

Benzene in Shoe Manufacturing
A Summary of Acute and Chronic Effects
From Occupational and Low-Dose Exposure

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Abstract

Low level and occupational exposure to benzene in shoe manufacturing and its subsequent toxicological effect on humans continues to be extensively researched and documented. Declared a Group A human carcinogen by the United States Environmental Protection Agency (U.S. EPA) (Bayliss et al.1998), the production of benzene each year ranks in the top ten of commodity chemicals (Watts 1998). Although benzene has several pathways of environmental release such as volatilization into the atmosphere and spills or intentional releases into ground and drinking water, direct occupational exposure poses the greatest risk to humans in terms of exposure concentrations. In addition, low-level chronic exposure, particularly in urban areas presents an intricate toxicological issue for researchers and regulators. Epidemiological data from occupational exposure indicate that manifestations of nonlymphocytic leukemia and numerous blood-related disorders occur at low level chronic exposure. Such results also indicate an apparent risk to populations near industrial areas. This paper investigates the sources, pathways, and receptors for benzene that result from its use in shoe manufacturing.

INTRODUCTION

Benzene: A Brief History of Use

Discovered by Michael Faraday in 1825, (Watts 1998) benzene is used extensively as an industrial intermediary in the production of medicinal chemicals, dyes, plastics, textiles, detergents, varnishes, paints, lacquers, waxes, artificial leather and rubber (Immig 1998). Its commercial production began in 1849 (Watts 1998) and has led to its further use as solvents for pesticides, inks, paints, rubber, adhesives, coatings, detergents and gasoline (Immig 1998). An individual may come into contact with Benzene via environmental, consumer product, and occupational exposure (ATSDR, 1989). Upon exposure, inhalation and dermal contact serve as the primary means of absorption of benzene into the body. Shoe manufacturing has contributed to benzene exposure through both occupational exposure pathways and environmental pathways. Its release in waste streams and unintentional spills as well as volatilization exposes employees and local populations to the toxic effects of benzene.

A Chemical of Concern

The controversy over benzene and its acute and chronic effects in humans has long been a subject of concern and debate (EPA-IRIS 2000). Through accidental occupational exposures of large amounts the acute end effects of benzene on humans have been observed and documented. These relatively sudden, short-lived, and reversible effects in humans range from moderate conjunctival and dermal irritation, headaches, giddiness, drowsiness, vertigo, and transient irritation at low doses (50-150 ppm) to ventricular fibrillation, pulmonary edema, unconsciousness and even death at inhaled concentrations of 19,000 ppm (Immig 1998). The EPA's Integrated Risk

Information System (EPA-IRIS 2000) has reported epidemiological studies of men and women working in industries such as shoemaking, oil refineries, and chemical production that provide the basis for investigating benzene as a carcinogen.

In 1986, following extensive research, epidemiological studies, and laboratory testing, benzene was classified as a known human carcinogen for all routes of exposure under the Environmental Protection Agency's Risk Assessment Guidelines (EPA-IRIS 2000). Although epidemiological data is notoriously inaccurate due to the inability to correlate absolute cause and effect relationships, these studies in addition to animal data, an improved understanding of biochemical mechanisms of action, and numerous studies of dermal absorption in humans and animals have confirmed the cancer causing potential of benzene (Bayliss et al. 1998).

DISCUSSION

SOURCES

Benzene is a naturally occurring substance produced by volcanoes and forest fires and present in many plants and animals (ATSDR 1989). In the shoe manufacturing industry, benzene is a component in the solvents, glues, and paints (Karacic et al. 1987). In production an increased potential for occupational exposure of employees working in its presence exists, as well as exposure of local populations. Employees are at risk due to the enclosed environment and potential for high exposure; local populations risk chronic exposure to more dilute levels when air is ventilated from the industrial facility, and when deliberate low-level release or small spills occur.

Due to its high volatility, the use of benzene in industry presents a source for concern, especially to employees working in its presence. In the early 1900's recorded peak exposure levels reached 1000 ppm under working conditions in shoe-manufacturing plants (Hricko 1994). Additional studies have recorded annual cumulative exposure levels greater than 500 ppm in industrial facilities (Bayliss et al. 1998). It was not until 1987 that the United States' Occupational Safety and Health Administration (OSHA) was able to impose a stringent maximum exposure level for benzene after years of legal battles with unions, chemical, oil and rubber companies. This regulation requires that occupational exposure levels remain below 1.0 ppm and employers must begin monitoring when levels reach 0.5 ppm (Hricko 1994). However, the controversy abroad remains, where shoe manufacturers such as Nike and Reebok are repeatedly accused of ignoring health and safety codes and the benzene exposure to employees is likely to be much higher than those recommended by experts (Hricko 1994).

In addition, the low level chronic exposure to populations surrounding an industrial facility cannot be ignored when benzene has been recognized as a human carcinogen. Benzene enters the atmosphere via fugitive emissions as well as intentional and accidental discharge to water. Because benzene has a relatively high vapor pressure and Henry's Law Constant ($0.00548 \text{ atm}\cdot\text{m}^3/\text{mol}$ at 25°C), once released to water, it volatilizes rapidly (half-life 2.7 hours reported by OGWDW 2000) and enters the atmosphere (Watts 1998). In addition, that which remains in water quickly undergoes oxidative processes that degrade benzene. As a result, exposure by means of ingestion is minimized or eliminated, but that due to inhalation increases. Because benzene is highly volatile, its potential for global contamination must be also considered.

Fortunately, benzene is susceptible to degradation in the atmosphere via photochemically produced hydroxyl radicals and its experimentally calculated half-life is 13.4 days (Watts 1998, OGWDW 2000). Oxygen and hydroxyl radicals act on benzene in the atmosphere to oxidize it creating phenol, catechol, cis-buconic acid and eventually carbon dioxide and water (see Figure 1.). Also, biodegradation and volatilization of benzene in soils prevent it from further contaminating the environment (OGWDE 2000).

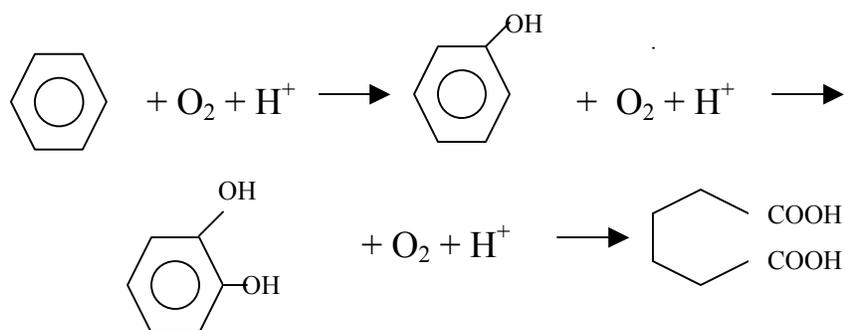


Figure 1. Stepwise oxidation of benzene to cis-buconic acid.

Thus, benzene is a non-persistent chemical and lacks potential to contaminate and intoxicate populations located great distances from its source.

PATHWAYS

The two primary pathways of exposure to benzene are through inhalation and dermal exposure. Pathways of exposure are heavily dependent upon the physical and chemical properties of a substance. A chemical's vapor pressure, water solubility, density, and octanol-water partitioning coefficient aid analysts in determining pathways

of transport and exposure in the environment. In the following paragraphs the properties of benzene are investigated with respect to its ability to intoxicate exposed humans.

Inhalation

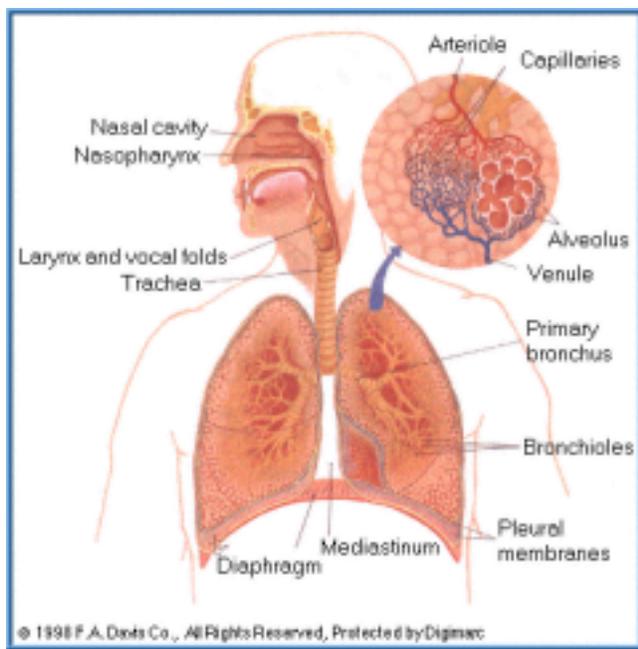


Figure 2. Diagram of Respiratory System (National Library of Medicine (NLM): Respiratory Tract).

who live in the local area surrounding a shoe manufacturing facility may also risk exposure to vapors that escape the facility confines as well as volatilized benzene from spills or intentional releases.

The respiratory system includes the nasopharyngeal, tracheobronchial, and pulmonary anatomical regions, see Figure 2 on the above (NLM: Respiratory Tract). In the pathway of respiratory exposure, benzene is inhaled deeply into the lungs in the vapor phase and comes into contact with the high surface area of the alveolar region.

Due to its relatively high volatility and high water solubility, exposure to benzene via inhalation poses a greater threat than through dermal contact. In fact, it has been estimated that as much as sixty percent of the amount inhaled is absorbed into the bloodstream whereas only one percent is absorbed through dermal contact (Immig 1998).

Employees in an occupational setting are exposed to benzene vapors released from solvents, paints and glue. Those

The alveolar region is very important to toxicant absorption due to its surface area (50 times that of skin) and thin membrane that separates the benzene vapors from the blood stream permit transport of volatile toxicants into the bloodstream (NLM: Respiratory Tract). Highly water soluble, therefore blood soluble, gases are easily transported into the blood stream via passive diffusion. Benzene has excellent potential to be absorbed into the blood stream due to its relatively high water solubility, 1779 mg/L (Watts, 1998). Once absorbed into the blood, benzene is transported throughout the body to major receptors.

Dermal Absorption:

When an individual is exposed to benzene via dermal contact, the skin provides an excellent barrier to its transport into the blood stream. Percutaneous absorption occurs via passive diffusion. By inspecting Figure 3 it becomes apparent that the epidermis lacks capillaries and that the toxin must reach the dermis

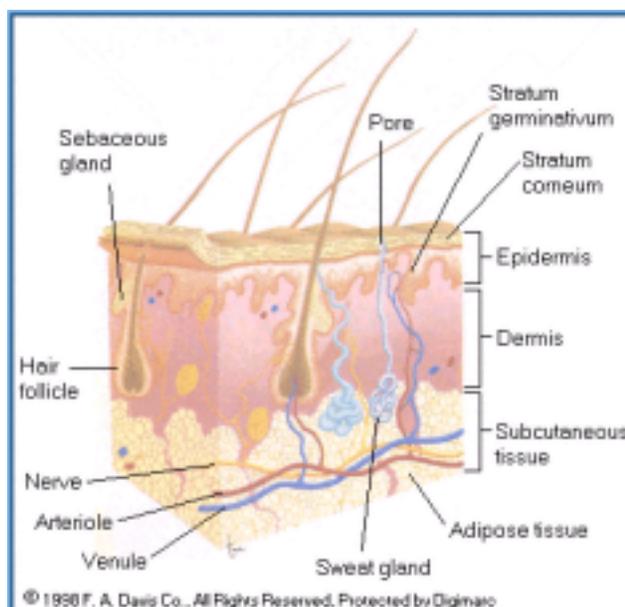


Figure 3. Diagram of Skin (NLM: Dermal Absorption).

before it can be absorbed into the blood stream via the venous and lymphatic capillaries (NLM: Dermal Route). The dose, lipid solubility, and length of exposure of the chemical are key to whether or not a toxin passes from the epidermis to the dermis. When benzene is exposed to the skin, the keratinized or hardened stratum corneum

coordinated with extracellular lipids act as a protective barrier to toxicants in the epidermis (Hughes, 1996). Note that if benzene enters a sweat gland or hair follicle, it bypasses this protective layer and transports directly into the dermis where these structures originate. Nonpolar, lipid-soluble toxicants such as benzene dissolve into the skin and diffuse through the lipid soluble keratinized layer (NLM: Dermal Route). Benzene is a relatively large molecule with moderate lipid solubility, $\log K_{ow} = 2.05$ (Watts, 1998), thus its potential to reach the blood stream via the skin is minimal. If it does manage to reach the blood stream, the exposure dose is generally a fraction of the absorbed dose, one percent as stated earlier.

In addition, length of exposure also plays a significant role in benzene intoxication via the dermal route. Thus, individuals working in an occupational setting are required to wear protective clothing and take immediate safety measures, such as cleansing the exposed area, when benzene is spilled directly on the skin. In addition, benzene has such a rapid volatilization rate that once it is spilled, a portion of it will volatilize and decrease potential for dermal absorption.

RECEPTORS:

Upon entering the blood stream after inhalation or dermal absorption, benzene targets many organs and cells. It has the potential to cause central nervous system (CNS) dysfunction, hematotoxicity, hepatotoxicity, and nephrotoxicity. Common acute end effects include epidermal, dermal and conjunctival irritation, headaches, giddiness, drowsiness, vertigo, impaired balance, convulsions, collapse, transient irritation, and CNS dysfunction (BP-Amoco 2000, Immig 1998). Epidemiological studies have

demonstrated that the primary chronic end effects include aplastic anemia and acute myelogenous leukemia (Bolton et al. 2000). In addition, the liver plays a fundamental role in benzene's toxicological end effects. Because the liver, kidneys, heart and brain have a high blood flow to mass ratio they receive a large portion of the total toxicant dose. For example, in one extreme case, results of an autopsy of a fatal benzene exposure case reported blood clots in the heart and main vessels, multi-organ congestion and pulmonary edema (Barbera et al. 1998). As predicted by the blood flow to mass ratios of these organs, victim's blood contained a benzene concentration of 31.67 $\mu\text{g/mL}$ and high concentrations were measured in the lungs (22.23 $\mu\text{g/g}$), liver (378.6 $\mu\text{g/g}$), brain (178.66 $\mu\text{g/g}$), heart (182.57 $\mu\text{g/g}$), and kidneys (75.15 $\mu\text{g/g}$) (Barbera et al. 1998). In addition, the liver, kidneys, and lungs also have the potential to metabolize and occasionally bioactivate a toxicant, as in the case of benzene in the liver.

When benzene is absorbed in the respiratory system, it has the potential to directly enter into pulmonary circulation by means of the pulmonary vein. This vein provides oxygen and other gases a direct route to the heart from the lungs (Hughes 1996). After being absorbed dermally, benzene distributes to tissues by means of the peripheral blood supply (Hughes 1996). Dermal absorption results in epidermal, dermal and conjunctival irritation or irritant contact dermatitis. Upon distributing to the various organs and tissues, these receptors respond by engaging, metabolizing, or otherwise eliminating the toxicant. The primary route of elimination takes place when benzene is metabolized to phenols and muconic acid then excreted in urine as conjugated sulfates

and glucuronides (Bayliss et al. 1998). However, when a toxicant is not eliminated, it has the potential to impart damage to the central nervous system and blood.

Benzene causes neurotoxicity, damage to central nervous system cells including the brain and nerves as well as the peripheral nervous system resulting from exposure to a toxicant. Benzene as a neurotoxin may act as an acetylcholinesterase inhibitor, bind to post synaptic receptors, or stimulate transport channels (Huges 1996) resulting in the reported symptoms of vertigo, giddiness, impaired balance, and convulsions. In addition, the mechanism of action for benzene as a neurotoxin is not widely known. However, reported incidence of CNS dysfunction has led to further studies. Varona et al. (1998) reported that acute exposure to benzene in rats generated a dose-related inhibition of the enzyme aminopeptidase in the hypothalamus and brain stem resulting in analgesia. Although the blood-brain barrier acts to inhibit passage toxic substances to the CNS, it cannot entirely prevent intoxication.

Hematotoxicity results when a xenobiotic directly affects the blood cells or bone marrow. Bone tissue is a constantly recycling tissue and subsequently very susceptible to intoxication. Extensive studies have been conducted on the toxicity of benzene and its link to leukemia and other bone diseases. Symptoms include fatigue, palpitations, difficulty breathing, gingival bleeding, and nosebleeds. Benzene itself is not likely to be the active toxicant because it is readily metabolized. As a result, it has been difficult to elucidate the pathway or many pathways of benzene toxicity.

Two primary benzene toxicity pathways have been postulated. The first involves hepatic metabolites (phenol, catechol, and hydroquinone) and the second entails the open-ring metabolites of benzene. In the liver benzene undergoes phase I and phase II

transformation by cytochrome P450 2E1, resulting in phenol, catechol, and hydroquinone (Bayliss et al. 1998). Bone marrow, which is “rich peroxidase activity”, enables further activation of these phenolic metabolites (Bayliss et al. 1998). In addition, hydroquinones undergo peroxidase activation resulting in covalent binding to protein and formation of DNA adducts (Levay et al. 1993). Myeloperoxidase (MPO) is available in high concentrations in bone marrow and may readily bioactivate phenolics, producing reactive quinones (Bayliss et al. 1998). Yet, phenol does not induce myelotoxicity, which is associated with benzene via the route described by the first hypothesis. Some scientists explain this discrepancy by suggesting that preferential conjugation of phenol takes place in the periportal region of the liver. Benzene, however, is metabolized in the pericentral region of the liver resulting in phenol then hydroquinones and data further supports this theory (Bayliss et al. 1998). Figure 4 on the following page conveys potential distribution and receptors of benzene in the human body.

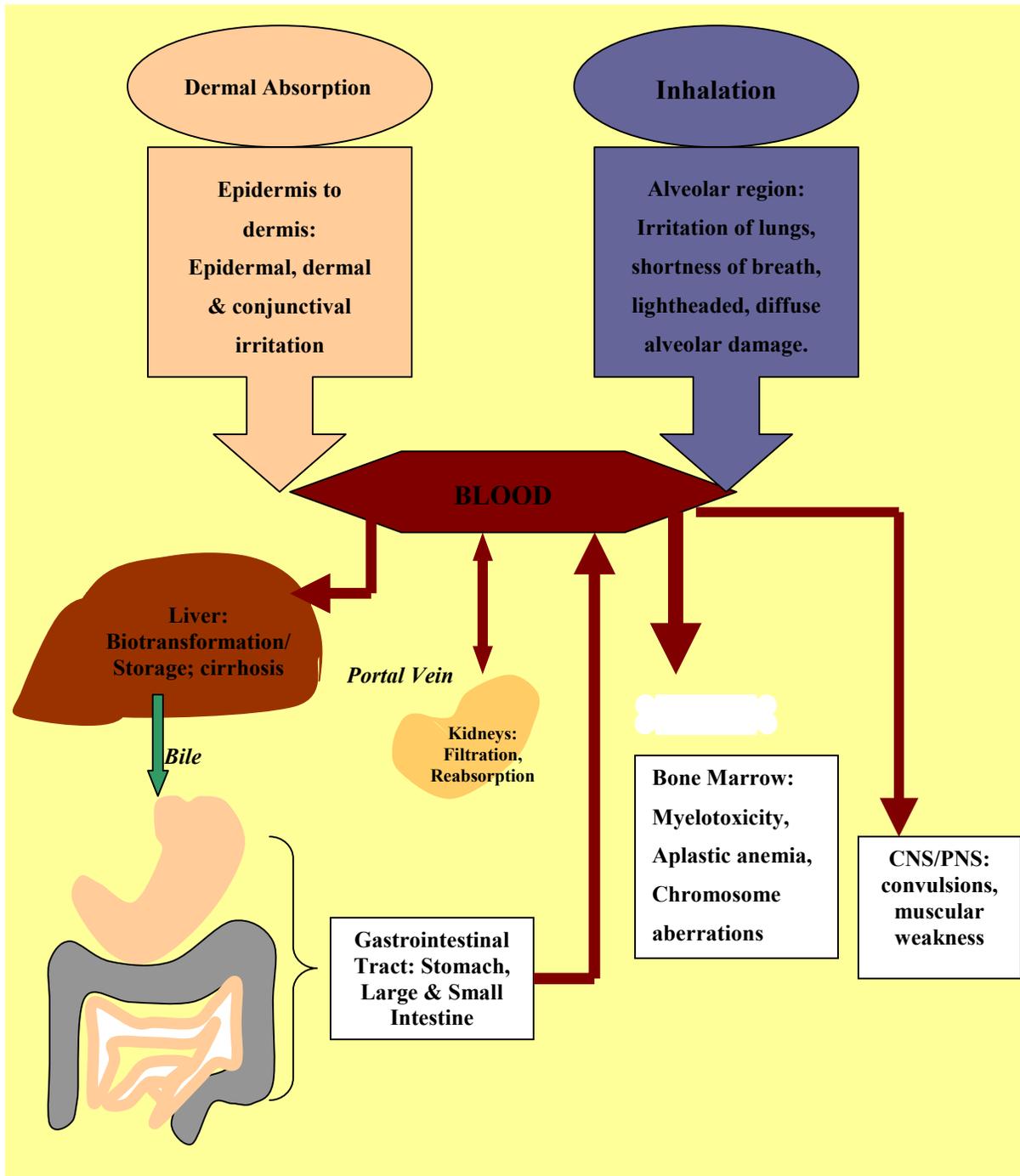


Figure 4. Diagram of toxicant flow path in human body and potential symptoms of intoxication.

The second hypothesis for the metabolic mechanism by which benzene induces hematotoxicity involves open-ring muconate derivatives of benzene. Trans, trans-muconic acid is often detected as the urinary metabolite of benzene. Trans, trans-muconaldehyde (MA) is a precursor to trans, trans-muconic acid and is proposed to be the most toxic species resulting from benzene metabolism. However, MA has never been reported as a metabolite in living organisms and its rapid metabolism may prevent scientists from isolating it *in vivo* (Bayliss et al 1998). Regardless of which of these hypotheses is correct, it is clear that the active toxicant is not benzene; rather its hepatic metabolites are responsible for disrupting bone tissue and blood production. Finally, it should be noted that chromosomal aberrations have also been noted in lymphocytes and bone marrow cells of patients with benzene-induced myelogenous leukemia, myelodysplastic syndrome, and pancytopenia (Bayliss et al. 1998).

CONTROLS:

There are two primary mechanisms of control and these include industrial use and government agency regulations. Well-conceived agency regulations in conjunction with appropriate work-place practices and training aid reduction of exposure to benzene. Government agencies provide guidelines for exposure limits based on scientific studies. Personal protective equipment such as aprons, gloves and masks with filters are made available by work-place management where needed, and they should be used according to agency recommendation (BP-Amoco 2000).

Federal agencies and legislation in the United States provide guidelines and regulations for hazardous waste emissions. Industries are required to comply with these

regulations with the threat of large fines or even closure. These agencies include the EPA and OSHA, which enforce regulations governing environmental release and occupational exposure respectively. Legislation such as the Clean Air Act, Clean Water Act, Safe Drinking Water Act (SDWA) Resource and Conservation and Recovery Act (RCRA) govern how much industries such as shoe manufacturing are permitted to pollute. Currently, the maximum contaminant level (MCL) for benzene is 0.005 mg/L, established under the SDWA. With an imposed maximum contaminant level goal (MCLG) of zero (EPA-OGWDW 2000), regulatory agencies in the U.S. are at work to minimize potential exposure to the local populations. The U.S. EPA has established that industries must use emission or process control devices to reduce their hazardous emissions by 95 percent. In addition, the total amount of benzene released to the atmosphere from a single facility cannot exceed 0.90 Mg/yr (EPA 1999). OSHA governs employee safety and exposure in the work place. As stated earlier, the current permissible level of vapor exposure is 1.0 ppm in an occupational setting averaged over an 8-hour period (NJDHSS 1994); however, air monitoring must be conducted when levels reach 0.5 ppm. In addition, dermal contact must be minimized through use of protective clothing and devices.

When chemical substitution is not possible, engineering control is the most effective way of reducing occupational exposure to benzene. Even though operations with benzene can be enclosed, exhaust ventilation must be provided at the site of chemical release. Personal protective equipment, for example, breathing protection, is sometimes necessary although less effective. Benzene is filtered with a mask and filter type A (for organic solvents with boiling point over 65⁰C). A helmet supplying fresh air is

often the preferred device due to its reliability. This equipment should be stored in an aseptic environment away from possible contact with solvent vapors. Not all materials can withstand benzene's ability to dissolve substances. Thus, gloves should be constructed of Viton or PVA. However, eventually these materials will also degrade and lose their protective capacity. Contaminated clothing must be changed promptly to avoid dermal absorption. Benzene should be stored in tightly closed containers in a cool well-ventilated area away from heat (BP-Amoco 2000). It must be noted that benzene reacts violently with oxidizing agents, such as permanganates, nitrates, peroxides, chlorates and perchlorates.

Unfortunately, many nations have not established stringent laws or governing bodies that provide and enforce regulations for toxic chemical release into the environment or in the work place. Even with the overwhelming evidence of its cancer-causing capabilities, some have chosen to ignore this evidence for the sake of economic gain. Reportedly, factories in China producing shoes for Nike and Reebok are accused of exposing their workers to high levels of benzene each day. Though the exposure concentrations are not available, the benzene levels are high enough to cause the acute symptoms of lightheadedness, headaches, imbalance, and nausea, symptoms, which occur at exposure levels of 50-150 ppm according to Immig (1998). The minimum risk level (MRL) established for intermediate neurological effects (ATSDR, 2000) is well below this range with a value of 0.004 ppm per day. In addition, this amount is well above the 31 ppm been noted to increase chromosome aberrations in the lymphocytes of exposed workers (Zhang et. al. 1999) increasing the potential for cancer.

CONCLUSION

Benzene is a contaminant of concern for many reasons, primarily because it has been a suspected and now decidedly known human carcinogen. Although the majority of the human population does not have to be concerned with occupational exposure to benzene via shoe manufacturing, the results of recent studies indicate that chronic low-level exposure may also increase the risk of cancer. Thus, the summation of minute amounts released to the environment via automobile emissions, coke ovens, nonferrous metal manufacture, ore mining, wood processing, coal mining, and textile manufacture in addition to shoe manufacturing are cause for concern, particularly in urban areas where several if not all of these processes take place. In fact, from 1987 to 1993 the Toxic Release Inventory reported that the total amount of benzene release to land by industry exceeded 1.5 million lbs and that released to water exceeded 500,000 lbs in the U.S. (EPA-OGWDW 2000). Although separately, the amounts may seem inconsequential, their combined effects are significant. With the U.S. production of benzene exceeding 12 billion lbs in 1993, this amount is expected to rise as the use of coal increasingly replaces the use of petroleum and natural gas for fuel (EPA-OGWDW 2000). Thus, the issue becomes more pertinent.

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