REVIEW ARTICLE

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Biomarker of Surgical Smoke as An Occupational Hazard for Health Care Workers in The Operating Room

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Surgical smoke generated by electrosurgical and energy-based instruments contains a complex mixture of hazardous substances, including volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), aldehydes, ultrafine particles and viable biological materials such as bacteria and viruses. Due to its highly heterogeneous composition, comprehensive monitoring of all constituents is not feasible because of analytical limitations, cost and the absence of validated biomarkers for many compounds. Therefore, identifying dominant chemical components with available and reliable biomarkers is essential for occupational exposure assessment in operating room personnel. Evidence from multiple studies consistently indicates that benzene, toluene, ethylbenzene and xylene (BTEX) are among the most dominant and relevant VOCs present in surgical smoke. This narrative review aims to identify practical and non-invasive biomarkers for monitoring internal chemical exposure from surgical smoke by synthesizing evidence from human biomonitoring studies focusing on urinary biomarkers. Particular emphasis is placed on BTEX-derived metabolites due to their well-characterized toxicokinetic, biological relevance and the availability of standardized and validated laboratory analytical methods. Urinary S-phenyl mercapturic acid (S-PMA), O-cresol, mandelic acid and methyl hippuric acids (o-, m-, p-MHA) were consistently detected among exposed healthcare workers, especially surgical nurses, indicating systemic absorption despite airborne concentrations generally remaining below occupational exposure limits. These findings suggest that chronic low-level exposure may still pose cumulative health risks. While BTEX biomarkers do not represent the entire toxic burden of surgical smoke, their dominance in smoke composition and the feasibility of reliable laboratory testing support their use as practical biomarkers for occupational health surveillance of medical personnel working in operating rooms. Future research should focus on longitudinal assessment and integrated biomarker panels to strengthen exposure–response evaluation.

Keywords: BTEX, healthcare workers, occupational exposure, PAHs, surgical smoke, urinary biomarkers

Introduction

Surgical smoke is produced when electrosurgical instruments, lasers, ultrasonic scalpels, or other energy-based devices generate heat sufficient to vaporize or coagulate biological tissue. This process releases a mixture of water vapor, particulate matter, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), viable cells, and infectious particles. Although water vapor accounts for most of the plume, a small fraction contains potentially hazardous substances that can pose respiratory and systemic health risks to operating-room personnel.[1,2,3]

Over the past decades, the use of energy-based surgical devices has increased substantially, leading to

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greater concern regarding occupational exposure to surgical smoke. Previous studies have characterized the chemical composition of surgical smoke and identified numerous toxicants, including benzene, toluene, ethylbenzene, and xylene (BTEX), as well as multiple PAHs. Experimental and human biomonitoring studies have confirmed that these compounds can enter the systemic circulation and be detected in biological samples from exposed healthcare workers. However, existing evidence remains fragmented, and exposure levels vary widely across studies.[4,5,6]

Despite the large body of research describing the composition and potential health effects of surgical smoke, a key gap is no standardized or validated biomarker that can be used to reliably assess exposure among healthcare workers. The chemical composition of surgical smoke is highly complex containing hundreds of compounds making comprehensive analysis impractical, expensive, and not feasible in routine occupational health monitoring. This highlights the need to identify specific biomarkers that are both analytically reliable and suitable for non-invasive biological sampling.

Therefore, the purpose of this narrative review is to synthesize current evidence on potential urinary biomarkers for assessing surgical smoke exposure, with a focus on metabolites of BTEX and PAHs. By evaluating biomarker specificity, sensitivity, feasibility, and clinical applicability, this review aims to propose the most appropriate biological indicators that can be used to monitor and manage occupational exposure among healthcare workers.

Methods

Evidence Search Strategy

The evidence search strategy employed in this systematic review was conducted systematically across multiple electronic databases, including PubMed, ScienceDirect, Scopus, and Cochrane, to identify relevant studies on biomarkers of surgical smoke exposure in healthcare workers. The search utilized a structured PICO (Population, Intervention, Comparison, Outcome) framework: the Population (P) consisted of healthcare workers exposed to surgical smoke; the Intervention (I) focused on biomarker exposure assessment; the Comparison (C) was implicitly made against control groups or occupational exposure limits; and the Outcome (O) aimed to identify rationale biomarkers for non-invasive sampling techniques and their availability. Keywords used in various combinations to refine the search results included: "Healthcare Worker," "Biomarker Exposure," "Surgical Smoke," "Operating Room," and "Urine Chemical Analysis."

Article Selection Process

The selection of relevant articles was conducted in a rigorous, multi-stage process based on predefined inclusion and exclusion criteria, as illustrated in **Figure 1**.

Initial Search and Duplication Removal

The initial search across the four databases yielded a total of 132 records (PubMed: 5, ScienceDirect: 107, Scopus: 20, Cochrane: 0). After removing duplicates, a total of 130 unique records proceeded to the screening stage.

Screening and Application of Criteria

The screening process was based on three main inclusion criteria: studies must involve human subjects, must focus on biomarker exposure assessment, and must be available as a full text in English. During this process, several records were excluded based on their content or format. Specifically, 3 studies were excluded because they involved animal models, 14 records were only available as an abstract, and 46 records were deemed not relevant to biomarker exposure. Furthermore, 41 conference abstracts, 3 records that were only single paragraphs, and 17 records consisting of book chapters, indexes, and encyclopedias were also excluded. This comprehensive screening process successfully reduced the initial pool of records to 6 relevant studies.

Results

Surgical smoke, also known as surgical plume, refers to the vapor generated during surgical procedures when tissue is disrupted. It is produced as aerosols containing various substances released by electrosurgical instruments. Surgical smoke is both visible and has a distinct odor, which comes from the gaseous by-products formed when tissue proteins and fats are vaporized and broken down during surgery.[1,2,7]

While water vapor makes up about 95% of surgical smoke, the remaining 5% consists of particulate matter and chemical substances that can pose health risks. This fraction may contain a variety of elements, including non-viable particles, chemical compounds, viable cells, and pathogens, with bacteria and viruses also potentially present within the smoke. Due to these components, healthcare workers in the operating room may face health hazards when exposed to surgical smoke during procedures.[1,2] A comparison of studies on surgical smoke exposure is presented in **Table 1**.

Mechanism of Surgical Smoke Formation

Surgical smoke is produced when energy-based surgical instruments interact with biological tissue through thermal or mechanical processes that cause vaporization, pyrolysis, or cellular disruption. A wide range of devices are capable of generating surgical smoke, including electrosurgery (diathermy), electrocautery, laser systems, ultrasonic scalpels, powered surgical drills, and high-speed burrs. Because human tissues contain a high percentage of water, the application of these devices results in rapid heating or vibration at the tissue interface, causing cell membrane rupture, release of intracellular water, and subsequent formation of aerosols containing both chemical and particulate components. These aerosols consist of gas-phase by-products, volatile organic compounds (VOCs), polycyclic aromatic hydrocarbons (PAHs), ultrafine particulate matter, and potentially viable biological materials.[1,8]

Different surgical instruments produce smoke with distinct characteristics depending on the mechanism of energy delivery. Electrosurgical devices and electrocautery generate smoke through high-temperature thermal destruction (>200°C), yielding ultrafine particles with mean diameters between 0.07–0.42 µm and high concentrations of VOCs including benzene, toluene, ethylbenzene, and BTEX. Laser systems operate via photothermal ablation, producing particles sized 0.1–0.8 µm and relatively higher concentrations of aldehydes and PAHs compared to electrosurgery. Conversely, ultrasonic scalpels utilize high-frequency mechanical vibration rather than heat, producing comparatively larger particles (0.35–6.5 µm) with lower VOC concentrations but containing more intact cellular debris and potentially viable pathogens, which may have infectious implications rather than chemical-toxicologic relevance.[3,8,9]

These differences demonstrate that biomarker selection must align with the dominant chemical profile generated by the type of surgical device. VOC-rich smoke generated by electrosurgical and laser instruments is more suitable for urinary biomarker monitoring using BTEX metabolites such as S-phenyl mercapturic acid (S-PMA), O-cresol, mandelic acid, and methyl hippuric acids, due to established toxicokinetic pathways and standardized analytical methods. Meanwhile, PAH exposure from laser-related procedures may be better reflected by biomarkers such as urinary 1-hydroxypyrene, and ultrasonic devices may not yield reliable urinary biomarkers due to the predominance of biological particles rather than chemically active compounds. Therefore, understanding the specific characteristics of each device is essential in supporting the rationale for selecting the most appropriate and feasible biomarker for occupational exposure monitoring.[2,9]

The mechanistic pathways involved in electrosurgery-induced smoke formation can be summarized as shown in **Figure 2**, illustrating both primary thermal processes and secondary electrochemical reactions.

During electrosurgical procedures, the interaction of high-frequency electrical energy with biological tissues primarily induces thermal decomposition and pyrolysis, leading to the breakdown of cellular structures and organic biomolecules into gases, condensable vapors, and ultrafine aerosolized particles. These thermally driven reactions produce a complex mixture of airborne contaminants, including VOCs, aldehydes, and PAHs, which represent the main chemical hazards relevant to internal dose monitoring. Although electrochemical reactions such as ion dissociation and limited electrolysis may occur due to the highly electrolytic nature of human tissues, these processes are considered secondary pathways and contribute minimally to the toxicologically significant compounds associated with occupational exposure.[10,11,12]

Pyrolysis, occurring in the absence or limited presence of oxygen, results in the fragmentation of complex organic molecules such as lipids, proteins, and carbohydrates into smaller volatile compounds and incomplete combustion products. This mechanism explains the release of aromatic hydrocarbons such as benzene, toluene, ethylbenzene, and BTEX, as well as PAH derivatives, which are metabolized in the human body and can be detected in urine as S-PMA, O-cresol, mandelic acid, and methyl hippuric acids. Meanwhile, electrolysis of tissue electrolytes may generate small inorganic byproducts, but these do not play a significant role in the biomarker selection process because they lack validated biological monitoring indicators and are not considered major contributors to the cumulative toxic burden.[10,11,12]

Composition of Surgical Smoke

As previously stated, surgical Smoke contains both chemical and organic matter. It can contain Carbon, Cellular Debris, Blood Products, Fecal Matter, Bacteria, Viral and Viable DNA, as well as HPV (Human Papilloma Virus) and HIV and Hepatitis B, among many others. More than 41 gases are present in surgical smoke, including

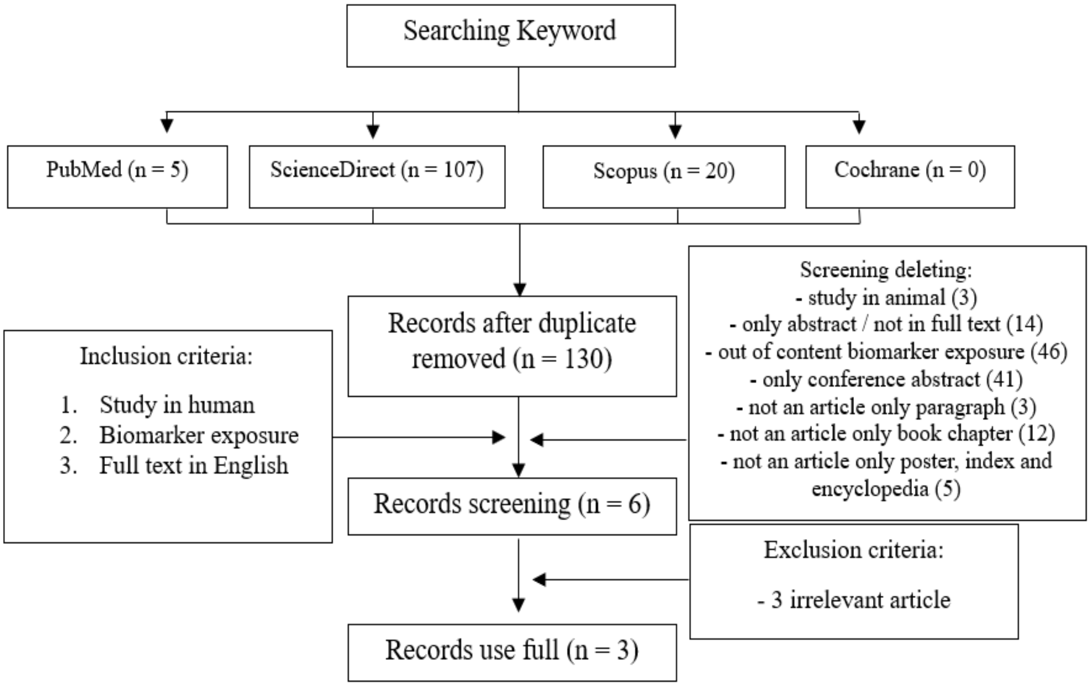

Figure 1. Process of article selection

some of the carbon and hydrocarbons, Benzene, Toluene, Xylene, Cyanide, as well as gaseous substances such as Carbon Monoxide and the highly toxic Formaldehyde. In addition, sevoflurane, a common anesthetic, has been found in surgical smoke. This means that the use of drugs can influence the composition of surgical smoke.[2,8]

The actual products of electrolysis depend on various factors, including the concentration of the sodium chloride solution and the presence of other ions that may affect the redox reactions. In a highly concentrated NaCl solution, the predominant products at the electrodes are likely to be chlorine gas at the anode and hydrogen gas at the cathode, with sodium hydroxide as a by-product. The production of small amounts of hydrogen and oxygen gases through the electrolysis of water. In the specific setting of electrosurgery, the generation of these substances can contribute to the composition of surgical smoke, which, as previously mentioned, the combination of these chemical reactions produces chemicals that can be found in surgical smoke like benzene.[10,11,12]

Redox reactions, or reduction-oxidation reactions, are a type of chemical reaction where there is an exchange of electrons between the atoms or molecules involved. In these reactions, one substance undergoes oxidation (loses electrons) and another substance undergoes reduction (gains electrons). In the context of electrosurgery, redox reactions are not the primary focus; instead, the procedure relies on the thermal effects of high-frequency electrical currents to cut, coagulate, or ablate tissue.[11,12]

The types and concentrations of VOCs present in surgical smoke vary depending on both the energy device used and the tissue being treated. For example, surgical smoke produced by electrocautery often contains significant amounts of hydrocarbons, nitrifying compounds, fatty acids, and phenols. In contrast, laser ablation of tissue typically generates smoke with higher levels of benzene, formaldehyde, acrolein, and polycyclic aromatic hydrocarbons (PAHs). When high-frequency electrosurgical devices are used on skin, the resulting smoke tends to have increased concentrations of toluene, ethylbenzene, and xylene, whereas procedures involving adipose tissue yield smoke with lower toluene but higher aldehyde levels. Research has shown that the VOC concentrations in smoke produced by ultrasonic scalpels during laparoscopic cholecystectomy are lower compared to those generated by electrocautery. Additionally, when

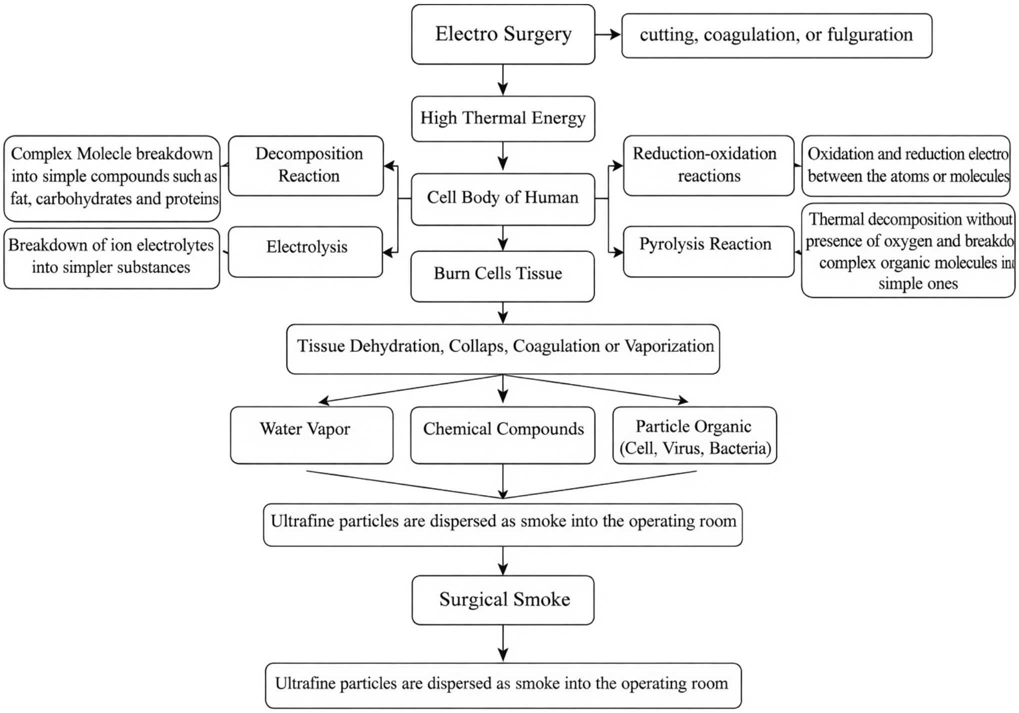

Figure 2. Schematic overview of surgical smoke formation mechanisms

liver tissue is cauterized with an electric knife, it can release more furfural than muscle tissue. The presence of carbon monoxide (CO) in surgical smoke is due to the incomplete combustion of tissue during these procedure.[3,8]

Benzene, toluene, and xylene are among the main chemicals detected in electrosurgical smoke. Although surgical smoke can contain various potentially harmful substances, the levels of hydrocarbons in electrosurgical smoke are much lower compared to those found in cigarette smoke.[13]

The Particles Size of Surgical Smoke

Particulate matter in surgical smoke is predominantly ultrafine, with 77% of particles smaller than 1.1 µm and a mean diameter of 0.07 µm. These aerosols contain a significant fraction of particles in the 10 nm to 1 µm range, which are too small to be captured by standard surgical masks (ineffective below 5 µm), posing a direct inhalation risk to operating room personnel.[3,8]

After understanding the characteristics and risks associated with particulate matter, it is important to consider particle size in relation to its health impact. The potential harm from inert particles is strongly linked to their size. Particle characteristics during surgery can vary depending on factors such as the type of tissue and the surgical energy device used. Electrocautery generates smoke particles ranging from 0.07 to 0.42 µm in diameter, laser devices produce particles between 0.1 and 0.8 µm, while ultrasonic scalpels generate comparatively larger particles, measuring around 0.35 to 6.5 µm in diameter.[2,8]

Based on measurement outcomes, tissues can be categorized into three groups according to particulate matter (PM) production: a high PM group (liver), a medium PM group (skeletal muscle, renal cortex, and renal pelvis), and a low PM group (lung, bronchus, subcutaneous fat, cerebral gray and white matter, and skin). Understanding the diameter of particles in surgical smoke is important because their size determines where they deposit in the respiratory tract, influencing the severity of potential harm. Particles around 5 µm or larger tend to settle in the nasal passages, pharynx, trachea, and bronchi, while particles under 2 µm can reach the bronchioles and alveoli, leading to lung inflammation. As a result, PM2.5 serves as a crucial indicator for assessing the potential health risks associated with exposure to s urgical smoke.[9,14]

Health Risks Associated With Surgical Smoke Exposure

Limiting the view of the operative field

Surgical smoke poses potential health risks due to its various properties. It can also disrupt surgical procedures by obscuring the operative field, particularly during laparoscopic surgeries where smoke accumulates within the abdominal cavity. In open surgeries, an assistant is frequently required to handle suction devices to clear the smoke and maintain visibility. During laparoscopic procedures, surgeons often need to pause their work to evacuate the smoke in order to regain a clear view. These interruptions can influence the efficiency and safety of surgical procedures to some extent.[2]

Causing iscomfort to medical staff and increasing the incidence of disease

In a questionnaire-based survey, almost half of the participating doctors and nurses reported experiencing various discomforts such as headaches, eye irritation, coughing, sore throat, lingering odors in their hair, nausea, drowsiness, dizziness, sneezing, and rhinitis. Surgical smoke contains a substantial quantity of fine particles with diameters under 2.5 μm (PM2.5). Exposure to PM2.5 is closely linked to conditions such as asthma and is recognized as an independent risk factor for mortality due to cardiovascular diseases, chronic obstructive pulmonary disease (COPD), and lung cancer. This association is due to the activation of multiple signaling pathways, including the activation of oncogenes and the suppression of tumor suppressor genes. Prolonged inhalation of PM2.5 consequently elevates the risk of developing lung cancer. When PM2.5 particles deposit in the lower airways, they can initiate inflammatory responses by activating Th2 cells and other inflammatory mediators, as well as inducing oxidative stress.[2,14,15]

Smoke generated during surgical procedures contains carcinogenic substances such as benzene and formaldehyde, and prolonged exposure to these chemicals can elevate cancer risk. Research indicates that inhalation of surgical smoke may lead to symptoms such as hypoxia, dizziness, coughing, headaches, nausea, vomiting, migraines, and irritation or pain in the eyes, nose, and throat. Additionally, the mutagenic potential of surgical smoke has been reported to be comparable to that of cigarette smoke. To address these hazards, the Occupational Safety and Health Administration (OSHA) and the National Institute for Occupational Safety and Health (NIOSH) have established recommended exposure limits (RELs) for various toxic substances in workplace environments.[10]

Surgical smoke contains a variety of toxic chemicals, including benzene, toluene, xylene, styrene, furfural, ethylbenzene, acetylene, hydrogen cyanide, and 1,3-butadiene, among others. The concentrations of these substances can sometimes exceed the occupational exposure limits set by NIOSH. Surgical smoke produced during electrocautery of human breast tissue and exposed human small airway epithelial cells (SAECs) and RAW 264.7 mouse macrophages to these samples. The findings demonstrated that exposure to surgical smoke resulted in about 25% cell death in SAECs and 40% in RAW cells compared to controls. Additionally, after 24 hours of exposure, there was a significant increase in lactate dehydrogenase (LDH) levels in the culture media, indicating that surgical smoke can damage cellular membranes.[2,15]

The mutagenic effects of surgical smoke on cells have been well documented, with some studies comparing its harmful impact to that of cigarette smoke. Research has shown that surgical smoke can cause significantly more DNA damage than cigarette smoke. It has been reported that the mutagenic potential of surgical smoke generated from electrocauterizing 1 gram of tissue is comparable to the mutagenicity of six cigarettes. Consequently, the amount of surgical smoke produced in a plastic surgery operating room in a single day may have a mutagenic effect equivalent to that of 27 to 30 cigarettes.[14,16]

Increasing the risk of disease transmission

There have been reports suggesting that medical personnel may contract HPV infections through exposure to surgical smoke. While hepatitis B virus (HBV) is primarily transmitted via blood, sexual contact, and from mother to child, it is known to cause hepatitis, liver cirrhosis, and liver cancer. The detection of HBV within surgical smoke raises the theoretical possibility of respiratory transmission of the virus. Additionally, the presence of viable cells in surgical smoke may contribute to the recurrence and spread of malignant tumors.[2]

Determinants of Valid and Feasible Biomarkers for Surgical Smoke Exposure

Surgical smoke consists out of various chemicals including Volatile Organic Compounds, Polycyclic Aromatic Hydrocarbons, Carbon Monoxide, Acrylonitrile, Hydrogen Cyanide and Formaldehyde. The complexity and diversity of chemicals in surgical smoke make it challenging to conduct a complete biomarker examination.[3]

The comprehensive examination of all potential biomarkers associated with surgical smoke exposure is constrained by several practical and methodological

Table 1. Comparison of studies on surgical smoke exposure.

Study Focus	Subject	Chemical Analyzed	Method	Key Findings	Ref
Occupational Exposure of operating room staff (surgeons, nurses, assistants).	Surgeons, scrub assistants, circulating nurses (n=15).	VOCs: Benzene, Toluene, Styrene, Ethylbenzene. PAHs: Naphthalene.	- Air Sampling & Urinary Biomonitoring. - Measured urinary metabolites (e.g., SPMA for benzene, o-cresol for toluene).	- Airborne chemical levels were below occupational limits. - Urinary o-cresol (toluene metabolite) was elevated, exceeding guidance levels	[6]
Occupational Exposure of operating room staff (including administrative personnel).	Administrative staff, surgical nurses, nurse anesthetists, surgeons (n=160).	VOCs: Toluene, Xylene.	- Urinary Biomonitoring only. Measured urinary metabolites (Hippuric Acid for toluene, Methyl Hippuric Acid for xylene).	- Administrative staff had the highest toluene exposure (via Hippuric Acid). - Surgical nurses had the highest xylene exposure (via Methyl Hippuric Acid). - All levels were below occupational limits.	[4]
Patient Exposure during laparoscopic cholecystectomy.	Patients undergoing laparoscopic surgery.	VOCs: Benzene, Toluene, Ethylbenzene, Xylene, Dioxins.	- Smoke Analysis & Urinary Biomonitoring. - Analyzed smoke composition and measured parent compounds (benzene, toluene) in urine.	- Patients absorbed smoke chemicals. - Post-operative urinary benzene and toluene increased significantly compared to pre-operative levels.	[5]

challenges. From an analytical perspective, the currently available laboratory techniques may not be capable of identifying or accurately quantifying the full spectrum of chemical constituents contained within surgical smoke. In addition, conducting a complete biomarker assessment requires substantial time and financial resources, making it less feasible for routine surveillance or large-scale occupational monitoring. Moreover, the technical capacity of diagnostic facilities varies, and not all laboratories possess the specialized equipment, validated methods, or trained personnel needed to process and analyze every possible biomarker, further limiting the practicality of a broad analytical approach.[4,8]

Instead, the focus is often on identifying and quantifying the most hazardous and abundant chemicals that pose significant health risks. By prioritizing the most relevant biomarkers, researchers and healthcare professionals can effectively monitor and mitigate the risks associated with surgical smoke exposure.[17]

The selection of biomarkers to assess surgical smoke exposure must be based on quantitative analysis of air samples from the surgical environment. This approach allows identification of the most abundant chemicals in surgical smoke, which can vary depending on the type of surgery and instruments used. Therefore, identifying the most prevalent compounds through air sampling is crucial for determining the appropriate biomarkers to monitor. The analysis of these biomarkers should be performed using noninvasive sampling techniques that do not interfere with the surgical process or the sterility of the environment. Moreover, it's essential to have standardized, quantitative, and validated analytical techniques available in the laboratory to ensure the reliability and accuracy of the results.[17,18]

The true health risks associated with surgical smoke depend on the extent to which its chemical components enter the body. These health risks are primarily influenced by the toxic properties of each individual chemical present in the smoke. Interactions between these chemicals may enhance (synergistic) or reduce (antagonistic) their toxic effects, thereby altering the impact of specific substances. Additionally, even low-level but continuous exposure to surgical smoke raises concerns due to the possibility of cumulative long-term effects. This suggests that the hazards posed by surgical smoke are relevant to anyone who spends time in an operating room.[2,17]

Some studies showed a predominance of a mixture of benzene, ethylbenzene, toluene and xylene in surgical smoke. Potential biomarker of surgical smoke exposure on the quantitative analysis of Volatile Organic Compounds through air sampling and urinary metabolites of benzene, ethylbenzene, toluene and xylene. The rationale for this selection is based on the availability of relevant associated biomarkers for a non-invasive sampling technique and the availability of a standardized, quantitative and validated analysis technique in the selected laboratory.[6]

It's also important to consider OSHA guidelines and other regulatory standards when selecting biomarkers, as these can provide thresholds for permissible exposure levels. By aligning the biomarker selection with these standards, healthcare facilities can better protect their staff from the potential health risks associated with surgical smoke exposure.[14,17]

Biological monitoring for benzene, toluene, ethylbenzene and xylene

Benzene, toluene, ethylbenzene, and BTEX are volatile organic compounds known to contribute to the development of various diseases, including cancer, upon human exposure. Biological monitoring is a critical component in assessing chemical exposure among workers, serving as a key element in managing and preventing adverse health outcomes. Effective exposure assessment is essential for the prevention of health risks related to chemical exposure and requires accurate metabolites and reliable analytical methods for their measurement in biological samples.18

To monitor exposure, air sampling in the breathing zones of workers can be conducted actively or passively. Active sampling utilizes a pump to draw air through a medium that captures the contaminants, while passive sampling employs badges or containers that collect chemicals through diffusion. Air monitoring helps determine the levels of contaminants inhaled by workers. However, to gain a comprehensive understanding of total exposure from all routes, biological monitoring should complement air sampling. The outcomes of biological monitoring are typically compared with Biological Exposure Indices (BEIs).[18]

Biological monitoring, alongside environmental monitoring and health surveillance, plays a vital role in preventing diseases associated with toxic agents in occupational and general environments. It assesses workers' exposure levels and related health risks by measuring the concentration of a chemical, its metabolites, or specific reversible biochemical changes in biological samples such as urine, blood, or exhaled air. This method reflects the total uptake of chemicals by individuals. The American Conference of Governmental Industrial Hygienists (ACGIH) has established reference guidelines through threshold limit values (TLVs) and BEIs, indicating the levels of biomarkers likely to be found in healthy workers exposed at the TLV-TWA. Typically, BEIs represent concentrations below which most workers should not experience adverse health effects.[17,18]

Toxicokinetic of BTEX

Absorption

Although benzene may enter the body through ingestion or, to a lesser degree, dermal contact, inhalation remains the dominant route of exposure. The compound is rapidly taken up through the lungs, reaching peak absorption of approximately 70–80% within the first few minutes, after which uptake declines quickly. Studies show that pulmonary absorption rates for benzene range between 47–52%, depending on exposure intensity. Toluene is likewise absorbed rapidly following inhalation and can be detected in the bloodstream within 10–15 minutes, whereas uptake from oral or dermal exposure occurs much more slowly. Moreover, inhaled toluene absorption increases during physical exertion compared with rest. Ethylbenzene shares a similar toxicokinetic pattern, demonstrating rapid respiratory absorption. For xylene, inhalation and ingestion serve as the main absorption pathways, with roughly 60% of inhaled xylene being retained and nearly 90% of ingested xylene absorbed, while skin absorption is relatively low.[18,19]

Distribution

Once absorbed into the bloodstream, benzene is distributed systemically and preferentially accumulates in adipose tissue due to its lipophilic characteristics. Among individuals exposed via inhalation, benzene has been detected in multiple organs and biological matrices, including blood, brain, liver, kidneys, stomach, bile, adipose tissue, and urine. Furthermore, evidence shows that benzene is capable of crossing the placental barrier, with concentrations in umbilical cord blood reported to be equivalent to or even higher than those measured in maternal circulation. Studies in both humans and experimental models have demonstrated a positive correlation between toluene levels in alveolar air and in blood. Data from in vitro and in vivo studies show that toluene distributes between plasma and red blood cells at ratios of approximately 1:1 and 1:2, respectively. Once absorbed, toluene tends to accumulate in lipid-rich and well-perfused tissues, including the brain, liver, and lungs.[18,19]

The retention of ethylbenzene in adipose tissue is estimated to be 5% of the total uptake. However, some studies suggest that the partitioning of ethylbenzene from air into adipose tissue in humans is similar to that observed in rats.[12] Following absorption, xylene is rapidly dispersed through systemic circulation, and all isomeric forms show comparable tissue distribution. Within the blood, xylene largely associates with serum proteins, while adipose tissue represents the primary reservoir, retaining approximately 4% to 10% of the absorbed amount. Experimental findings demonstrate that m-xylene and p-xylene, along with their metabolites, are mainly detected in lipid-rich tissues such as adipose tissue and the brain, as well as in highly vascularized organs including the liver and kidneys.[18,20]

Biotransformation

Benzene

Benzene is chiefly cleared from the body via renal elimination of its metabolites, with a smaller fraction removed through pulmonary exhalation in its unmetabolized form. Only trace quantities of unchanged benzene are detectable in urine. Its metabolic fate is concentration-dependent: at low exposure levels, benzene undergoes efficient biotransformation and is predominantly excreted in urine as conjugated metabolites, whereas at higher doses, metabolic pathways may become saturated, leading to a greater proportion of unaltered benzene being expelled through respiration.[18,19]

Benzene undergoes biotransformation through several metabolic routes. In the initial phase, cytochrome P-450 2E1 (CYP2E1) catalyzes its oxidation to benzene oxide. The major downstream product of this reaction is phenol, which can be further oxidized by CYP2E1 to yield catechol and hydroquinone. These metabolites may subsequently be converted by myeloperoxidase, producing 1,2-benzoquinone from catechol and 1,4-benzoquinone from hydroquinone, and can also be further oxidized by CYP2E1 to form 1,2,4-benzenetriol. Phenolic metabolites (phenol, catechol, hydroquinone, and 1,2,4-benzenetriol) are then subjected to phase II conjugation with sulfate or glucuronic acid. In addition, benzene oxide may follow two alternative pathways: conjugation with glutathione (GSH) leading to the formation of S-phenyl mercapturic acid (PMA), or iron-mediated ring cleavage resulting in the production of trans,trans-muconic acid (tt-MA).[18,20]

Both trans,trans-muconic acid (tt-MA) and S-phenyl mercapturic acid (PMA) are recognized as sensitive and valid biomarkers for monitoring benzene exposure. At lower airborne benzene concentrations (8-hour TWA below 0.3 ppm), PMA is considered a more reliable marker due to its higher specificity. Additionally, PMA's longer elimination half-life makes it a preferable biomarker for non-standard work schedules, such as 12-hour shifts. Conversely, at higher benzene concentrations (8-hour TWA above 1 ppm), tt-MA is also reliable and may be favored because it is easier to measure than PMA. The ACGIH has recommended using both tt-MA and PMA as biomarkers for occupational benzene exposure, with Biological Exposure Indices (BEIs) set at 500 μg/g creatinine for tt-MA and 25 μg/g creatinine for PMA. Furthermore, measuring benzene levels in exhaled breath and blood provides additional reliable indicators of benzene exposure. Urinary benzene and urinary 8-hydroxydeoxyguanosine (8-OHdG) are also utilized to detect early genotoxic effects associated with environmental benzene exposure.[18,21]

Toluene

The metabolism of toluene begins with cytochrome P450 (CYP)-mediated methyl group and ring hydroxylation. In human liver microsomes, the primary pathway involves methyl hydroxylation, leading to the formation of benzyl alcohol as the main initial metabolite. In contrast, ring hydroxylation, which produces ortho- and para-cresols (o-cresol and p-cresol), contributes to less than 5% of the total metabolites formed. Among the CYP isozymes, CYP2E1 plays a major role in the production of benzyl alcohol, while CYP1A2 and CYP2E1 are involved in the formation of o- and p-cresols.[18]

The enzymes involved in toluene metabolism vary depending on the level of exposure. At lower exposure levels, CYP2E1 primarily facilitates the formation of benzyl alcohol and p-cresol, while CYP1A1/2 contributes to the production of o- and p-cresols. In contrast, at higher toluene concentrations, CYP2B1 and CYP2C11/6 are involved in generating benzyl alcohol and o- and p-cresols. Benzyl alcohol undergoes further metabolism through sequential oxidation by alcohol dehydrogenase and aldehyde dehydrogenase to form benzoic acid. This benzoic acid can then conjugate with glycine, a process catalyzed by acyl-CoA synthetase and acyl-CoA: amino acid N-acyltransferase, to produce hippuric acid (HA), which accounts for approximately 83–94% of the urinary toluene metabolites in rats. Additionally, benzoic acid may conjugate with glucuronic acid to form benzoyl glucuronide, contributing to about 3–9% of urinary metabolites. Overall, HA is recognized as the primary urinary metabolite of toluene.[18]

The level of o-cresol levels in urine correlate well with airborne toluene concentrations, the variability of creatinine-corrected o-cresol measurements is higher compared to urinary toluene, and o-cresol levels are also more influenced by smoking habits. The study concluded that urinary toluene serves as a valuable alternative to o-cresol and may be considered the preferred biomarker for assessing toluene exposure. The ACGIH recommends using toluene levels in blood (0.02 mg/L) and urine (0.03 mg/L), along with urinary o-cresol (0.3 mg/g creatinine), as indicators for monitoring occupational exposure to toluene.[18]

Ethylbenzene

The metabolism of ethylbenzene involves hydroxylation facilitated by liver microsomal enzymes, with CYP2E1 and CYP2B6 playing key roles in this initial step. These enzymes hydroxylate the ethyl side chain of ethylbenzene to produce 1-phenylethanol, which can be directly excreted in the urine, primarily as glucuronide conjugates, or further oxidized to acetophenone. Both 1-phenylethanol and acetophenone may appear in urine as minor metabolites or undergo additional metabolic transformations. Through further oxidation, they can form 2-hydroxyacetophenone, 1-phenyl-1,2-ethanediol, mandelic acid (MA), and phenylglyoxylic acid (PGA). In individuals exposed to ethylbenzene through inhalation, MA and PGA are the predominant urinary metabolites, accounting for approximately 70% and 25% of metabolites, respectively. However, following dermal exposure, only about 4.6% of absorbed ethylbenzene is excreted as MA. The ACGIH has recommended using the combined urinary levels of MA and PGA (0.15 g/g creatinine) as an indicator for monitoring occupational exposure to ethylbenzene.[18]

Xylene

Xylene metabolism involves hydroxylation by liver microsomal enzymes (mixed-function oxidases). The primary metabolic pathway includes the oxidation of the methyl side chain of xylene to produce methyl benzoic acids, which subsequently conjugate with glycine to form methyl hippuric acids (MHA). This pathway accounts for nearly the entire absorbed dose of xylene. A secondary pathway, responsible for less than 10% of the absorbed dose, involves the excretion of unchanged xylene in exhaled air and urine, as well as further metabolism to produce methylbenzyl alcohols, o-toluic acid glucuronide, xylene mercapturic acid, and dimethylphenols. The ACGIH has recommended measuring MHA levels in end-of-shift urine samples (1.5 g/g creatinine) as a marker for monitoring occupational exposure to xylene.[18]

Excretion

For unmetabolized BTEX compounds, pulmonary excretion represents the principal elimination pathway. Evidence indicates that approximately 16.4–41.6% of absorbed benzene is eliminated via exhalation, with no significant sex-related variation, and the greatest proportion expelled within the first hour post-exposure. In addition, benzene undergoes biotransformation in humans to phenol and trans,trans-muconic acid (tt-MA), which are subsequently excreted in urine mainly as sulfate- and glucuronide-conjugated metabolites.[18,22]

After short-term inhalation exposure, toluene is predominantly eliminated via urine in the form of metabolites, while a smaller fraction (around 7–20% of the absorbed dose) is excreted unchanged through respiration and, to a lesser degree, urine. Most inhaled toluene is cleared relatively quickly, whereas the portion sequestered in adipose tissue is released more gradually. Although the renal excretion of unmetabolized toluene represents a minor elimination pathway, its kinetic profile still supports its relevance for biological monitoring in occupational settings. In previous controlled study, male volunteers exposed to 50 ppm of deuterated toluene ($^2H_8$-toluene) for two hours exhaled approximately 13% of the retained dose as unmetabolized $^2H_8$-toluene, while urinary metabolites were quantified as 75% $^2H_5$-hippuric acid, 0.31% ^{2}H7-o-cresol, 0.53% $^2H_7$-m-cresol, and 11% $^2H_7$-p-cresol.[18,23]

Ethylbenzene is rapidly metabolized in the body, with the majority of the absorbed compound eliminated as urinary metabolites. Exhalation represents an additional clearance pathway and follows a multiphasic pattern, beginning with a fast elimination phase with a half-life of less than one hour, which is substantially shorter than that of its urinary metabolites. Among these, mandelic acid (MA) and phenylglyoxylic acid (PGA) are excreted with estimated half-lives of roughly 3–5 hours and 10–12 hours, respectively. The elimination profile of MA exhibits two phases, comprising an initial rapid phase with a half-life of approximately 3.1 hours followed by a slower terminal phase with a half-life of about 25 hours. In exposed individuals, peak urinary excretion of metabolites is typically observed between 6 and 10 hours after exposure.[18,23]

In humans, around 95% of absorbed xylene is metabolized and excreted as urinary metabolites, predominantly as MHA, while about 5% is expelled unchanged via exhalation. The excretion of MHA is rapid, with most being detectable in urine within two hours after exposure, and the excretion rate continues to rise with time. Of the total absorbed xylene isomers, only about 0.005% is excreted unchanged in urine, and around 2% is excreted as xylenols. The elimination of MHA also follows biphasic kinetics, with half-lives of approximately one hour for the rapid phase and 20 hours for the slower phase. Physical activity can enhance xylene absorption, thereby increasing the urinary excretion of m-MHA and 2,4-xylenol.[18,23]

Strategies to Protect Healthcare Workers from Surgical Smoke Exposure

Surgical masks, N95 masks and masks containing activated carbon

Surgical masks are the most commonly used protective equipment among healthcare workers during daily procedures. They offer a degree of protection by blocking droplets, splashes of bodily fluids, and larger dust particles. However, these masks are not capable of fully protecting medical personnel from all hazardous components present in surgical smoke, as they can only filter particles with diameters larger than 5 micrometers. Their filtration efficiency significantly decreases for particles smaller than 5 micrometers, which include various pathogens and VOCs. Consequently, surgical masks do not provide sufficient protection against these smaller particles found in surgical smoke.[2,13]

N95 masks are approved by NIOSH in the United States, with a filtration efficiency exceeding 95% for particles with aerodynamic diameters of 0.075 ± 0.020 micrometers. Given that the average particle size in surgical smoke from electrocautery procedures is around 0.07 micrometers, N95 masks provide superior protection against surgical smoke compared to standard surgical masks. The use of high-filtration masks like N95 respirators is therefore recommended. Additionally, the fit of the mask to the wearer's face significantly impacts its protective effectiveness. This is an advantage of N95 masks, as they are designed to form a better seal on the face. Healthcare workers should check the fit of their N95 masks to ensure proper use, as the escape of exhaled air around the mask indicates an inadequate seal. If this occurs, the mask should be adjusted immediately to maintain airtightness. It is also advisable to use devices to monitor airborne particle levels in the environment and within the respirator before healthcare workers enter their work areas.[2,7]

Experimental evidence demonstrates that activated carbon has a strong adsorption capacity for VOCs, leading to a reduction in their levels within surgical smoke. Consequently, respiratory protective masks incorporating activated carbon filtration components may decrease VOC uptake through inhalation and offer an additional protective measure for healthcare personnel.[2,24]

Smoke evacuation devices

Another key protective measure involves the use of smoke evacuation systems. In clinical settings, suction devices are commonly operated by surgical assistants to remove smoke generated during procedures. For optimal effectiveness, the suction tip must be maintained at a distance of no more than 5 centimeters from the emission point, with an airflow velocity of approximately 31–46 meters per minute. The orientation of the device is also important, as a 45-degree angle maximizes smoke capture efficiency. Nonetheless, maintaining the ideal positioning may be challenging in practice, as it can interfere with the surgeon's visual field when coordination is insufficient.[16,25]

During laparoscopic procedures, evacuating smoke via the trocar using an aspirating device can cause a rapid drop in pneumoperitoneal pressure, subsequently reducing the available intra-abdominal working space and potentially disrupting surgical performance. Furthermore, when the trocar is withdrawn at the end of the operation, the concentrated surgical smoke that has accumulated inside the abdominal cavity may be released directly into the operating room environment. This concern can be mitigated by utilizing disposable trocars integrated with filtration systems, which may help limit the emission of hazardous compounds such as benzene, toluene, and butyraldehyde into the surroundings.[25,26,27]

Most portable smoke evacuation units are equipped with either high-efficiency particulate air (HEPA) or ultralow particulate air (ULPA) filtration systems. HEPA filters can trap approximately 99.7% of particles larger than 0.3 µm, while ULPA filters are designed to remove at least 99.999% of airborne particles exceeding 0.12 µm in diameter. These filtration mechanisms are intended to prevent the recirculation of hazardous particulate matter from surgical smoke into the operating room atmosphere. It should also be noted that the overall performance of smoke extraction is affected by both the orientation of the suction device and the airflow velocity. Optimal capture efficiency has been reported when surgical cutting occurs at a 45-degree angle and the suction device operates at a flow rate of approximately 10,500 m^3/h.[16,25,26]

Proper implementation of portable smoke evacuation systems has been shown to efficiently remove surgical plume and is therefore advised for routine clinical use. Nevertheless, their broader utilization remains limited in practice, primarily due to concerns regarding operational noise. Experimental findings indicate that evacuation systems designed to clear smoke while simultaneously maintaining stable CO_2 insufflation pressures offer advantages during gastrointestinal endoscopy procedures. These observations imply that similar technology could be beneficial in laparoscopic surgery, enabling effective smoke removal without compromising pneumoperitoneal pressure.[24,26,28]

Several commercial developers have introduced integrated systems that incorporate disposable smoke evacuation tubing directly into electrosurgical instruments. This configuration enables the evacuation mechanism to maintain an ideal proximity to the operative field without the need for continuous manual positioning by an assistant. Consequently, it can decrease procedural workload and operational burden while promoting a more efficient surgical workflow.[26,29]

A circulating pneumoperitoneum system has been developed for laparoscopic surgery that enables filtration and recirculation of intraperitoneal gases, thereby facilitating smoke clearance while maintaining consistent intra-abdominal pressure. Despite its technical advantages, its application in routine clinical practice remains limited. In addition, certain surgical groups have proposed low-cost techniques using underwater-seal evacuation systems equipped with filters to remove smoke, although these methods still require further clinical evaluation to confirm safety and effectiveness. Beyond the use of engineering controls and protective devices, it is also possible for surgeons to implement basic behavioral strategies to reduce exposure. For instance, during open procedures where smoke extraction is less effective, surgeons and scrub assistants may avert their faces from the plume source to avoid direct inhalation of concentrated smoke, thereby reducing potential exposure risk.[29,30]

Operating Room Ventilation

During surgical procedures, some surgical smoke inevitably escapes into the operating room environment. Research has indicated that during laparoscopic surgeries, smoke can leak through gaps between instruments and the trocar, contributing to low levels of surgical smoke in the operating room air. Ensuring effective ventilation within the operating room is essential to minimize the accumulation of smoke in the environment. Utilizing positive pressure ventilation in the operating room can help direct airborne particles, including potentially infectious agents, away from the surgical area, thereby maintaining cleaner air conditions during procedures.[2,29]

In addition, an interesting study investigating the difference between different types of ventilation in the operating room showed that hybrid ventilation provides more effective protection than upward displacement ventilation. Hybrid ventilation results in a 10-50-fold reduction in colony forming units (CFUs) in the protected area close to the patient's wound. Thus, having an effective ventilation system in the operating room is essential.[2,29]

Enhancing the awareness of protection

The protective strategies outlined above are intended to minimize the potential health risks of surgical smoke exposure among healthcare workers. However, in clinical practice, protection against surgical smoke is often not prioritized, and most medical personnel do not routinely use high-efficiency filtration masks such as N95 respirators. This gap between recommended measures and actual practice underscores the urgent need for structured training programs to improve awareness, risk perception, and understanding of effective protective strategies against surgical smoke exposure.[2]

Surgical smoke is generated during tissue dissection, coagulation, or ablation using electrosurgical, laser, or other energy-based instruments. Although approximately 95% of the plume consists of water vapor, the remaining fraction contains hazardous components, including ultrafine particulate matter, VOCs, PAHs, biological cells, and viral particles.[1,2] The quantity and composition of surgical smoke vary depending on the type of device used, power settings, tissue characteristics, and operator technique, resulting in heterogeneous occupational exposure among operating room personnel.[1,3,8] Continuous exposure over the course of a medical career, combined with other occupational carcinogenic risks, raises concerns regarding long-term respiratory, cardiovascular, and oncologic outcomes.[3] Evidence indicates that PM2.5 and ultrafine particles present in surgical smoke are associated with airway irritation, chronic inflammation, and oxidative injury,[2,14,15] and may also facilitate viral transmission, including HPV and HBV.[2]

Evidence of internal exposure has been demonstrated across three reviewed studies through the detection of urinary metabolites derived from VOC exposure among healthcare workers.[4,5,6] Although measured concentrations were generally below established occupational biological exposure indices (BEIs), elevated levels of O-cresol particularly among surgical nurses and assistants-suggest the presence of cumulative and role-dependent exposure.[6] These findings highlight that repeated low-dose exposure may still contribute to clinically meaningful long-term health risks, emphasizing the need for prospective biomonitoring and improved exposure-control strategies in operating room environments.

Urinary metabolites derived from BTEX compounds, including S-phenyl mercapturic acid, O-cresol, mandelic acid, and methyl hippuric acids, are considered suitable biomarkers due to their well-characterized toxicokinetic profiles, biological specificity, and feasibility for non-invasive monitoring.[14,18] In contrast, urinary formaldehyde is not recommended as a biomarker because of its very short biological half-life, significant environmental confounding, and limited specificity for surgical smoke exposure.[14] Consequently, urinary BTEX metabolites currently represent the most practical and reliable indicators for assessing internal chemical exposure related to surgical smoke in occupational settings.

From a toxicokinetic perspective, S-PMA is a highly specific and sensitive biomarker for benzene exposure, particularly at low concentrations, and is superior to t,t-muconic acid in irregular work schedules due to its longer elimination half-life.[14,18] Hippuric acid and O-cresol are established biomarkers for toluene exposure, with O-cresol being more appropriate in low-dose environments such as operating rooms.[6,14,18] Mandelic acid serves as a reliable biomarker for ethylbenzene exposure, demonstrating dose-dependent elimination kinetics, while o-, m-, and p-methyl hippuric acids reflect exposure to corresponding xylene isomers and enable integrated exposure assessment when specific sources cannot be distinguished.[4,14,18] Collectively, these biomarkers support occupational surveillance efforts aimed at protecting healthcare workers in surgical settings.

Preventive strategies to mitigate the risks associated with surgical smoke exposure include the consistent use of high-efficiency smoke evacuation systems, maintenance of adequate operating room ventilation, and the use of fit-tested N95 or equivalent respiratory protection when smoke evacuation is insufficient or unavailable.[2,24,25,26] These engineering controls should be reinforced by administrative measures such as mandatory training programs, standardized operating procedures, and regular hazard communication to ensure comprehensive and sustained protection for healthcare workers.[2]

Conclusion

Findings from the three included studies indicate that surgical smoke consistently contains a mixed profile of benzene, toluene, ethylbenzene, and BTEX, suggesting these volatile organic compounds as common and relevant exposure constituents. Accordingly, S-PMA, urinary O-cresol, urinary mandelic acid, and urinary o-, m-, and p-methyl hippuric acids represent feasible biomarker options for evaluating internal exposure due to their specificity, suitability for non-invasive sampling, and established analytical availability. Exposure to surgical smoke may contribute to adverse health effects, including asthma, chronic obstructive pulmonary disease, cardiovascular diseases, and lung cancer, particularly following repeated or cumulative exposure. Therefore, preventive efforts should prioritize the use of N95 respirators, smoke evacuation systems, adequate operating room ventilation and filtration, and continuous education for operating room personnel regarding the occupational hazards associated with surgical smoke.

Authors' Contribution

SS was responsible for conceptualization of the review, methodology design, literature search, data curation, formal analysis and writing original draft. MI and BP contributed to writing review and editing by providing critical intellectual revisions and ensuring methodological accuracy. MI and BP also provided supervision throughout the development of the manuscript. All authors approved the final version of the manuscript prior to submission.

Conflict of Interest

The authors declare no competing interests.

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