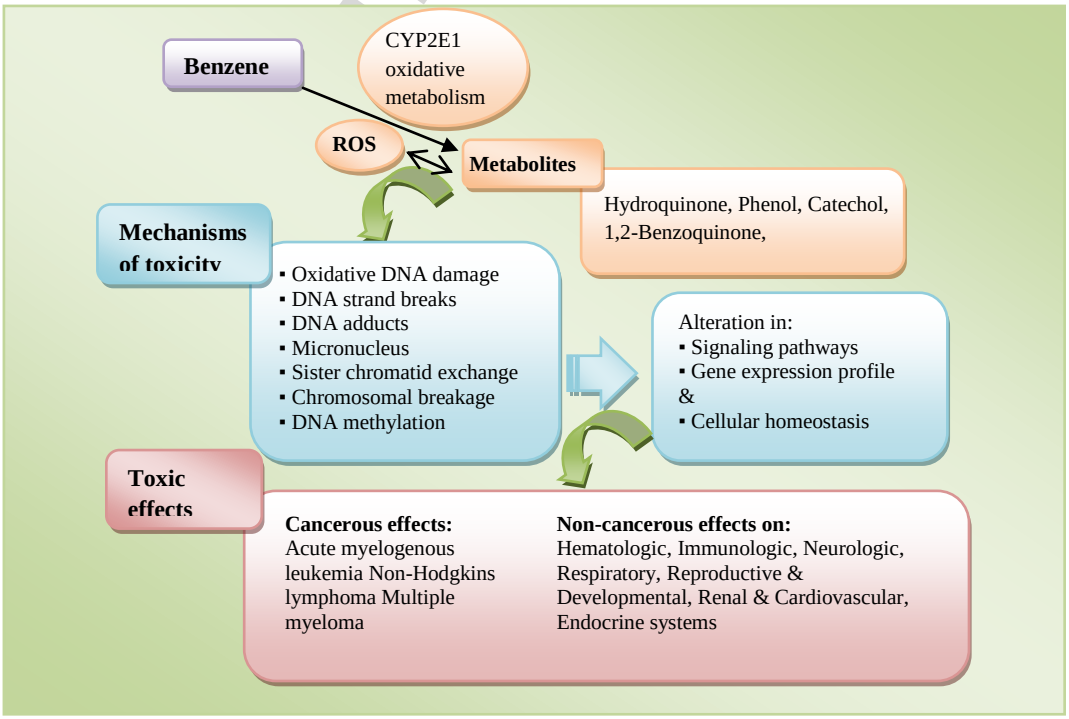

Figure 3: A schematic figure illustrating benzene metabolism, mechanisms of toxicity, and toxic effects in a biological system

Discussion & Conclusion

The concern of the existence of chemical air pollutants and their possible role in causing various chronic diseases is very long, but due to lack of comprehensive monitoring system, health outcomes associated with air pollutants are poorly characterized (Briggs, 2003).

Benzene is one of the chemical air pollutants and is ubiquitous in our environment released from various sources posing a silent threat to human health. It is worth mentioning that in most of the countries, where benzene is being monitored poorly, non communicable disease like diabetes, cancer, human infertility, neurological disease, birth defects and cardiovascular problems are commonly widespread, however there are difference in the prevalence rate from country to country and urban and rural areas (Shaw et al., 2010, Ramachandran et al., 2010, Ghaffar et al., 2004, Lawes et al., 2008, Kearney et al., 2005, Goyal and Yusuf, 2006, Ferri et al., 2005, Akbari et al., 2012, Yasseen et al., 2001, Evens, 2004, Durkin, 2002, Motlagh et al., 2009, Ombelet et al., 2008, W.H.O., 2011). Diabetes, lungs and breast cancers are the most common diseases of India, Bangladesh, Pakistan, Iran, Egypt, Saudi Arabia, UAE, Malaysia and Indonesia. In some countries (India, Bangladesh, Pakistan, Iran and Egypt) diabetes is a very swiftly multiplying disease (Shaw et al., 2010, Al-Nozha et al., 2004, Esteghamati et al., 2008). Although U.S.A, China, Australia and European countries have regulated the contents of benzene in petrochemicals, as per CDC, and other governmental organizations of concerned countries and world health organization report no substantial decline has been noted in the prevalence of chronic diseases such as cancers, diabetes and cardiovascular problems, which puts a question mark on the safe limit of benzene (http://www.aihw.gov.au/diabetes/prevalence (W.H.O., 2011, Busse et al., 2010).

Besides causing cancer of blood components, benzene in animal studies has also been reported to induce mammary cancer (Austin et al., 1988, Wolff et al., 1996). However, few human studies exist to suggest benzene as one of the risk factor for causing breast cancer. The results of an epidemiological cohort study of female workers dealing with benzene based glues in a shoe making factory in Italy supported that chronic exposure to benzene can be one of the risk factor for breast cancer (Costantini et al., 2009). Another case control study published by Petralia et al. (1999) had already suggested that benzene exposure is one of the risk factors for causing breast cancer in women (Petralia et al., 1999).

Moreover, benzene has been listed as an endocrine disrupting chemical, but its association in causing metabolic diseases particularly diabetes mellitus has not been studied in details. Both epidemiologic and experimental evidences are lacking in this regard. Few studies suggest that benzene exposure in animals affect the gluconeogenesis and certain enzymes involved in glucose metabolism (Khan and Yusufi, 2009).

Benzene acts as double edge sword. It exerts toxic effects via ROS formation and oxidative stress along with genotoxicity. The relationship of ROS in causing neurodegenerative diseases, diabetes, endocrine dysfunctions, cardiovascular diseases, immune system disturbances and cancer has been studied in detail in other studies (Saeidnia and Abdollahi, 2013; Mostafalou and Abdollahi, 2013). Generated free radicals/ROS cause damage to all cell components including the DNA. Based on these mechanisms of benzene toxicity it may be logically said that chronic exposure to benzene is one of the risk factors in causing above mentioned chronic disorders.

Considering epidemiologic and experimental evidence brought in this review, further epidemiologic research is still needed in regions with high prevalence of diabetes, lung and breast cancer in order to collect more evidences to quantify the role of air pollution with benzene in causing these serious health effects. Of course more experimental studies in these areas will be of great help in better understanding the molecular mechanisms involved in the pathogenesis of these disorders.

Conclusion

The current study presents accumulated data both experimental and epidemiologic on benzene-induced health toxicities with particular emphasis on non-cancerous health effects. Based on the mechanism of toxicity of benzene, it could reasonably be said that benzene may be one of the risk factors in the incidence of chronic diseases such as diabetes, lung and breast cancers in the developing countries. There are enough evidences available which suggest that environmental pollutants are among the risk factors in occurrence of chronic diseases. Benzene is a much studied chemical toxicant in respect of blood components, but its role in the incidence of chronic disorders like diabetes and breast and lung is still unclear. So we are of the view, that the concern of benzene exposure is far more than carcinogenicity of blood components and should be evaluated both in epidemiologic and experimental studies from the aspect of interactions and

mechanism of toxicity in relation to human general health problems especially endocrine disturbances with particular reference to diabetes and breast and lung cancers.

Chronic benzene exposure should be matter of concern for population of all countries with special focus of those regions where benzene is reported to be in high concentration. Our analysis is to either eliminate or control the sources of exposure of benzene and implement integrated environmental monitoring systems in order to avoid the hazards of the benzene. For this purpose, integrated research activities are needed in those regions of the world where benzene concentration is high. Health and environmental pollution follow up system should be developed in each country to identify the source and health outcome of air pollutants.

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HIGHLIGHTS

- Benzene is a volatile organic air pollutant and human blood carcinogen
- Benzene exposure needs to be evaluated in relation to diabetes, breast and lung cancer
- Chronic diseases are highly widespread in most of the countries where benzene has being poorly monitored
- The incidence of chronic diseases remained unaltered instead of reducing the contents of benzene in petrochemicals in some parts of the world
- Strong regulatory interventions over petroleum products are needed, besides searching for environment friendly alternative to benzene