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Systematic Review

Biological Monitoring of Occupational Exposure to Nitrous Oxide, Sevoflurane, and Desflurane in Healthcare Workers: A Systematic Review

Nastaran Ostvar [1], Laura Campo [1,2] and Silvia Fustinoni [1,2,*]

[1] Department of Clinical Sciences and Community Health, University of Milan, 20122 Milan, Italy; nastaran.ostvar@studenti.unimi.it (N.O.); laura.campo@unimi.it (L.C.)
[2] Laboratory of Toxicology, Fondazione IRCCS Ca' Granda Ospedale Maggiore Policlinico, 20122 Milan, Italy
* Correspondence: silvia.fustinoni@unimi.it

Abstract

Anesthetic gases are widely used in healthcare settings. Biological monitoring has been applied to assess internal exposure, but the available evidence has never been comprehensively synthesized. This systematic review summarizes studies of occupational exposure to nitrous oxide, sevoflurane, and desflurane, evaluates reported relationships between airborne exposure and biological concentrations, and assesses biomarker suitability. Following PRISMA guidelines, PubMed and Scopus were searched for studies published in English or Italian from 1969 to 2026. Eligible biomarkers included nitrous oxide in blood, urine, or exhaled air, sevoflurane and hexafluoroisopropanol (HFIP) in urine, and desflurane in urine. Thirty-nine studies were included. More recent studies generally reported lower airborne and biomarker concentrations. Positive relationships between airborne and biological concentrations were reported. Regression-derived urinary nitrous oxide concentrations corresponding to 50 ppm airborne exposure ranged from 25 to 35 µg/L, clustering around 30 µg/L. At contemporary low exposures, unmetabolized urinary sevoflurane and desflurane were frequently below analytical detection limits, whereas HFIP remained measurable. Urinary nitrous oxide is the best-characterized biomarker. Urinary HFIP appears promising for low-level sevoflurane exposure, although between-study variability currently prevents definition of a biological guidance value. Evidence for urinary desflurane remains limited.

Keywords: biomonitoring of exposure; operating room; healthcare workers; nitrous oxide; sevoflurane; desflurane

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1. Introduction

Anesthetic gases have played a fundamental role in medical practice since the introduction of ether anesthesia in the mid-nineteenth century. Today, inhalational anesthetics are widely used for the induction and maintenance of general anesthesia during surgical procedures, for sedation in critical care settings, and for analgesia and conscious sedation in dentistry, emergency medicine, obstetrics, and various outpatient procedures.

Over the past decades, substantial technological advances and the introduction of new anesthetic agents with improved safety profiles have transformed inhalational anesthesia. Modern anesthesia delivery systems, together with more efficient scavenging technologies, have contributed to keeping environmental contamination and occupational exposure to waste anesthetic gases (WAGs) under control. In operating rooms and intensive care units, anesthetic administration is commonly performed using continuous-flow anesthesia

workstations connected to the patient's respiratory system through tracheal intubation or supraglottic devices. These systems operate within semi-closed or closed breathing circuits, allowing partial recovery and recirculation of anesthetic gases and thereby minimizing their release into the workplace atmosphere [1].

However, anesthetic gases are also frequently administered through face masks, particularly during procedural sedation, pediatric anesthesia induction, dental care, and labor analgesia. Although mask systems may incorporate scavenging devices, their efficiency is inherently limited by leakage around the patient interface, or through an open mouth in the case of dentistry, resulting in the release of anesthetic gases into the surrounding environment. Moreover, even in the case of anesthesia performed with semi-closed or closed breathing circuits, some leakages can occur, for example, during the vaporizer filling and anesthesia induction and extubation [2].

Consequently, healthcare workers may still experience measurable occupational exposure, especially during the use of masks, prolonged procedures or in settings where scavenging systems are absent or inadequately maintained.

Currently, the most widely used inhalational anesthetics in human medicine are nitrous oxide, sevoflurane, and desflurane. Nitrous oxide is commonly administered through face masks for conscious sedation in dentistry, pediatric emergency care, and labor analgesia, while it is also used in combination with volatile halogenated anesthetics during general anesthesia. Sevoflurane and desflurane are predominantly delivered through anesthesia workstations; however, sevoflurane may be administered by mask during inhalational induction in pediatric patients when intravenous access is not readily available.

Occupational exposure to WAGs has been a matter of concern since the 1970s because of the potential adverse health effects associated with chronic low-level exposure, including neurological symptoms, reproductive disorders, genotoxic effects, and oxidative stress, although the available evidence remains inconsistent and often limited by methodological constraints.

Numerous studies have therefore investigated environmental concentrations of anesthetic gases in healthcare settings, and biological monitoring has been widely employed to assess the internal dose absorbed by exposed workers. Compared with environmental monitoring, biological monitoring provides a more direct estimate of individual exposure by integrating inhalation uptake, work practices, and interindividual variability in toxicokinetics [3].

While occupational exposure limits for airborne anesthetic gases have been established or recommended by several national and international agencies or scientific papers (reviewed in [2,4]), biological guidance values and biological limits remain scarce.

For biological monitoring of exposure, the biomarkers useful for anesthetic gases are very few. In Italy, the Italian Ministry for Health, back in 1989 [5], recommended the use of nitrous oxide in end of shift urine sample for the biological monitoring of occupational exposure to nitrous oxide, with a guidance value of 27 μg/L, corresponding to an occupational exposure limit value of 50 ppm of nitrous oxide in air. The American Conference of Governmental Industrial Hygienists since 2011, recommended urinary fluorides for the biological monitoring of exposure to fluranes with a biological exposure index (BEI) of 3 mg/L in the end of shift sample; the note on non-specificity and significant background limit its use for the evaluation of low exposures [6]. In 2026, the German Research Foundation (DFG) proposed the biological tolerance values (BAT) of 4 μg/L for both urinary sevoflurane or isoflurane or their sum in end of shift/end of exposure samples [7].

The limited availability of validated biomarkers hampers the interpretation of biomonitoring data and restricts the routine application of biological monitoring in occupational health surveillance programs. Moreover, despite the body of literature, evidence on biologi-

cal monitoring of occupational exposure to modern anesthetic gases remains fragmented, and no comprehensive synthesis of available data has been published so far.

The aim of this systematic review is therefore to identify and critically evaluate all studies on biological monitoring of occupational exposure to nitrous oxide, sevoflurane, and desflurane among healthcare workers published up to March 2026. The review encompasses studies investigating nitrous oxide in blood, urine, and exhaled air, sevoflurane and its principal metabolite hexafluoroisopropanol (HFIP) in urine, and desflurane in urine. In addition to summarizing the available evidence, this review examines temporal trends in biomarker concentrations, summarizes the reported relationships between biological biomarker concentrations and corresponding airborne exposure levels, and discusses the biological concentrations associated with currently proposed occupational exposure limits. By providing a comprehensive overview of available biomonitoring data, this review aims to support the development of evidence-based strategies for occupational health surveillance of healthcare workers exposed to anesthetic gases.

2. Materials and Methods

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) [8]. No review protocol was prospectively registered in PROSPERO or another repository.

2.1. Study Strategy

The literature search was conducted using the search strategy presented in Table 1. Three main aspects were included in the query: exposure, focusing on nitrous oxide, sevoflurane and desflurane, biomarkers/biological monitoring and health care personnel. The scientific literature was searched from Scopus and PubMed databases. The periods of investigation were from 1969 to 26 March 2026 in PubMed and 1980 to 26 March 2026 in Scopus. We considered only papers written in English or Italian.

Table 1. Keywords to construct the search query used to search in PubMed and Scopus.

Databases Used	Search Query
Scopus and PubMed	(“waste anesthetics*” OR “anesthetic gas*” OR “anesthetic gases*” OR “inhalation anesthetic*” OR “volatile anesthetic*” OR sevoflurane OR desflurane OR “nitrous oxide” OR N2O) AND (“biological monitoring” OR biomonitoring OR “biological assessment*” OR biomarker* OR “exposure biomarker*” OR “biological indicator*” OR “urinary concentration” OR “serum concentration” OR urine OR blood OR “biological trace”) AND (“health care worker*” OR “hospital staff” OR “clinical personnel” OR “anesthesia personnel” OR anesthetist* OR “nurse anesthetist*” OR “nurse*” OR “operating room personnel” OR “operating theatre staff” OR “surgical staff” OR “OR staff” OR “OR personnel” OR “hospital staff” OR “hospital worker*” OR “medical staff” OR “clinical staff” OR “surgical team” OR “anesthesia provider*” OR “staff” OR “personnel” OR “operating suite personnel” OR “hospital operating room”)

2.2. Eligibility Criteria

Studies were considered eligible when they met the following criteria:

- population: healthcare workers occupationally exposed to anesthetic gases, including anesthetists, surgeons, nurses, technicians, dentists, dental assistants, midwives, and other healthcare personnel;
- occupational setting: healthcare environments in which nitrous oxide, sevoflurane, or desflurane were used, including operating rooms, dental settings, procedural sedation units, post-anesthesia care units, and other clinical settings;
- exposure: occupational exposure to nitrous oxide, sevoflurane, or desflurane;
- biological matrices and biomarkers: nitrous oxide measured in urine, blood, or exhaled air; sevoflurane or its metabolite hexafluoroisopropanol (HFIP) measured in urine; and desflurane measured in urine;
- study design: original studies reporting biological monitoring data from occupationally exposed healthcare workers;
- eligible outcomes: quantitative concentrations of exposure biomarkers in biological samples, with or without corresponding airborne exposure measurements, and/or quantitative relationships between airborne and biological concentrations.

Studies were excluded if they:

- investigated biomarkers of biological effects or health outcomes without measuring a biomarker of exposure;
- investigated patients rather than occupationally exposed healthcare workers;
- were reviews, editorials, conference abstracts without sufficient original data, or duplicate reports;
- were experimental studies not involving occupational exposure;
- did not provide quantitative biological monitoring data for the biomarkers considered in this review.

2.3. Data Collection Process

The study selection process is summarized in the PRISMA flow diagram (Figure 1). The database search identified 578 records, including 378 from Scopus and 200 from PubMed. After removal of 49 duplicates, 529 records remained for title screening. Following title screening, 364 records were excluded as not relevant, and 165 articles were retained for abstract review.

During abstract screening, additional studies were excluded for several reasons, the most common being studies on biomonitoring of effect (n = 80) and review articles (n = 18). After this step, 48 articles were assessed for full-text eligibility. Full texts could not be retrieved for five articles, leaving 43 studies available for detailed evaluation. A total of 34 studies met the eligibility criteria and were included in the review. An additional five eligible studies were identified through supplementary searching: three through backward citation searching [9–11], and two from publications previously known to the authors [2,12]. The same eligibility criteria applied to records identified through the database searches were also applied to these additional records. These studies were added to the database-derived records, resulting in a final set of 39 studies included in the qualitative synthesis.

The screening of each paper was performed independently by two reviewers. Relevant information was extracted and collected in structured tables, one for each anesthetic gas. Study inclusion was determined through discussion between the reviewers until consensus was reached.

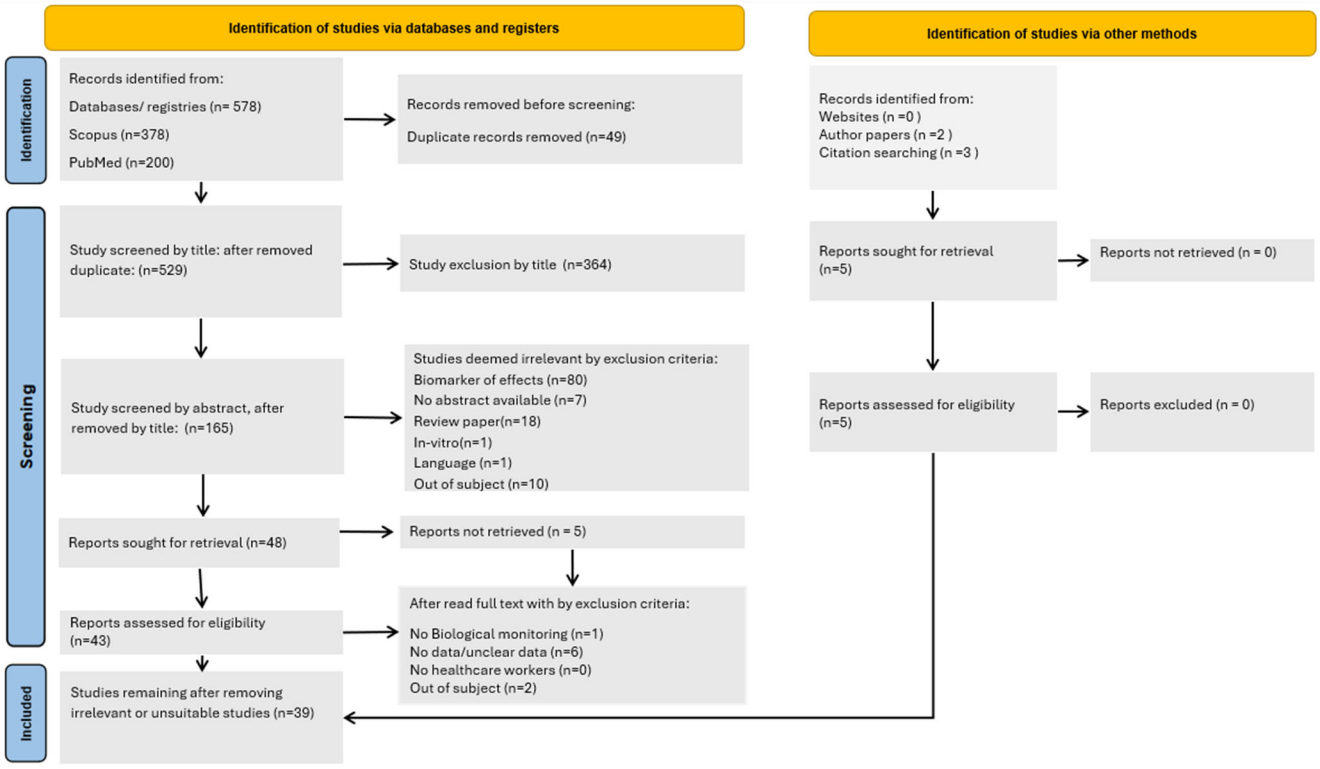


Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow diagram indicating systematic review on biological monitoring and exposure to anesthetic gases among healthcare workers.

2.4. Methodological Quality Appraisal

An initial attempt was made to assess the reporting quality of the included studies using a quantitative adaptation of the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) checklist, tailored to biological and environmental exposure assessment studies. The STROBE initiative was developed to improve the transparency and completeness of reporting in observational research and provides reporting recommendations rather than a formal risk-of-bias assessment tool [13]. Preliminary application of the adapted checklist showed that the resulting scores were strongly influenced by publication year, with older studies consistently receiving lower scores because several items included in current reporting standards were not routinely reported at the time. Therefore, a quantitative STROBE-based assessment was considered inappropriate for comparing the methodological quality of studies spanning almost five decades.

Instead, a domain-based qualitative appraisal framework was developed to evaluate methodological aspects specifically relevant to occupational biomonitoring. The following study characteristics and methodological domains were considered: study period; participant selection and eligibility criteria; job title and number of participants; biomarker measured; availability of repeated measurements; exposure duration; timing of biological sample collection; analytical method; reporting of limits of detection and/or quantification (LOD/LOQ); treatment of non-detects; adjustment for relevant factors; and statistical reporting. The assessment was intended to identify methodological strengths and limitations relevant to the interpretation and comparability of biomonitoring results rather than to generate an overall numerical quality score. The results of this appraisal are reported in Supplementary Table S1.

2.5. Data Organizations and Synthesis

The studies included in this review were categorized according to the type of anesthetic gas, with each category presented in a separate table. Within each table, the papers were arranged chronologically, from the oldest to the most recent. For each study, key information is reported, including the occupational setting, the number of workers investigated, and their job titles, when available.

Airborne exposure data, when possible representing personal exposure, are presented by worker group or job title and compared with the corresponding concentrations of biomarkers measured in biological specimens collected at the end of exposure or at the end of the work shift. In Tables 2, 4 and 6, to facilitate comparison among studies, airborne exposure to anesthetic gas was given in ppm and biomarker concentration was expressed in μg/L. When urinary concentrations were originally reported after adjustment for creatinine, conversion to volume-based concentrations was performed assuming a urinary creatinine concentration of 1.5 g/L.

Studies that reported a regression/correlation between personal exposure to anesthetic gases and biomarker levels in specific biological fluids were summarized in separate Tables 3, 5 and 7. These tables include information on the number of paired observations and the correlation coefficient, as reported in the original paper. When only the coefficient of determination (R^2) from a simple linear regression was reported, the corresponding correlation coefficient was derived as the square root of R^2, with a positive sign according to the direction of the reported relationship. The use of log-transformed data in the original analyses has also been indicated in the relevant table footnotes. When available, the biological concentrations corresponding to selected airborne exposure levels were also reported. In this case the concentrations were retained in the units used in the original studies (see exhaled nitrous oxide in Table 3, reported in ppm and HFIP in Table 5, reported in mg/L). No correlation analysis was performed.

Finally, graphical figures are presented to provide a descriptive visualization of the temporal distribution of personal airborne concentrations of anesthetic gases and corresponding biomarker concentrations reported in the studies conducted in operating rooms. The plotted values are those reported by the individual studies and may represent arithmetic means, geometric means, or medians. Studies conducted in dental settings were excluded because of the substantially different exposure conditions associated with nitrous oxide sedation. The y-axis represents the airborne concentration of the anesthetic gas or the corresponding urinary biomarker concentration, whereas publication year is shown on the x-axis. Publication year was used as a surrogate temporal indicator because the actual year of workplace sampling was seldom reported. For graphical purposes, central estimates reported below the LOQ were represented as one-half of the LOQ. This substitution was used solely to allow non-quantifiable values to be displayed on the logarithmic scale and should be interpreted cautiously because LOQs differed among studies. Given the heterogeneity in summary statistics, study populations, exposure conditions, sampling strategies, and analytical methods, these figures are intended solely as descriptive visualizations and not as formal quantitative analyses of temporal trends.

3. Results

3.1. Methodological Appraisal

Supplementary Table S1 summarizes the study characteristics and the domain-based methodological appraisal of the included studies, which are presented in chronological order. The reviewed studies seldom reported the actual study period or explicit participant eligibility criteria beyond occupational exposure to anesthetic gases. In some studies, the

number of individual workers could not be clearly determined because the number of biological samples or measurements, rather than the number of participants, was reported.

Exposure duration, when reported, was commonly approximately 4 h, corresponding to the duration of a morning work period in several studies. Biological samples were generally collected at the end of exposure or at the end of the work shift; however, these sampling times were not always clearly distinguished, limiting comparability across studies.

Analytical methods for biomonitoring were consistently based on gas chromatography coupled with different detection systems, although information on the detector was incomplete or unclear in some publications [14,15]. For the determination of unmetabolized anesthetic gases, most studies used headspace sampling of the biological specimen prior to gas chromatographic analysis. From the 1990s onwards, electron capture detection (ECD) was progressively replaced by mass spectrometric detection. Reporting of analytical sensitivity also improved over time, with information on limits of detection (LOD) and/or quantification (LOQ) becoming more frequent in later studies. The first included study explicitly reporting an LOQ was published in 2001 [16]. Similarly, information on non-detects was generally absent from earlier publications, whereas studies published after 2000 increasingly reported the number or proportion of samples below the LOD or LOQ.

Stratification of biomonitoring results was most commonly performed according to job title and/or the presence of ventilation or scavenging systems. Descriptive statistics were predominantly reported as arithmetic means and standard deviations, often accompanied by minimum and maximum values.

Overall, the number of methodological items classified as not reported (NR) was greater in earlier studies, indicating substantial temporal differences in reporting completeness that should be considered when comparing biomonitoring results across the nearly five decades covered by this review.

3.2. Nitrous Oxide

Table 2 summarizes the studies on biological monitoring of occupational exposure to nitrous oxide. Between 1978 and 2026, 24 studies were performed in five different countries: Italy (n = 18), the United Kingdom (n = 3), Finland (n = 1), Jordan (n = 1), and Sweden (n = 1). Most studies were performed in operating rooms, while others were conducted in dental settings, one in midwifery unit, and one in an oncological pediatric sedation room. The investigated workers included anesthetists, surgeons, nurses, technicians, dentists, dental assistants, dentistry nurses, sedation machine operators, midwives, and other operating room personnel. Sample sizes ranged from 4 to 1521 exposed workers, with or without repeated measurements.

Air nitrous oxide concentrations showed a marked decline over time, ranging from values exceeding 2000 ppm in early studies conducted without scavenging systems to concentrations below 1 ppm in more recent investigations (Table 2 and Figure 2). Studies directly comparing workplaces with and without scavenging systems consistently demonstrated substantial reductions in exposure when scavenging technology was implemented [14,15,17,18].

Blood and urinary nitrous oxide were the most frequently investigated biomarkers of exposure, with early investigations mainly measuring nitrous oxide in blood, whereas later studies predominantly evaluated urinary nitrous oxide. In addition, two early studies evaluated nitrous oxide in exhaled breath [19,20]. Only one study investigated both urinary and blood nitrous oxide [21] and one study measured both urinary nitrous oxide and nitrous oxide in breath [19].

For blood nitrous oxide, reported mean concentrations ranged from 21 to 2651 µg/L, with the highest concentrations generally observed in the absence of scavenging systems [14].

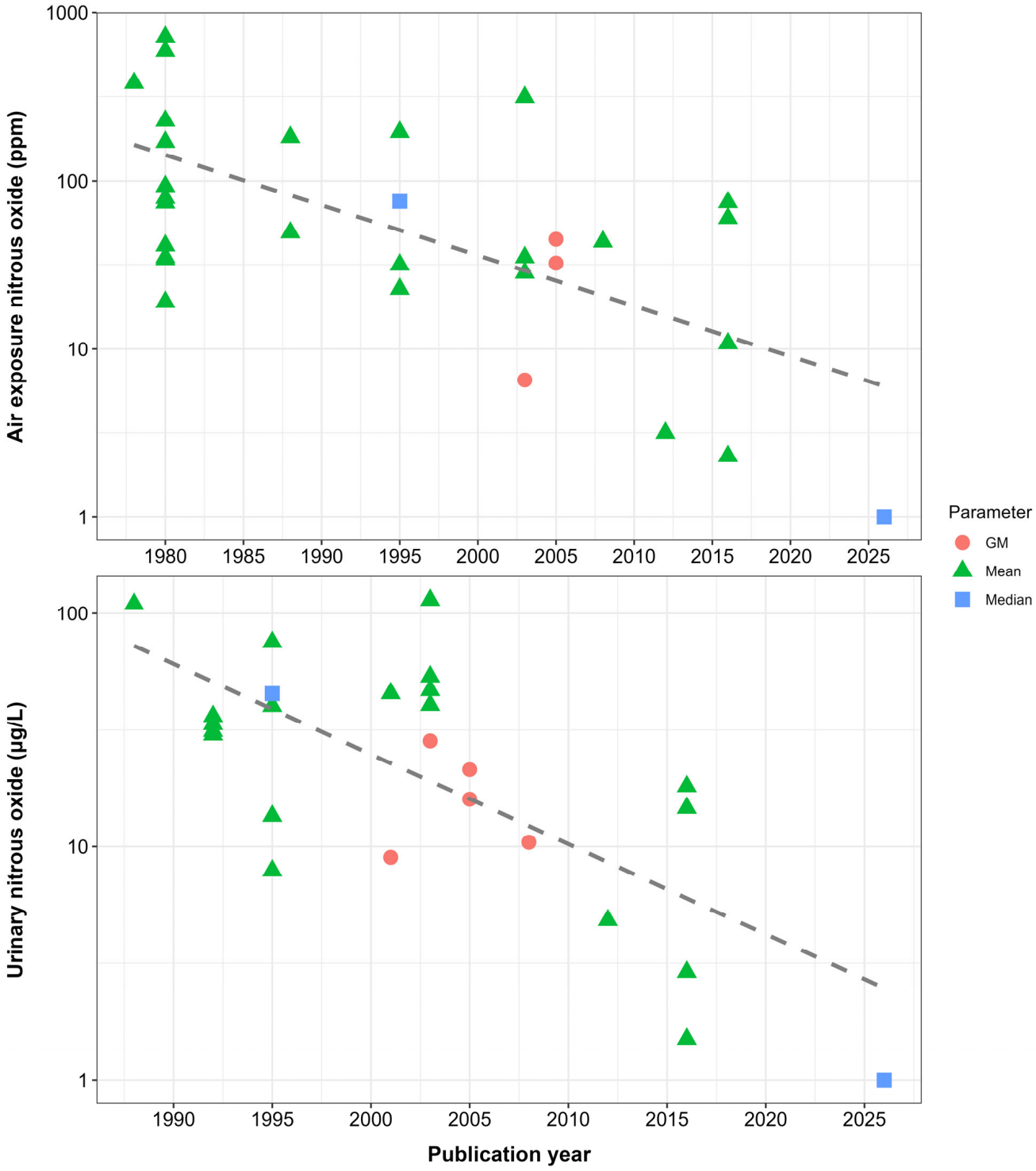


Figure 2. Airborne and urinary nitrous oxide concentrations reported in studies performed in hospital settings (excluding dentistry), plotted according to publication year. Each point represents the mean, geometric mean, or median concentration reported in an individual study. Publication year was used as a surrogate temporal indicator because the actual year of workplace sampling was not consistently reported. Values below the LOQ were plotted as LOQ/2 solely for graphical purposes and should not be interpreted as estimates of the actual concentrations. The figure is intended to illustrate broad trends in reported concentrations rather than to provide a quantitative analysis of temporal changes in exposure.

For urinary nitrous oxide, reported concentrations decreased markedly over time, from values over 2000 µg/L in studies conducted during the 1980s to concentrations below the analytical detection limit (<2 µg/L) in more recent investigations [2,12]. Most studies reported mean or geometric mean values below 50 µg/L (Table 2, Figure 2).

Nitrous oxide in breath was evaluated in an early study by Korttila (1978) [20], who reported mean end-tidal concentrations of 75 ± 39 µg/L, alongside blood levels of 153 ± 111 µg/L. Additionally, another study evaluated breath nitrous oxide levels from about 50 to 190 µg/L [19]. Only one study compared biological matrices suggesting that urinary concentrations may exceed blood concentrations under comparable exposure conditions; however, as this observation is based on a single study, it requires further confirmation [21]. Among the investigated work settings, dental sedation procedures generally showed the highest exposure levels. Across occupational groups, exposure patterns were largely determined by proximity to the emission source. In operating rooms, anesthetists generally experienced the highest exposures, whereas dentists represented the most highly exposed professional category in dental settings [2,14].

Table 3 summarizes the studies reporting positive linear regressions between personal air exposure and biological concentration of nitrous oxide in end of shift/end of exposure samples of urine, blood and exhaled air. Urinary nitrous oxide showed a consistent positive linear relationship with personal airborne exposure. The linear regressions were obtained with varying numbers of paired observations (from 11 to 835) and varying correlation strengths, with correlation coefficient ranging from 0.64 to 0.949 indicating moderate to very strong correlations. A regression derived concentration of urinary nitrous oxide ranging from 25 to 35.5 µg/L was calculated corresponding to a personal exposure of 50 ppm Some papers further proposed a biological equivalent exposure limit (BEEL) corresponding to an occupational limit value of 50 ppm, defined as the 95th lower confidence interval of the regression line [19,22–24]. This BEEL ranges from 20.6 to 27 µg/L of urinary nitrous oxide corresponding to 50 ppm.

Nitrous oxide in blood also showed a positive correlation with personal air exposure. The correlations were obtained with a variable number of observations (from 80 to 116) and a degree of strength, ranging from 0.59 to 0.82 [14,15,21]. At 50 ppm air concentration, blood nitrous oxide was estimated at 25 µg/L [21].

Evidence for exhaled-air nitrous oxide was limited, with only one study reporting a positive correlation between personal exposure and biological concentration, with a correlation coefficient of 0.911 [19].

Comparing the three different biomarkers, while the previous experiences were mostly performed using blood nitrous oxide, in the last decades urinary nitrous oxide was largely preferred. This is due to the similar performance of the two biomarkers, but a much easier and more convenient urine sampling. The limited use of exhaled-air nitrous oxide may reflect practical challenges related to sample collection and storage, together with the absence of clear advantages over urinary monitoring.

Table 2. Summary of studies evaluating the exposure to nitrous oxide in health care workers using biomarkers of exposure.

First Author, Year	Country	Setting	Scavenging System	Investigated Worker/Samples	Air Exposure	Biomarker of Exposure	Biomarkers Concentration (End of Exposure, µg/L)
Korttila K et al., 1978 [20]	Finland	Operating room	Semi-open system	10 nurses	380 ppm	Nitrous oxide in blood	Mean ± SD: 153 ± 111 µg/L
						Nitrous oxide in the end- tidal air	Mean ± SD: 75 ± 39 µg/L
Krapez JR et al., 1980 [15]	UK	Operating Room 1	Absent	17 anesthetist samples, 16 nurse samples	Anesthetists Mean (range): 721 (96–2001) ppm Nurses Mean (range): 93 (23–203) ppm	Nitrous oxide in blood	Anesthetists Mean (range): 655.6 (149.6–2208.8) µg/L Nurses Mean (range): 127.6 (39.6–365.2) µg/L
			Passive scavenging		Anesthetists Mean (range): 79 (15–203) ppm Nurses Mean (range): 19 (8–75) ppm		Anesthetists Mean (range): 92.4 (<39.6–202.4) µg/L Nurses Mean (range): <39.6 µg/L
		Operating Room 2	Absent	22 anesthetist samples, 8 surgeon samples	Anesthetists Mean (range): 591 (52–2385) ppm Surgeons Mean (range): 170 (133–194) ppm		Anesthetists: Mean (range): 585.2 (136.4–2002.0) µg/L Surgeons: Mean (range): 184.8 (114.4–268.4) µg/L
			Passive scavenging		Anesthetists Mean (range): 41 (8–112) ppm Surgeons Mean (range): 34 (3–125) ppm		Anesthetists: Mean (range): 57.2 (<39.6–127.6) µg/L Surgeons: Mean (range): <39.6 (<39.6–39.6) µg/L
		Operating Room 3	Absent	15 anesthetist samples, 8 surgeon samples	Anesthetists Mean (range): 227 (78–676) ppm Surgeons Mean (range): 716 (96–1931) ppm		Anesthetists: Mean (range): 277.2 (189.2–558.8) µg/L Surgeons: Mean (range): 739.2 (96.8–1500.4) µg/L
			Passive scavenging		Anesthetists Mean (range): 35 (6–72) ppm Surgeons Mean (range): 74 (25–207) ppm		Anesthetists: Mean (range): <39.6 (<39.6–52.8) µg/L Surgeons: Mean (range): 88.0 (<39.6–387.2) µg/L

Table 2. *Cont.*

First Author, Year	Country	Setting	Scavenging System	Investigated Worker/Samples	Air Exposure	Biomarker of Exposure	Biomarkers Concentration (End of Exposure, µg/L)
Hillman KM, 1981 [14]	UK	Dentist	Absent	44 dentist samples, 12 dental assistant samples	Mean ± SD (range): 2445.2 ± 1536.9 (266–6281) ppm	Nitrous oxide in blood	Dentist: Mean ± SD (range): 2651.44 ± 1379.84 (646.8–7150) µg/L Dental assistants: Mean ± SD (range): 893.64 ± 374 (431.2–1623.6) µg/L
			Present	46 dentist samples, 14 dental assistant samples	Mean ± SD (range): 351.2 ± 260.8 (92–1228) ppm		Dentist: Mean ± SD (range): 334.4 ± 319.44 (52.8–1795.2) µg/L Dental assistants: Mean ± SD (range): 74.8 ± 45.76 (30.8–211.2) µg/L
Sonander H, 1983 [25]	Sweden	Operating room	Partial	4 anesthetists and anesthetist nurses	NR	Nitrous oxide in urine	Range: 2000–23,000 µg/L
Imbriani M, 1988 [24]	Italy	Operating room	Partial	145 exposed (32 anesthetists, 38 surgeons, 75 nurses)	Mean ± SD (range): 181.5 ± 134.2 (4–675) ppm	Nitrous oxide in urine	Mean ± SD (range): 109.6 ± 89.6 (5.5–463.5) µg/L
Trevisan A, 1990 [19]	Italy	Operating room	Absent	20 exposed (5 surgeons, 5 anesthetists and 10 nurses)	Range of means: 92–444 ppm	Nitrous oxide in urine	Range: ≈50–520 µg/L
						Nitrous oxide in breath	Range: ≈50–190 µg/L
Bolzoni G, 1992 [26]	Italy	Operating room	Absent	54 samples (9 anesthetist samples, 19 surgeon samples, 9 nurse samples, 17 other staff samples)	Range of means: 95–746 ppm	Nitrous oxide in urine	Anesthetists: Mean (range): 30.2 (3–82) µg/L Surgeons: Mean (range): 31.3 (3–76) µg/L Nurses: Mean (range): 36.2 (2–92) µg/L Other staff: Mean (range): 33.5 (2–95) µg/L
Brugnone F, 1995 [21]	Italy	Operating room	NR	>700 exposed	Mean ± SD (range): 49 ± 45 (0.5–170) ppm	Nitrous oxide in urine	Mean ± SD (range): 40 ± 182 (1–3805) µg/L
						Nitrous oxide in blood	Mean ± SD (range): 21 ± 18 (1–75) µg/L

Table 2. *Cont.*

First Author, Year	Country	Setting	Scavenging System	Investigated Worker/Samples	Air Exposure	Biomarker of Exposure	Biomarkers Concentration (End of Exposure, µg/L)
Imberti R, 1995 [17]	Italy	Operating room	Absent with open circuit anesthesia	49 samples (Anesthetists and nurses)	Mean ± SD: 194.6 ± 15.2 ppm	Nitrous oxide in urine	Mean ± SD: 75.0 ± 6.7 µg/L
			Present with open circuit anesthesia		Mean ± SD 31.6 ± 4.1 ppm		Mean ± SD: 13.5 ± 1.7 µg/L
			Present with low flow anesthesia		Mean ± SD 22.7 ± 1.8 ppm		Mean ± SD: 7.9 ± 0.7 µg/L
Imbriani M, 1995 [22]	Italy	Operating room	Partial	1521 exposed (anesthetists, surgeons and nurses)	Median value (range): 75.5 (0.9–3340) ppm	Nitrous oxide in urine	Median (range): 45.18 (0.5–1781) µg/L
Poli D, 1999 [27]	Italy	Operating room	NR	12 operating room staff	NR	Nitrous oxide in urine	Range: 3.8–22.0 µg/L
Accorsi A, 2001 [16]	Italy	Operating room	partial	713 samples (140 anesthetist samples, 77 surgeon samples, 105 surgical nurse samples, 302 generic staff samples, 89 auxiliary staff samples)	NR	Nitrous oxide in urine	Overall Mean ± SD (range): 45.3 ± 123.5 (0.4–1415.9) µg/L Anesthetists Mean (range): 61.3 (0.4–722) µg/L Surgeons Mean (range): 17.2 (1.1–207) µg/L Surgical nurses Mean (range): 67.7 (0.7–1063) µg/L Auxiliary staff Mean (range): 36.3 (1–353) µg/ Generic staff Mean (range): 23.4 (0.8–1416) µg/
Scapellato ML, 2001 [28]	Italy	Operating room	NR	229 exposed	NR	Nitrous oxide in urine	Overall Range of means: 4.47 to 116.31 (0–342.4 µg/L)
Accorsi A, 2003 [23]	Italy	Operating room	NR	124 exposed (31 anesthetists, 4 surgeons, 26 surgical nurses, 63 operating room personnel)	Geometric mean (range): 6.5 (0.2–123.6) ppm	Nitrous oxide in urine	Geometric mean (range): 9.0 (0.5–74.9) µg/L

Table 2. *Cont.*

First Author, Year	Country	Setting	Scavenging System	Investigated Worker/Samples	Air Exposure	Biomarker of Exposure	Biomarkers Concentration (End of Exposure, µg/L)
Henderson K A, 2003 [29]	UK	Midwifery units	NR	46 midwives	Mean ± SD (range): 313 ± 358 (2.4–1300) ppm	Nitrous oxide in urine	Mean ± SD (range): 114 ± 191 (0–1102) µg/L
Trevisan A, 2003 [18]	Italy	Operating room	Open circuit/Semi-closed circuit	61 exposed (surgeons, assistant surgeons, anesthetists, nurses)	Overall–Mean (range): 31.3 (0.9–111.6) ppm	Nitrous oxide in urine	Mean ± SD: 46.7 ± 54.4 µg/L
					Open circuit–Mean (range): 34.9 (0.9–99.45) ppm		Mean ± SD: 53.4 ± 65.3 µg/L
					Semi-closed circuit–Mean (range): 28.3 (0.9–111.6) ppm		Mean ± SD: 40.4 ± 45.4 µg/L
Rovesti S, 2005 [30]	Italy	Operating room	NR	>80 exposed (surgeons, assistant surgeons, anesthetists, nurses)	First survey GM (range): 44.7 (37.1–53.9) ppm	Nitrous oxide in urine	First survey GM (range): 28.4 (3.9–161) µg/L
					Second survey GM (range): 32.3 (27.5–38.0) ppm		Second survey GM (range): 21.4 (2.4–105) µg/L
Scapellato ML, 2008 [31]	Italy	Operating room	NR	38 surgical nurses	NR	Nitrous oxide in urine	Monday GM (range): 15.9 (3.0–137) µg/L Friday GM (range): 10.4 (1.8–73.3) µg/L
Al-Ghanem S, 2008 [32]	Jordan	Operating room	NR	18 exposed	Mean ± SD (range): 43.2 ± 39.3 (0.0–136.0) ppm	Nitrous oxide in urine	Mean ± SD (range): 1234 ± 836 (247–3182) µg/L
Fustinoni S, 2009 [12]	Italy	Operating room	NR	75 exposed (24 surgeons, 25 nurses, 13 technicians, 13 anesthetists)	Range: <0.5 to 6.9 ppm, 81% quantified samples	Nitrous oxide in urine	<2 µg/L, 0% quantified samples
Fustinoni S. 2012 [33]	Italy	Operating room	NR	180 exposed	Mean (range): 3.15 (0.13–142) ppm	Nitrous oxide in urine	Mean (range): 4.85 (<2–658 µg/L), 20% quantified samples

Table 2. *Cont.*

First Author, Year	Country	Setting	Scavenging System	Investigated Worker/Samples	Air Exposure	Biomarker of Exposure	Biomarkers Concentration (End of Exposure, µg/L)
Messeri A, 2016 [34]	Italy	Pediatric sedation room of the oncology department	Face mask	90 samples	Mean (range): 74.5 (33.2–105.6) ppm	Nitrous oxide in urine	Mean (range): 18.1 (15.3–37.4) µg/L
			Face mask connected to demand valve		Mean (range): 59.7 (31.3–102.4) ppm		Mean (range): 14.6 (12.4–29.1) µg/L
			Double face mask		Mean (range): 10.8 (7.1–13.4) ppm		Mean (range): 2.9 (2.6–4.8) µg/L
			Double face mask connected to demand valve		Mean (range): 2.3 (1.0–5.8) ppm		Mean (range): 1.5 (1.2–2.3) µg/L
Zaffina S, 2019 [35]	Italy	Dentist (pediatric)	NR	21 exposed (10 dentists 11 assistants)	Mean ± SD (range): 24.17 ± 16.16 ppm	Nitrous oxide in urine	Dentists Mean ± SD: 9.94 ± 6.92 µg/L Assistant Mean ± SD: 8.23 ± 4.90 µg/L
Campo L, 2026 [2]	Italy	Operating room	Present	54 samples (surgeons, anesthetists, surgical nurses, nurses, auxiliary)	Median (5th–95th): 1.0 (<0.5–33.7) ppm, 89% quantified samples	Nitrous oxide in urine	Median (5th–95th): <2 (<2–10) µg/L, 37% quantified samples
		Dentist	Present	23 samples (dentists, sedation machine operator, dentistry nurses, auxiliary)	Median (5th–95th): 28.3 (3.3–363.9) ppm, 100% quantified samples		Median (5th–95th): 7 (<2–118) µg/L, 70% quantified samples

NR = Not reported, GM = Geometric mean; SD = standard deviation.

Table 3. Linear regressions between biological concentrations of nitrous oxide in end of exposure or end of shift samples and the corresponding personal exposure.

First Author, Year	Nitrous Oxide in End of Exposure/Shift Urine			Nitrous Oxide in End of Exposure/Shift Blood			Nitrous Oxide in End of Exposure/Shift Exhaled Air		
	N Paired Data	Correlation Coefficient	Regression Derived Concentration (Corresponding Air Exposure)	N Paired Data	Correlation Coefficient	Regression Derived Concentration (Corresponding Air Exposure)	N Paired Data	Correlation Coefficient	Regression Derived Concentration (Corresponding Air Exposure)
Krapez J R, 1980 [15]				116	0.82 *	-			
Hillman KM, 1981 [14]				NR	0.77 *	-			
Sonander H, 1983 [25]	11	0.99 *	-						
Imbriani M, 1988 [24]	145	0.89	20 µg/L (25 ppm) 13 µg/L (25 ppm) ‡ 35 µg/L (50 ppm) 27 µg/L (50 ppm) ‡ 65 µg/L (100 ppm) 55 µg/L (100 ppm) ‡						
Trevisan A, 1990 [19]	20	0.760	20.6 µg/L (50 ppm)				20	0.911	29.6 ppm (50 ppm)
Brugnone F, 1995 [21]	76	0.64	25 µg/L (50 ppm)	80	0.59	25 µg/L (50 ppm)			
Imberti R, 1995 [17]	49	0.95 *							
Imbriani M,1995 [22]	835	0.89	30 µg/L (50 ppm) 25 µg/L (50 ppm) ‡						
Accorsi A, 2001 [16]	73	0.86	-						
Accorsi A, 2003 [23]	104	0.93	22.3 µg/L (25 ppm) 17.1 µg/L (25 ppm) ‡ 35.5 µg/L (50 ppm) 26.4 µg/L (50 ppm) ‡						
Rovesti S, 2005 [30]	96	0.92	30.7 µg/L (50 ppm)						
Zaffina S, 2019 [35]	10 dentists 11 assistants	0.786 * 0.918 *	-						
Campo L, 2026 [2]	76	0.65 *							

* Repeated measurements; ‡ Biological Equivalent Exposure Limit (BEEL) proposed considering the 95th lower confidence limit of the regression line.

3.3. Sevoflurane

The first biomonitoring study on occupational exposure to sevoflurane was published in 2000, approximately two decades after the first studies on nitrous oxide [36]. This reflects the later introduction of sevoflurane into clinical practice. Between 2000 and 2025, 18 studies on occupational exposure to sevoflurane using exposure biomarkers were performed in five different countries, including Italy (n = 12), Germany (n = 3), Belgium (n = 1), Iran (n = 1), and Jordan (n = 1). Investigated workers were anesthetists, surgeons, nurses, technicians, auxiliary personnel, and other healthcare personnel. Most of the studies were performed in operating rooms, two of which were pediatric [37,38], and one in a post-anesthesia care unit (PACU) [11]. The number of study workers ranged from 8 to a few hundred (see Table 4).

The concentration of air sevoflurane ranged from <0.10 to 139.9 ppm; the highest concentration was found in the oldest study [36], that was performed with on open/semi open circuit. Airborne sevoflurane concentrations showed a marked decline over time; typical concentrations measured in the last 10 years are often below 0.5 ppm, as illustrated in Figure 3.

Urinary sevoflurane and urinary hexafluoro isopropanol (HFIP), the main metabolite of sevoflurane, were reported in 12 and 12 studies, respectively; 6 studies investigated both.

For urinary sevoflurane, studies published until 2015 reported concentrations between 0.1 and a few μg/L. In the most recent investigations, urinary sevoflurane was below the analytical detection limit in all samples [39,40].

For urinary HFIP, the first study using this biomarker reported a mean concentration of 7400 μg/L with anesthesia administered with an open/semi-open circuit [36]; the following studies reported much lower concentrations with mean/median values of some hundreds of μg/L in the first decades and of few tens of μg/L in the latest studies. A clear trend toward lower concentrations was observed for urinary HFIP, mirroring the decline in airborne sevoflurane concentrations (Figure 3).

Across studies simultaneously measuring both biomarkers, urinary HFIP concentrations exceeded those of unmetabolized sevoflurane by factors ranging from 38-fold to more than 800-fold. This supports previous observations reporting that the adsorbed sevoflurane is excreted about two orders of magnitude more for HFIP than for unmetabolized sevoflurane [9,11,37,39–41].

No consistent differences in urinary sevoflurane or HFIP concentrations were observed among operating rooms, pediatric operating rooms, and PACU.

Exposures were reported to be higher in anesthetists, similarly to what has been reported for nitrous oxide.

Urinary sevoflurane shows positive linear regression with air exposure, sometimes after log transformation of data (Table 5). The linear regressions were obtained with a different number of observations (from 10 to 104) and a variable degree of strength, ranging from 0.49 to 0.86, indicating weak to strong associations between airborne and urinary sevoflurane concentrations. At 2 ppm air concentration, urinary sevoflurane levels were generally around 3–4 μg/L [23,37,41].

Similarly, HFIP shows positive linear regression with air exposure, sometimes after log transformation of data (Table 5). The linear regressions were obtained with a different number of observations (from 22 to 533) and different levels of correlation strength, with correlation coefficient ranging from 0.456 to 0.88. For exposure to air sevoflurane of 2 ppm, the concentration of HFIP ranged from 318 to 2773 μg/L [10,41].

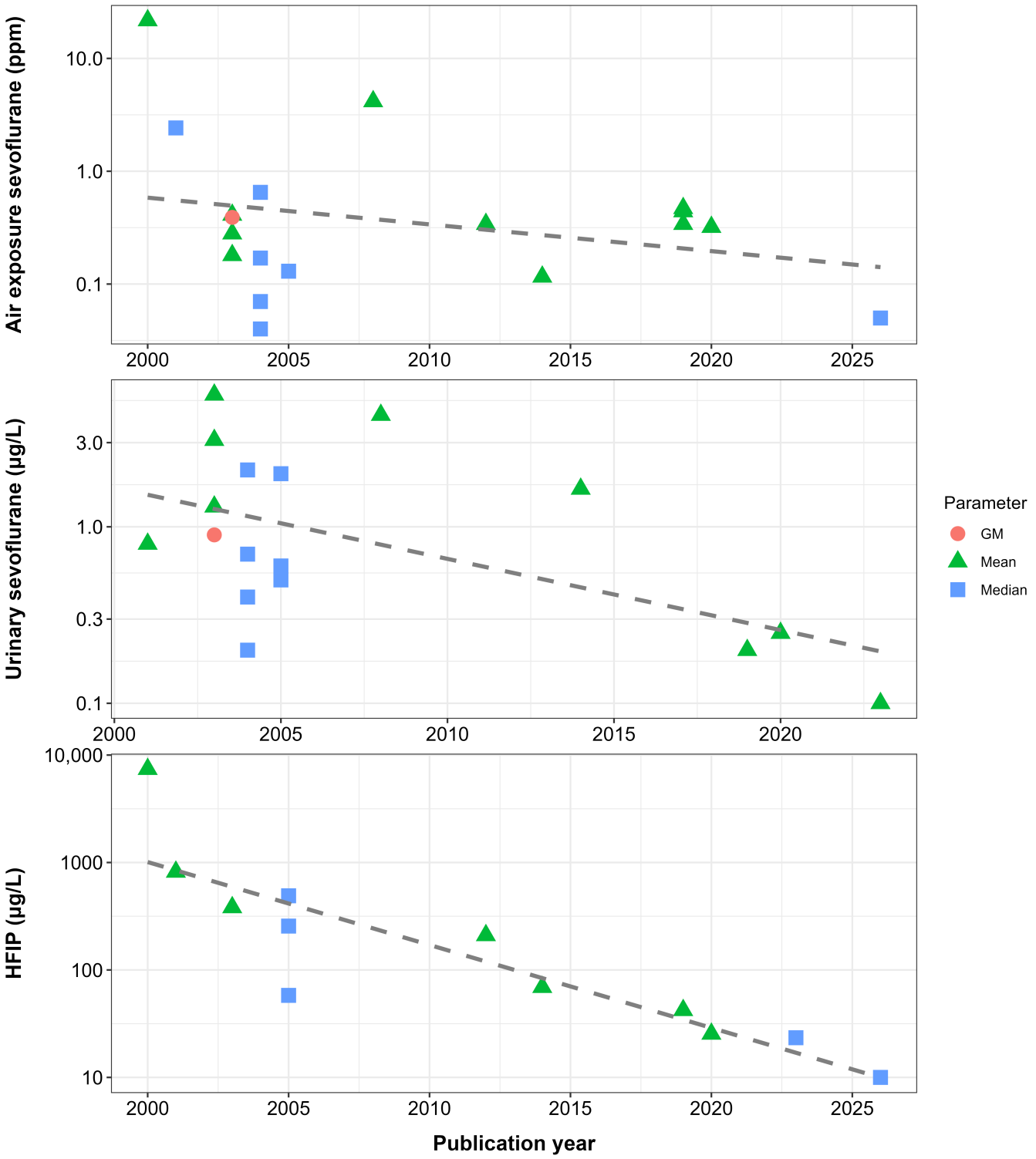


Figure 3. Airborne and urinary sevoflurane and HFIP concentrations reported in studies performed in hospital settings, plotted according to publication year. Each point represents the mean, geometric mean, or median concentration reported in an individual study. Publication year was used as a surrogate temporal indicator because the actual year of workplace sampling was not consistently reported. Values below the LOQ were plotted as LOQ/2 solely for graphical purposes and should not be interpreted as estimates of the actual concentrations. The figure is intended to illustrate broad trends in reported concentrations rather than to provide a quantitative analysis of temporal changes in exposure.

Table 4. Summary of studies evaluating the exposure to sevoflurane in health care workers using biomarkers of exposure.

First Author, Year	Country	Setting	Scavenging System	Investigated Worker/Samples	Air Exposure	Biomarker of Exposure	Biomarkers Results (End of Exposure, µg/L)
Haufroid V, 2000 [36]	Belgium	Operating room	Close circuit	50 exposed	Mean (range): 0.1 (<0.1–0.3) ppm	HFIP in urine	Mean (range): <500 µg/L
			Open/semi-open circuit		Mean (range): 21.7 (2.2–139.9) ppm		Mean (range): 7400 (<500–58,800) µg/L
Accorsi A, 2001 [16]	Italy	Operating room	NR	707 samples	NR	Sevoflurane in urine	Mean ± SD (range): 0.8 ± 3.6 (0–46) µg/L
Imbriani M, 2001 [42]	Italy	Operating room	NR	145 exposed (anesthetists, surgeons, nurses)	Mean (range): 2.42 (0.05–27.9) ppm	HFIP in urine	Mean (range): 818 (20–7730) µg/L
Accorsi A, 2003 [23]	Italy	Operating room	NR	124 exposed (31 anesthetists, 4 surgeons, 26 surgical nurses, 63 room personnel)	Geometric mean (range): 0.39 (0.05–3.0) ppm	Sevoflurane in urine	Geometric mean (range): 0.90 (0.1–5.0) µg/L
Barbic F, 2003 [10]	Italy	Operating room	NR	86 exposed	Mean ± SD (range): 3.25 ± 10.22 (0.01–26,700) mg/m^3	HFIP in urine	Mean ± SD (range): 382.2 ± 816.6 (2–5028) µg/L
Trevisian A, 2003 [18]	Italy	Operating room	Open circuit/semi-closed circuit	61 exposed (surgeons, assistant surgeons, anesthetists, and nurses)	Overall Mean (range): 0.28 (0–1.88) ppm	Sevoflurane in urine	Mean ± SD: 3.1 ± 8.2 µg/L
					Open circuit Mean (range): 0.41 (0.02–1.88) ppm		Mean ± SD: 5.6 ± 12.1 µg/L
					Semi-closed circuit Mean (range): 0.18 (0–1.4) ppm		Mean ± SD: 1.3 ± 2.5 µg/L

Table 4. *Cont.*

First Author, Year	Country	Setting	Scavenging System	Investigated Worker/Samples	Air Exposure	Biomarker of Exposure	Biomarkers Results (End of Exposure, µg/L)
Gentili A, 2004 [38]	Italy	Pediatric operating room	Present	36 exposed (10 anesthetists, 10 surgeons, 12 nurses, 4 auxiliary nurses)	Anesthetists Median, IQR: 0.65, 1.36 ppm	Sevoflurane in urine	Anesthetists Median, IQR: 2.1, 2.6 µg/L
					Surgeons Median, IQR: 0.07, 0.4 ppm		Surgeons Median, IQR: 0.4, 0.3 µg/L
					Nurses Median, IQR: 0.17, 0.25 ppm		Nurses Median, IQR: 0.7, 0.9 µg/L
					Auxiliary personnel Median, IQR: 0.04, 0.01 ppm		Auxiliary personnel Median, IQR: 0.2, 0.3 µg/L
Accorsi A, 2005 [37]	Italy	Pediatric operating room	NR	36 exposed (10 anesthetists, 8 surgeons, 14 nurses, 4 auxiliary personnel)	Median (range): 0.13 (0.03–18.82) ppm, 100% quantified samples	Sevoflurane in urine	Median (range): 0.60 (<0.03–18.5) µg/L, 99% quantified samples
						HFIP in urine	Median (range): 490 (<10–6830) µg/L, 73% quantified samples
Accorsi A, 2005 [9]	Italy	Operating room	NR	10 exposed (3 anesthetists, 7 other workers)	NR	Sevoflurane in urine	Anesthetists Median: 2 µg/L Other workers Median <1 µg/L
						HFIP in urine	Anesthetists Median: 256 µg/L Other workers Median: 58 µg/L
Al-Ghanem S, 2008 [32]	Jordan	Operating room	NR	18 exposed	Mean ± SD (range): 4.16 ± 14.86 (0.02–73.07) ppm	Sevoflurane in urine	Mean ± SD (range): 4.3 ± 5.0 (0.0–30.0) µg/L

Table 4. *Cont.*

First Author, Year	Country	Setting	Scavenging System	Investigated Worker/Samples	Air Exposure	Biomarker of Exposure	Biomarkers Results (End of Exposure, µg/L)
Fustinoni S, 2009 [12]	Italy	Operating room	NR	75 exposed (24 surgeons, 25 nurses, 13 surgical nurses, 13 anesthetists)	Ranged: <0.1 to 0.9 ppm, 30% samples quantified	HFIP in urine	Range: 20 to 1220 µg/L, 90% quantified samples
Fustinoni S, 2012 [33]	Italy	Operating room	NR	180 exposed	Mean (range): 0.34 (0.07–1.46) ppm	HFIP in urine	Mean: 210 (<20–5070) µg/L, 79% quantified samples
Scapellato ML, 2014 [41]	Italy	Operating room	NR	100 exposed (19 anesthetists, 25 surgeons, 14 surgery nurses, 9 anesthetist nurses, 33 operating room nurses)	Mean ± SD (range): 0.116 ± 0.213 (<0.010–0.940) ppm	Sevoflurane in urine	Mean ± SD (range): 1.64 ± 3.09 (<0.10–17.28) µg/L
						HFIP in urine	Mean ± SD (range): 69.2 ± 101.7 (<1.0–5 50.0) µg/L
Jafari A, 2018 [43]	Iran	Operating room	NR	45 exposed	Median (range): 0.004 (ND-0.53) ppm 6.7% quantified samples	Sevoflurane in urine	Median (range): 0.004 (<0.1–2.41) µg/L 6.7% quantified samples
Herzog-Niescery J, 2019 [11]	Germany	post anesthesia care unit (PACU)	Absent	10 exposed	In the middle of PACU Mean ± SD: 0.34 ± 0.07 ppm Above the patient's face Mean ± SD: 0.44 ± 0.10 ppm Corridor: Mean ± SD: 0.47 ± 0.06 ppm	Sevoflurane in urine	Mean ± SD: 0.20 ± 0.06 µg/L
						HFIP in urine	Mean ± SD: 42.18 ± 27.82 µg/L
Herzog-Niescery J, 2020 [39]	Germany	Operating room	Present	8 exposed (surgeons)	Mean ± SD: 0.32 ± 0.09 ppm	Sevoflurane in urine	<0.5 µg/L
						HFIP in urine	Mean ± SD: 25.42 ± 21.39 µg/L, 100% quantified samples

Table 4. *Cont.*

First Author, Year	Country	Setting	Scavenging System	Investigated Worker/Samples	Air Exposure	Biomarker of Exposure	Biomarkers Results (End of Exposure, µg/L)
Selke S, 2023 [40]	Germany	Operating room	NR	28 exposed (24 anesthetists, 4 surgeons)	NR	Sevoflurane in urine	<0.2 µg/L
						HFIP in urine	Median: 23.4 (<3–145) µg/L, 78% quantified samples
Campo L, 2026 [2]	Italy	Operating room	Present	551 samples (140 surgeons, 93 anesthetists, 63 nurses, 50 surgical nurses, 24 auxiliary personnel)	Median (5th–95th): <0.1 (<0.1–0.5) ppm, 32% quantified samples	HFIP in urine	Median (5th–95th): <20 (<20–320) µg/L, 43% quantified samples

NR = Not reported; ND = not detected; GM = Geometric mean; SD = standard deviation; IQR = interquartile range.

Table 5. Linear regressions between urinary concentrations of sevoflurane biomarkers in end of shift samples and the corresponding personal exposure.

First Author, Year	Sevoflurane in Urine			HFIP in Urine		
	N Paired Data	Correlation Coefficient	Regression Derived Concentration (Corresponding Air Exposure)	N Paired Data	Correlation Coefficient	Regression Derived Concentration (Corresponding Air Exposure)
Haufroid V, 2000 [36]				50	0.89 $	0.8 mg/L (2 ppm) 6.8 mg/L (20 ppm) 16.7 mg/L (50 ppm)
Accorsi A, 2001 [16]	74	0.663				
Imbriani M, 2001 [42]				145	0.79 $	0.160 mg/L (0.5 ppm) ‡ 0.488 mg/L (2 ppm) ‡
Accorsi A, 2003 [23]	104	0.87 $	3.6 µg/L (2 ppm) 3.0 µg/L (2 ppm) ‡			
Barbic F, 2003 [10]				86	0.88	2773 µg/L (2 ppm)

Table 5. *Cont.*

First Author, Year	Sevoflurane in Urine			HFIP in Urine		
	N Paired Data	Correlation Coefficient	Regression Derived Concentration (Corresponding Air Exposure)	N Paired Data	Correlation Coefficient	Regression Derived Concentration (Corresponding Air Exposure)
Gentili A, 2004 [38]	21 anesthetists	0.76 $				
	29 nurses	0.84 $				
Accorsi A, 2005 [37]	76 *	0.835 $	1.4 µg/L (0.5 ppm) 3.9 µg/L (2 ppm)	73 *	0.749 $	0.820 mg/L (0.5 ppm) 2.66 mg/L (2 ppm)
Fustinoni S, 2009 [12]				75	0.456	0.86 mg/L (2 ppm)
Scapellato ML, 2014 [41]	100	0.49 $	2.1 µg/L (0.5 ppm) 3.7 µg/L (2 ppm)	100	0.52 $	131 µg/L (0.5 ppm) 318 µg/L (2 ppm)
Herzog-Niescery J, 2019 [11]	10	0.69	-			
Herzog-Niescery J, 2020 [39]				22 *	0.85 #	
Campo L, 2026 [2]				533 *	0.48 $#	

* Repeated measurements; $ after log-transformation of data; # multiple regression model; ‡ Biological Equivalent Exposure Limit (BEEL) proposed considering the 95th lower confidence limit of the regression line.

3.4. Desflurane

There are only two published studies investigating biological monitoring of occupational exposure to desflurane, both conducted in Italian operating room settings [2,44] (Table 6). The investigated workers included anesthetists, surgeons, nurses, surgical nurses, auxiliary personnel. Sample size ranged from 21 to 35 exposed workers. In both cases, urinary desflurane is used as biomarker.

Table 6. Summary of studies evaluating the exposure to desflurane in health care workers using biomarkers of exposure.

First Author, Year	Country	Setting	Scavenging System	Investigated Worker/ Samples	Air Exposure	Biomarker of Exposure	Biomarkers Results (End of Exposure, Original Unit)
Alessio A, 2003 [44]	Italy	Operating room	NR	21 exposed (Anesthetists, surgeons, nurses)	Mean ± SD (range): 3.43 ± 4.69 (0.29–13.18) ppm	Desflurane in urine	Mean ± SD (range): 2.10 ± 1.06 (0.20–6.13) µg/L
Campo L, 2026 [2]	Italy	Operating room	Present	35 exposed (9 surgeons, 7 anesthetists, 11 nurses, 7 surgical nurses, 2 auxiliary personnel)	Median (5th–95th): <0.1 (<0.1–2.0) ppm, 46% quantified samples	Desflurane in urine	Median (5th–95th): <0.3 (<0.3–2.04) µg/L, 34% quantified samples

NR = Not reported.

Airborne desflurane concentrations were substantially higher in the earlier study, with a mean value of 3.43 ppm and a median of 1.60 ppm (range: 0.29–13.18 ppm) [44] while the recent study reported markedly lower exposure levels with a median below 0.1 ppm and a 95th percentile of 2.0 ppm [2]. This reflects the trend toward lower exposures already shown for the other anesthetic gases.

Both investigations confirm a positive correlation between environmental desflurane and end of exposure urinary desflurane (Table 7). The linear correlations were obtained with a variable number of observations (from 21 to 34) and variable levels of strength, and correlation coefficient ranging from 0.49 to 0.916. At 2 ppm a biological equivalent exposure limit of 0.9 µg/L, corresponding to the 95th lower confidence interval of the regression line, was proposed [44].

Table 7. Linear regressions between urinary concentrations of desflurane in end of shift samples and the corresponding personal exposure.

First Author, Year	Desflurane in Urine		
	N Paired Data	Correlation Coefficient	Regression Derived Concentration (Corresponding Air Exposure)
Alessio A, 2003 [44]	21	0.916 $	0.9 µg/L (2 ppm) ‡
Campo L, 2026 [2]	34 *	0.49 $#	

* Repeated measurements; $ after log-transformation of data; # multiple regression model; ‡ Biological Equivalent Exposure Limit (BEEL) proposed considering the 95th lower confidence limit of the regression line.

The earlier study also demonstrated rapid urinary elimination kinetics, suggesting that urinary desflurane primarily reflects very recent exposure [44].

4. Discussion

This systematic review identified 39 studies investigating biological monitoring of occupational exposure to nitrous oxide, sevoflurane, and desflurane in healthcare workers. Four main findings emerged: (i) occupational exposure levels have markedly decreased over the last four decades; (ii) biological concentrations have declined in parallel with airborne exposure; (iii) strong positive and quantitative relationships between environmental and biological measurements have been consistently reported; and (iv) the suitability of biomarkers differs substantially among anesthetic gases under contemporary exposure conditions.

The exposure to anesthetic gases in healthcare personnel greatly decreased over the period of more than four decades covered by this review. This is evidenced by both the airborne concentration of gases and by the concentration of exposure biomarkers. The most prominent decrease was that of nitrous oxide, which was more than 2000 ppm in the very first studies and is now three orders of magnitude lower in the operation rooms, where nitrous oxide is used at a low percentage in a mixture with fluranes and is administered via intratracheal tube for the maintenance of anesthesia [2]. Two orders of magnitude decrease was also seen in dentistry with sedation, where nitrous oxide is administered via nose masks, which may allow significant leakage through the patient's mouth during treatment, resulting in elevated environmental contamination and worker exposure (reported by [2,14,35]). Another reason is the high concentrations of N_2O administered in the mixture during dentistry sedation (up to 70%) and the fact that dentistry sedation is often applied to non-collaborative patients.

For sevoflurane, a similar trend is observed, even if the gas was introduced much later than nitrous oxide and the first studies were published in the beginning of the year 2000; at that time a concentration of sevoflurane as high as 140 ppm was reported [36], even if in numerous operating rooms risk management measures were already in place, such as a high ventilation rate (in Italy an air exchange per hour of 15 is required for the authorization of surgery theatres since 1997, DPR 14/01/97) [45] and the scavenging systems to trap waste anesthetic gases. The latest studies support the presence of very low levels of sevoflurane, often below the quantification limit of 0.1 ppm [2]. In these applications, sevoflurane was administered in close circuits, through tracheal tube, and in low percentage, typically from 1 to 3%; a more dispersive use is the pediatric administration with facial mask in the induction phase of anesthesia, but this typically lasts few seconds. Overall, both uses of sevoflurane are associated with a very limited air dispersion.

The data on desflurane are very limited, even if the two available studies suggest a similar trend as sevoflurane [2,44].

Altogether, several risk management measures have been undertaken during the decades, and now the widespread introduction in operating room of high ventilation rate, low flow anesthesia, close circuits with scavenging systems, an improved system to connect the vaporizer to the anesthesia workstations and the higher awareness and better education of the healthcare workers, has greatly improved the hygienic conditions in the operating rooms. Some residual criticisms may be still present in open circuit use, where the administration of nitrous oxide is performed with mask and in poorly controlled conditions or on-demand use, such as in midwifery [29].

The lower airborne concentrations of anesthetic gases reported in more recent studies are paralleled by lower concentrations of the corresponding biomarkers, as descriptively illustrated in Figures 2 and 3. In addition, several studies reported positive correlations between biological markers and personal airborne exposure (Tables 3, 5 and 7), supporting the ability of these biomarkers to reflect occupational exposure. Biological monitoring has some practical characteristics that may facilitate its application in healthcare settings, as it generally requires the collection of a spot urine sample at the end of the exposure

period and provides an integrated measure of internal exposure from different sources and routes. Personal/environmental monitoring requires dedicated sampling devices, which may need to be worn by workers, as well as specialized personnel for their deployment and management; personal sampling devices may also interfere to some extent with routine activities in surgical settings. On the other hand, personal/environmental monitoring characterizes external exposure and can provide important information on exposure sources and the effectiveness of control measures. Overall, biological and personal/environmental monitoring should be regarded as complementary approaches, and the choice between them, or their combined use, should depend on the specific objectives of the occupational exposure assessment.

When it comes to the different anesthetic gases and the possible biomarkers, we observe different outcomes for the different gases.

For nitrous oxide, after the first use of nitrous oxide in blood [14,15,20] and few attempts to introduce nitrous oxide in exhaled breath [19,20], the measure of nitrous oxide in urine has become the universally used biomarker of exposure. The available studies consistently support a relationship between urinary concentrations and occupational exposure levels, allowing the estimation of biological concentrations corresponding to selected airborne exposure levels (Table 3). Several studies reported regression-derived urinary nitrous oxide concentrations of approximately 25–35 µg/L corresponding to an airborne exposure of 50 ppm, with several estimates clustering around 30 µg/L. Despite differences in study period, analytical methods, exposure conditions, sampling strategies, and study populations (see also Supplementary Table S1), this clustering suggests that approximately 30 µg/L may represent a candidate biological equivalent concentration for an airborne exposure of 50 ppm. However, this concentration should not be interpreted as a formally validated biological limit value; establishment of such a value would require further evaluation of analytical performance, toxicokinetics, intra- and inter-individual variability, sampling strategy, and validation under present occupational exposure conditions.

Considering sevoflurane, two biomarkers have been investigated: urinary sevoflurane and HFIP (Table 4). For urinary sevoflurane, a linear correlation with personal airborne exposure has been consistently reported (Table 5). Three studies reported urinary sevoflurane concentrations of 3.6–3.9 µg/L, corresponding to an exposure of 2 ppm of sevoflurane [23,37,41]. Moreover, recently a biological tolerance value (BAT) of 4 µg/L has been included in the BAT list by the German Research Foundation (DFG) corresponding to a maximum workplace concentration of 2 ppm [7]. However, at the current occupational exposures to sevoflurane, concentrations of urinary sevoflurane were frequently below the analytical limit of quantification [2,39,40]. For these reasons, urinary sevoflurane cannot be considered the biomarker of choice for the biological monitoring of exposure to sevoflurane.

In contrast, urinary HFIP is present at concentrations that are roughly two orders of magnitude higher than those of urinary sevoflurane. Consequently, it remains quantifiable in most biological samples, even at exposure levels well below current occupational exposure limits. In addition, a linear relationship with airborne exposure has been demonstrated. An elimination half-life of 19 h has been reported for HFIP [46], which provides a wider sampling window in comparison with the unmetabolized biomarkers, and less critical timing for sample collection. Overall, urinary HFIP appears to be a promising biomarker for the biological monitoring of current sevoflurane exposure.

Nevertheless, substantial variability is observed in the proposed HFIP concentrations corresponding to an airborne sevoflurane exposure of 2 ppm, with values ranging from 318 to 2773 µg/L (Table 5). This variability may reflect the reported long elimination half-life of HFIP [46], which may result in carry-over from exposures occurring during previous work shifts, as well as differences among studies in exposure duration and intensity, timing of

biological sample collection, interindividual variability [36,37], analytical methods, and the regression approaches used to estimate biological equivalent concentrations (see also Supplementary Table S1). In particular, biological sampling time and differences in exposure duration, number of procedures performed, interval between the end of exposure and sample collection, and previous exposure greatly affect the biomarker concentrations and limit direct comparability among studies. End-of-exposure and end-of-shift sampling should not be considered equivalent, especially for rapidly eliminated unmetabolized anesthetic gases, because biomarker concentrations may decrease substantially after exposure ceases.

Therefore, although HFIP appears suitable for detecting low-level occupational exposure to sevoflurane, the available evidence is not yet sufficiently consistent to support the definition of a single biological guidance value. Further studies using standardized exposure assessment and biological sampling protocols would be needed to establish a more reliable biological equivalent concentration and to evaluate its potential use as a biological guidance value.

For desflurane, urinary desflurane is the only biomarker that has been investigated for the assessment of occupational exposure. Given its rapid elimination, unmetabolized urinary desflurane primarily reflects recent exposure, making the timing of biological sample collection particularly relevant. However, the available evidence is limited to only two studies [2,44], both involving relatively small numbers of exposed workers. Although both studies reported positive relationships between airborne and urinary desflurane concentrations, this very limited evidence base precludes firm conclusions regarding the validity and practical utility of urinary desflurane as a biomarker of exposure. Moreover, the most recent study reported that only 34% of urinary samples were quantified [2], which may reflect the very low airborne exposure levels currently encountered in occupational settings and further limits its practical applicability. Finally, the use of desflurane is progressively declining because of its substantial environmental impact and contribution to greenhouse gas emissions [47,48], further reducing the practical relevance of developing biological monitoring approaches specifically for this anesthetic.

The main knowledge gaps identified by this review include the lack of standardized biological sampling times, differences in analytical sensitivity among studies, limited information on intra- and inter-individual variability, the geographical concentration of the available evidence, and the limited number of multicenter studies simultaneously assessing personal airborne exposure and biological concentrations under low-exposure conditions. These gaps are particularly important for HFIP and urinary desflurane and should be addressed in future biomonitoring studies.

An important consideration when interpreting these findings is the geographical concentration of the available evidence. Most studies were conducted in Italy, including 18 of the 24 studies on nitrous oxide and 12 of the 18 studies on sevoflurane. Therefore, the exposure patterns and biomarker–exposure relationships identified in this review largely reflect the Italian occupational and healthcare context, although recent studies from Germany have reported similar findings [11,39,40]. Consequently, the quantitative findings should be generalized to other countries with caution. This is particularly relevant because occupational exposure may be influenced by technological factors, such as ventilation and anesthetic gas scavenging systems; anesthesia practices, including equipment maintenance procedures; and occupational health and safety regulations in surgical units. Multicenter studies conducted across different countries and healthcare systems would be useful to confirm the external validity and generalizability of the observed biomarker–exposure relationships.

Among the strengths of this work are its focus on biological monitoring of anesthetic gases over a temporal period of almost 50 years and the comparison of biomonitoring results with contextual environmental monitoring data. However, several limitations should

be considered. The included studies were heterogeneous in terms of study population, occupational setting, exposure conditions, biological sampling strategy, analytical methodology, and reporting standards, with some information being incompletely reported (see Supplementary Table S1). Analytical methods for the measurement of anesthetic gases and biomarkers have also evolved considerably over the period covered by the review, becoming more specific and sensitive (see Supplementary Table S1). These methodological differences may affect the comparability of reported concentrations across studies and should be considered when interpreting Figures 2 and 3. In particular, these figures illustrate differences in concentrations reported across publication years rather than quantitatively established temporal changes in occupational exposure.

Moreover, the proportion of quantifiable samples depends not only on exposure levels but also on analytical sensitivity. This is especially relevant for unmetabolized urinary sevoflurane and desflurane, which are currently present at very low concentrations. However, a systematic quantitative assessment of the influence of analytical sensitivity was not possible because LOD and LOQ values were frequently not reported, particularly in earlier studies (Supplementary Table S1). Moreover, the literature search was restricted to PubMed and Scopus and included only studies published in English or Italian, and therefore relevant studies indexed in other databases or published in other languages may have been missed. Publication bias cannot be excluded. In addition, biological sampling times differed among studies, particularly with respect to end-of-exposure and end-of-shift sampling, which may contribute to variability in biomarker concentrations. Studies also reported different summary statistics, including arithmetic means, geometric means, and medians, limiting direct quantitative comparison across studies. Evidence for desflurane biomonitoring was particularly limited. Furthermore, the review was not prospectively registered, and no predefined protocol was available, which limits the ability to verify whether methodological decisions were established a priori. Finally, although we introduced a structured domain-based study characteristics and methodological quality appraisal, this assessment was intended to identify methodological strengths and limitations relevant to occupational biomonitoring and should not be considered equivalent to a formal risk-of-bias assessment. Furthermore, differences in participant selection, occupational tasks, exposure conditions, biological sampling strategies, analytical performance, and adjustment for potential confounding factors may contribute to the heterogeneity observed across studies. These differences, systematically documented in Supplementary Table S1, limit the direct comparability of biomonitoring results and should be considered when interpreting the strength and generalizability of the reported exposure–biomarker relationships.

The findings of this review support urinary nitrous oxide as a well-characterized biomarker of occupational exposure, with several studies reporting a candidate biological equivalent concentration of approximately 30 μg/L corresponding to an airborne exposure of 50 ppm. The review also highlights the potential of urinary HFIP as a biomarker of low-level sevoflurane exposure. Further multicenter studies using harmonized personal airborne and biological monitoring protocols are needed to strengthen the evidence supporting HFIP as a suitable biomarker and to provide a basis for establishing biological guidance values.

5. Conclusions

The available literature shows an overall pattern of lower occupational exposure to waste anesthetic gases in more recent studies. Urinary nitrous oxide is the best-characterized biomarker, with regression-derived concentrations of approximately 25–35 μg/L corresponding to an airborne exposure of 50 ppm and several estimates clustering around 30 μg/L, suggesting this value as a candidate biological equivalent concentration. For sevoflurane, urinary HFIP remains measurable under low-exposure conditions and appears promising,

although substantial between-study variability currently prevents the definition of a biological guidance value. Evidence for urinary desflurane remains insufficient because only two studies are currently available.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/jox16070215/s1, Table S1: Study characteristics and methodological quality appraisal of the reviewed studies according to aspects considered relevant to biological monitoring; File S1: PRISMA 2020 Checklist. Reference [49] are cited in the supplementary materials.

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