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Occupational Exposure to Inhalation Anesthetics in Operating Room and Adverse Health Outcomes: A Systematic Review

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Summary: *Volatile anesthetics (VA) are essential agents for inducing and maintaining unconsciousness during specific surgical procedures, but they pose several health risks for exposed workers. The aim of the systematic review was to assess the effects of long-term VA occupational exposure in operating rooms. The review was conducted in accordance with the PRISMA Statement, and the search was conducted in PubMed, Scopus, and Web of Science to identify articles published between January 1, 1994, and December 31, 2024, that reported data from observational, quasi-experimental, and experimental studies. The protocol was registered in PROSPERO (ID: CRD42024500838). The quality of the studies was assessed using the standard Newcastle-Ottawa Scale versions for cohort and case–control studies, and an adapted version for cross-sectional studies. A total of 65 studies were included. Adverse effects were categorized into four groups: reproductive and adverse pregnancy or offspring outcomes, neurotoxic alterations, laboratory parameter changes, and cyto- and genotoxicity. Overall, no significant associations were found between VA exposure and reproductive or pregnancy outcomes. One study reported neurological alterations (prolonged reaction times). Additionally, some studies have documented impairments in immune function and minor alterations in renal and hepatic function parameters. Finally, several studies indicated an increased risk of genotoxicity and oxidative stress. Given this evidence, protective measures and health surveillance for exposed workers remain crucial preventive measures.*

1. Introduction

About 266 million surgeries are performed each year, many of which require general inhalation anesthesia [1]. This large surgical volume exposes a broad range of healthcare workers (HCW) including anesthesiologists, nurse anesthetists, operation rooms (ORs) nurses, operating room technicians/personnel, recovery room nurses, and surgeons to volatile anesthetics (VA), with a gradient of median exposure based on occupation (anesthesiologist more than scrub nurses, more than surgeons, more than circulation nurses). It has recently been estimated that 10% of HCW are exposed to VA, and, given 6 million HCW worldwide, the number of potentially exposed individuals could be as high as 600.000 [1].

Before the 1970s, the most commonly used anesthetics, such as ether and chloroform, were found to be neurotoxic and hepatotoxic. In the 1970s, exposure levels to halogenated anesthetics such as halothane were often high, up to several hundred ppm, due to underestimating inhalation risks and

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the almost total lack of evacuation systems, the poor efficiency of environmental ventilation systems, and the use of high-flow systems in anesthesia techniques. In Italy, considerable improvements have been made by adapting the ventilation system to the rules of the Ministry of Health indicated in 1989, which provided certain values for nitrous oxide but did not refer to a value for halogenates, recommending that efforts be made to respect the National Institute of Occupational Safety and Health (NIOSH) limit values established in 1977, i.e., for N_2O 25 ppm, for halogenates alone 2 ppm 'C' Ceiling, and for halogenates in combination with N_2O 0.5 ppm [2, 3]. Conversely, the American Conference of Governmental Industrial Hygienists (ACGIH) in 2011 recommended a higher global standard for occupational exposure (TLV-TWA) to halogenated gases for halothane and N_2O(50 ppm) and for enflurane and isoflurane (75 ppm). ACGIH did not set any biological exposure index for VA, even though the concentration of unmetabolized VA or their metabolites in urine has been found to be a reliable tool. Health authorities have also developed technical procedures (e.g., sampling methods, active air treatment systems, maintenance procedures, and leak tests of the machinery used for anesthesia) to minimize VA concentrations and have determined the medical surveillance of exposed workers. Moreover, in clinical practice, there has been a shift toward sevoflurane, desflurane, and isoflurane, displacing the obsolete halothane (peak use in the 1970s) and reducing N2O to a large extent. Nonetheless, despite improvements in anesthetic techniques and instrumentation, the risk of exposure to VA remains in operating rooms [4, 5] and continues to be a matter of concern, given the long exposure for HCW, which can exceed 20 years. Numerous studies have examined the acute or chronic effects of VA on mutagenic and carcinogenic risk in operating room personnel, using in vivo and in vitro approaches. The main VA are degraded into potentially toxic products. Enflurane, isoflurane, and desflurane generate carbon monoxide, a potential cause of poisoning [6]. Halothane and sevoflurane generate difluoroethylene, haloalkane, and trifluoromethyl vinyl ether (commonly known as "compound A"). In chronically exposed individuals, compound A may cause hepatotoxicity, nephrotoxicity, carcinogenesis, immunodeficiency, impairment of fertility, and adverse effects on fetal development [7, 8]. Hoerauf et al. [9] showed that inhaled exposure to traces of VA can affect HCW. Several authors suggested that chronic exposure to VA could change the genome of the target cell [4, 10].

In addition to the effect on HCWs, recent studies have analyzed the effect of VA on the environment and have pointed out that volatile anesthetics such as N_2O, as well as the highly fluorinated gases sevoflurane, desflurane, and isoflurane, are greenhouse gases and ozone-depleting agents, although to a smaller extent (0.1%) than CO_2 [1]. Although limited, there are still workplaces without artificial ventilation and scavenging systems, and hospitals where halothane is still in use. The aim of the present systematic review was to assess the effects of long-term occupational exposure to VA among HCWs working in operating rooms, using a 30-year period from 1994 to 2024.

2. Materials and Methods

2.1. Search Strategy

The systematic review was carried out in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [11]. The review protocol was registered in PROSPERO with the reference number CRD42024500838. The review question focuses on adverse outcomes associated with long-term occupational exposure to inhalation anesthetics in healthcare personnel of all genders working in the operating rooms. The studies selection procedure used the "PICOS" methodology (P stands for patient, population or problem; I for intervention; C for control group or comparison; O for outcome; S for study design) to generate the search query, and adherence to the following eligibility criteria was required: the population was made up of adult workers of all genders, occupationally exposed to inhalation anesthetics; the intervention/exposure was the occupational exposure to inhalation anesthetics in the operating rooms; the outcome was the evaluation of adverse outcomes for human health associated to the occupational exposure to

inhalation anesthetics; study design included observational, quasi-experimental, and experimental studies. For the purpose of this review, quasi-experimental studies were defined as non-randomized intervention or before–after designs conducted in occupational settings. We queried three electronic databases to search for articles: PubMed, Scopus, and Web of Science. The search was conducted from February 15th 2025 to February 28th 2025. The full search strategies for each database, including Boolean operators, is: (("Anesthetics Inhalation" OR "Volatile anesthetics" OR "Anaesthetic Gases" OR "Desflurane" OR "Isoflurane" OR "Nitrous oxide" OR "Sevoflurane" OR "Xenon" OR "haloflurane" OR "enflurane") AND ("Health Personnel" OR "health care worker*" OR "HCW" OR " operating rooms" OR " Operating Theatre") AND ("Occupational Diseases" OR "occupational health" OR "Occupational surveillance" OR "occupational exposure" OR "risk assessment" OR "occupational risk assessment")).

2.2. Inclusion/Exclusion Criteria

Articles were considered eligible if they included data from observational, quasi-experimental, or experimental studies of adult workers occupationally exposed to VA in operating rooms, regardless of gender or age. We included only items published in English or Italian from 01 January 1994 to 31 December 2024. These criteria were chosen because of changes in experiences, laws, and the use of VAs: since the 1970s, many studies have examined the potential health risks associated with exposure to VAs. For this reason, many countries have introduced regulatory limit values for VA concentrations in operating rooms. Operating rooms have also been upgraded through the introduction of scavenging systems, closed dispensing systems, and strict air-exchange protocols. Most of these improvements became widespread after 1990. For these reasons, we decided to assess the potential risk of exposure over the past 30 years to reflect the current situation and minimize bias in our study.

Studies that included data from the general population or workers exposed to VA but not in operating rooms were excluded. We also excluded studies of HCWs not occupationally exposed to inhalation anesthetics, in vitro studies, and animal studies. Other types of studies, such as reviews, meta-analyses, case studies, qualitative investigations, book chapters, editorials, and commentaries, were not considered.

The titles and abstracts from the three databases were imported into the reference management software Zotero (version 7.0.6) to conduct the initial relevance assessment. The next phase involved title and abstract screening, during which potentially suitable studies were independently reviewed by five authors (AC, KV, LC, ADG, and SG). Subsequently, the full texts of these studies were independently examined by the same two authors, and a discussion took place regarding their potential inclusion in the review. Any disagreements were resolved through consensus among the authors. All steps were supervised by two other investigators (CP and MV).

The collected data were summarized in tables that presented bibliographic details (including author, year of publication, and country of origin), sample size, participant age and gender. The tables also included information on employment characteristics, inhalation anesthetics, associated effects, confounding and interfering variables considered, and the key findings of the selected studies.

2.3. Study Quality and Evaluation

We conducted the quality assessment using the Newcastle–Ottawa Quality Assessment Scale (NOS) [12]. The standard NOS versions were applied for cohort and case–control studies. For cross-sectional studies, we used an adapted version of the NOS based on previously proposed modifications, maintaining the original three-domain structure (Selection, Comparability, and Outcome/Exposure). The adapted scale for cross-sectional studies included a maximum of 7 points: Selection (maximum 3 points), Comparability (maximum 2 points), and Outcome (maximum 2 points. For case-control and cohort studies: good quality (3 or 4 criteria in selection domain, 1 or 2 criteria in comparability domain, and 2 or 3 criteria in outcome domain); fair quality (2 criteria in selection domain, 1 or 2 criteria in comparability domain, and 2 or 3 criteria

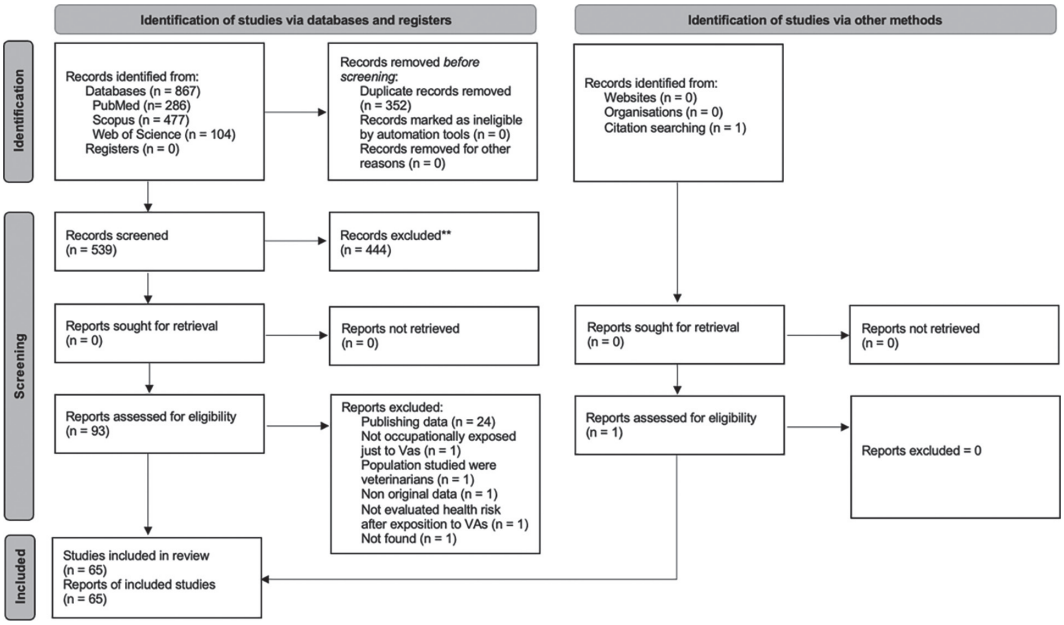

Figure 1. Article selection process used for the systematic review following the PRISMA guidelines.

in outcome domain); poor quality (0 or 1 criterion in selection domain, 0 criteria in comparability domain, or 0 or 1 criteria in outcome domain).

Each study was scored by five authors (AC, KV, LC, ADG and SG), and any discrepancies were resolved through consensus among all the authors.

3. RESULTS

3.1. Article Selection

Figure 1 shows article selection process used for the systematic review following the PRISMA guidelines.

A total of 1,062 articles were found in all searched databases (351 from PubMed, 694 from Scopus, and 97 from Web of Science). After duplicate deletion, 819 records were screened for inclusion and, of the remaining studies, 725 were deleted after analyzing the title and abstract. Then, the full texts of 94 articles were assessed for eligibility and they were evaluated considering the inclusion and exclusion criteria. After the evaluation, 29 articles were excluded because of the exclusion criteria and specifically for the following reasons: 24 articles because they were published before 01 January 1994, 1 article considered exposure not just to VAs but mixed with other substances, 1 studied exposure of veterinarians, 1 did not used original data, 1 did not evaluated health risk after exposure and 1 because it was not found. Finally, 65 articles met the inclusion criteria, and were included in the analysis.

3.2. Main Characteristics of the Included Studies

Figure 2 shows the global distribution.

The included articles involved almost all continents, with 39 from Europe, 2 from North America, 16 from Asia, 8 from South America. In particular, the studies were performed in the following countries: 12 in Italy [6, 13-23], 11 from Turkey [24-34], 9 from Iran [35-43], 8 from Brazil [44-51], 6 from Poland [10, 52-56] and 3 from Croatia [57-59]. Other countries were less represented: Canada [60, 61], China [62, 63], Germany [64, 65] and Saudi Arabia [66, 67] had two studies each. Only one study was conducted each in Austria [68], Czech Republic [69], France [70], India [4], Ireland [71], Pakistan [72], Slovenia [73] and Taiwan [74].

The studies were grouped based on the main health risk: fertility and pregnancy (Table 1), neurotoxicity (Table 2), laboratory and immunology (Table 3) and cytogenetic effects (Table 4).

Figure 2. Distribution of included articles according to the geographical areas.

Table 1. Characteristics of studies on fertility and pregnancy outcomes associated with exposure to volatile anesthetics.

Author(Y)	Design/ Country	Sample	VA Exposure	Exposure	Main Findings	Quality ecaluation according to NOS Scale
Teschke (2011)	Retrospective cohort, Canada	9433 F	Multiple halogenated agents + N_2O	NS	↑congenital anomalies with ↑exposure; OR>2 for halothane, isoflurane, sevoflurane	Poor (3)
Uzun (2014)	Cross-sectional, Turkey	60 F, 31±6 y	Desflurane, isoflurane, sevoflurane, N_2O	6.8±7 y	No differences in pregnancy-related lab markers	Poor (3)
Zanetti (2004)	Longitudinal, Italy	61 F	Mainly sevoflurane + N_2O (max 7.8 ppm; 590 ppm)	16 y	No infertility or adverse offspring outcomes; abortivity↑only in doctors (confounders)	Poor (3)

NS = not specified

These groups were chosen based on presenting studies divided on the main clinical parameters they investigated, to let us show the results merged based on the clinical evaluation. Some of these studies (n = 4) have been reported in more than 1 domain due to the outcomes investigating more areas of health risk. All the studies included subjects with an average age of 34.32 years (minimum average 26, maximum average 45) with a sample size ranging from 23 individuals [44] to 9,433 [23] (average 254.53). Most of the studies involved both males and females, while nine studies including only females [23, 28, 34, 53, 55, 56, 60, 73, 74], four only males [41, 66, 67, 72], and seven did not state the

Table 2. Neurobehavioral and neurological effects of occupational exposure to volatile anesthetics.

Author (Year)	Design / Country	Sample	VA Exposure	Exposure	Main Findings	Quality ecaluation according to NOS Scale
Isolani (1998)	Longitudinal, Italy	37 HCW	N_2O	NS	No relation between N_2O levels and vigilance/mood tests; only daily arousal variation	Poor (3)
Kozanhan (2017)	Cross-sectional, Turkey	60 exp / 51 ctrl	Desflurane, sevoflurane, N_2O	≥5 h/day ≥1 y	Altered thiol/disulfide homeostasis after adjusting for anxiety	Poor (3)
Lucchini (1995)	Cross-sectional, Italy	62 exp / 46 ctrl	Etrane, N_2O (1.3 / 62.6 ppm)	8.4±5.9 y	Higher SRT in exposed workers after shift	Good (7)
Lucchini (1996)	Cross-sectional, Italy	30 exp / 20 ctrl	N_2O (≈5–54 ppm)	4.2±4.3 y	↑ SRT and PRL only with gaseous anesthesia; cortisol unchanged	Good (7)
Lucchini (1997)	Cross-sectional, Italy	112 exp / 135 ctrl	Isoflurane 0.4 ppm, N_2O 23.2 ppm	9.7±7.5 y	No correlation between atmospheric and biological indicators	Fair (5)
Proietti (2000)	Cohort, Italy	300 HCW	Isoflurane 1.5–3.2 ppm, N_2O 40–88 ppm	10 y	Subjective symptoms (anxiety) but no blood alterations	Poor (3)
Scapellato (2008)	Cross-sectional, Italy	38 exp / 23 ctrl	Isoflurane, N_2O	9.3±7.5 y	Non-linear dose–effect trend for N_2O and neurobehavioral impairment	Fair (5)
Tran (1994)	Cross-sectional, Canada	99 exp / 182 ctrl	N_2O (TWA 43–62 ppm)	NS	Symptoms more frequent in controls due to poor IAQ	Fair (5)
Vouriot (2005)	Cross-sectional, France	53 exp / 53 ctrl	Desflurane, isoflurane, sevoflurane, N_2O	>5 y	Worse static/dynamic balance; ↑ reliance on visual input	Fair (5)

NS = not specified

Table 3. Hematologic, immunologic, neuro-renal and reproductive effects associated with occupational exposure to volatile anesthetics.

Author (Year)	Design/ Country	Sample (n)	VA (summary)	Exposure (mean)	Key finding (summary)	Quality ecaluation according to NOS Scale
Amiri (2018)	Cohort, Iran	52 exp / 52 ctrl; 34.0±6.3 y	Isoflurane, sevoflurane, N_2O (2.4;0.2;851 ppm)	10.8±5.6 y	↓Hb, Hct, MCH, MCHC, RBC in exposed vs controls	Good (7)
Bakhshaei (2017)	Cross-sectional, Iran	75 exp / 75 ctrl;NS	Halothane 1.5±1.4 ppm	NS	Urinary Br correlated with exposure; ↑abnormal ALT/ AST in exposed women	Fair (5)
Bargellini (2001)	Cross-sectional, Italy	51 exp / 20 ctrl; 34.9±5.6 y	Isoflurane, N_2O (not specified)	Exposure score (months)	Altered lymphocyte subpopulations (↓CD3, ↓CD4; ↑NK)	Poor (3)
Casale (2013)	Cross-sectional, Italy	119 exp / 184 ctrl; 41.6±9.0 y	Enflurane, halothane, isoflurane, N_2O (ns)	14.0±6.1 y	Altered liver markers; ↓ neutrophils, ↑ lymphocytes	Fair (5)
Chaoul (2015)	Cross-sectional, Brazil	15 exp / 15 ctrl; 28.2±1.5 y	Isoflurane, sevoflurane (>7 ppm); N_2O (100 ppm)	3 y	↑IL-8 (pro-inflammatory) in exposed staff	Poor (3)
Emara (2020)	Cross-sectional, Saudi Arabia	120 exp / 60 ctrl; 34.3±5.6 y	Multiple VAs + N_2O (ns)	7.3±2.0 y	↑ inorganic F, HFIP, liver toxicity markers; hematologic disturbances	Fair (5)
Goto (2000)	Cross-sectional, Ireland	20 exp / 10 ctrl; 35.6±9.1 y	Isoflurane, sevoflurane, N_2O (SI/UI reported)	NS	Reduced neutrophil apoptosis at 24 h in exposed workers	Poor (3)
Gruber (2002)	Cross-sectional, Austria	48 exp / 10 ctrl; 35.5 y	Not specified	NS	Urinary neopterin within normal range; higher in <35 y	Poor (3)
Hua (2021)	Cross-sectional, China	68 exp / 82 ctrl; 30.6±5.8 y	Sevoflurane 1.1±0.7 ppm	8.3±5.2 y	↓ SOD and vital organ parameters; ↑ MDA, bilirubin, creatinine, QT/QTc	Poor (3)

Table 3 continues

Author (Year)	Design/ Country	Sample (n)	VA (summary)	Exposure (mean)	Key finding (summary)	Quality ecaluation according to NOS Scale
Jafari (2018)	Cross-sectional, Iran	42 exp / 30 ctrl; 31.3±10.1 y	Isoflurane, sevoflurane (median 1.3 ppm)	Ventilation 15 ACH	Oxidative stress: ↑ transaminases, ↓ antioxidants, ↑ MDA	Good (7)
Ji (2021)	Cohort, China	28 exp / 28 ctrl; 33.1±5.2 y	Sevoflurane 1.0 (0.0–2.2) ppm	2–20 y	No significant effects on lymphocyte apoptosis, cell cycle, subsets or Ig levels	Good (7)
Krajewski (2007)	Cross-sectional, Poland	95 exp / 90 ctrl; 37.6 y	Halothane, isoflurane, sevoflurane, N_2O (mg/m^3)	Ventilation varied; scavenging	↓Vit B12 and ↑tHcy in exposed, worse above exposure limits	Fair (5)
Nasiri& Hosseinimehr (2006)	Cross-sectional, Iran	70 exp / 70 ctrl; 31±9 y	Halothane (ns)	NS (>1 y)	↑SGOT in exposed (within normal limits)	Fair (5)
Neghab (2020)	Historical cohort, Iran	52 exp / 52 ctrl; 34.0±6.3 y	Isoflurane, sevoflurane, N_2O (ns)	10.8±5.6 y	↑ALT, AST, ALP, GGT, α-GST;↑KIM-1, creatinine; α-GST	Fair (5)
Neghab (2023)	Historical cohort, Iran	30 exp / 30 ctrl; 35.7±6.3 y	Isoflurane, sevoflurane, N_2O (ns)	10.9±6.7 y	↑IL-4, ↑IFN-γ and ↑IFN-γ/IL-4 ratio →Th1 shift	Fair (5)
Trevisan (2003)	Cross-sectional, Italy	61 exp / 43 ctrl; 39.5±9.8 y	Sevoflurane 0.3 ppm; N_2O 31.3 ppm	NS	Slight ↑ urinary total protein; dose–response for sevoflurane suggested	Good (7)
Uzun (2014)	Cross-sectional, Turkey	60 exp; 31±6 y; 100% F	Desflurane, isoflurane, sevoflurane, N_2O Scavenging present	6.8±7.0 y	No differences in homocysteine, folate, B12, anticardiolipin/ antiphospholipid Abs	

NS = not specified

Table 4. Genotoxic, oxidative, immunologic, and other biological effects associated with occupational exposure to volatile anesthetics.

Author (Year)	Design / Country	Sample (n)	VA (summary)	Exposure (mean)	Key finding (summary)	Quality ecaluation according to NOS Scale
Al-Rasheedi (2021)	Cross-sectional Saudi Arabia	120 exp / 60 ctrl; 34.3±1.2 y	Desflurane, isoflurane, sevoflurane (ns)	7.3±0.4 y	↑ plasma fluoride, ↑ IFN-γ, ↑ IL-2; IL-4 higher in anesthesiologists; oxidative stress markers altered	Fair (5)
Aun (2018)	Cohort, Brazil	26 exp; 26.8±2.1 y	Desflurane, isoflurane, sevoflurane, N_2O	1 y	No early cytotoxicity/ genotoxicity in first residency year	Poor (3)
Aun (2023)	Cohort, Brazil	23 exp; 26.1±2.5 y	Desflurane, isoflurane, sevoflurane, N_2O	~41.2 h/wk (OR)	↑ lipid peroxidation, DNA damage, altered antioxidant gene expression during residency	Poor (3)
Baysal (2008)	Cross-sectional Turkey	30 exp / 30 ctrl; 32.5±5 y	Multiple VAs + N_2O (ns)	7±4 y	↑ leukocyte DNA damage, ↑ TOS/ OSI, ↓ TAS in exposed	Good (7)
Bilban (2005)	Cross-sectional Slovenia	153 exp / 350 ctrl; 37 y	Isoflurane, halothane, N_2O (range)	15.9±7.5 y	↑ SCE, SCE frequency and MN in anesthesia group vs controls	Good (7)
Bozkurt (2002)	Cross-sectional Turkey	16 exp / 16 ctrl; 32.0±4.1 y	Halothane, isoflurane, sevoflurane, N_2O	0.2–16 y	Higher SCE/ HFC% in exposed (not statistically significant)	Fair (5)
Braz (2018)	Cross-sectional Brazil	30 exp / 30 ctrl; 28.6±1.7 y	Isoflurane, sevoflurane, N_2O (5–155 ppm)	3.1±0.5 y	↑ micronuclei, karyorrhexis, pyknosis in buccal cells	Good (7)
Braz (2020)	Cross-sectional Brazil	32 exp / 31 ctrl; 28.1±1.8 y	Isoflurane, sevoflurane, N_2O (5–180 ppm)	3 y; 37 h/ wk	↑ basal DNA damage, ↑ IL-17A; slight ↑ MN; oxidative markersNS	Good (7)
Çakmak (2019)	Cross-sectional Turkey	46 exp / 21 ctrl; 33±6.1 y	Sevoflurane (0.3–0.6 ppm)	5 y	↑ MN in PBLs (~2×) and BECs (~3×); urinary sevoflurane high	Good (7)

Table 4 continues

Author (Year)	Design / Country	Sample (n)	VA (summary)	Exposure (mean)	Key finding (summary)	Quality ecaluation according to NOS Scale
Cegin (2016)	Cross-sectional Turkey	32 exp / 32 ctrl; 34.9 y	Desflurane, sevoflurane, N_2O (ns)	6.9 y	↑ MPO and lipid hydroperoxides; ↓ catalase and sulfhydryl groups	Fair (5)
Cerit (2014)	Cross-sectional Turkey	25 exp; 37 y (100% F)	Isoflurane, sevoflurane (ns)	80 h/ month	↓ ARE and TAS; ↑ TOS and OSI in anesthesia personnel	Fair (5)
Chandrasekhar (2006)	Cross-sectional India	45 exp / 45 ctrl; 38.9±9.0 y	Multiple VAs + N_2O (ns)	11.0±4.5 y	↑ DNA damage (comet), ↑ chromosomal aberrations and MN	Good (7)
Chang (1996)	Cross-sectional Taiwan	18 exp / 18 ctrl; 36±1.8 y	N_2O (ns)	13.7±1.2 y	In vitro evidence of DNA repair errors; correlation with years of employment	Poor (3)
Costa Paes (2014)	Cross-sectional Brazil	15 exp / 15 ctrl; 27.4±2.1 y	Isoflurane, sevoflurane, N_2O (ns)	8–22 months (30 h/wk)	↑DNA damage; changes in plasma thiols and GPx over time	Poor (3)
Eroglu (2006)	Cross-sectional Turkey	25 exp / 25 ctrl; 34.4±7.1 y	Sevoflurane, N_2O (8.9;119 ppm)	~6.6 y (78.9±74.3 mo)	↑SCE in anesthesiologists; SCE decreased after 2-month leave	Good (7)
Hoerauf (1999)	Cross-sectional Germany	27 exp / 27 ctrl; 33.3 y	Isoflurane, N_2O (0.5;11.8 ppm)	3 months (8 h/day)	↑SCE frequency after exposure	Fair (5)
Hua (2021)	Cross-sectional China	68 exp / 82 ctrl; 30.6±5.8 y	Sevoflurane 1.1±0.7 ppm	8.3±5.2 y	↓SOD; ↑MDA, bilirubin, creatinine, QT/QTc	Poor (3)
Jafari (2018)	Cross-sectional Iran	42 exp / 30 ctrl; 31.3±10.1 y	Isoflurane, sevoflurane (median 1.3 ppm)	Ventilation 15 ACH	↑transaminases, ↑MDA, ↓antioxidants (oxidative stress)	Good (7)
Kargar Shourok (2018)	Cross-sectional Iran	60 exp / 60 ctrl; 35.7±6.9 y	Isoflurane, sevoflurane, N_2O (2.4;0.2;851 ppm)	NS	↑MN and chromosomal aberrations; genotype modifies susceptibility	Good (7)
Khisroon (2020)	Cross-sectional Pakistan	50 exp / 49 ctrl; 32.1±8.8 y	Not specified	Mean job 6.5±4.7 y	↑comet assay TCS; exposure duration and GST polymorphisms affect DNA damage	Fair (5)

Table 4 continues

Author (Year)	Design / Country	Sample (n)	VA (summary)	Exposure (mean)	Key finding (summary)	Quality ecaluation according to NOS Scale
Kozanhan (2017)	Cross-sectional Turkey	60 exp / 51 ctrl; 34.7±6.5 y	Desflurane, sevoflurane, N_2O	≥5 h/day ≥1 y	Disturbed thiol/ disulfide homeostasis after anxiety adjustment	Poor (3)
Lewinska (2005)	Cross-sectional Poland	46 exp / 28 ctrl; 39.0±7.1 y	Isoflurane, sevoflurane, N_2O (range)	17.7±10.1 y	↑MN frequency in exposed nurses	Good (7)
Malekirad (2005)	Cross-sectional Iran	66 exp / 66 ctrl; 32 y	Halothane, N_2O (ns)	9.3 y	↑lipid peroxidation; ↓thiol groups; TAC unchanged	Fair (5)
Musak (2013)	Cross-sectional Czech Rep	247 exp / 250 ctrl; 37±9.8 y	Isoflurane, sevoflurane (mg/m^3)	12.8±9.6 y	↑chromosomal damage indices (CATot, CTA, CSA) vs unexposed	Good (7)
Neghab (2020)	Cross-sectional Iran	60 exp / 60 ctrl; 35.7±6.9 y	Isoflurane, sevoflurane, N_2O (2.4;0.2;851 ppm)	≥6 h/day; 11.0±5.6 y	↑MN/CA, ↑MDA, ↓TAC and SOD; antioxidant status inversely correlates with MN/CA	Good (7)
Pasquini (2001)	Cross-sectional Italy	46 exp / 66 ctrl; 39.7±6.9 y	Enflurane, N_2O (ns)	12.2±16.3 y	Mixed SCE results; sex and smoking influenced outcomes	Fair (5)
Rozgaj (1999)	Cross-sectional Croatia	129 exp / 41 ctrl; 38.7±7.8 y	Halothane, N_2O (350 mg/m^3; 350–400 ppm)	11.8±7.8 y	↑ chromosome breaks, acentric fragments, dicentrics in exposed	Fair (5)
Rozgaj (2001)	Cross-sectional Croatia	43 exp / 26 ctrl; 35.1±7.4 y	Halothane, N_2O (ns)	12.1±7.7 y	↑ chromosomal aberrations and MN; women higher RR for MN	Fair (5)
Rozgaj (2009)	Cross-sectional Croatia	50 exp / 50 ctrl; 38.7±7.6 y	Isoflurane, sevoflurane, N_2O (ns)	13.0±9.0 y	↑ comet assay tail length/moment and MN frequency in exposed	Fair (5)
Santovito (2014)	Cross-sectional Italy	21 exp / 21 ctrl; 35.7±5.7 y	Not specified	8.6±4.4 y	↑ SCE in exposed; GSTT1 null associated with higher SCE	Fair (5)
Sardaş (1998)	Cross-sectional Turkey	66 exp / 41 ctrl;NS	Halothane, isoflurane, N_2O (ns)	1–17 y	↑ comet assay DNA damage in exposed; smoking also increased damage	Fair (5)

Table 4 continues

Author (Year)	Design / Country	Sample (n)	VA (summary)	Exposure (mean)	Key finding (summary)	Quality ecaluation according to NOS Scale
Sardaş (2006)	Cross-sectional Turkey	17 exp / 19 ctrl; 33.3±3.5 y	Desflurane, isoflurane, sevoflurane, N_2O	>8 y	Vitamin C+E supplementation ↓ comet TCS in exposed (12 wks)	Fair (5)
Silva (2023)	Cross-sectional Brazil	100 exp / 93 ctrl; 34.0±12.1 y	Isoflurane, sevoflurane, N_2O (TWA 7–165 ppm)	9 (1–30) y	↑ buccal MN and NBUD; oxidative stress and instability with longer exposure; genotype effects	Good (7)
Souza (2016)	Cross-sectional Brazil	30 exp / 27 ctrl; 41.5±15.0 y	Desflurane, isoflurane, sevoflurane, N_2O	>2 y, Inadequate scavenging (0–8 ACH)	(Study truncated in file) — genomic instability and oxidative markers assessed	Good (7)

NS = not specified

gender of the participants [10, 19, 32, 35, 43, 61, 70]. All the included studies were observational studies, most of them were cross-sectional studies [4, 6, 10, 13, 15-18, 20-22, 24-30, 32-34, 36-40, 42, 46-59, 61, 62, 65-74], and other articles presents the results of longitudinal studies [14, 19, 23, 35, 41, 43-45, 60, 63]. Even though the methodology of the studies were similar, they have been run in different times, in particular from 1994 to 2004 we included 19 studies [10, 13-19, 22, 23, 25, 31, 57, 59, 61, 64, 68, 71, 74], from 2005 to 2014 we included 23 studies [4, 6, 20, 21, 24, 28, 29, 32-34, 39, 40, 49, 53-56, 58, 60, 65, 69, 70, 73], from 2015 to 2024 23 studies [26, 27, 30, 35-38, 41-43, 45-48, 50-52, 62, 63, 66, 67, 72]. This distribution emphasizes the importance of the theme in the scientific world nowadays.

The main results are reported in the following four main classes: the area "Fertility and pregnancy" (Table 1), the area "Neurotoxicity" (Table 2), the area "Laboratory and immunology" (Table 3), the area "Cytogenetic effects" (Table 4). The full scoring criteria for each study design is shown in each Table.

The area "Fertility and pregnancy" included three articles [23, 34, 60], two of them stated that there was not significant evidence about their main outcome. One of these studies, conducted on 9,433 mothers that were nurses exposed to halothane and this exposure was probably connected with possible congenital anomalies. Concerning the quality assessment of these studies, they all were evaluated as Poor.

The area "Neurotoxicity" included nine articles [14-17, 19, 21, 30, 61, 70]. The main outcomes were poorer neurobehavioral performance, measured by a specific test, and personal feelings of anxiety. An important note is that three studies stated that there was not significant evidence in the field of neurotoxicity. As the quality assessment of these studies, two were marked as Good, four as Fair, and three as Poor.

The area "Laboratory and immunology" included 17 articles [6, 13, 22, 34-37, 40, 42, 44, 48, 55, 62, 63, 67, 68, 71], the main outcome was also the oxidative stress, marked by the increasing of pro-inflammatory cytokines or for example the alteration of some blood parameters, such as transaminases and lymphocytes. About the quality assessment of these studies, four were marked as Good, seven as Fair, and six as Poor.

In total, 40 articles were included in the area "Cytogenetic effects" [4, 10, 18, 20, 24-33, 37-39, 42, 44-47, 49-54, 56-59, 62, 64-66, 69, 72-74]. The main outcome was the correlation between exposure and

oxidative stress, and some of them reported different types of reversible DNA damage (sister chromatid exchange, micronuclei frequencies, specific type of cells such as leukocytes, etc). Considering the quality assessment of these studies, 17 were marked as Good, 17 as Fair and six as Poor.

4. Discussion

Waste anesthetic gases (WAGs) are small releases of anesthetic gases that leak from a patient's anesthetic breathing circuit during delivery of or recovery from anesthesia. WAGs include N_2O and halogenated anesthetics such as halothane, enflurane, isoflurane, desflurane and sevoflurane. The halogenated anesthetics are often administered in combination with N_2O and may pose a hazard to hospital workers. The anesthetic breathing circuit includes the mask, endotracheal tube, anesthetic gas machine, ventilator, pumps, scavenging devices that limit WAG releases, plus connecting tubing and other elements, depending on EPHB Report No. 2022-DFSE-822 [75], the delivery system and are typically only used in the operating room (OR) [76].

In the USA, in a survey among USA anesthesiologists [77], 97% of them reported using anesthesia machines with scavenging systems, showing a great adherence to the NIOSH recommendation [78]. However, not only the recommendations from countries may vary, but also access to scavenging and/or exhaustion systems. These factors may therefore reduce adherence and lead to the exposure of healthcare workers to WAGs [79]. Nonetheless, we must highlight that it does not exist a global indication toward the exposure limits. The first regulations [80] were established in the USA, in 1977, when the National Institute for Occupational Safety and Health (NIOSH) determined a threshold of 25 ppm of nitrous oxide (N_2O) measured as a time-weighted average (TWA) during the administration of the drug, and 2 ppm of the other volatile anesthetics. Others have assigned a threshold of 50 ppm for N_2O for an 8-h working day [77, 81].

The European Union (EU) uses its own threshold values and exposure limits, which tend to be higher than the North American. Large discrepancies in threshold limits remain; for example, isoflurane threshold levels range from a maximum of 5 ppm in Denmark to 50 ppm in Spain. In the United Kingdom (UK), the maximum permitted levels per anesthetic under an 8-h TWA are 100 ppm for N_2O, 50 ppm for isoflurane, and 10 ppm for halothane; however, there are no defined values for sevoflurane or desflurane. In general, because absolute safe levels have not been scientifically established, most guidelines and policies regarding inhaled anesthetics are advisory rather than mandatory.

4.1. Reproductive and Pregnancy Outcomes

The evidence regarding reproductive and pregnancy outcomes among healthcare workers occupationally exposed to volatile anesthetics appears overall inconsistent and does not support a clear association under contemporary operating room conditions. In a meta-analysis [82], a 50% increase in risk of spontaneous abortion was calculated with exposure to anesthetic gases. Across the studies included in this review, reproductive outcomes were investigated mainly through retrospective cohort and cross-sectional designs, often relying on registry data [60] or self-reported reproductive histories. Sample sizes were generally moderate to large; however, exposure assessment was frequently qualitative or indirect, and information on scavenging systems and ventilation was often incomplete. Most studies conducted after the widespread introduction of scavenging systems and improved ventilation standards did not report a statistically significant increase in infertility, spontaneous abortions, or congenital anomalies among exposed workers compared with controls. When associations were observed, they were often limited to specific subgroups or historical periods characterized by higher exposure levels, particularly involving halothane and nitrous oxide. Importantly, several studies suggested that non-chemical occupational factors—such as night shifts, workload, stress, and work–life imbalance—may have contributed to adverse reproductive outcomes, potentially confounding the relationship with anesthetic exposure.

Taken together, these findings suggest that, under current exposure scenarios and with modern

anesthetic agents, occupational exposure to volatile anesthetics is unlikely to represent a major determinant of adverse reproductive or pregnancy outcomes. Nevertheless, the heterogeneity in study design, exposure metrics, and outcome definitions limits the ability to draw definitive conclusions, and residual confounding cannot be excluded.

4.2. Neurotoxicity and Neurobehavioral Effects

In the 1970s, many studies focused on neurotoxicity from VA. With new anesthetics and the lowering of exposure, neurotoxicity seemed to be set aside. In fact, studies investigating neurotoxic and neurobehavioral outcomes were relatively few and heterogeneous in terms of design, outcome measures, and exposure characterization. Most evidence derives from cross-sectional studies assessing cognitive performance, reaction times, mood, or subjective symptoms using standardized neurobehavioral tests. Overall, most studies conducted at exposure levels below or near occupational limits did not identify clinically relevant neurobehavioral impairment. Some investigations reported subtle alterations [16], such as prolonged reaction times, changes in vigilance, or increased subjective symptoms (e.g., fatigue, headache, reduced concentration), particularly at the end of work shifts or workweeks. These effects were generally mild, reversible, and not consistently correlated with biological or environmental exposure indicators.

Notably, studies that identified neurobehavioral changes often involved exposure to N_2O, either alone or in combination with halogenated anesthetics, and were conducted in settings with suboptimal ventilation or incomplete scavenging. Conversely, studies performed in operating rooms equipped with modern air-exchange systems and scavenging devices tended to report null or weak associations.

Overall, the available evidence does not support a strong or consistent neurotoxic effect of long-term occupational exposure to volatile anesthetics at current exposure levels. However, the limited number of high-quality longitudinal studies and the reliance on cross-sectional assessments preclude firm conclusions, particularly regarding subtle or cumulative effects.

4.3. Laboratory and Immunological Alterations

A larger body of evidence addressed laboratory and immunological parameters, including hematological indices, liver and kidney function markers, oxidative stress biomarkers, and immune cell profiles. These studies were predominantly cross-sectional, with some cohort designs, and generally involved small to moderate sample sizes. Several studies reported statistically significant differences between exposed workers and controls in liver enzymes, renal markers, inflammatory cytokines, and oxidative stress indicators. However, in most cases, these alterations remained within clinical reference ranges and were interpreted as subclinical or early biological effects rather than overt disease. Immune-related findings, such as changes in lymphocyte subpopulations or cytokine profiles, suggested a possible modulation of immune function, although results were not uniform across studies. Exposure levels varied widely, and positive findings were more frequently reported in studies conducted in environments lacking adequate scavenging systems or involving higher concentrations of anesthetic gases, particularly nitrous oxide. However, studies with documented low-level exposure and effective ventilation often failed to detect significant laboratory abnormalities.

These findings suggest that chronic occupational exposure to volatile anesthetics may be associated with mild and potentially reversible biological alterations, particularly related to oxidative stress and immune modulation. Nonetheless, the cross-sectional nature of most studies and the limited control for confounding factors—such as smoking, alcohol consumption, concurrent chemical exposures, and work-related stress—limit causal inference.

4.4. Cyto- and Genotoxicity and Oxidative Stress

Some studies, especially in vitro, found increased DNA damage, higher frequency of chromosomal aberrations, sister chromatid exchange or micronuclei in lymphocytes, while others, especially in vivo, did not [18]. A substantial number of studies, including several of good methodological quality, documented increased frequencies of micronuclei,

sister chromatid exchanges, chromosomal aberrations, and markers of oxidative DNA damage in exposed workers compared with controls. These effects were observed across different countries and study populations and were often accompanied by evidence of oxidative stress imbalance, characterized by increased lipid peroxidation and reduced antioxidant defenses. Importantly, some studies reported dose–response relationships and correlations with duration of exposure, supporting a potential causal link. Genetic susceptibility, such as polymorphisms in detoxification enzymes (e.g., GST genes), also appeared to modulate individual vulnerability to genotoxic effects. Many studies deepen the role of VA on oxidative stress, especially in its chronic form, which may lead to several irreversible effects, such as fibrosis, necrosis, atrophy, vascular damage and DNA breakage. Malekirad et al. [39] investigated oxidative stress induced by chronic exposure to VA and Sardas et al. [32] studied the effect of antioxidant supplementation in HCW, obtaining that supplementation of the diet with vitamin C and vitamin E results in significant decrease in the DNA damage. From a clinical point of view, there is currently much discussion on the proinflammatory, proangiogenic, and antiapoptotic cellular effect of VA [83]; based on this, VA should be detrimental in patients with cancer, although this is unproved [84].

Although many of these studies involved relatively young and otherwise healthy workers, and the observed alterations were subclinical, the consistency of findings across different settings raises concern regarding long-term health implications. Even in studies conducted under modern operating room conditions, low-level exposure to volatile anesthetics was sometimes associated with measurable genotoxic biomarkers, suggesting that current exposure limits may not fully prevent early biological effects.

4.5. Overall Interpretation and Relevance to Current Operating Room Settings

Taken together, the evidence reviewed over the last three decades indicates a gradient of effects associated with occupational exposure to volatile anesthetics. While reproductive outcomes and neurotoxicity appear weakly or inconsistently associated with exposure under contemporary conditions, laboratory alterations and, more notably, genotoxic and oxidative stress markers show more consistent associations. It is important to emphasize that many of the included studies are subject to methodological limitations, including cross-sectional designs, limited exposure assessment, and incomplete adjustment for confounders. Nevertheless, the convergence of findings on genotoxic endpoints across multiple independent studies suggests that even low-level, chronic exposure to waste anesthetic gases may induce early biological effects that warrant attention. Differences in exposure levels, laboratory methods, possible insufficient statistical power and lack of control for confounding aspects may explain these conflicting results. Future research should prioritize longitudinal designs, standardized exposure metrics, and harmonized outcome definitions, with particular attention to modern anesthetic agents and current operating room technologies. Such approaches are essential for clarifying the long-term health implications of observed subclinical alterations and informing evidence-based occupational health policies. Nowadays another technique to induce anesthesia is the Total Intravenous Anesthesia (TIVA). With this technique, the risk of exposure does not exist; however, the VAs technique cannot yet be substituted for TIVA.

4.5. Limitations of the Systematic Review

The present systematic review has some limitations. First, the results cannot be considered definitive because the included studies employed different exposure assessment methods, used different analytical methods, had insufficient statistical power, and lacked control for confounding variables. Secondly, grey literature was excluded because we considered only peer-reviewed studies. Moreover, we included articles published in Italian or English; consequently, some studies published in other languages may have been excluded. However, limiting systematic reviews to English-language publications has little impact on effect estimates or conclusions. Finally, we did not conduct a meta-analysis due to heterogeneity in the assessment methods and results across the included studies.

5. Conclusion

The reviewed articles highlight that occupational exposure to VA remains a subject of debate. Further studies are needed to evaluate the risk of chronic VA exposure in controlled operating rooms, considering factors such as ventilation systems and VA limits.

Most studies report a statistically significant increase in early-effect biomarkers, particularly cytogenetic ones, among workers exposed to VA compared with control groups, underscoring the importance of these biomarkers in biomonitoring studies. Minimizing VA exposure in work environments is crucial through the use of appropriate ventilation systems and continuous monitoring of VA levels in ppm. Moreover, it is essential to establish an international consensus on uniform, adequate global limits to protect all workers, as the adverse effects of chronic exposure beyond European and American limits are real and irreversible.

Overall, evidence over the last three decades most consistently supports an association between occupational exposure to waste anesthetic gases and early biomarkers of genetic/oxidative damage, while findings on reproductive outcomes and neurotoxicity are less consistent. Future studies should prioritize standardized exposure assessment, control for major confounders, and harmonized outcome definitions to improve comparability across settings.

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