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Nada O F Kassem
San Diego State University

Robert M. Strongin
Portland State University

Andrea M. Stroup
Behavioral Health and Health Policy Practice

Marielle C. Brinkman
The Ohio State University

Ahmad El-Hellani
The Ohio State University

See next page for additional authors

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Authors

Nada O F Kassem, Robert M. Strongin, Andrea M. Stroup, Marielle C. Brinkman, Ahmad El-Hellani, Hanno C. Erythropel, Arash Etemadi, Maciej L. Goniewicz, Eleanore G. Hansen, Noura O. Kassem, and multiple additional authors

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Running head: Toxicity of Waterpipe Tobacco Smoking

Nada O.F. Kassem DrPH[1]*, Robert M. Strongin PhD[2], Andrea M. Stroup PhD[3], Marielle C. Brinkman BS[4], Ahmad El-Hellani PhD[5], Hanno C. Erythropel PhD[6], Arash Etemadi MD, PhD[7], Maciej L. Goniewicz PhD[8], Eleanore G. Hansen MS[9], Noura O. Kassem MPH[1], Dongmei Li PhD[10], Sandy Liles MPH[1], Alexandra Noël PhD[11], Mary Rezk-Hanna PhD[11], Qixin Wang PhD[12], Irfan Rahman PhD[13]

[1] Nada O.F. Kassem
Health Promotion and Behavioral Science, San Diego State University, San Diego, CA 92182, U.S.
Hookah Tobacco Research Center, San Diego State University Research Foundation, San Diego, CA 92123, U.S.
[2] Robert M. Strongin, Department of Chemistry, Portland State University, Portland, OR 97207-0751, U.S.
[3] Andrea M. Stroup, Behavioral Health and Health Policy Practice, Westat, Rockville, MD 20850, U.S.
[4] Marielle C. Brinkman,
College of Public Health, The Ohio State University, Columbus, OH 43210, U.S.
Center for Tobacco Research, The Ohio State University Comprehensive Cancer Center, Columbus, OH 43214, U.S.
[5] Ahmad El-Hellani
Division of Environmental Health Sciences, College of Public Health, The Ohio State University, Columbus, OH 43210, U.S.
Center for Tobacco Research, The Ohio State University Comprehensive Cancer Center, Columbus, OH 43214, U.S.
[6] Hanno C. Erythropel
Department of Chemical and Environmental Engineering, Yale University, New Haven, CT 06511, U.S.
Yale Center for the Study of Tobacco Products (YCSTP), Department of Psychiatry, Yale School of Medicine, New Haven, CT 06511, U.S.
[7] Arash Etemadi, Metabolic Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, NIH, Bethesda, MD 20892, U.S.
[8] Maciej L. Goniewicz, Department of Health Behavior, Roswell Park Comprehensive Cancer Center, Buffalo, NY 14263, U.S.
[9] Eleanore G. Hansen, Division of Environmental Health Science, School of Public Health, University of Minnesota, Minneapolis, MN 55455, U.S.
[1] Noura O. Kassem, Hookah Tobacco Research Center, San Diego State University Research Foundation, San Diego, CA 92123, U.S.
[10] Dongmei Li, Department of Clinical and Translational Research, Obstetrics and Gynecology, Public Health Sciences, University of Rochester Medical Center, Rochester, NY 14642, U.S.

[1] Sandy Liles, Hookah Tobacco Research Center, San Diego State University Research Foundation, San Diego, CA 92123, U.S.
[11] Alexandra Noël, Department of Comparative Biomedical Sciences, School of Veterinary Medicine, Louisiana State University, Baton Rouge, LA, 70803, U.S.
[11] Mary Rezk-Hanna, School of Nursing, University of California, Los Angeles, Los Angeles, CA 90095, U.S.
[12] Qixin Wang, Ragon Institute of Mass General, MIT, and Harvard, Cambridge, MA, USA, 02139, U.S.
[13] Irfan Rahman, Department of Environmental Medicine, University of Rochester Medical Center, Rochester, NY 14642, U.S.

* *Corresponding author:*
Nada O.F. Kassem
Director and Founder of the Hookah Tobacco Research Center
San Diego State University Research Foundation
9245 Sky Park Court, Suite 250, San Diego, CA 92123
nkassem@sdsu.edu
Cell: 858-422-7814

ORCID IDs
Nada O.F. Kassem https://orcid.org/0000-0002-5403-7234

Robert M. Strongin https://orcid.org/0000-0003-3777-8492

Andrea M. Stroup https://orcid.org/0000-0003-2895-460X

Marielle C. Brinkman https://orcid.org/0000-0002-4315-649X

Ahmad El-Hellani https://orcid.org/0000-0002-1047-0597

Hanno C. Erythropel https://orcid.org/0000-0003-3443-9794

Arash Etemadi https://orcid.org/0000-0002-3458-1072

Maciej L. Goniewicz https://orcid.org/0000-0001-6748-3068

Eleanore G. Hansen https://orcid.org/0000-0002-6606-2912

Noura O. Kassem https://orcid.org/0009-0000-5702-7624

Dongmei Li https://orcid.org/0000-0001-9140-2483

Sandy Liles https://orcid.org/0000-0003-3240-7799

Alexandra Noël https://orcid.org/0000-0001-5634-8151

Mary Rezk-Hanna https://orcid.org/0000-0001-9926-5276

Qixin Wang https://orcid.org/0000-0001-9051-8388

Irfan Rahman https://orcid.org/0000-0003-2274-2454

ABSTRACT

Waterpipe tobacco (WPT) smoking is a public health concern, particularly among youth and young adults. The global spread of WPT use has surged since the introduction of pre-packaged flavored and sweetened WPT, which is widely marketed as a safer tobacco alternative. Besides flavorants and sugars, WPT additives include humectants, which enhance the moisture and sweetness of WPT, act as solvents for flavors, and impart smoothness to the smoke, thus increasing appeal to users. In the United States (U.S.), unlike cigarette tobacco flavoring (with the exception of menthol), there is no FDA product standard or policy in place prohibiting sales of flavored WPT. Research has shown that the numerous fruit, candy, and alcohol flavors added to WPT entice individuals to experience those flavors, putting them at an increased risk of exposure to WPT smoke-related toxicants. Additionally, burning charcoal briquettes—used as a heating source for WPT—contributes to the harmful health effects of WPT smoking. This review presents existing evidence on the potential toxicity resulting from humectants, sugars, and flavorants in WPT, and from the charcoal used to heat WPT. The review discusses relevant studies of inhalation toxicity in animal models and of biomarkers of exposure in humans. Current evidence suggests that more data are needed on toxicant emissions in WPT smoke to inform effective tobacco regulation to mitigate the adverse impact of WPT use on human health.

Keywords: Waterpipe, hookah, flavorants, humectants, sugars, charcoal

1. Introduction

Waterpipe tobacco (WPT) smoking is a centuries-old tobacco use method in which burning charcoal heats tobacco, producing smoke that passes through a water-filled bowl before reaching the user's mouth, lungs, and circulatory system [Figure 1 (Rezk-Hanna & Benowitz, 2019)]. The use of a waterpipe, also known as hookah, shisha, and narghile, to smoke tobacco has become increasingly popular worldwide, particularly among youth and young adults in several eastern Mediterranean, eastern European, and Western countries, including the United States (U.S.) (Jawad et al., 2018; Zheng et al., 2022). Nationally representative data from the Population Assessment of Tobacco and Health (PATH) Study from 2013-2018 indicated that among U.S. adolescents (12–17 years) and young adults (18-24 years), 4.8% and 18.5% of individuals who never-used WPT initiated WPT use during that period, respectively, and 10.6% and 14.1% of individuals who ever-used WPT increased the frequency of WPT use during the same period, respectively (Gautam et al., 2022).

There are many adverse health consequences associated with WPT use, including lung and esophageal cancer, and diminished parameters of cardiopulmonary and cardiovascular function (Al Ali et al., 2020; Hassane et al., 2022; Mahfooz et al., 2023; Montazeri et al., 2017; Qasim et al., 2019; Raad et al., 2011). Nevertheless, there continues to be broad social acceptance of use in the U.S. and worldwide due in part to misinformation about the associated risks (Cobb et al., 2010). WPT is often perceived as safe or a safer alternative to other combustible tobacco products, and this perception may lead to initiation and continued use of WPT (Kuk et al., 2022). For example, data from Wave 1 of the PATH Study (2013-2014) showed that U.S. adolescents (12-17 years) who perceived WPT to be neither harmful nor addictive were 173% more likely to initiate WPT ever use, and 166% more likely to first report past 30-day use, compared to their counterparts who considered WPT to be both harmful and addictive (Kuk et al., 2022). Common misbeliefs about WPT use that may encourage initiation and continued use include: (1) WPT smoking is less addictive than cigarettes, (Elton-Marshall et al., 2020) thus misguiding users about their ability to quit WPT use; (2) water through which the smoke passes “filters out” toxicants, resulting in the misperception that WPT is a safer product (Cobb et al., 2010); and (3) WPT use is a social activity not typically occurring on a daily or frequent basis, leading users to assume that intermittent use is safe despite the substantial exposure levels of smoke toxicants (Cobb et al., 2010). This lack of perceived harm has enhanced the social acceptance of WPT use (Cobb et al., 2010).

The growing popularity of WPT use has been attributed to several factors: (1) the introduction of flavored and sweetened WPT providing pleasant, smooth smoke; (2) the availability of WPT in numerous desirable aromatic flavors, including fruit, candy and alcohol flavors; (3) increased accessibility to WPT through sales in convenience stores, tobacco retailers, and online; (4) unregulated advertisements and marketing claims fueling misperceptions of reduced harm compared to cigarette use; (5) flourishing of WPT discussions on social media platforms; and (6) rapid emergence and proliferation of hookah lounges/cafes in close proximity to colleges providing patrons a social setting with food, drinks, and entertainment, or a place to study with friends while smoking and sharing a waterpipe (Kassem et al., 2015; Kassem et al., 2019; Ma et al., 2022; Maziak, 2010, 2011; Maziak, Ward, et al., 2004).

WPT is available in three forms: (1) unflavored tobacco (known as Ajami, Isfahani or Tumbak/Tombak), which consists of dry tobacco leaves; (2) unflavored sweetened tobacco (known as ma’assel), which consists of tobacco leaves infused with honey, molasses, and other sweet syrups; and (3) flavored and sweetened tobacco (also known as flavored ma’assel), which consists of tobacco leaves infused with honey, molasses, and other sweet syrups and a variety of flavoring agents. This review focuses on flavored and sweetened waterpipe tobacco, also referred to hereafter as *flavored waterpipe tobacco, waterpipe tobacco,* or *WPT*.

This review examines the following aspects of flavored and sweetened WPT: Toxicity of WPT smoke in animal models, nicotine intake and biomarkers of exposure in humans, biomarkers of secondhand smoke exposure, and toxicity resulting from humectants, sugars, flavorants, and charcoal. We conclude with a review of WPT regulations in the U.S. and provide suggestions for future research that could be leveraged to help mitigate the adverse impacts of WPT use on public health.

2. Toxicity of WPT Smoke

a. Toxicity of WPT Smoke in Animal Models

Acute and chronic animal exposure to WPT smoke has been shown to induce lung inflammation and injury (*Table 1*). For example, in mice, WPT smoke exposure elevated oxidative stress and inflammatory responses in the lungs with increased recruitment of leukocytes and respective cytokines (Khabour et al., 2018; Nemmar et al., 2013). WPT smoke exposure resulted in increased expression of matrix metalloproteinases, MMP9 and MMP12, in the lungs of mice, indicating potential chronic lung injury, inflammatory responses, and extracellular matrix (ECM) remodeling (Greenlee et al., 2007; Khabour et al., 2015). WPT smoke exposure can result in a dysregulation of the circadian clock gene profile in the lungs, which has been associated with multiple chronic lung diseases (Khan et al., 2019). Daily exposure to WPT smoke for 2 months showed severe DNA damage in the lungs, kidneys, bone marrow, and liver of mice (Abi-Gerges et al., 2020). Prenatal exposure to WPT smoke has been shown to increase asthmatic risk in offspring of mice, elevate inflammation and oxidative stress in the lung and hippocampus, and potentially contribute to short- and long-term memory impairment in offspring rats (Al-Sawalha et al., 2018; Al-Sawalha et al., 2017). To gain a more complete toxicological profile of WPT use in animal models, future research should investigate different WPT products with carefully manipulated additives and smoking durations.

b. Biomarkers of Exposure to WPT Smoke

Although WPT is not directly burned, the temperature that WPT reaches during smoking (~150°C) can result in toxicant generation (Brinkman, Teferra, et al., 2020). Toxicants stem primarily from the thermal degradation of WPT constituents or from the heating source itself (e.g., charcoal), and include polycyclic aromatic hydrocarbons (PAHs), carbon monoxide (CO), and volatile organic compounds (VOCs) (Jacob et al., 2011; Kassem, Kassem, et al., 2014; Monzer et al., 2008; Olsson & Petersson, 2003). The uptake of these toxicants in the body is assessed by quantifying biomarkers of exposure similar to those measured from cigarette smoking. Biomarkers measured in people who smoke WPT include the metabolites of nicotine, tobacco-specific nitrosamines (TSNA), PAHs, and VOCs (Etemadi et al., 2023).

Levels of NNAL (4-(methylnitrosamino)-1-(3-pyridyl)-1-butanol), a metabolite of the carcinogenic nicotine-derived nitrosamine ketone (NNK), were higher in urine samples of participants who smoke WPT exclusively compared to participants who do not use any tobacco (Kassem et al., 2017). Another study found that children ≤ 5 years old living in homes of participants who exclusively smoked WPT daily had 37.3 times significantly higher levels of urinary NNAL than their counterparts living in homes of participants who did not smoke any tobacco (Kassem, Daffa, et al., 2014). However, TSNA emissions from WPT smoking and resulting NNAL biomarker levels were generally lower than those reported for cigarette smokers

(Jacob et al., 2013; Radwan et al., 2013). WPT smoking is associated with high urinary concentrations of hydroxy-PAH metabolites, especially those of high molecular weight PAHs (e.g., hydroxypyrene) (Jacob et al., 2013). Many VOC metabolites are also increased in the urine of people who smoke WPT, especially those of benzene (Kassem, Kassem, et al., 2014), which stems primarily from the use of charcoal (Olsson & Petersson, 2003). Using charcoal as the heating source for WPT increases users' exposure to benzene, PAHs, and CO (Monzer et al., 2008).

Other toxic compounds found in WPT smoke are the semivolatile furans (Brinkman, Teferra, et al., 2020), especially 5-(hydroxymethyl)-2-furaldehyde and 2-furaldehyde, which were present in WPT smoke at 3900 and 230 times higher levels, respectively, than in cigarette smoke (Brinkman, Teferra, et al., 2020). Some urinary furan metabolites were higher in participants who exclusively smoked WPT compared to participants who did not use any tobacco (Kassem et al., 2020).

Several studies have measured acute biomarkers of exposure in controlled experimental settings and natural settings such as homes and hookah lounges/bars. Irrespective of the timing of the most recent WPT use, people who smoke WPT had significantly higher concentrations of all of the biomarkers mentioned above (Etemadi et al., 2019). This indicates that people who smoke WPT are chronically exposed to many toxicants and carcinogens.

Moreover, biomarkers of harm, including inflammation, oxidative stress, immunity, tissue injury, and repair were elevated in people who smoke WPT (Khan et al., 2020). For example, plasma levels of biomarkers of oxidative stress and inflammation, such as IL-1β, IL-6, IL-8, and TNFα, were significantly higher in people who smoke WPT compared to people who do not smoke any tobacco, indicating elevated systemic inflammation response (Khan et al., 2020). Similarly, urinary biomarkers of oxidative stress and inflammation, such as 8-isoprostanes, MPO, RAGE, En-RAGE, and MMP-9, were also elevated in people who smoked WPT (Khan et al., 2020). Analyses of nationally representative data from Wave 1 of the PATH Study (2013-2014) showed that cardiovascular disease-related biomarkers of potential harm, including serum sICAM-1 and urinary F2-isoprostane, were lower among people who smoke WPT exclusively than people who smoke cigarettes exclusively (Rezk-Hanna, Adolfo, et al., 2023). However, these findings represent patterns of WPT smoking predominantly shared among U.S. adults who report non-daily intermittent use of WPT and do not reflect solitary, daily use (Rezk-Hanna, Adolfo, et al., 2023).

c. Nicotine Intake from WPT

Although many people who smoke WPT believe that WPT is not addictive (Maziak, Eissenberg, et al., 2004; Primack et al., 2008; Smith-Simone et al., 2008), emerging studies have shown that its use is associated with nicotine dependence (Aboaziza & Eissenberg, 2015). When people who smoke cigarettes and are nicotine-dependent smoke low-nicotine-yield cigarettes, they compensate by smoking more intensely (more frequent and larger volume puffing) to attain their accustomed level of nicotine intake (Benowitz, 2001). Similarly, compensation occurs among people experienced with smoking WPT when they smoke WPT with lower nicotine emissions (Brinkman, Kim, et al., 2020).

WPT typically contains cut-up tobacco leaves and up to ~70 weight-% of additives. The additives-to-tobacco ratio drives the nicotine content of WPT (e.g., WPTs with higher concentrations of additives have lower nicotine concentrations). The reported nicotine content of WPT ranges from 0.5-6.3 mg/g of head-filler (Hadidi & Mohammed, 2004; Kulak JA, 2017). Some nicotine is lost to the water when the smoke is pulled through the waterpipe (Edwards et al., 2021). Data obtained from smoking machines show that water in the bowl reduced nicotine content in WPT mainstream smoke between 1.4- and 3.1-fold; the nicotine content of water-filtered WPT mainstream smoke ranged from 13 to 46 µg per puff (Erythropel et al., 2021); and total nicotine inhaled for a typical WPT smoking session can be as high as 9,000 µg/session (Shihadeh et al., 2015).

WPT use is associated with significant nicotine intake. For example, a study of 55 participants who smoke WPT found a 4-fold increase in cotinine (a urinary biomarker of nicotine) following smoking WPT at a hookah bar (St Helen et al., 2014). Similarly, a study of 105 participants who exclusively smoke WPT found 8.6- and 8.4-fold increases in urinary cotinine levels following smoking WPT at a hookah lounge (n=55) and following smoking WPT in a home setting (n=50), respectively (Kassem, Kassem, Liles, Jackson, et al., 2018). Another study found a substantial increase in plasma nicotine concentration among 16 participants who smoked WPT in a clinical research ward (Jacob et al., 2011). Overall, a significant uptake of nicotine from WPT smoking underscores its addiction potential.

d. WPT and Secondhand Smoke Exposure

People who do not smoke any tobacco but live in homes where WPT is used are also exposed to nicotine, toxicants, and carcinogens. For example, a study found that children ≤5 years old living in homes of people who smoke WPT daily had significantly higher levels of urinary cotinine, NNAL, and 3-HPMA (a metabolite of acrolein) compared to children of people who do not smoke any tobacco (Kassem, Daffa, et al., 2014). Another study found that adults who do not smoke WPT but socialize with people who smoke WPT had significantly higher levels of urinary cotinine and 3-HPMA following social gatherings where only WPT was used, and about half (47%) had detectable levels of NNAL in urine (Kassem et al., 2017; Kassem,

Kassem, Liles, Jackson, et al., 2018; Kassem, Kassem, Liles, Zarth, et al., 2018). Indeed, more studies are needed to investigate exposure to WPT secondhand and thirdhand smoke, particularly among people who reside in homes where WPT is smoked, such as children, women of reproductive age or pregnant, adolescents, and older adults with pre-existing cardiopulmonary diseases.

3. Contribution of Additives to the Toxicity of WPT

a. Humectants

The most common WPT consumed worldwide, flavored and sweetened WPT, called ma'assel (Maziak, 2015), has been shown to contain up to 70 weight-% of the humectants glycerol and propylene glycol (Schubert, Heinke, et al., 2012). Humectants in WPT enhance WPT's moisture and sweetness, act as solvents for flavors, and impart smoothness to the smoke, thus increasing the product's appeal (Adetona et al., 2020; Keller-Hamilton et al., 2022; Wagener et al., 2021). Humectants may replace more expensive ingredients such as molasses or honey to reduce the price of mass-produced hookah tobacco (Brinkman, Teferra, et al., 2020). Since WPT does not burn self-sustainably and is instead heated indirectly by charcoal, the maximum temperature of WPT is much lower than the combustion zone of a burning cigarette, 150 ºC and 950 ºC, respectively(Baker, 2004; Shihadeh & Saleh, 2005). As a result, this leads to the intact transfer of most WPT humectants to the smoke, forming up to 23% of the collected total particulate matter (TPM), namely tar (Schubert et al., 2011).

Humectants make limited contributions to aldehyde emissions in cigarettes (e.g., glycerol generally only present at 1–3 weight-%) (Yip et al., 2010), but when present as the main ingredients in e-cigarettes (e.g., glycerol, propylene glycol present in the range of 80-99 weight-%), they do contribute substantially to the emission of aldehydes and other toxicants (AlGemayel et al., 2022; El-Hage et al., 2020; Ooi et al., 2019; Saliba et al., 2018; Strongin, 2019). A study indicates that the presence of acrolein in WPT smoke is positively related to the humectant (glycerol) content of the unburned WPT (Almomen et al., 2023). Another study showed that glycerol in WPT notably contributed to VOC in mainstream WPT smoke (Perraud et al., 2019).

The presence of glycerol and propylene glycol in WPT strongly correlates with WPT flavorant levels. For example, one flavored WPT brand contains 20 times higher levels of humectants compared to an unflavored WPT brand (Adetona et al., 2020). Humectants also increase smoke production, as they can constitute up to 23% of the tar thereby facilitating nicotine delivery and greater smoking satisfaction (Keller-Hamilton et al., 2022). There is a need to further study the impact of humectants on toxicant generation in WPT smoke.

b. Sugars

Reducing sugars (e.g., glucose and fructose) can make up 34 weight-% of WPT as seen in Table 1 in Jaccard et al. 2020 (Jaccard et al., 2020). Total sugar content levels, or the sum of fructose, glucose, and sucrose, were comparable between a flavored brand and those in an "unflavored" WPT brand by a factor of ~two (Adetona et al., 2020). WPT is enriched with ~15-50 times higher concentrations of simple sugars than other combustible tobacco products such as cigarettes (Maziak & Sharma, 2020). The sweet sensory perceptions associated with flavored and sweetened WPT are cited as reinforcing factors for WPT use (Martinasek et al., 2011). Flavorings and other additives, especially sweeteners (e.g., sugars, honey, syrup), contribute to the appeal and uptake of WPT smoking among youth (Ben Taleb et al., 2020; Hoffman et al., 2016; Martinasek et al., 2011; Maziak et al., 2020; Wagener et al., 2021). Indeed, an analysis of WPT-related tweets on the social media platform X (formerly Twitter) found that most flavors mentioned and preferred were associated with sweet sensations: fruit, sweets, and beverage/alcohol (Feliciano et al., 2023).

People who smoke WPT are exposed to toxicants from the thermal degradation of the sugar additives in WPT, which pyrolyze to form respiratory toxicants (Jaccard et al., 2020; van Nierop et al., 2019). The thermal degradation of sugar additives in WPT leads to the emission of toxicants and carcinogens, including carbonyls, aldehydes, and semivolatile furans (Daher et al., 2010; Kassem, Kassem, Liles, Zarth, et al., 2018; Perraud et al., 2019; Schubert, Bewersdorff, et al., 2012; Shihadeh et al., 2015; Soussy et al., 2016; Talhout et al., 2006). Compared to cigarette smoke, WPT smoke contains several orders of magnitude higher concentrations of semivolatile furans, including furfural and 5-hydroxymethylfurfural, both sugar degradation products (Brinkman, Teferra, et al., 2020; Schubert, Bewersdorff, et al., 2012). However, the lack of acute and chronic inhalation toxicity data for semivolatile furans is a significant gap in the current understanding of WPT toxicology and is thus a barrier to effective tobacco control (Maziak & Sharma, 2020).

c. Flavorants

WPT smokers have reported higher enjoyment, liking, satisfaction, and calmness when using flavored WPT than when using unflavored varieties (Ben Taleb et al., 2019; Leavens et al., 2018; Maziak et al., 2020). One study reported that out of 237 commercial WPT products (including steam stones and herbal molasses) sold in the European Union (EU) countries, 75% were “fruit” flavored, and authors categorized these into 8 main flavor categories and 48 unique flavor subcategories (Bakker-'t Hart et al., 2022). The most frequently detected flavoring chemicals (excluding sugars) included vanillin, ethyl vanillin (both typical “dessert” flavorants), dihydrocoumarin (“spice”), ethyl butyrate, ethyl acetate, ethyl-2-methylbutyrate, isoamyl acetate (all “fruity”), maltol (“dessert”), menthol (“minty”), and benzyl alcohol ("fruity/floral”). The popularity of flavored WPT among young people indicates that flavors facilitate nicotine initiation, which is concerning due to nicotine's well-known effects on the developing brain and other organs and its addictiveness (Alomari et al., 2018; CDC, 2012; Colyer-Patel et al., 2023).

Numerous WPT flavors have been reported (Javed et al., 2017; Schubert et al., 2013), with each flavored WPT typically containing a mixture of several flavoring chemicals (Schubert et al., 2013), some of which possess allergenic, irritant, and toxicological properties (Gupta et al., 1991; Hua et al., 2019; Schubert et al., 2013; Silverman, 1946).The adverse health effects associated with inhaling flavored WPT smoke are understudied, with very little available clinical and pre-clinical data (Nemmar et al. 2020a; Schubert et al. 2013).

The chemical flavorings in WPT smoke can lead to additive or synergetic toxicological responses compared to unflavored WPT smoke, as seen in animal models (Nemmar et al. 2020a; Nemmar et al. 2020b). In a mouse model, one experimental study evaluated the effects of unflavored, apple-flavored, or strawberry-flavored WPT smoke on pulmonary responses (Nemmar et al. 2020a). Following one month of exposure, authors found that unflavored and flavored WPT smoke induced significant lung function and structure changes compared to air-exposed control mice (Nemmar et al. 2020a). While apple and strawberry-flavored WPT smoke altered levels of IL-6 and catalase, nitric oxide and cleaved caspase-3 levels were only significantly changed in the strawberry WPT smoke-exposed group (Nemmar et al. 2020a). Thus, different toxicities between flavored and unflavored WPT were observed, with strawberry-flavored WPT smoke being the most harmful to mice.

Further, another study evaluated the effect of unflavored and apple-flavored WPT smoke on the cardiovascular system of mice over one month (Nemmar et al. 2020b). It found that, compared to air, inhaling WPT smoke increased blood pressure levels and altered markers for thrombosis and blood vessel reactivity (Nemmar et al. 2020b). The addition of the apple flavor led to increased cardiovascular dysfunction with increased oxidative stress and inflammation in the heart (Nemmar et al. 2020b). These two studies confirm, at the pre-clinical level, a differential cardiopulmonary toxicity potential of flavored WPT smoke vs. unflavored WPT smoke (Nemmar et al. 2020a; Nemmar et al. 2020b).

The remainder of this section describes research findings for several different flavorant classes and their related compounds. This is expanded in *Supplementary Material Table 1*, which lists select flavor-related compounds, grouped by their chemical classification and flavor category.

Esters and Lactones. Esters were either the most or second most abundant class of flavorants across all flavored WPT products studied (Farag et al., 2018). For example, lactones (cyclic esters) were characteristic of peach-flavored products (Farag et al., 2018). At elevated temperatures, esters may form harmful carboxylic acids (Narimani et al., 2022).

Ketones. Of significant concern is the finding of 2,3-butanedione (diacetyl) (Farag et al., 2018). Diacetyl, the notorious "buttery" flavor identified as the causative agent of Bronchiolitis obliterans ("popcorn lung") (Harber et al., 2006), is a known respiratory toxicant (Silverman, 1946; van Rooy et al., 2007). Carvone, a terpenoid ketone and the principal flavorant in spearmint, possesses insecticidal properties, and, interestingly, has also been described to be present in cinnamon-flavored WPT, likely to add a minty undertone.

Terpenes and terpenoids. Terpenes and terpenoids were the second most common class of flavorants found in apple- and licorice-flavored WPT products (Farag et al., 2018). Terpenes are somewhat prone to thermal degradation, potentially forming toxicants such as formaldehyde and isoprene during heating (Meehan-Atrash et al., 2017). While some terpenes, such as βcaryophyllene, show anti-inflammatory, antioxidant, and cytoprotective effects, most terpenes, especially monoterpenes, have demonstrated high cytotoxicity in several model organisms, α-terpineol (Supplementary Material Table 1) and terpinolene are among the most toxic terpenes, along with humulene and β-linalool. Limonene, found in watermelon WPT products (Farag et al 2018). exhibited cytotoxicity and inflammatory responses in naïve monocytes (Morris et al. 2021).

Nitrogen-containing compounds. Nitrosoazetidine was found at trace levels in apple- and melon-flavored WPT products (Farag et al., 2018). Nitrosoazetidine, when administered by gavage, is a liver carcinogen in animals (Lijinsky et al., 1984); however, its inhalation safety needs to be investigated.

***Aldehydes*.** Aldehydes can cause varying degrees of mucus membrane irritation, eventually resulting in inflammation when inhaled at sufficient concentrations and frequency (Dinu et al., 2020). Cinnamaldehyde, the principal component of cinnamon flavor, is cytotoxic (Behar et al., 2016). Human embryonic stem cells are sensitive to low concentrations of cinnamaldehyde (Behar et al., 2014), a potentially significant concern for pregnant women using WPT. Flavorant molecules can also break down during heating to form toxic levels of formaldehyde, acetaldehyde, acrolein, and glyoxal (Khlystov & Samburova, 2016). Ethyl vanillin, an aldehyde commonly found in "dessert" flavors but also in green grape-flavored WPT, was found to be cytotoxic to human bronchial epithelial cells treated with the flavorant (Morris et al., 2021).

Semivolatile furans. Semivolatile furans, such as furfural, can impart sweet, caramel, and almond (*The Good Scents Company Information System*; Zhang et al., 2010) aromas to WPT smoke and can lead to pulmonary irritation upon inhalation (Gupta et al., 1991). As noted above, semi-volatile furans can be generated from the thermal degradation of sugars.

Aromatic compounds. Aromatic compounds were abundant in mango-flavored WPT (Farag et al., 2018). Diphenyl ether, which has a harsh metallic aroma, irritates the mucus membranes and the upper respiratory tract. Prolonged exposure can damage multiple organs (Stanfill et al., 2006).

Alcohols. Of the alcohols, β-linalool is a non-irritant but auto-oxidizes to an allergenic product (Christensson et al., 2009). Overexposure to 1-hexanol, found mainly in apple and melon-flavored WPT, can lead to eye and respiratory tract irritation as well as central nervous system depression (Cometto-Muñiz et al., 1997; Mckee et al., 2015).

d. Implications of the findings on flavorant classes

Additional research will expand the inhalation toxicity knowledge base of flavorants and toxicants arising from the thermal breakdown of specific WPT flavorants during smoking. There is a clear need to correlate the presence and concentration of volatile flavoring compounds in flavored WPT smoke with altered pathophysiological cardiopulmonary responses. Despite the scarcity of studies on this topic, a diversity of research efforts provides evidence of the possible inhalation toxicity of 13 flavoring chemicals used in WPT (*Table 2*).

4. Contribution of the Heating Source to the Toxicity of WPT

WPT is an assisted-combustion tobacco product, and an external source of heating is needed due to the presence of high levels of humectants in WPT that prevent self-sustained combustion (Maziak, Ward, et al., 2004). Traditionally, the most widely used external heating source has been charcoal. Charcoal is known to naturally contain a large variety of trace elements and heavy metals (Elsayed et al., 2016). Studies have demonstrated the presence of heavy metals such as lead, arsenic, cadmium, and chromium, as well as VOCs, such as benzene, in WPT charcoal emissions (Schubert et al., 2015; Shihadeh et al., 2015). As a result, WPT users are exposed to these harmful compounds via mainstream smoke, generally at levels higher than from combustible cigarettes (Schubert et al., 2015; Shihadeh et al., 2015).

As with all incomplete combustion of carbon, the burning of charcoal yields carbon monoxide (CO), a compound that, when inhaled, preferentially binds to blood hemoglobin over oxygen, thereby reducing oxygen distribution in the body (Bleecker, 2015). There is ample evidence that WPT use will result in much higher CO exposure compared to combustible cigarette use (Rezk-Hanna & Benowitz, 2019), and studies have concluded that as much as 90% of CO and PAH emissions from WPT use stem from the charcoal briquettes rather than the WPT itself (Monzer et al., 2008). Moreover, different types of charcoal may contribute differently to emissions, with quick-light charcoal emitting significantly higher levels of CO compared to natural charcoal (Medford et al., 2015). Unfortunately, there exist ample medical case studies from across the globe describing cases of CO poisoning due to WPT use (Ashurst et al., 2012; Medford et al., 2015; Retzky, 2017; Verweij et al., 2019).

More recently, electric heaters for waterpipes have been introduced, likely due to the known health risks associated with charcoal heating (El Hourani et al., 2019). Replacing charcoal with an electric heater was found to reduce CO and PAH levels by up to 90%, consistent with the evidence laid out above, yet an increase in the emission of acrolein was found, likely resulting from increasing degradation of humectants (El Hourani et al., 2019; Monzer et al., 2008). One clinical study found that using electrical heaters to heat WPT resulted in a reduction of nicotine delivery and in a reduction of exposure to CO and benzene compared to charcoal-based WPT use

(Brinkman, Kim, et al., 2020). However, the study also reported that participants puffed greater volumes of smoke more aggressively to compensate for lower nicotine emissions, ultimately increasing tobacco-related exposures. A machine-smoking study reported that using electric heaters instead of charcoal reduced mainstream CO and PAH but increased semivolatile furan yields (El Hourani et al., 2019). One concern with electric heating devices is potential metal exposure from the heating element, similar to e-cigarette elements (Williams et al., 2017). Concerning the health effects of combustible charcoal-heated vs. electrically-heated WPT, a study found that, similar to cigarette smoking, electrically-heated WPT smoking acutely impairs endothelial function, one of the earliest signs of development of atherosclerotic cardiovascular disease (Rezk-Hanna et al., 2019). Furthermore, in traditional charcoal-heated WPT smoking, the acute vascular dysfunction is masked by the effects of high levels of CO, which acts as a vasodilator (Rezk-Hanna et al., 2019).

An emerging concern is the availability of WPT charcoal in various enticing flavors, e.g., apple, pineapple, orange, lemon, mint, peach, strawberry, and watermelon,(*Starlight Charcoal*) which may contribute to the appeal of WPT use and/or increase toxicant exposure. Furthermore, manufacturers of coconut shell charcoal are using descriptors implying reduced harm, such as “environment-friendly” or “chemical-free”(*Starlight Charcoal*).

5. WPT Package Labeling Concerns

Without adequate regulations specific to WPT marketing and package labeling, WPT companies advertise their products as comprising mainly molasses and dried fruit, touting them as harmless tobacco alternatives (Jawad, 2015; Rezk-Hanna et al., 2014; World Health Organization, 2015). However, current scientific evidence does not support these claims (Al Ali et al., 2020; Hassane et al., 2022; Montazeri et al., 2017; Raad et al., 2011).

One concern is the inaccurate labeling of WPT constituents, such as nicotine. Although data on nicotine content and its yields in smoke delivered from WPT are essential to assessing the addictive potential of these products, one study that measured plasma nicotine levels in people who smoke WPT found that nicotine labeling on WPT packaging did not necessarily correlate with nicotine delivery (Vansickel et al., 2012). This finding indicates inaccurate labeling of WPT products, which may mislead those who smoke WPT (Vansickel et al., 2012). More research is needed to assess the accuracy of nicotine labeling on WPT packaging, such as comparing measured nicotine levels in neat WPT with levels indicated on the packaging label.

Of particular concern is the marketing and advertisement of WPT flavorings. *Table 3* lists WPT package labeling concerns that have been shown to promote widespread WPT use, social acceptance of the behavior, and misperceptions about the addictive potential and adverse health effects of using these products, particularly among youth and young adults (Maziak et al., 2020; Soneji et al., 2021; Villanti et al., 2017). *Table 3* provides examples of labeling concerns, such as the use of attractive names of flavorings, lack of disclosure of product ingredients, and use of reduced harm descriptors. Global regulatory bodies are encouraged to consider these WPT package labeling concerns to mitigate misleading messages of safety of use.

6. Regulation of Flavored and Sweetened WPT in the U.S.

The U.S. Food and Drug Administration (FDA) first gained legal authority to regulate cigarettes, smokeless, and roll-your-own tobacco in 2009 when the U.S. Congress passed the Family Smoking Prevention and Tobacco Control Act (TCA) (U.S. Government Printing Office, 2009). In 2016, the FDA's regulatory authorities were extended to all tobacco products, including WPT and its associated components and parts (FDA, 2016). Despite those regulatory efforts, there continues to be an increase in WPT popularity, lack of user awareness of potential harms, and availability of WPT in appealing flavors (Aljarrah et al., 2009; Maziak, 2011).

The regulatory context for WPT in the U.S. is complicated by differing, and often conflicting, federal, state, and local regulations. A 2015 study surveying Clean Indoor Air Acts (CIAA) from each of the 50 states and the District of Columbia found that policies varied greatly between states, and that many state CIAAs contained language that resulted in WPT exclusion from the regulation in question. This was especially significant for waterpipe venues (e.g., hookah lounges, bars), with as many as 24 states allowing waterpipe venues to be exempt from the state CIAA, and a further 14 states having "percentage of sales requirements" for tobacco that could enable exemptions for the venues (Martinasek et al., 2015). In another example of conflicting regulations, a 2017 study evaluating local and statewide WPT-relevant policies in Pennsylvania found that local-level reform attempts were prevented or rolled back by preemptions from the state, and some state regulations were constrained by federal preemptions (Colditz et al., 2017). Ultimately, tobacco control policies at federal, state, and local levels in the U.S. must be amended to be effective, consistent, and specific in their verbiage around WPT, and to reduce constraints from preemptions.

7. Conclusion

Despite the known health risks associated with flavored and sweetened WPT use, particularly from additives and heating sources, WPT use remains a global phenomenon. The public, particularly youth and young adults, may be more susceptible to initiate or continue WPT use because of availability of enticing flavors and additives, packaging tactics, and lack of regulation, as well the influence of societal norms. Those factors could intensify toxicant exposure and adverse health outcomes including nicotine addiction. This review summarizes our cumulative knowledge of the association of WPT flavors, additives, and charcoal with the ensuing toxicity as determined by animal models and biomarkers of exposure in clinical and epidemiological studies. We also highlight gaps in the existing literature and regulations of flavored and sweetened WPT toxicity.

8. Future Directions

Based on the findings in this review, *Table 4* suggests future research related to the toxicity of WPT additives (e.g., humectants, sweeteners, flavorants), heating sources and other device components, impact of WPT marketing and advertisements, and misleading or inaccurate communications of WPT (e.g., point-of-sale advertising, product packaging inserts and labeling), as well as health education strategies to increase awareness of the toxicity and associated health risks of WPT use. Effective WPT-related policy and regulatory efforts depend on high-quality independent evidence. Thus, research funding specifically tailored to WPT is critical so that new data can continue to inform federal, state, and local regulation of WPT production, marketing, and sales, to protect public health.

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Disclaimer
The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the authors' institutions, the National Institutes of Health (NIH), the U.S. Food and Drug Administration (FDA), or the Tobacco-Related Disease Research Program (TRDRP).

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Table 1. **Toxicity of flavored and sweetened waterpipe tobacco (WPT) smoke in animal studies.**

Species/Strain	Exposure type	Duration	Puff profile	WPT Flavor (Brand)	Toxicity (target organs)
Balb/c mice	whole body	6 weeks (180 puffs/day)	a	Two Apples (Nakhla)	Airway inflammation (Khabour et al., 2018).
Balb/c mice	whole body	7 days (180 puffs/day)	a	Two Apples (Nakhla)	Increased inflammation responses and oxidative stress in lungs: (Khabour et al., 2012).
Balb/C mice	nose only	1 month	b	Plain and Apple (Al Fakher)	Increased the risk of thrombogenicity, and heart inflammatory response (Nemmar et al., 2019).
Balb/c mice - male	whole body	2 or 8 weeks (180 puffs/day)	a	Two Red Apples (Nakhla)	Increased oxidative stress and levels of MMP1, 3, and 9 in heart (Rababa'h et al., 2019).
C57BL/6 mice	whole body	7 days (180 puffs/day)	a	Double Apple (Nakhla)	Increased the risk of thrombosis (Alarabi et al., 2020).
C57BL/6 mice	whole body	2 months (180 puffs/day)	a	Double Apple (Nakhla)	Lung inflammation, DNA damage noticed in lung, kidney, liver, and bone marrow (Abi-Gerges et al., 2020).
C57BL/6 mice	nose only	1 month (30 puffs/day)	b	Apple (Al Fakher)	Inflammation and DNA damage were noticed in the lungs after WPT smoke exposure (Nemmar et al., 2019).
C57BL/6 mice	nose only	3 months (30 puffs/day)	b	Apple (Al-Fakher)	Increased the risk of thrombosis, oxidative stress, and DNA damage in heart (Nemmar et al., 2022).
C57BL/6 mice	nose only	1 month (30 puffs/day)	b	Plain, Apple & Strawberry (Al Fakher)	Increased lung inflammation, oxidative stress, DNA damage, and asthmatic risk (Nemmar, Al-Salam, Beegam, Yuvaraju, & Ali, 2020).
C57BL/6 mice	nose only	6 month (30 puffs/day)	b	Honey (Al Fakher)	Increased DNA damage, oxidative stress and the risk of interstitial fibrosis in heart (Nemmar et al., 2017).
Wister rats	whole body	4 weeks (180 puffs/day)	a	Two Apples (Nakleh)	Oxidative stress was elevated in brain; induced short- or long-term memory loss (Alzoubi et al., 2015).
Wistar rats	whole body	19 weeks (360 puffs/day)	a	Two Apples (Nakhla)	Blood pressure & fasting glucose level were increased after WPT smoke exposure (Al-Sawalha et al., 2020).
Wistar rats - male	whole body	4 weeks (180 puffs/day)	a	Double Apples (Nakhla)	WPT smoke exposure caused memory loss (Alzoubi et al., 2019).
Balb/c mice	nose only	5 days (30 puffs/day)	b	Honey (Al Fakher)	Increased inflammation in heart and risk of thrombus (Nemmar, Yuvaraju, et al., 2015).

Balb/c mice	nose only	1 month (30 puffs/day)	b	Honey (Al Fakher)	Lung inflammation and oxidative stress were noticed after WPT smoke exposure (Nemmar et al., 2013).
BALB/C mice	nose only	1 or 4 weeks (30 puffs/day)	b	Honey (Al Fakher)	Inflammation, oxidative stress, and DNA damage were noticed in kidney (Nemmar, Beegam, et al., 2020).
Balb/c mice	nose only	5 days (30 puffs/day)	b	Honey (Al Fakher)	WPT smoke induced inflammation and oxidative stress were noticed in lung (Nemmar, Al Hemeiri, et al., 2015).
Balb/c mice	nose only	1 month (30 puffs/day)	b	Honey (Al Fakher)	Induced lower levels of antioxidant, testosterone and luteinizing hormone in plasma (Ali et al., 2015).
C57BL/6 mice - female	nose only	6 months (180 puffs/day)	a	Blue Mint & Exotic Pirate's Cave (Starbuzz)	Lymphocyte activity was inhibited by WPT smoke (Reyes-Caballero et al., 2020).
Gprc5a or Lcn2 KO mice	whole body	Days 4-21 of lactation (171 puffs/day)	a	Double Apple (Nakhla)	Increased the risk of lung tumor development (Hassane et al., 2022).
Wistar rats	whole body	Days 4-21 of lactation (360 puffs/day)	a	Double Apple (Nakhla)	Dysregulated the male hormonal levels and increased oxidative stress in testes (Al-Sawalha et al., 2021).
Balb/c mice	whole body	Prenatal exposure (360 puffs/day)	a	Two Apples (Nakhla)	Increased lung inflammation and oxidative stress, and the allergic risk in offspring (Al-Sawalha et al., 2017).
Wistar rats	whole body	Prenatal exposure (360 puffs/day)	a	Two Apples (Nakhla)	Either short- or long-term memory were affected. Catalase level in brain was increased in late gestation and whole gestation WPT smoke exposure (Al-Sawalha et al., 2018).
Wister rats	whole body	Prenatal exposure (360 puffs/day)	a	Two Apples (Nakhla)	Lower body weight and survival rate in offspring (Al-Sawalha et al., 2018).

[a] 2.6/3s puff duration with 17s interval; [b] 2s puff duration with 58s interval.

Table 2. **Selected WPT Flavorants, Related Compounds, Odor, and Applicable Toxicity Studies**

Compound Class	WPT Flavorants and Related Compounds	Characteristic Odor	Relevant WPT flavors	Toxicity Studies
Esters	2-Hexenol acetate	Fruity	Melon, Apple, Unflavored	Acute inhalation toxicity at dosage of 500ppm (Silverman, 1946).
	Ethyl cinnamate	Spices/Cinnamon	Guava	Cytotoxicity in lung fibroblast and epithelium (Behar et al., 2018).
	n-Hexyl acetate	Fruity	Melon	Acute inhalation toxicity at dosage of 500ppm (Silverman, 1946).
	Triacetin	Odorless	Green grape	Cytotoxicity in lung fibroblast and epithelium (Behar et al., 2018).
Ketones	2,3-Butanedione (diacetyl)	Buttery	Melon, Unflavored	Peribronchial inflammation, mild nasal and laryngeal injury after exposure of diacetyl 100-400ppm for at least 4 weeks (Morgan et al., 2008).
Terpenes and Terpenoids	Limonene	Citrus/Fruity	Watermelon	Cytotoxicity and induced inflammatory responses in naïve monocyte (Morris et al., 2021).
Aldehydes and Furans	Ethyl vanillin	Vanilla/Dessert	Green grape	Induced cytotoxicity in lung epithelium and associated with lung obstructive or restrictive diseases (Hua et al., 2019).
	p-Anisaldehyde	Spices	Licorice	Cytotoxicity in lung fibroblast and epithelium (Behar et al., 2018).
	Furfural	Sweet	Caramel, Almond	Irritated when inhaled and induced injury in parenchymal area (Gupta et al., 1991).
	Furaneol	Fruity	Strawberry	Cytotoxicity to lung epithelium (Hua et al., 2019).
Aromatic compounds	Phenol	Sweet	Apple, Green grape, Guava, Melon	Phenol exposure at 1.7mg/mL showed cytotoxicity and mitochondrial activity inhibition in ex vivo human lung slice (Galina et al., 2018).
Alcohols	2-Ethyl-1-hexanol	Odorless	Melon	Acute exposure to 1mg/m^3 caused irritation to nasal, throat, and respiratory track (Ernstgard et al., 2010).
	Eugenol	Spice/Clove	Green grape	Cytotoxicity in lung fibroblast and epithelium (Behar et al., 2018).

Table 3. **Flavored and Sweetened Waterpipe Tobacco (WPT) Package Labeling Concerns.**	
Labeling Concerns	Characteristics
Use of attractive names of flavorings	Use of fruit, candy, and alcohol flavoring names attracting youth, such as apple martini, sweet passion fruit, peaches n cream, bubble gum, gummy bears, tequila sunrise, Arabian coffee, etc.
Lack of disclosure of product ingredients	Inaccurate labeling of tobacco product constituents, including nicotine concentrations (Vansickel et al., 2012); lack of disclosure on specific ingredients, including sugar and sweetener levels (Rezk-Hanna, Talhout, et al., 2023); and use of misleading label information about product ingredients (e.g., zero tar) (Jawad et al., 2017).
Use of reduced harm descriptors	Use of descriptors implying reduced harm (e.g., "healthy", "clean", "pure", "organic" and "fresh"); Use of large size pictures implying "safe and healthy" tobacco products (e.g., fruits, vegetables, and herbs) (Jawad et al., 2017).

Table 4. **Suggested Future Research for Flavored and Sweetened WPT and Health Education Strategies.**

Suggested Future Research for WPT

- Determine hazards from inhalation of humectants, sugars and flavorants, and breakdown products thereof, during WPT use.
- Correlate toxicants in WPT smoke with WPT ingredients, for example, by using isotopic labeling.
- Determine hazards from inhalation of WPT charcoal breakdown products during WPT use.
- Evaluate the marketing of flavors that appeal to youth.
- Assess the sales trends of the numerous flavors of WPT products and WPT charcoal, particularly flavors that appeal to youth.
- Develop and test WPT-specific cessation interventions.

Suggested Health Education Strategies

- Incorporate known health risks associated with exposure to WPT smoke in educational campaigns.
- Enhance current educational strategies by countering misleading information that may result in misperceptions of the potential health risks of smoking WPT.

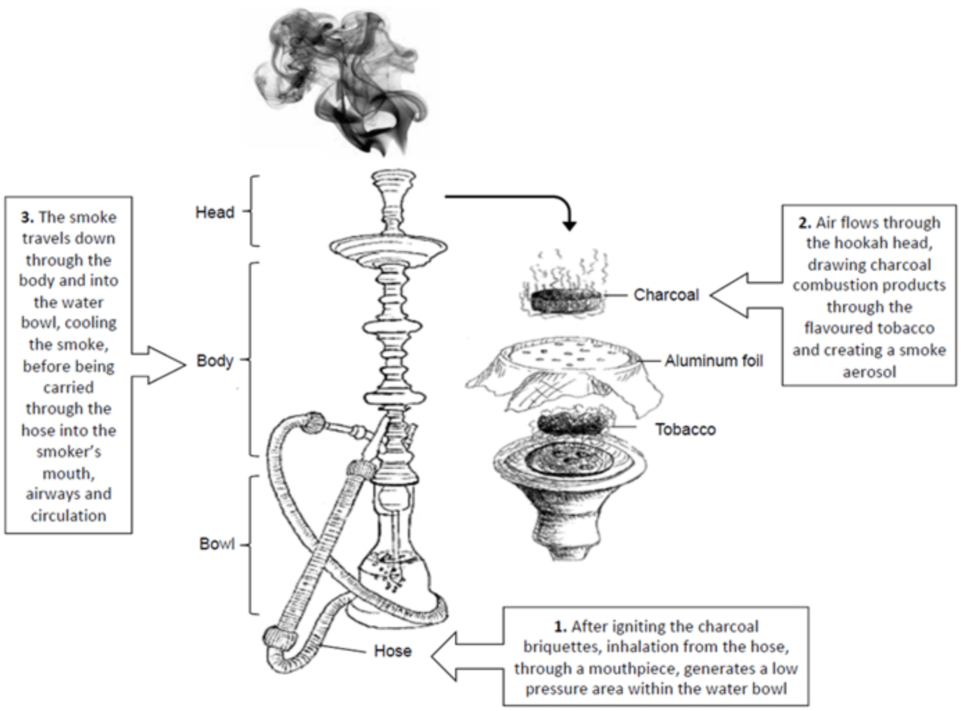

Figure 1. Diagram of waterpipe elements

60x43mm (300 x 300 DPI)