Exposure to chemicals and pathophysiological disorders with special reference to a benzene metabolite:1,4-Benzoquinone

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Abstract

Humans are exposed to several chemicals through daily use of different products like food supplements, cosmetics, pharmaceuticals, pesticides, etc. Occupational exposure to chemicals is one of the major routes in which workers of different industries and factories are dreadfully affected. Benzene is such a widely used chemical often required as raw material in the manufacturing of different products like detergents, insecticides, dyes, lubricants, etc. It is a common environmental toxin that is ubiquitously present in the air, water, and soil. This review focuses on general chemical exposure with a specific focus on the potent benzene metabolite parabenzoquinone (p-BQ).The results of this study show that exposure to chemicals from numerous sources poses a major hazard to human health, resulting in a variety of pathophysiological problems. Benzene causes toxicity in various organs by producing reactive intermediates, the most potent of which being p-BQ. The toxicity generated by the benzene metabolite, p-BQ, in several organs sheds more light on the aetiology of cell and tissue damage.

Keywords: 1,4-Benzoquinone, Benzene, pathophysiology, chemicals, exposure.

1. Introduction

The majority of occupational exposures are present in the environment at large or in consumer goods that includes food, drinks, pharmaceuticals, and cosmetics etc. There may be numerous erroneous distinctions. Although things like cigarette smoke, sunlight, and immunosuppressive medications are not often thought of as occupational exposures, there are employees whose jobs put them in proximity with these substances (Siemmiatycki, 2014). As best, benzene, and radon gas are all known to be industrial carcinogens, but they are also frequently found in the general population, and it is likely that many more people are exposed to these substances outside of the workplace than within.Additionally, some carcinogens are substances that are utilised in research and to which very few individuals will ever be exposed, whether at workplace or outside of it. The somewhat peculiar character of the evidence is a second source of ambiguity. In some cases, humans are aware that an occupational or industrial group is more likely to get risk of cancer than the general population and we are fairly certain of the cause, such as scrotal cancer in chimney sweeps and Polycyclic Aromatic Hydrocarbons (PAHs) in soot, or lung cancer in asbestos miners and asbestos fibres (Waldron, 1983; IARC, 2012).

2. Chemical Exposures and Diseases

Asbestos-related incidence of cancer is one of the health issues that has gathered the most public attention, debate, and price. Asbestos refers to a group of naturally occurring fibrous silicates that have a wide range of chemical and physical properties and have been utilised extensively in both industrial and consumer products for more than a century (Selikoff et al, 1984). The two main forms of fibre are chrysotile and amphibole. Many vocations, including mining and milling, the creation of products containing asbestos, and the usage of these products, have exposed workers to asbestos fibres. Due to the application and removal of asbestos products and building demolition, construction and maintenance

personnel currently make up the biggest group of workers exposed to asbestos in industrialised nations (Dement et al, 1983). Throughout the 20th century, asbestos exposure at work was one of the most common.Early in the 1960s, reports began to surface connecting asbestos exposure to mesothelioma, a pleura and peritoneum tumour that had previously gone undiagnosed. By the middle of the 1960s, it was obvious that the very high and essentially uncontrolled exposure levels that were common at the time may cause mesothelioma and lung cancer (Lynch et al, 1935).

Bladder cancer among aluminium industry employees and lung cancer among painters are examples of situations where we are aware that a group was at increased risk but the underlying cause is unknown or at the very least unverified (IARC 2012).There are multiple levels of evidence for an association. The evidence of increased risk seems unambiguous for some correlations, such as those between bladder cancer and benzidine and liver angiosarcoma and vinyl chloride monomer. The data is only suggestive for some correlations, such as those between breast cancer and shift work or bladder cancer and occupation as a painter. There are thousands of agents in the industrial environment that have been demonstrated to have some effect in tests of mutagenicity or genotoxicity, and hundreds of them have been found to be carcinogenic in some animal species despite the lack of human data regarding their carcinogenicity. Thus the attempt to compile a list of occupational exposures to various xenobiotics is complicated by these factors (IARC 2012; Siemmiatycki, 2014).

Among the various kinds of controllable risk factors for cancer, occupational carcinogens hold a distinct place. The study of the pathophysiology of human cancer in the workplace has been incredibly beneficial. In fact, occupational carcinogens account for close to half of all known human carcinogens. Although it is crucial to identify occupational carcinogens in order to prevent occupational cancer, there may be benefits that extend outside

of factories as well because most occupational exposures make their way into the general environment, sometimes at elevated concentrations than at work and, for some agents, with more people exposed than in the workplace (Guha et al, 2010).A number of research on smoking and lung cancer in the 1950s marked the beginning of the current age of cancer epidemiology. In the field of occupational cancer epidemiology, significant research on gas and asbestos workers, and chemical industry workers who produce dyestuffs were conducted during this time. Significant workplace risks were brought to light by the results of these early studies, and occupational cancer research has been significantly affected by the techniques these early scientists devised for investigating occupational cohorts.Extensive experimental effort aiming at evaluating the carcinogenic potential of various compounds were conducted concurrently with the explosion of epidemiologic research on cancer and the environment. While this was first done in an unorganised manner, national organisations, most prominently the National Toxicology Program in the USA, have since put in place systematic techniques to evaluate a huge number of compounds using standardised, cutting-edge, lengthy animal experiments(Silvermann et al, 2012;Siemmiatycki, 2014).

In the majority of nations, lung cancer is the most prevalent tumour reported in men affecting the lungs and chest, with an estimated 1,6 million new cases and 1.4 million fatalities per year, along with pleural malignant mesothelioma (Bofetta et al, 2014). After the second half of the 20th century, malignant mesothelioma incidence substantially rose, with over 90% of cases being linked to pleural mesothelioma. 250,000 new cases of malignant mesothelioma are anticipated over the following decades, with the peak in incidence occurring between the years of 2015 and 2020, according to some authors (Ferlay*et al*, 2010; Robinson, 2012). In addition to tobacco use, which is without a doubt the primary cause of lung cancer, occupational and environmental risk factors are also quite important. According to reports, the attributable percentage for lung cancer caused by occupational exposures

ranges from 7-15% in males and 2-9% in women, with projected mortality tolls of 29300 and 3200, respectively (Jemal et al, 2011). Asbestos, diesel engine emissions, various mixtures of polycyclic aromatic hydrocarbons, crystalline silica, arsenic, and some heavy metals are the main contributors with sufficient information in humans. While acid mists and welding fumes are the agents with inconclusive information.Although asbestos is still used in several industrialised nations, the World Health Organization describes it as "the most important occupational carcinogen" that "causes about half of the fatalities from occupational cancer." Also, it is believed that asbestos fibres are to blamed for more than 80% of all pleural malignant mesothelioma cases worldwide, which are on the rise. Malignant pleural mesothelioma and lung cancer risk cannot be exclusively attributed to occupational factors. Genes may alter theresponse to individual in such a way that the likelihood of the host contracting a disease is increased or decreased.The aetiology and severity of these disorders may be significantly influenced by variation in genes involved in xenobiotic and oxidative metabolism (Phase I and Phase II enzymes) or in DNA repair pathways, according to numerous research published in the last ten years. An important candidate gene for lung cancer and pleural mesothelioma susceptibility among them is the glutathione S-transferase family of genes due to its function in the metabolism of certain carcinogens, occupational toxins, and environmental toxins (Neri et al, 2006; Neri et al, 2008). Occupational exposures, genetic polymorphisms, lung cancer, and mesothelioma are all related in some way, and this systematic review seeks to summarise our current understanding of that link.

3. Parabenzoquinone-the potent metabolite of benzene

Parabenzoquinone (1,4-benzoquinone or 1,4-BQ or p-BQ), a nonaromatic six-membered ring molecule that is produced by the oxidation of 1,4-hydroquinone, a byproduct

of benzene metabolism has been observed to contain in diesel and cigarette smoke . It can have negative effects on the eyes, skin, and respiratory system (Banerjee et al, 2008; Gieselhert et al, 1997; Jakober et al, 2007). By creating reactive oxygen species and adducts with the DNA bases in cultured mammalian cell lines, this bioactive quinone has been shown to have significant genotoxic effects. It also causes apoptosis (Levay et al, 1991; Pathak et al, 1995; Hirakuet al, 1996; Baigi et al, 2008). Michael adducts are covalently bonded quinine-thiol complexes that are formed when parabenzoquinone reacts with biological nucleophiles like free thiol groups in proteins, glutathione (GSH), and N-acetylcysteine (NAC) (Wang et al, 2006). It is a substance found in cigarette smoke that has been shown to damage lung epithelial cells and prevent T lymphocyte activation. Smokers frequently experience lung tissue damage, which is defined by a condition known as emphysema. Chronic obstructive pulmonary disease (COPD), one of the main causes of death and morbidity worldwide (Tuder et al., 2003; Demedts et al., 2006), frequently results in emphysematous lung destruction, and p-BQ plays a significant role in this severe lung damage (Das et al, 2010).

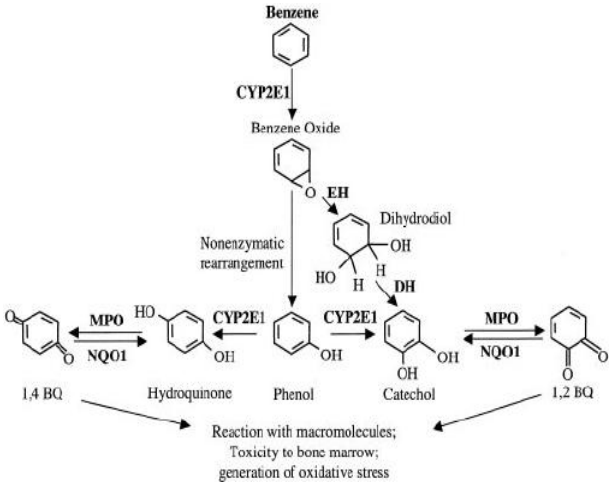

Fig:1 Formation of 1,4-BQ from Benzene and metabolism of benzene in liver and bone-marrow. CYP2E1 is present in liver which oxidizes benzene to benzene oxide followed by several possible routes of metabolism. NQO1 detoxifies the BQs in the bone marrow to the less toxic metabolites, hydroquinone and catechol. BQ:benzoquinone; DH:benzenedihydrodiol dehydrogenase, EH:microsomal epoxide hydrolase, MPO:myeloperoxidase (Bauer et al, 2003).

Chronic human benzene exposure has been linked to a number of hematopoietic disorders, including leukaemia and lymphomas. Certain benzene metabolites, such as benzoquinone (BQ), are mutagenic and genotoxic. Bone marrow stem cells are highly susceptible to benzene-induced cytotoxicity and DNA damage, which could lead to changes in the genome of these progenitor cells, leading to erythroid disorders and malignancies. Human bone marrow CD34 hematopoietic progenitor cells (HPC) were exposed to 1,4-BQ in vitro to assess cytotoxicity, genotoxicity, and DNA damage responses, as well as the molecular mechanisms involved. CD34-HPC from 10 men and 10 women were exposed to 0, 1, 5, 10, 15, or 20 M of 1,4-BQ for 72 hours before being analysed. Apoptosis and cytotoxicity were dose-dependent, with 10 M 1,4-BQ causing approximately 60% cytotoxicity when compared to untreated controls. In cultures treated with 1,4-BQ, the percentage of micronucleated CD34-cells risen exponentially. Furthermore, the p21 mRNA level was increased in 1,4-BQ-treated cells, indicating that human CD34 cells use the p53 pathway in response to 1,4-BQ-induced DNA damage. However, there were no significant changes in mRNA levels of the DNA repair genes ku80, rad51, xpa, xpc, and ape1 as well as p53 following treatment with 1,4-BQ. Although there were interindividual differences in the cellular response to 1,4-BQ, there was no gender difference in the overall response. These findings show that human CD34 cells are highly susceptible to 1,4-BQ toxicity and respond to genomic instability via the p53 DNA damage response pathway. Human CD34 HPC will be useful in determining the toxicity of other benzene metabolites and hematotoxic chemicals (Abernethy et al, 2004).

Haematological diseases and cancers are mediated in part by the metabolism of benzene. Benzene is primarily metabolised in the liver, although it is also metabolised in the lung and bone marrow on a secondary level. In essence, cytochrome P450 2E1 oxidises

benzene to benzene oxide at the commencement of the metabolism of benzene (CYP2E1). The spontaneous transformation of benzene oxide into phenol produces catechol and/or hydroquinone metabolites, both of which can be further transformed into hazardous metabolites (Meek and Klaunig 2010; McHale et al. 2012). In contrast, benzene oxide can undergo further metabolism to become benzene dihydrodiol, which can then be transformed into catechol.The possibility of the ring opening of benzene and the subsequent generation of aldehyde metabolites is also present. For instance, inactivation happens as a result of an enzymatic interaction with glutathione (Snyder and Hedli 1996; Meek and Klaunig 2010). Some of the reactive metabolites develop in the bone marrow where myeloperoxidases and other heme-protein peroxidases activate phenolic metabolites to semiquinone radicals generating free radicals, causing oxidative damage to different progenitor cells and different areas of bone marrow. Myeloperoxidase (MPO) in the bone marrow will further oxidise HQ to form the extremely genotoxic metabolite 1,4-benzoquinone (1,4-BQ) (Tuo et al. 1996; Hartwig 2010; McHale et al. 2012; Mathialagan et al, 2020).

A characteristic hazardous byproduct of benezene is 1,4-benzoquinone (1,4-BQ), which is considered to be a highly reactive benzene metabolite capable of inducing cytotoxicity and apoptosis in vitro and playing a substantial role in hematotoxicity (Chen et al, 2017).

It is commonly known that benzene must first undergo a number of reactive intermediates before it may cause damage. 1,4-Benzoquinone (1,4-BQ), a byproduct of benzene metabolism, may influence the degree of cell death by inducing apoptosis (Son et al, 2016). Previously, it was discovered that Caspase-9 targeting by miR-133a was a putative mechanism of H_2O_2 induced apoptosis in cardiomyocytes, which was associated with benzene-induced hematotoxicity (Bai et al, 2014; Xu et al, 2014; Yin et al, 2013). As a result,

it is possible to speculate that the underlying mechanism of miR-133a in benzene-induced hematotoxicity involves apoptosis (Chen et al, 2016).

Another study found a substantial correlation between 1,4-BQ-Alb and benzene exposure in those who were exposed to the chemical at workplace, and this new study indicates that the same is true for benzene oxide (BO) adducts. This suggests that 1,4-BQ and BO, at least in highly exposed individuals, are both available for binding to plasma proteins in humans exposed to benzene and that 1,4-BQ-Alb, BO-Alb, and BO-Hb can act as biomarkers of benzene exposure.

Recent research has demonstrated a connection between maternal benzene exposure and the development of juvenile leukaemias, indicating that these leukaemias may begin in utero (Sirotkin et al, 2017; Zhou et al, 2014). Benzene penetrates the placental barrier, although the processes underlying its toxicity in pregnancy are still poorly understood. The DNA repair enzyme foetal topoisomerase IIa (TopoIIa) is impaired by the benzene metabolite benzoquinone (BQ). Following a 24-hour exposure to BQ, an increase in TopoIIa-DNA covalent adducts was discovered (Holmes & Winn, 2019).However, after 24 hours of BQ administration, higher levels of the double-stranded DNA break marker cH2AX were found, indicating that TopoIIa-induced breaks were more prevalent in BQ-treated cells which demonstrated that BQ causes changes in foetal TopoIIa, indicating that this protein is a target of benzene and may be connected to in utero benzene toxicity (Holmes and Winn, 2019).

Fetal murine hematopoietic cells from pZK1 transgenic mice were used in a previous in utero investigation to examine the effects of p-BQ on DNA recombination, DNA damage, including DNA DSBs as detected by g-H2A.X foci and oxidative DNA damage, and the formation of reactive oxygen species (ROS). At different times after exposure to BQ, a considerable rise in recombination was seen (Tung et al, 2012).

HIF-1a overexpression in the K562 cell line may have an impact on the toxicity of 1,4-BQ. In a prior study, HIF-1a overexpression K562 cell line was created using a lentiviral vector, and it was discovered that both control K562 cells and HIF-1a overexpression cells exposed to 1,4-BQ had considerably higher levels of HIF-1a. HIF-1a overexpression significantly decreased ROS levels, apoptosis, and cell cycle during G2/M phase as compared to 1,4-BQ exposed control cells. Moreover, Nox4 was downregulated while Bcl-2 was upregulated as a result of HIF 1a overexpression. Moreover, at the same 1,4-BQ dose, HIF-1a overexpression cells had a considerably greater lactic acid (LD)/pyruvic acid (PA) ratio than control cells.Moreover, HIF-1a overexpression cells showed a considerable rise in the expression levels of Glut1, Ldha, Pkm2, Pgk1, Pdk1, Pfkl, and Pfkfb3 and thus they suggested that 1,4-BQ-induced ROS and apoptosis could be reduced by HIF-1a overexpression by targeting Nox4, Bcl-2, and important glycolysis enzymes (Sun et al, 2019).

Very recent researches revealed significant alterations in histoarchitecture and oxidative stress biomarker enzymes of liver and kidneys in p-BQ induced wistar rats (Mishra et al,2022). Additionally structural chromosomal abnormalities, higher frequency of micronuclei induction and higher rate of DNA fragmentation were also observed (Mishra et al, 2023).

4. Conclusion

To sum up, the findings of the present study reveals life threatening use of chemicals and its exposure which ultimately lead to serious health disorders. The toxicity caused by benzene metabolite, p-BQ in different organs provide further insight into mechanism of pathogenesis of cell and tissue injury.

5. Author Contribution

The first author has contributed in write-up of the manuscript. The second and third authors have provided suggestions during preparation and edited the manuscript.

6. Conflict of interest

The authors declare that they have no conflict of interest in preparation of the manuscript.

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