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Review

Inhaled toxins: A threat to male reproductive health

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ABSTRACT

Exposure to air pollutants is known to be an important risk factor in reducing semen quality in men across the world. Poor semen quality results in decline in the global fertility rate and significant personal stress, dysfunctional sexual relationships, and psychosocial problems. Continuous monitoring and effective efforts to reduce air pollution in industries and the environment and making positive changes in daily lifestyle can prevent adverse effects on semen quality and reduce the high prevalence of men infertility. This review aims to summarize studies associating pollutant concentrations of polycyclic aromatic hydrocarbons (PAHs), formaldehyde (FA), and BTEX (benzene, toluene, ethyl-benzene, and xylene) on semen quality. In this systematic review, Scopus, PubMed and Web of Science databases were searched until November 13, 2022. The PECO statement was formulated to clarify the research question, and articles that did not satisfy the criteria outlined in this statement were excluded. Generally, 497 articles were obtained through searching databases, and after the investigations, 26 articles that met the entry criteria were extracted and finally considered in the systematic review. The results showed that occupational and environmental exposures to PAHs, formaldehyde, and BTEX were associated with increased metabolite concentration of toxic pollutants in body fluids. These toxin-associated pollutants directly or indirectly cause detrimental effects on sperm motility, vitality, DNA fragmentation, and morphology. There is evidence on the impact of PAHs, formaldehyde, and BTEX pollutants on the reduction of semen quality. Therefore, proving the relationship between air pollutants and testicular function in semen quality can play an effective role in macro policies and adopting stricter laws to reduce the emission of air pollutants and promote a healthy lifestyle to improve reproductive health in young men.

1. Introduction

Infertility is considered a severe public health problem worldwide amid increased life expectancy and low and falling fertility levels, with 60 % of the world population living in countries currently at or below the replacement rate of 2.1 children per woman. The abrupt decline in the global fertility rate from 5.3 in 1963 to 2.4 in 2019 is a serious concern, and the role of air pollutants has to be put in the equation (UN, 2022).

Infertility is prevalent in which 8–12 % of couples are involved; in 50 % of cases, male factors are the leading cause (Agarwal et al., 2021). Calculated global data showed that 2.5–12 percent of men in different countries suffer from infertility problems (Agarwal et al., 2015). A key variable in men's reproductive health is semen quality, which includes semen volume, sperm concentration, count, motility, morphology, and DNA fragmentation (Kumar and Singh, 2022). The World Health Organization (WHO), by publishing the laboratory manual for the examination and processing of human semen, has published the values of each seminal fluid parameter in fertile men (Appendix A1) (WHO, 2021). This booklet is a reference document for procedures and methods for the laboratory examination and processing human semen, intended to maintain and sustain the quality of analysis and the comparability of results from different laboratories across the world. Based on this

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manual, the normal values for each seminal fluid parameter were determined as follows:

Volume $\geq$ 1.4 mL, concentration $\geq 16\times10^6$, total motility $\geq$ 42 %, progressive motility $\geq$ 30 %, total sperm count $\geq$ 60 million/ejaculate, and normal morphology >4 %.

However, during the last two decades, due to the increase in the rate of infertility and azoospermia in men, there has been a growing concern about the gradual decrease in semen quality, especially for sperm concentration and morphology (Wu et al., 2017). There is an extensive list of risk factors for infertility including: smoking (tobacco, marijuana, and E-cigarettes), overweight, obesity, use of illicit drugs (amphetamines, cocaine, and opioids (Holmboe et al., 2020; Nielsen et al., 2019)); alcohol, chronic diseases, mental stress, exposure to environmental and industrial toxins, i.e., air pollution has potential effects on semen quality (Karavolos et al., 2020).

Common air pollutants such as formaldehyde, polycyclic aromatic hydrocarbons (PAHs) and Benzene, Toluene, Ethylbenzene and Xylenes also called BTEX chemicals, can cause adverse effects on spermatogenesis, steroidogenesis, and sperm dysfunction and reduce male fertility (Katukam et al., 2012; Kumar and Singh, 2022). Exposure to these pollutants can increase the concentration of their metabolites in the body, including monohydroxylated PAHs (OH-PAHs) for polycyclic aromatic hydrocarbons and phenol-hydroquinone and catechol for benzene (Jacob and Seidel, 2002; Li et al., 2008; Mandani et al., 2013). Finally, these metabolites can have adverse effects on sperm quality by disrupting the secretion of reproductive hormones, such as testosterone (Chen et al., 2011), and causing oxidative stress (Mandani et al., 2013; Pan et al., 2008), and then they are excreted through urine (Li et al., 2008; Mandani et al., 2013).

So far, many studies worldwide have proven the relationship between exposure to air pollutants and the reduction of semen quality. The results of a study conducted in Egypt on 66 infertile men under the age of 45 showed that chronic exposure to PAHs was associated with increased urinary metabolite levels of 1-hydroxypyrene (1-OHP), 1-hydroxynaphthalene (1-OHNa), and 2-hydroxynaphthalene (2-OHNa) in the infertile group. In addition, 30 % fragmentation of sperm DNA was observed in semen samples (Saad et al., 2019). Chen et al. (2021) also investigated the effect of PAHs on sperm quality and male reproductive hormones. The results of this study proved that the increase in the levels of urinary metabolites of this pollutant has a negative relationship with the morphology and motility of sperms (Chen et al., 2021). In addition, results obtained from a recent cohort study indicated that long-term occupational exposure to formaldehyde was significantly associated with poor semen quality, including sperm motility, morphology, and DNA fragmentation index (Lv et al., 2022).

Although the effect of air pollutants on sperm quality and male infertility has been proven, there is still a significant difference of opinion in this field, (Ling et al., 2016; Nobles et al., 2018; Zhou et al., 2021) including the study by Axelsson et al. (2022) (Axelsson et al., 2022). In this study, PAH metabolites 1-OHP and 2-hydroxyphenanthrene (2-OHPh) were examined in the urine of 381 men selected from two groups of young Swedish men, and no correlation was observed between the levels of biomarkers of this pollutant and DNA fragmentation (Axelsson et al., 2022).

Given the importance of global infertility and semen quality changes from the perspective of public health, this systematic review has the following aims to: (1) investigate the concentration of formaldehyde, PAHs and BTEX pollutants in the air and body fluids of volunteers and (2) evaluate the effect of the concentration of such pollutants on the semen quality, including sperm count, volume, abnormal morphology/normal %, sperm telomere length, motility (linearity (LIN), velocity of the curved line (VCL), average path velocity (VAP), velocity of straight line (VSL), BCF (beat cross frequency), ALH (amplitude of lateral head displacement), MAD (mean angular displacement) and progressive motility, sperm apoptosis, DNA fragmentation, and sperm aneuploidy (%).

2. Methods

2.1. Search strategy

To the best of our knowledge, this is the first systematic review conducted to investigate the effects of formaldehyde, PAHs, and BTEX on semen quality in humans. The current study is based on the Preferred Reporting Items for Systematic Review and Meta-analyses statement (PRISMA). The review protocol was registered and published in the International Prospective Register of Systematic Reviews (PROSPERO, CRD42022375439).

To create a research question with a clear structural framework, a PECO (population, exposure, comparator, and outcome) statement was formed (Table 1). With the help of this statement, it is possible to draw an approach for defining research goals, conducting systematic reviews, and formulating entry/exit criteria.

To access studies focused on the effects of formaldehyde, PAHs, and BTEX on human semen quality, a systematic search was conducted in Scopus, PubMed, and Web of Science databases, without date restrictions until November 13, 2022. The keywords used in this study are as follows:

1. **Exposure to pollutants:** PAH*, “polycyclic aromatic hydrocarbon*”, formalin, formaldehyde, methanal, formal, “methylene oxide”, BTEX, benzene, toluene, ethyl-benzene and xylene*
2. **Outcomes of exposure:** “semen quality”, “sperm volume”, “sperm concentration”, “sperm count”, “sperm motility”, “sperm morphology”, and “sperm DNA fragmentation”
3. **Media for pollutant concentration measurement:** Biomonitoring, “biologic monitoring”, urine, “body fluids”, blood, serum, plasma, and air.

In addition, the hand searching and reference checking of the selected articles were also performed to identify potential additional studies that met the inclusion criteria.

2.2. Selection criteria

In this review, studies on the effects of formaldehyde, BTEX, and PAHs on the reproductive outcome combined with the effects of lifestyle-related factors (smoking, caffeine, alcohol consumption, and stress) were excluded. In addition, the inclusion of studies that investigated the synergistic effect of several pollutants, without considering the independent effect of each of the mentioned pollutants, was also avoided. Animal research, laboratory studies, review and conference articles, books and letters to the editor were also omitted. In the present study, only the final published original articles with peer review and in the English language were extracted.

Table 1
PECO (Population, Exposure, Comparator, and Outcome) statement.

PECO	Evidence
Population	All adult men (≥18 years) referred to infertility centers or men who voluntarily participated in the studies.
Exposure	Inhalational exposure to FA, BTEX, and PAHs.
Comparator	Comparison of values obtained from semen quality parameters including sperm count, volume, abnormal morphology/normal (%), sperm telomere length, head morphology, motility (LIN, VCL, VAP, VSL, BCF*), ALH (amplitude of lateral head displacement), mean angular displacement (MAD) and progressive motility, sperm apoptosis, DNA fragmentation, and sperm aneuploidy (%) in the studied men with the values recommended by the WHO laboratory manual for the examination and processing human semen.
Outcome	Decreasing the quality of semen below the limit recommended by WHO due to inhalational exposure to FA, BTEX, and PAHs pollutants.

PAH: Polycyclic Aromatic Hydrocarbons, **FA**: Formaldehyde, **BTEX**: Benzene, Toluene, Ethyl-benzene, and Xylene

[*] Note: BCF is beat cross frequency

2.3. Data extraction

At this stage, the following information was extracted from each selected study and summarized in standard forms:

Authors, country, year of publication, study design, number and age of patients/volunteers, type and concentration of pollutant, media for measuring pollutant concentration, and instruments for measuring metabolites and semen parameters. In addition, semen quality parameters including sperm count, volume, concentration, abnormal/normal morphology (%), sperm telomere length and head morphology, motility (LIN, VCL, VAP, VSL, BCF (beat cross frequency), ALH (amplitude of lateral head displacement), MAD (mean angular displacement) and progressive motility, vitality, sperm apoptosis, DNA fragmentation, and sperm aneuploidy (%).

2.4. Quality control

Two researchers (A.H.Kh and M.M.) evaluated the quality of studies using the Joanna Briggs Institute (JBI) checklist. This checklist evaluates the risk of bias in studies by examining 8 questions in 4 areas of sample selection criteria, exposure assessment, confounding factors, and results and appropriate statistical analysis. Each question can be answered with one of the options "yes", "no", "uncertain" or "not applicable". Finally, depending on which of the answers contains more than 50–75 % of the total questions, the article is classified into 3 groups (Table 2).

Finally, all the articles having the adequate quality were included in the study.

2.5. Result synthesis

In this systematic review, meta-analysis was not possible due to heterogeneity in methodological and contextual aspects. Therefore, the results obtained from the selected studies, which included the type and mean concentration of FA, BTEX and PAHs pollutants and the quality parameters of semen, were combined narratively (Tables 3 and 4). At this stage, after summarizing the results, the correlation within and between studies was explored to investigate the relationship between the levels of exposure to pollutants and the severity of the outcome.

Fig. 1 shows the process of conducting the current systematic review by the members of the research team. This process includes 5 steps of keyword extraction, systematic search and integration of articles in EndNote X20 software, data screening and extraction, resolving contradictions and ambiguities, and results synthesis and writing original draft.

3. Results and discussion

3.1. Selection process and characteristics of articles

The selection process of the articles included in the present systematic review is shown in Fig. 2. Accordingly, 79 articles were retrieved from PubMed, 243 articles from Scopus and 175 articles from Web of Science, which brings the total number of studies to 497. After merging the studies in EndNote software, 194 duplicates were removed and 303 studies entered the screening stage, which resulted in the exclusion of 264 studies. Therefore, 39 full texts were further evaluated to check entry and exit criteria as well as quality assessment. Finally, 26 studies were extracted, and 13 articles were removed due to the lack of inclusion criteria (N= 7), reporting the cumulative effects of several pollutants on semen quality (N= 4), investigating the effect of air pollution on the sex ratio of human sperm (Y:X chromosome ratio of sperm) (N= 1) and high risk of bias (N= 1).

Table 2
Classification of articles based on quality (Yu et al., 2020).

Name of the group	Response percentage	Quality degree	Risk of bias
Q1	Yes ≥ 50–75 %	High	Low
Q2	Unclear ≥ 50–75 %	Moderate	Unclear
Q3	No ≥ 50–75 %	Low	High

Specifically, the studies included in the present systematic review include 5 cohort studies, 5 case-control and 16 cross-sectional studies that were conducted in several countries around the world: Sweden, Egypt, India, Cuba, Mexico and USA (1 in each country), 4 in Taiwan, 14 in China and 2 in Poland (Table 3).

3.2. Summary of collected data and discussion

Overall, researchers measured formaldehyde, PAH and BTEX metabolites in urine (73 %), blood (19.23 %) and semen (7.7 %). The results emphasized the potential impact of the targeted pollutants on semen quality (Table 4) (Chen et al., 2021; Hsu et al., 2006; Jeng et al., 2013b, 2018; Ji et al., 2013; Jurewicz et al., 2013; Katukam et al., 2012; Lv et al., 2022; Radwan et al., 2016; Recio-Vega et al., 2018; Rendón et al., 1994; Saad et al., 2019; Song et al., 2013; Wang et al., 2015; Xia et al., 2009a, 2009b; XIAO et al., 2001; Yang et al., 2020, 2017a, 2017b). Reduction in sperm motility, vitality, DNA fragmentation, sperm head size, telomere and neck morphology alterations and decrease in total sperm count, volume and concentrations were the key findings and most certainly related to infertility; which has a direct relationship with concentration of biomarkers of pollutants in body fluids.

The process of spermatogenesis includes a critical period of 90 days (epididymal storage, development of sperm motility, and spermatogenesis) (Huang et al., 2020). Targeting the exposures of air pollutants to a specific period result in different effects. Henry et al. (2021) showed that exposure to fine $PM_{2.5}$ and coarse PM_{10} during the early phase of spermatogenesis is associated with abnormal sperm head morphology, while exposures in the late phase are associated with a significant decrease in sperm concentration (Henry et al., 2021). Interestingly, $PM_{2.5}$ was more deleterious than the coarse fraction and since $PM_{2.5}$ varies in chemical composition of organic and inorganic components, the results are subjected to the region sampled across the world. DNA methylation is likely to play a key role in spermatogenesis and DNA methyltransferases (DNMT) are expressed in spermatogonia (DNMT1, DNMT3A) and DNMT3B accumulate in spermatocytes and spermatids. The DNMTs dynamic expression during spermatogenesis (Uysal et al., 2016) is likely compromised upon exposure to air pollutant components.

Montjean et al. (2015) found a positive correlation between DNA methylation levels and sperm motility in a cross-sectional study. This finding strongly suggested that low levels of methylation indicate defective spermatogenesis (Montjean et al., 2015). In addition, reactive oxygen species (ROS) also can damage the integrity of DNA in the sperm nucleus and affect their count and motility (Homa et al., 2019). According to the studies, most air pollutants, including NO_2, SO_2, PMs, O_3 and PAHs, can produce ROS after being transformed by CYP450 dihydro-dehydrogenase. Stimulation of ROS production in this way takes place after the production of quinone redox and the catalysis of electron transfer reactions (Carré et al., 2017). Although certain amounts of ROS are required for the physiological function of sperm, especially the fertilization process, its excessive and uncontrolled amount results in damage to sperm (Dutta et al., 2020).

Indeed, the presence of polyunsaturated fatty acids in the sperm membrane, in addition to maintaining fluidity, makes the sperm very sensitive to oxidative stress. The peroxidation of these fatty acids can cause the loss of sperm fluidity and reduce the activity of membrane enzymes and ion channels; this affects sperm motility and some of the key mechanisms required for egg fertilization. Also, studies have shown that breaking DNA strands and genetic mutations caused by peroxidation of sperm DNA bases can lead to a decrease in fertilization potential and changes in the subsequent growth of the fetus. Other ROS effects, include the change in sperm function due to the splitting of polypeptide chains and the accumulation of protein masses, as well as the alterations

Table 3
Characteristics of selected articles.

Reference	Country	Study design	N	Age (year)	Pollutant	Media	Mean ± SD concentration	Instrument
(Rendón et al., 1994)	Cuba	Case and control	Case= 24 Control= 24	Case= 36.0 ± 9.9 Control= 35.2 ±8.95	PAH BTEX (Toluene)	Blood and air	Benzo[*a*]pyrene (BaP)= 1 ng/m^3 Toluene= 118.9 mg/m^3	BaP: gas-liquid chromatography Toluene: spectrophotometry Sperm quality: Sperm count by hemocytometer and sperm morphology by Papanicolau method.
(XIAO et al., 2001)	China	Case and control	Case= 24 Control= 37	Case= 33.18 ± 6.88 Control= 31.78 ± 6.36	BTEX (Benzene, Toluene, Xylene)	Blood	**[μmol/L]:** Benzene= 4.40 Toluene= 1.42 Xylene= 1.32	Benzene, toluene, and xylene in blood: headspace chromatographic method Sperm quality: WHO guideline
						Semen	Benzene= 1.85 Toluene= 0.22 Xylene= 5.67	
(Hsu et al., 2006)	Taiwan	Cross-sectional	48	Sideoven workers= 36.5 ±10.5 Topside-oven workers= 39.0 ±7.2	PAH	Urine	**1-OHP [ug/g CR*]:** Sideoven workers= 54.0 ± 44.8 Topside-oven workers= 207.8 ± 176.4	Urinary 1-OHP: HPLC fluorescence method. PAHs analysis: Chromatogram/ quadrupole mass spectrometer (GC-MS). WHO guidelines: Sperm count, morphology, and motility. Determination of sperm DNA fragmentation: SCSA
						Ambient	**1-OHP [ng/m^3]:** Sideoven workers= 1123.1 ± 1829.3 Topside-oven workers= 3436.1 ± 3411.0	
(Xia et al., 2009a)	China	Case-control	542	Case= 28.70 ±4.69 Control= 28.93±3.92	PAH	Urine	**1-OHP [μg/g]:** 1-hydroxynapthalene (1-N)=2.13 2-hydroxynapthalene (2-N) = 4.26 1-OHP= 1.11 2-OHF= 2.79	Urinary concentrations of PAHmetabolites: LC-MS/MS sperm quality: WHO guideline (computer-aided semen analysis (CASA))
(Xia et al., 2009b)	China	Case-control	Case= 513 Control= 273	Case= 28.65 ±4.51 Control= 29.32±3.14	PAHs	Urine	**1-N [μg/g CR]:** Case= 2.15 Control= 1.98 **2-N [μg/g CR]:** Case= 4.29 Control= 3.60 **1-OHP [μg/g CR]:** Case= 1.15 Control= 1.10 **2-OHF [μg/g CR]:** Case= 2.77 Control= 2.52	Urinary PAH metabolites: LC-MS/MS. Sperm quality: WHO guideline using computer-aided semen analysis – CASA. Semen volume, concentration and motility.
(Han et al., 2011)	China	Cross-sectional	232	20–40	PAH	Urine	**[μg/g CR]:** 2-OHNa= 7.72 2-OHFlu= 2.95 9-OHPh= 1.92 1-OHP= 0.66	PAH metabolites: HPLC-FD Semen quality, sperm apoptotic markers with Annexin V assay sperm DNA damage: comet assay.
(Katukam et al., 2012)	India	Case and control	Case= 160 Control= 200	Case= 31.48 ± 7.91 Control= 29.54 ± 7.61	Benzene	Blood	26.92 ± 21.33 μmol/dL	Body fluid benzene analysis: Head space chromatography. The sperm DNA integrity: modified alkaline single-cell gel electrophoresis or the comet assay method.
						Semen	2.47 ± 2.53 μmol/dL	
(Ji et al., 2013)	China	Cross-sectional	433	28.4 ± 3.3	PAH	Semen	60.53±22.14 MFI	Semen quality analysis: computer assisted semen analysis (CASA). DNA fragmentation analysis= The Tdt-mediated dUTP nick-end labeling (TUNEL) assay. PAH-DNA adducts determination: Immunofluorescence staining.
(Song et al., 2013)	China	Cross-sectional	53	<24 - >33	PAHs	Blood	**[ng/g]:** benzo[*k*]fluoranthene (BkF)= 1583 ± 972 Acenaphthene (Ace)= 314 ± 263 Acenaphthylene (Acy)= 109 ± 67 Fluorine (Fl)= 376 ± 195 Naphthalene (Na)= 291 ± 374 Phenanthrene (Phe)=	Blood investigation: GC–MS. WHO guidelines: Concentration, volume, and sperm motility.

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Table 3 (*continued*)

Reference	Country	Study design	N	Age (year)	Pollutant	Media	Mean ± SD concentration	Instrument
							234 ± 113 Chrysene (Chr)= 66 ± 48 Fluoranthene (Fu)= 2344 ± 2385 Benzo[*b*]fluoranthene (BbF)= 122 ± 83 Benzo[ghi]perylene (BghiP)= 569 ± 365 Anthracene (Ant)= 358 ± 392 Benzo[*a*]anthracene (BaA)= 4653 ± 3129 BaP= 335 ± 310 Dibenz[*a*,*h*]anthracene (DahA)= 207 ± 182 Indeno[1,2,3-cd]pyrene (IPy)= 58 ± 46 Pyrene (Py)= 47 ± 31	
(Jeng et al., 2013b)	Taiwan	Cross-sectional	36	High exposure group (N= 16)= 43.9 ± 8.9 Low exposure group (N= 20)= 38.3 ± 9.4 Control (N= 15)= 35.6 ± 9.2	PAH	Urine	**1-OHP [μg/g CR]:** High exposure group= 12.8 ±12.9 Low exposure group= 4.4 ± 4.3 Control= 0.3 ± 0.2	Measurement of PAHs in air: GC-MS Measurement of urinary 1-OHP: HPLC system with a fluorescence detector Semen quality: WHO guidelines Detection of DNA fragmentation: terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) assay DNA concentration: the absorbance method DNA adducts: nuclease P1-enhanced 32 P-postlabeling assay
						Air	**1-OHP [ng/m^3]:** High exposure group= 41620.3 ± 17697.6 Low exposure group= 19887.6 ± 1378.1 Control= 57.0 ± 18.1	
(Jeng et al., 2013a)	USA	Cross-sectional	65	44.5	PAH	Breathing zone Urine	1-OHP= 3075.3 ± 2537.5 ng/m^3 1-OHP= 9.4 ± 8.5 μg/g CR	PAH measurement: GC-MS Semen and urine analysis: WHO guidelines Urinary 1-OHP measurement: HPLC Measurements of DNA fragmentation: terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) assay Measurement of 8-oxodGuo: LC-MS/MS Analyses of bulky DNA adducts: two dimensional
(Jurewicz et al., 2013)	Poland	Cross-sectional	277	32.0± 4.6	PAH	Urine	1-OHP= 0.33±0.31 μg/L	1-OHP: HPLC Sperm quality: WHO guideline (computer-aided semen analysis (CASA))
(Wang et al., 2015)	China	Cross-sectional	Reference group= 76 FA exposure group= 114	Reference group= 29.26 ± 3.51 FA exposure group= 29.84 ± 4.06	Formaldehyde	Air	0.22–2.91 mg/m^3	formaldehyde investigation: formaldehyde detector Semen analyses: computer-automated semen analysis system (CASA)
(Jeng et al., 2015)	Taiwan	Cross-sectional	112	Case= 41±10 Control= 38 ± 11	PAHs	Urine	**1-OHP [μg/g CR]:** Case= 14.2 ±12.6 Control= 3.8±4.5	1-OHP measurement: HPLC with a fluorescent detector Semen analysis: WHO guidelines
(Radwan et al., 2016)	Poland	Cross-sectional	181	32.1	PAH	Urine	1-OHP= 0.29 μg/g CR	Sperm aneuploidy analysis: multicolour FISH analysis Measurement of 1-hydroxypyrene in urine: HPLC
(Ling et al., 2016)	China	Cohort	666	21.4 ± 1.2	PAHs	Urine	**[μg/g CR]:** 2-OHFlu= 0.413 ± 1.838 1-OHPyr= 0.020 ± 4.065 1-OHNap= 0.068 ± 7.195 2-OHNap= 0.650 ± 2.099 1-OHPhe= 0.084 ± 3.986	Urinary PAH: LC-MS/MS Semen analysis: WHO guidelines (computeraided sperm analysis (CASA System)) Sperm apoptosis assay: flow cytometry

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Table 3 (*continued*)

Reference	Country	Study design	N	Age (year)	Pollutant	Media	Mean ± SD concentration	Instrument
							2-OHPhe= 0.175 ± 1.838 3-OHPhe= 0.190 ± 1.856 4-OHPhe= 0.007 ± 4.393	
(Yang et al., 2017a)	China	Cross-sectional	933	32.05 ± 5.30	PAH	Urine	**[μg/L]:** 1-OHNa= 4.43 ± 6.16 2-OHNa= 9.70 ± 8.93 2-OHFlu= 3.85 ± 4.11 9-OHFlu= 3.53 ± 2.64 1-OHPh= 1.00 ± 0.88 2-OHPh= 1.57 ± 1.59 3-OHPh= 1.32 ± 1.19 4-OHPh= 1.57 ± 1.16 9-OHPh= 2.32 ± 1.28 1-OHP= 1.37 ± 1.10	PAH Metabolites Analysis: GC-MS Semen Quality: WHO guidelines
(Ling et al., 2017)	China	Cohort	666	19->24	PAHs	Urine	**[μg/g CR]:** 1-OHNap= 0.265 ± 0.543 2-OHNap= 0.898 ± 1.141 1-OHPhe= 0.143 ± 0.127 2-OHPhe= 0.214 ± 0.163 3-OHPhe= 0.233 ± 0.180 4-OHPhe= 0.025 ± 0.054 2-OHFlu= 0.498 ± 0.386 1-OHPyr= 0.049 ± 0.080	Urinary PAH metabolites measurement: HPLC-MS/MS mtDNA copy number (mtDNAcn) analysis: eal-time quantitative PCReal-time quantitative PCR mtDNA integrity analysis: long PCR Mitochondrial membrane potential (MMP) analysis: flow cytometry
(Yang et al., 2017b)	China	Cross-sectional	793	31.97 ± 5.24	PAHs	Urine	**[μg/g CR]:** 1-OHNa= 2.08 2-OHNa= 4.7 2-OHFlu= 2.54 9-OHFlu= 1.76 1-OHPh= 1.04 2-OHPh= 1.62 3-OHPh= 0.77 4-OHPh= 0.66 9-OHPh= 0.84 1-OHP= 0.83	PAH metabolites analysis: GC-MS Sperm DNA damage: Comet assay Sperm apoptosis: Annexin V/PI assay
(Jeng et al., 2018)	Taiwan	Cross-sectional	106	High exposure group= 44 ± 8 Low exposure group= 37 ± 9 Control= 38 ± 9	PAH	Urine	**1-OHP [μg/g CR]:** High exposure group= 14.70 ± 12.88 Low exposure group= 4.01 ± 4.28 Control= 0.24 ± 0.19	Urinary 1-OHP measurement: HPLC with a fluorescence detector Semen quality analysis: WHO guidelines Detection of DNA fragmentation: The terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling (TUNEL) assay
(Recio-Vega et al., 2018)	Mexico	Cross-sectional	Case= 35 Control= 35	Case= 30.36 ± 11.0 Control= 28.82 ± 8.00	PAHs	Urine	**1-OHP [μmol/mol CR]:** Case= 0.67 ± 0.89 Control= 0.13 ± 0.17	Urinary 1-OHP analysis: HPLC Semen analysis: WHO criteria DNA damage analysis: single cell gel electrophoresis (comet assay)
(Saad et al., 2019)	Egypt	Cross-sectional	66	<45	PAH	Urine	**[nmol/mmol CR]:** 1-OHP= 1.7 ± 1.68 1-naphthol= 6 ± 5.11 2-naphthol= 19.3 ± 31.71	Quantification of 1-hydroxypyrene in urine: HPLC. Semen analysis: Sperm count na motility using a computer program (Mira Lab ISO 9001). Assessment of DNA fragmentation: Halosperm.
(Yang et al., 2020)	China	Cross-sectional	111	31.4 ± 4.7	PAHs	Urine	**[μg/g CR]:** 1-hydroxynaphthalene (1-OHNa)=2.30 2-hydroxynaphthalene (2-OHNa)= 4.51 2-hydroxyfluorene (2-OHFlu)= 1.80 9-hydroxyfluorene (9-OHFlu)= 2.50 1-hydroxyphenanthrene (1-OHPh)= 0.74 2-hydroxyphenanthrene	Urinary OH-PAH: GC-MS Semen analysis: WHO manual (computer-aided semen analysis)

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Table 3 (*continued*)

Reference	Country	Study design	N	Age (year)	Pollutant	Media	Mean ± SD concentration	Instrument
							(2-OHPh)= 0.71 3-hydroxyphenanthrene (3-OHPh)= 0.73 4-hydroxyphenanthrene (4-OHPh)= 0.84 9-hydroxyphenanthrene (9-OHPh)= 1.17 1-OHP= 0.60	
(Chen et al., 2021)	China	Cohort	1452	20 (Median)	PAH	Urine and Air	**Baseline investigation [ug/g CR]:** 1-OHNap= 0.508 ± 2.353 2-OHNap= 1.415 ± 6.702 1-OHPhe= 0.286 ± 2.094 2-OHPhe= 0.382 ± 2.753 3-OHPhe= 0.412 ± 2.683 4-OHPhe= 0.137 ± 1.111 1-OHPyr= 0.083 ± 0.707 2-OHFlu= 0.959 ± 6.671 **Follow-up investigation [ug/g CR]:** 1-OHNap= 0.265 ± 0.537 2-OHNap= 0.897 ± 1.134 1-OHPhe= 0.153 ± 0.119 2-OHPhe= 0.214 ± 0.160 3-OHPhe= 0.232 ± 0.178 4-OHPhe= 0.069 ± 0.061 1-OHPyr= 0.049 ± 0.080 2-OHFlu= 0.497 ± 0.382	Air: GC-Mass Sperm quality: WHO guideline. Sperm DNA fragmentation index (DFI): sperm chromatin structural assay (SCSA) Urinary OH-PAHs metabolites: HPLC-MS/MS.
(Lv et al., 2022)	China	Cohort	205	29.49 ± 3.64	Formaldehyde	Air	1.49 ± 0.61 mg/m^3	Concentration of FA in breathing zone: formaldehyde detector Semen analyses: WHO guidelines (computer automated semen analysis system (CASA)) Sperm morphology analysis: smears
(Axelsson et al., 2022)	Sweden	Cohort	381	17–21	PAH	Urine	**[ng/mmol CR]:** 1-OHP= 0.17 ± 0.29 ng/mL 1-OHP= 11 ± 16 2-OHPH= 0.35 ± 0.44 2-OHPH= 25 ± 43	Analyses of the biomarkers: Liquid Chromatography with tandem mass spectrometry (LC-MS/MS). Determination of sperm DNA fragmentation: Sperm Chromatin Structure Assay (SCSA) test.

[*] Note: Creatinine = CR

in the integrity of the mitochondrial membrane. These processes can be accelerated by damage to DNA and sperm membrane and leading to a decrease in sperm count (Chianese and Pierantoni, 2021; Muratori et al., 2015). Rubes et al. found evidence of gene-environment interaction between glutathione-S transferase M1 (GSTM1) and air pollution (probably c-PAHs). This study found a statistically significant association between GSTM1 null genotype and increased percentage of sperm with fragmented DNA (DFI %) (β = 0.309; 95 % CI: 0.129, 0.489) and showed men homozygous null for GSTM1, having less capacity to detoxify PAHs metabolites and as a result are more sensitive to the effects of air pollution on sperm chromatin (Rubes et al., 2007).

Studies indicate that inhalation exposure to pollutants damage sperm telomere length (STL) (Zhou et al., 2021), which was consistent with the results of the study by Ling et al. (2016). This study showed that there was a negative relationship between STL and urinary PAH metabolites (Ling et al., 2016). Also, Yang et al. (2023) in a recent study investigated the relationship between PAH exposure and telomere length in the adult general population (Yang et al., 2023). This study proved that for each unit increase in base-10-logarithm-transformed 2-napthol and 2-fluorene concentration, telomere length decreased by 1 % (Yang et al., 2023). The results of these studies were consistent with the investigations conducted on other air pollutants, including the study by Zhou et al. (2021) (Zhou et al., 2021). In a recent cross-sectional study in China, the effect of ambient air pollutants on semen quality parameters was investigated and the results showed that exposure to $PM_{2.5}$ and PM_{10} in 70–90 days delay had an inverse and significant relationship with STL (Zhou et al., 2021). Lu et al. (2023) also obtained similar results in investigating the role of exposure to O_3 in reducing sperm quality (Lu et al., 2023). The results of this research showed that an increase of 10 $\mu g/m^3$ O_3 in inhaled air was associated with a decrease in STL, sperm

Table 4
Effects of exposure to formaldehyde, PAH, and BTEX on semen quality.

Reference	Volume (mL)	Concentration (10^6/mL)	Total sperm count (10^6/ ejaculate)	Abnormal morphology (%)	Sperm telomere length	DNA fragmentation	Sperm aneuploidy (%)	Vitality (%)
(Rendón et al., 1994)	Case= 3.13 Control= 3.50	Case= 62.2 Control= 28.4	_	**normal morphology:** Case= 40.1 Control= 52	_	_	_	Case= 60 Control= 52.02
(XIAO et al., 2001)	Case= 2.34 ± 1.47 Control= 2.90 ± 0.95	_	**(× 10^9 spermatozoa/ L):** Case= 173.44 ± 155.71 Control= 232.09 ± 141.47	_	_	_	_	Case= 58.95 ± 15.60 Control= 72.63 ± 6.98
(Hsu et al., 2006)	Sideoven= 2.8 ±1.4 Topside-oven= 2.4±1.4	_	Sideoven= 128.3±102.7 Topside-oven= 113.3 ±106.3	Sideoven= 14.6 ±7.8 Topside-oven= 32.3±31.3	_	Sideoven= 198.1 ±30.3 for αT 19.3±13.9 % for COMPαT Topside-oven= 246.2 ±49.5 for αT 34.8±14.4 % for COMPαT	_	_
(Xia et al., 2009a)	Case= <2 Control= ≥2	Case= <20 Control= ≥20	Case= <40 Control= ≥40	_	_	_	_	_
(Xia et al., 2009b)	_	Case= 36.48 Control= 48.81	Case= 118.40 Control= 67.28	_	_	_	_	_
(Han et al., 2011)	_	_	_	12.93	_	**tail DNA (tail%)**= 32.24	_	_
(Katukam et al., 2012)	Case (Group I)= 2.64 ± 1.19 Case (Group II)= 2.41 ± 1.11 Case (Group III)= 2.28 ± 0.92 Control= 2.48 ± 1.04	_	Case (Group I)= 26.35 ± 8.64 Case (Group II)= 23.26 ± 7.75 Case (Group III)= 19.92 ± 7.79 Control= 58.08 ± 8.89	Case (Group I)= 59.69 ± 8.31 Case (Group II)= 62.30 ± 9.14 Case (Group III)= 66.26 ± 8.02 Control= 26.57 ± 8.60	_	**Sperm DNA comet tail length (µm):** Case (Group I)= 4.98 ± 2.44 Case (Group II)= 5.86 ± 2.46 Case (Group III)= 6.13 ± 2.11 Control= 1.89 ± 0.28	_	_
(Ji et al., 2013)	_	72.8 ± 54.2	251.7 ± 225.5	_	_	18.7 ± 11.5 %	_	_
(Song et al., 2013)	3.30 ± 1.50	99.0 ± 70.3	_	_	_	_	_	_
(Jeng et al., 2013b)	High exposure group= 2.1 ± 1.3 Low exposure group= 2.0 ± 1.1 Control= 2.2 ± 1.3	High exposure group= 122.6 ± 114.4 Low exposure group= 104.8 ± 77.9 Control= 121.9 ± 102.7	_	**Normal morphology:** High exposure group= 14.5 ± 3.4 Low exposure group= 15.0 ± 3.1 Control= 34.5 ± 2.6 **Total head defects:** High exposure group= 79.2 ± 7.8 Low exposure group= 79.6 ± 5.5 Control= 61.3 ± 5.5 **Total coiled tail:** High exposure group= 6.3 ± 6.3 Low exposure group= 5.6 ± 6.2	_	**DNA fragmentation (%):** High exposure group = 37.8 ± 21.1 Low exposure group = 32.9 ± 20.0 Control= 27.1 ± 7.8 **Bulky DNA adducts (in 10^9 nucleotides):** High exposure group = 70.5 ± 33.2 Low exposure group = 68.3 ± 30.4 Control = 26.0 ± 12.9	_	High exposure group= 61.9 ± 19.2 Low exposure group= 71.0 ± 24.1 Control= 84.4 ± 14.3

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Table 4 (*continued*)

Reference	Volume (mL)	Concentration (10^6/mL)	Total sperm count (10^6/ ejaculate)	Abnormal morphology (%)	Sperm telomere length	DNA fragmentation	Sperm aneuploidy (%)	Vitality (%)
				Control= 4.2 ± 4.2				
(Jeng et al., 2013a)	–	4.6±0.9	–	**Normal morphology:** 15.3±6.8	–	36.3±22.36 %	–	72.4±19.4
(Jurewicz et al., 2013)	3.46 ± 1.46	49.65 ± 54.02	–	Head abnormalities= 30 Neck abnormalities= 15 Tail abnormalities= 6	–	16 %	–	–
(Wang et al., 2015)	median Reference group= 2.5 Low FA-exposed group= 2.7 High FA-exposed group= 2.3	median Reference group= 52.2 Low FA-exposed group= 52.1 High FA-exposed group= 54.9	median Reference group= 134.3 Low FA-exposed group= 121.6 High FA-exposed group= 126.3	–	–	–	–	–
(Jeng et al., 2015)	–	Case= 113.3 ±96.6 Control= 123.4 ±102.4	Case= 226.6 ±124.2 Control= 227.3 ±112.5	**Normal form:** Case= 29.3 ±3.2 Control= 35.5 ±2.6 **Head defects:** Case= 54.3 ±7.4 Control= 49.9 ±6.1 **Coiled tail:** Case= 5.6±4.3 Control= 4.1 ±3.2	–	**TUNEL (Terminal deoxynucleotidyl transferase-mediated dUTP nick end-labeling) (%):** Case= 38.7±21.25 Control= 29.1 ±9.4 **SCSA (%):** Case= 11.9±9.9 Control= 9.2 ±8.35 **8-oxodGuo (/10^6 dG):** Case= 23.45± 18.1 Control= 20.3 ±8.6 **Bulky DNA adducts (10^9 nucleotides):** Case= 65.25± 28.05 Control= 31.15 ±20	–	Case= 74.5 ±19.2 Control= 82.5 ±17.5
(Radwan et al., 2016)	–	50.71	–	**Normal sperm morphology** = 46	–	**Total chromosome disomy**= 1.72	X-Y−18 = 1.30 X-X−18 = 0.28 Y-Y−18 = 0.61	–
(Ling et al., 2016)	–	–	–	–	0.951 ± 1.324	–	–	–
(Yang et al., 2017a)	2.96	52.15	142.58	**Normal morphology** =20.02 **Abnormal head**= 66.92	–	–	–	–
(Ling et al., 2017)	–	–	–	–	–	MMP (%) = 70.050 ± 13.672 mtDNAcn= 3.680 ± 3.216 mtDNA integrity= 1052.042 ± 862.523	–	–
(Yang et al., 2017b)	–	–	–	–	–	Tail (%)= 34.85 Tail length (µm)= 72.18 TDM (µm)= 15.24 Comet length (µm)= 148.12	–	–
(Jeng et al., 2018)	High exposure group= 2.2 ± 1.3 Low exposure group= 2.1 ± 1.1 Control= 2.1 ± 1.3	High exposure group= 123.2 ± 115.2 Low exposure group=	–	High exposure group= 13.9 ± 3.3 Low exposure group= 16.8 ± 2.4 Control= 35.2 ± 2.6	–	High exposure group = 39.2 ± 24.2 Low exposure group = 33.2 ± 20.0 Control=30.1 ± 8.60	–	High exposure group= 71.5 ± 17.8 Low exposure group= 76.3 ± 21.0

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Table 4 (*continued*)

Reference	Volume (mL)	Concentration (10^6/mL)	Total sperm count (10^6/ ejaculate)	Abnormal morphology (%)	Sperm telomere length	DNA fragmentation	Sperm aneuploidy (%)	Vitality (%)
		105.2 ± 78.1 Control= 122.9 ± 102.7						Control= 82.9 ± 13.2
(Recio-Vega et al., 2018)	Case= 2.29 ± 1.2 Control= 2.91 ± 1.3	Case= 61.74 ± 24.2 Control= 37.93 ± 24.2	Case= 90.40 ± 79.3 Control= 173.6 ± 98.6	**Normal morphology:** Case= 50.00 ± 15.0 Control= 67.25 ± 11.3	–	**Tail length (μ):** Case= 42.07 ± 10.0 Control= 29.61 ± 9.0 **Tail moment (μ):** Case= 8.11 ± 4.8 Control= 4.07 ± 3.5 **Tail migration (μ):** Case= 23.19 ± 11.2 Control= 11.37 ± 8.9	–	Case= 50.32 ± 14.7 Control= 59.67 ± 17.1
(Saad et al., 2019)	–	–	Control= 87.5 ± 15.45 Group II-a= 26.8 ± 25.78 Group II-b= 23.7 ± 20.07	–	–	–	–	–
(Yang et al., 2020)	–	36.38	125.17	–	–	–	–	–
(Chen et al., 2021)	Baseline (median)= 3.42 Follow-up= 3.56	Baseline (median)= 53.80 Follow-up= 51.80	Baseline (median)= 183.64 Follow-up= 193.45	**Normal morphology:** Baseline (median)= 8.37 Follow-up= 10.50	–	**High DNA stainability (HDS):** Baseline investigation= 3.85 Follow-up= 3.15	–	–
(Lv et al., 2022)	2.5 (Median)	54.07 (Median)	128.79 (Median)	Normal sperm (Median)= 10	–	18.85 ±7.99 %	–	–
(Axelsson et al., 2022)	–	–	–	–	–	14 ± 11 %	–	–

Reference	Motility (μm/s)									Sperm apoptosis (%)
	LIN	VCL	VAP	VSL	BCF	ALH	MAD	Progressive (%)	Total (%)	
(Hsu et al., 2006)	–	–	–	–	–	–	–	–	Sideoven= 54.7±21.6 Topside-oven= 51.5 ±27.1	–
(Xia et al., 2009a)	–	–	–	–	–	–	–	–	Case= <50 Control= ≥50	–
(Han et al., 2011)	–	–	–	–	–	–	–	–	30.6	Annexin V^{-}/PI^{-} spermatozoa= 67.46 Annexin V^{+}/PI^{-} spermatozoa =6.25 PI^{+} spermatozoa =17.20
(Ji et al., 2013)	0.5777	41.53	–	35.3	–	–	–	–	55.3 ± 26.1	–
(Song et al., 2013)	–	–	–	–	–	–	–	–	Grade semen motility= 9.02 ± 9.12 Grade b semen motility= 18.97 ± 12.30 Grade a + b semen motility= 27.99 ± 19.31	–
(Jeng et al., 2013b)	–	–	–	–	–	–	–	High exposure group= 6.7 Low exposure group= 8.3 Control= 13.3	–	–

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Table 4 (*continued*)

Reference	Volume (mL)	Concentration (10^6/mL)		Total sperm count (10^6/ ejaculate)	Abnormal morphology (%)	Sperm telomere length	DNA fragmentation		Sperm aneuploidy (%)	Vitality (%)
(Jeng et al., 2013a)	–	–	–	–	–	–	–	–	55.9 ± 20.6	–
(Jurewicz et al., 2013)	–	78.3±16.9	52.70 ±11.32	43.6±10.6	26.37±3.81 Hz	3.55 ±0.76	–	–	0.56	–
(Wang et al., 2015)	Reference group= 66.25 ± 7.84 Low FA-exposed group= 63.88 ± 9.98 High FA-exposed group= 65.15 ± 6.61	Reference group= 52.31 ± 10.02 Low FA-exposed group= 48.87 ± 9.64 High FA-exposed group= 47.16 ± 10.15	Reference group= 38.56 ± 8.24 Low FA-exposed group= 35.07 ± 7.25 High FA-exposed group= 33.96 ± 7.52	Reference group= 35.48 ± 8.12 Low FA-exposed group= 32.08 ± 7.35 High FA-exposed group= 31.16 ± 7.34	–	Reference group= 3.46 ± 1.11 Low FA-exposed group= 3.44 ± 1.24 High FA-exposed group= 3.41 ± 1.03	Reference group= 35.48 ± 8.12 Low FA-exposed group= 32.08 ± 7.35 High FA-exposed group= 31.16 ± 7.34	median Reference group= 49.9 Low FA-exposed group= 38.6 High FA-Exposed= 36	median Reference group= 59.5 Low FA-exposed group= 49.8 High FA-exposed group= 43.8	–
(Jeng et al., 2015)	–	–	–	–	–	–	–	–	Case= 14.8 Control= 16.8	–
(Radwan et al., 2016)	–	–	–	–	–	–	–	–	56.00	–
(Ling et al., 2016)	–	–	–	–	–	3.44 ± 1.12	–	–	–	Annexin V$^-$/PI= 68.264 ± 1.219 Annexin V$^+$ = 18.084± 1.472 Annexin V$^-$/ PI$^+$= 9.579 ± 1.737
(Yang et al., 2017a)	0.6358	43.98	–	27.67	–	–	–	0.4313	0.5051	–
(Yang et al., 2017b)	–	–	–	–	–	–	–	–	–	Annexin V$^-$/PI$^-$ spermatozoa= 71.79 Annexin V$^+$/ PI$^-$spermatozoa= 5.00 PI$^+$ spermatozoa =10.73
(Jeng et al., 2018)	–	–	–	–	–	–	–	–	High exposure group= 54.1 ± 20.3 Low exposure group= 74.5 ± 24.3 Control= 81.4 ± 15.1	–
(Recio-Vega et al., 2018)	–	–	–	–	–	–	–	Case= 35.96 ± 22.1 Control= 49.03 ± 15.7	Case= 54.35 ± 19.7 Control= 67.25 ± 13.7	–
(Saad et al., 2019)	–	–	–	–	–	–	–	Control = 69.5 ± 6.66 Group II-a= 29.5 ± 21.24 Group II-b =39.1 ± 18.48	–	–
(Yang et al., 2020)	–	–	–	–	–	–	–	39.58	46.70	–
(Chen et al., 2021)	–	–	–	–	–	–	–	Baseline (Median)= 55.50 Follow-up= 57	–	–
(Lv et al., 2022)	65.21± 8.23	49.74± 10.14	36.13 ±7.96	33.16± 7.86	5.09 ± 1.03	3.44 ± 1.12	53.86± 8.05	40.13 (Median)	51.01 (Median)	–

Abbreviation: LIN= Linearity, **VAP**= Average Path Velocity, **VCL**= Velocity of the Curved Line, **VSL**= Velocity of Straight Line, **BCF**= Beat Cross Frequency, **ALH**= Amplitude of Lateral Head displacement, **MAD**= Mean Angular Displacement

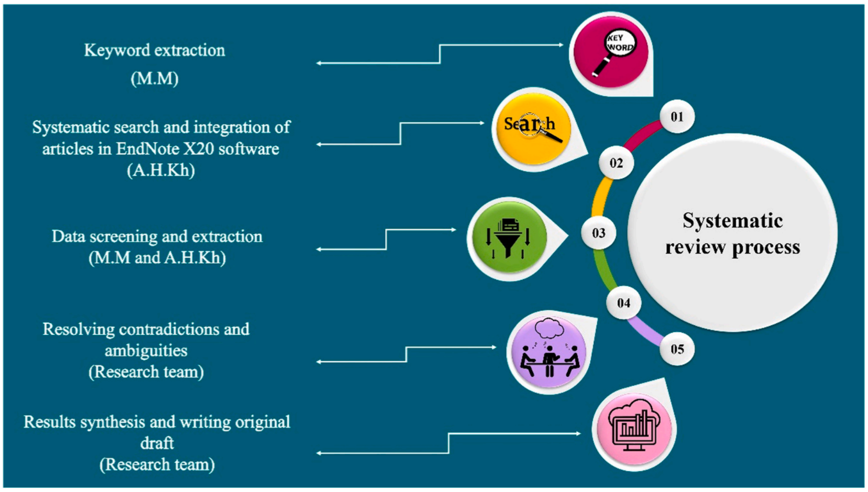

Fig. 1. The process of conducting the systematic review.

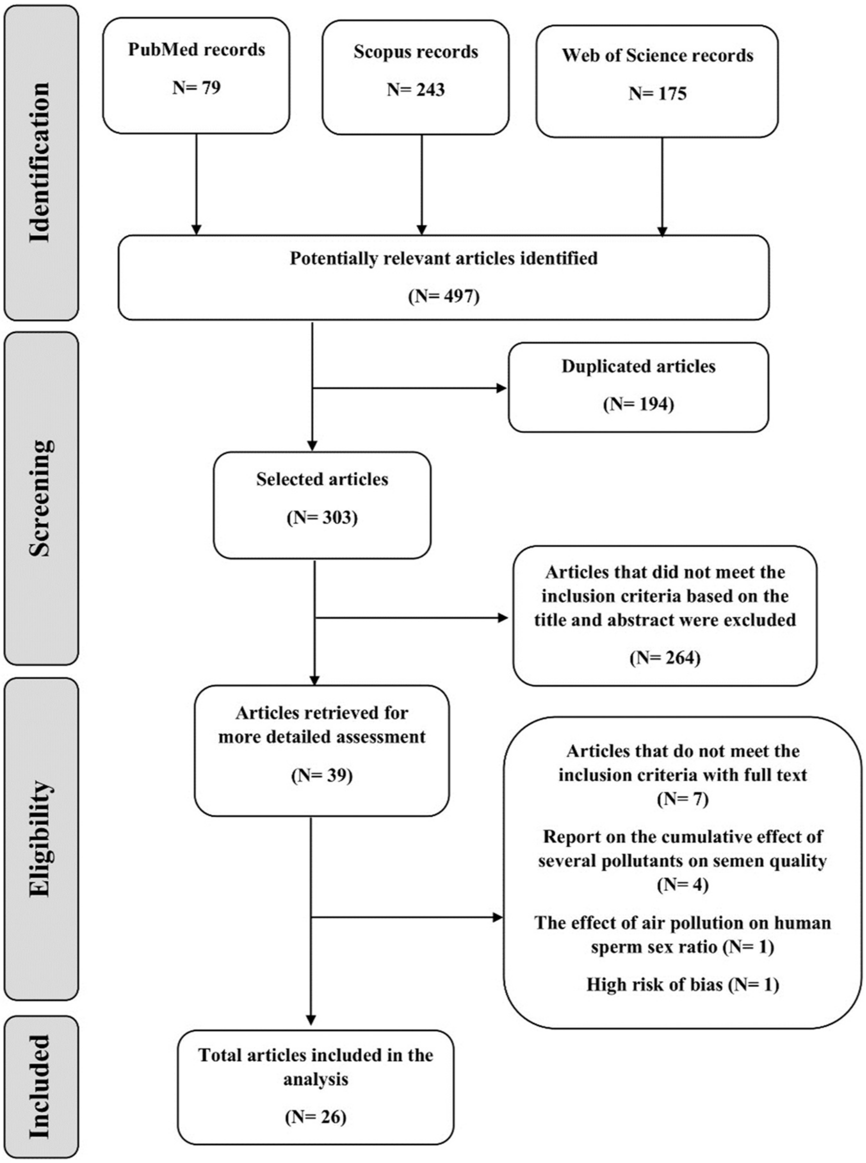

Fig. 2. PRISMA flow diagram of the literature search.

volume, sperm concentration, total count, and total motile sperm number (Lu et al., 2023).

Based on the investigations, in addition to DNA integrity, STL has also been proposed as an important index for evaluating sperm quality and playing an effective role in total sperm motility (Rocca et al., 2016; Zhang et al., 2016). Total mobility is a sensitive parameter to assess long-term and short-term exposure, which is very important in male fertility. This parameter relates to sperm fertilization ability and reflects the structural integrity and sperm vitality (Tang et al., 2017).

The results of Yang et al., (2017) showed that an increase in the levels of urinary PAH metabolites is associated with a decrease in vital Annexin V negative sperm counts, which plays a role in the process of sperm apoptosis (Yang et al., 2017b). Exposure to PAHs and formaldehyde can promote the apoptosis of sperm cells and reduce their quality by causing oxidative stress and producing free radicals (Lv et al., 2022; Vogel et al., 2020). The Yang et al., study in Wuhan, China, examined semen and urine samples from men of reproductive age showing that urinary 9-OHFlu is associated with DNA damage and increased sperm apoptosis (Yang et al., 2017b). Exposure to formaldehyde significantly decreases the levels of superoxide dismutase (SOD) and glutathione peroxidase (GSHPx), both antioxidant enzymes that protect cells from oxidative damage, as well as increases the level of malondialdehyde (MDA) in tissue (Lv et al., 2022). The work of Lv et al., indeed demonstrated formaldehyde in the occupational setting is strongly associated with poor semen quality and high levels of testicular oxidative stress (Lv et al., 2022).

In a recent study, Saad et al. (2019) investigated the impact of environmental and occupational exposure on the semen quality in idiopathic male infertility in Egypt (Saad et al., 2019). In this study, it was observed that the total sperm count in the control group (87.5 ± 15.45 $\times 10^6$/ejaculate) was significantly higher than the environmental (26.8 ± 25.78 $\times 10^6$/ejaculate) and occupational exposure group (23.7 ± 20.07 $\times 10^6$/ejaculate) connected with PAH (Saad et al., 2019). The high concentration of pollutants in occupational environments can cause acute exposure to these inhaled toxins, so the more severe adverse health effects in the occupational exposure group are not far from expected. The results of this research were consistent with the results of Recio-Vega et al. (2018) (Recio-Vega et al., 2018). In this case-control study, it was observed that following occupational exposure to PAHs, urinary levels of 1-OHP in brick kiln workers (case group) were 5 times that of healthy officer workers (control group). In addition, it was found that the volume and total sperm count in the case group is lower than the control group (Recio-Vega et al., 2018). Wang et al. (2015) also obtained similar results in the study of the effect of occupational exposure to FA on semen quality (Wang et al., 2015). This study proved that exposure to high levels of this pollutant can have adverse effects on volume and total sperm count (Wang et al., 2015).

Rapid and continuous cell division requires a high level of oxygen consumption and makes the testicular tissue more vulnerable to hypoxia and hypoxia in turn, inhibits spermatogenesis and reduces sperm count by promoting spermatogenic cell apoptosis (Zhou et al., 2021). Exposure to air pollutants disrupts the function of the Hypothalamic-Pituitary-Gonadal (HPG) axis and the secretion of the testosterone. Testosterone low levels indirectly affect spermatogenesis, maturation, and semen quality (Comar et al., 2017; Fischer et al., 2019). After evaluating the possible relationship between exposure to benzene and testosterone levels, Rosati et al., (2017) concluded that exposure to low concentrations of benzene can also have a significant effect on the testosterone blood (Rosati et al., 2017). These results are consistent with the evidence presented by Kubincová et al., (2019) investigating the effect of PAHs, chemicals with a disrupting endocrine regulation, on testicular gap junctional intercellular communication (GJIC) of key importance for the prime functioning of testicular function (Kubincová et al., 2019). Kubincová and coworkers described lower molecular weight PAHs quickly dysregulated GJIC in Leydig TM3 cells by transference of major testicular gap junctional protein connexin 43 (Cx43) from plasma membrane to cytoplasm. The longer the exposures to PAHs, the more severe the GJIC dysregulation in testes. The authors concluded that PAHs contribute to male reproductive dysfunction through testicular GJIC and junctional and/or non-junctional functions of Cx43.

Saad et al., (2019) showed a significant increase in the prolactin level in the blood serum of men with more PAHs exposure versus less exposure (Saad et al., 2019). Hyperprolactinemia is known to suppress testosterone synthesis and male fertility through the excessive secretion of adrenal corticoids or by inhibiting the secretion of the gonadotropin-releasing hormone through prolactin receptors on hypothalamic dopaminergic neurons. PAHs are also associated with binding to estrogen receptors or androgen receptors with agonistic or antagonistic effects (Carré et al., 2017). Estrogen receptor alpha (ESR1) may be down-regulated in case of hypoxia. This protein is selectively expressed in testicular cells and the epididymal epithelium and plays a role in regulating the count and morphology of sperm in both the testis and epididymis (Dumasia et al., 2016). Aberrant testicular expression of ESR1 can affect regular estrogen signaling and lead to reduced sperm output (Dumasia et al., 2016; Rago et al., 2018).

The current evidence suggests that PAHs can affect sperm function by binding and stimulating aryl hydrocarbon receptors (AhR). This mechanism also occurs in dioxins and polychlorinated biphenyls (Nebert et al., 2004). However, there is still a controversial issue given that a small number of articles included in the present study did not find a relationship between PAHs and semen quality (Han et al., 2011; Jeng et al., 2015; Ling et al., 2016, 2017). Cannarella et al., (2019) reported that the total sperm concentration in individuals living in industrialized areas was significantly lower than those living in less industrialized areas (Cannarella et al., 2019) in Sicily. The authors suggested that there is a need for effective control of air pollution based on its negative impact on human reproductive health.

Based on the reviewed studies, it is clear that the difficulty of pinpointing the air pollutant components involved in the damage to reproductive male tissues and both the outdoor and the occupational exposures are relevant to patient's evaluation. The use of different biomarkers is key to determine the severity of the exposures and can be effective for statistical data. 1-OHP is the main metabolite of pyrene, one of the most widespread PAHs produced from gasoline and diesel combustion in urban environments. This metabolite is a good biomarker to identify PAH exposure levels from different sources, ambient air, indoor air and food (Saad et al., 2019). In addition, exposure dose, pollutant concentration, duration of exposure, age, occupation, tobacco and marijuana exposures and alcohol intake, comorbidities and racial and ethnic differences can also affect the final outcome (Kumar et al., 2018).

4. Strengths and limitations

The present systematic review had several potential strengths that distinguish it from other relevant review studies. First, this study is the first and most up-to-date published systematic review related to the effect of PAHs, FA, and BTEX on men's semen quality. Second, in our systematic search, we did not impose any restrictions on study design, geographic scope, and publication time of articles. This allowed us to obtain the most comprehensive results. Third, we conducted a systematic search of the largest and most authoritative databases available to ensure the inclusion of all eligible studies. Fourth, due to the inclusion of an acceptable number of articles in this systematic review, the results obtained from 8873 subjects were examined, which indicates the comprehensiveness and generalizability of the results of the present study. Fifth, this study tried to examine all the parameters related to semen quality to increase the comprehensiveness of the study. Although this study had several strengths, but limitations including the lack of access to the full text of some studies and the limited number of pollutants examined were unavoidable.

5. Gaps and recommendations

The results of a comprehensive review of published studies show the existence of some gaps in this important area of health. According to the studies, despite the wide spread of FA in various indoor, outdoor and occupational environments, few studies have been conducted to investigate the effect of this pollutant on the semen quality. Therefore, it is recommended to conduct more cohort studies to increase knowledge and identify other adverse effects of FA on semen quality and male infertility.

One of the potentially important questions that arise after studying the results of the selected articles is, "can simultaneous exposure to several pollutants have a synergistic effect on their toxicity to reduce sperm quality?". Therefore, conducting various laboratory, cell and animal studies to answer this question seems mandatory.

Although the adverse effect of exposure to air pollutants on the reduction of semen quality has been proven, some researchers have reached contradictory results. Therefore, designing studies to investigate the effect of genetic factors on the response to the studied pollutants in reducing semen quality is highly encouraged.

Also, many men have acute and chronic exposure to many inhaled pollutants at work. However, few studies have investigated the semen quality in industrial workers. Therefore, considering the growth of industries, especially in developing countries, it is recommended to conduct more studies in this field.

6. Conclusion

The results of this systematic review showed that chronic inhalation exposure to PAHs, FA, and BTEX pollutants is associated with an increase in the concentration of metabolites of these pollutants in blood, urine and semen, which can cause a potential decrease in semen quality, including decreased motility, vitality, DNA fragmentation, and abnormal sperm morphology.

Infertility is a serious public health problem worldwide and the abrupt decline in the global fertility rate ought to be a serious concern along with the detrimental impact of air pollutants upon the health of millions of people worldwide.

One thing is clear: if air pollutants are crucial players in male reproductive problems, we can protect individuals from their exposures by controlling environmental pollution and, indeed occupational exposures.

Therefore, continuous monitoring to reduce air pollution in industries and the environment, encouraging workers to use personal protective equipment (PPE) to reduce exposure levels to pollutants and making positive changes in daily lifestyle can prevent these adverse effects on semen quality and reduce the high prevalence of men infertility. Moreover, due to the magnitude of inhalation exposures to PAHs, formaldehyde and BTEX in different environments, it is essential to increase the awareness of people and government authorities to control emissions of these pollutants.

CRediT authorship contribution statement

Tommaso Cai: Writing – review & editing. **Mahdiyeh Mohammadzadeh:** Software, Project administration, Methodology, Investigation, Data curation, Conceptualization. **Amir hossein khoshakhlagh:** Writing – original draft, Supervision, Software, Investigation, Formal analysis, Data curation, Conceptualization. **Walter D. Cardona Maya:** Writing – review & editing. **Lilian Calderón-Garcidueñas:** Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Appendix A1

Distribution of semen examination results from men in couples starting a pregnancy within one year of unprotected sexual intercourse leading to a natural conception

Parameters	N	Centiles									
		2.5th	5th	(95 % CI)	10th	25th	50th	75th	90th	95th	97.5th
Semen volume (mL)	3586	1.0	1.4	(1.3–1.5)	1.8	2.3	3.0	4.2	5.5	6.2	6.9
Sperm concentration (10^6 per mL)	3587	11	16	(15–18)	22	36	66	110	166	208	254
Total sperm number (10^6 per ejaculate)	3584	29	39	(35–40)	58	108	210	363	561	701	865
Total motility (PR + NP, %)	3488	35	42	(40–43)	47	55	64	73	83	90	92
Progressive Motility (PR, %)	3389	24	30	(29–31)	36	45	55	63	71	77	81
Non-progressive Motility (NP, %)	3387	1	1	(1–1)	2	4	8	15	26	32	38
Immotile Spermatozoa (IM, %)	2800	15	20	(19–20)	23	30	37	45	53	58	65
Vitality (%)	1337	45	54	(50–56)	60	69	78	88	95	97	98
Normal forms (%)	3335	3	4	(3.9–4.0)	5	8	14	23	32	39	45

Data Availability

Data will be made available on request.

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