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Field Report

Exposure of paediatric healthcare personnel to nitrous oxide in paediatric care units

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Abstract: Nitrous oxide (N_2O) was found responsible for genetic and reproductive toxicities, whereas it is widely used in paediatric care units where most healthcare providers are women of childbearing age. This motivated investigating occupational overexposure and overexposure factors in several paediatric hospital units. A cross-sectional study was carried out in seven healthcare units. On each of 34 healthcare providers, air samples were extracted (portable pumps and Tedlar® bags) and N_2O quantified (gas chromatography, pulsed discharge ionization detection, and infrared spectrometry). The data allowed calculating mean instantaneous exposures. The mean instantaneous exposure was: i) four times higher in closed vs. open treatment rooms; ii) two times higher in case of use vs. non-use of N_2O; iii) significantly higher in junior vs. senior healthcare providers (by 12%); and, iv) higher during presumably short vs. presumably long procedures (by 20%). Overexposures to N_2O were mainly seen in the emergency unit and in day hospitals for thoracic/abdominal diseases and nephrology. Overexposures were frequent during short-duration procedures; among 88 N_2O measurements, 77 (87.5%) exceeded the 200 ppm threshold over 15 minutes. The overexposures call for dedicated treatment rooms (with adequate equipment and ventilation), more efficient anaesthetic practices, appropriate training, and regular checks.

Key words: Anaesthetics, Anaesthetic gases, Nitrous oxide, Occupational exposure, Paediatric hospitals, Paediatric nursing, Risk assessment, Risk factors

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Introduction

Over the last decades, the need to alleviate care-related pain increased progressively the use of nitrous oxide (N_2O or, precisely, EMONO, an equimolar mix of oxygen and N_2O) in care units, especially paediatric units. However, N_2O is potentially toxic[1]; the medical literature has reported evidence of short- and long-term neurologic, haematologic hepatic, renal, genetic, and reproductive toxicities[2–7].

Among these toxicities, reproductive toxicity has been very concerning because most healthcare providers (HCPs) in paediatric units are women (up to 75% of paediatricians[8] and up to 99.7% of paediatric nurses)[9]. In the early nineties, Rowland *et al.*[10, 11] observed significant increases in time-to-pregnancy and abortion risks among dental assistants exposed to N_2O for 5h/week. Shortly after, Ahlborg *et al.*[12] found similar results among midwifes and Bodin *et al.*[13] reported increased risks of premature birth and low birthweight. A decade ago, Shirangi *et al.*[14, 15] observed increased risks of abortion and premature birth in female veterinarians and, more recently, a French official report[16] considered that N_2O is potentially responsible for impaired fertility and first-trimester abortions.

Since 1977 in the USA and later in France, health authorities have recommended reducing air pollution by anaesthetic vapours and set exposure limits for all HCPs. In France, one recommendation stipulated that treatment rooms should be equipped with devices to remove anaesthetic vapours[17]. During anaesthetics administration, these devices should be able to reduce air concentration of N_2O to <25 ppm (parts per million) as average exposure value (AEV) at close distance to patients and HCPs.

For the time being, there is still no international consensus on the thresholds of exposure to N_2O. Over the European continent, AEVs differ between countries: 100 ppm in Germany, UK, Norway, Denmark, Sweden, and Switzerland[18]. In the USA, the National Institute for Occupational Safety and Health (NIOSH) has recommended a much lower exposure limit: 25 ppm as a time-weighted average (TWA) during the period of anaesthetic administration[19].

Currently, not all countries have set short-term exposure limits (STELs, 15 min). In some countries of the European Union, the STELs range between 200 and 500 ppm[18, 20]. In France, no specific value was set, but the ANSES (Agence Nationale de Sécurité Sanitaire de l'Alimentation, de l'Environnement et du Travail) has recommended to keep this value <5 times the AEV (i.e., <125 ppm) over 15 min[21].

At present, in France, the exposure to anaesthetic vapours in operating rooms is decreasing; however, the levels of N_2O in other treatment rooms are not known; thus, probably inadequately controlled. In fact, most studies on the subject are rather old and have mainly targeted delivery rooms or dental care rooms[22]. The most recent studies in the paediatric department of an old hospital and in various units of a recent hospital have found levels that exceeded the 8h-TWA limit in 4 out of 6 treatment rooms[23].

Given the latter facts and because of a substantial large number of HCP complaints, it was decided to check previous preliminary results[23] and carry out an accurate investigation of on-the-job risks of exposure of HCPs to N_2O in various paediatric units of a large hospital that implemented new procedures for N_2O use. The investigation had to confirm or disprove the existence of an occupational risk for HCPs according to the current exposure limits set by the French laws.

Subjects and Methods

In April 2015, this cross-sectional observational study carried out N_2O measurements in several units of a university children's hospital (117 beds, 82,000 visits, and 19,000 admissions per year) where 80% of HCPs (480/600) were women of childbearing age.

The hospital's procurement services helped identifying the units that used the highest quantities of EMONO; i.e., Emergency (3,350 l/yr), Visceral & urologic surgery (750 l/yr), Conventional hospital (CH) for thoracic & abdominal diseases (655 l/yr), Day hospital (DH) for thoracic & abdominal diseases (480 l/yr), DH for nephrology (365 l/yr), and CH for endocrinology (270 l/yr). A seventh unit (CH for neurology, nephrology, & rheumatology) was added to this list despite a relatively low use of EMONO (65 l/yr) because similar units are seldom mentioned in the specialized literature.

In the seven units under study and for minor interventions, EMONO was administered with portable equipment (bottles and masks). The paediatric mask (Ambu® UltraSeal Paediatric, King Systems, Noblesville, IN, USA) had an evacuation system to remove expired air and waste gas (Int'Air Medical, Bourg-en-Bresse, Ain, France). EMONO was administered in a continuous flow because the device was devoid of an on-demand control valve.

The whole study was carried out over 12 successive days of which four were dedicated to mere observation of HCPs' environments, tasks, and practices (no measurements); this 'on-the-job' observation allowed identifying typical procedures worthy of study and analysis. The investigators

planned then data collection on 33 typical independent procedures carried out by 34 HCPs, all voluntary participants, almost all women.

The data collected were the position of each HCP, the type of procedure, its location, the time spent, the means used to decrease HCP exposure to N_2O, the factors likely to limit air exchange, and accurate measurements of N_2O on each HCP.

In each of nearly 90 procedures monitored, EMONO was collected only during anaesthetic release. Each collection used a portable auto-regulated GilAir™ air sampling pump (Sensidyne, LP, St Petersburg, FL, USA) and the samples were immediately stored in Tedlar® gas-sampling bags (CEL Scientific Corporation, Cerritos, CA, USA). Thus, the pump and the bag were carried by the HCP. The admission valve of the pump was opened at the start and closed at the end of each procedure and the flow could not change with temperature or humidity. The flow rates were set at 50 ml/min with 1-l Tedlar bags for presumably short procedures (roughly <15 min) and at 20 ml/min with 2-l Tedlar bags for presumably long procedures (roughly >15 min). Most importantly, on each HCP, EMONO was collected from the breathing zone; precisely, the inlet of the sampling tube was fixed at the HCP's shoulder to be brought near the nose and mouth when the HCP would bend over the patient.

Samples were analysed in a single laboratory by gas chromatography coupled to pulsed discharge helium ionization detection (GC-PDHID). The chromatograph (Perkin Elmer® Clarus® 500, Shelton, CT, USA) was equipped with a Carboxen® 1010 Plot 30 m x 0.53 mm capillary column (Sigma-Aldrich, Allentown, PA, USA) at an oven temperature of 130°C. The injector and detector were at 250°C and the carrier-gas flow rate was 3 ml/min. GC-analysis was calibrated by gas standards analysed in the same conditions. The retention time of N_2O was 5 minutes. The limit of quantification was estimated at 2 ppm. Over ten reproducibility tests with gas standards at 3.2, 40, and 500 ppm N_2O, the coefficients of variation were 2.94, 1.74, and 0.3%, respectively. All Tedlar bag samples were analysed within 24 h of collection. According to a previous kinetic work, the stability of N_2O in those bags is excellent. In a study by California Air Resources Board, "N_2O concentration dropped by less than 0.2% after 7 hours in the first experiment, and by less than 2% after 96 hours in the second experiment" and the authors added: "Unlike other oxides of nitrogen, nitrous oxide is stable (…) for at least 4 days"[24]. A later report confirmed: "The stability of the nitrous oxide in the Tedlar™ bags was found to be at least four days."[25] and a third more recent report demonstrated that "after ten days in a Tedlar bag, an initial concentration of 300 ± 15 nmol mol–1 N_2O was still 300.69 (Standard deviation/%: 1.01)[26]. In our own tests, gas losses from Tedlar bags did not exceed 2% over a 24-hour storage period but at very low contents (H_0 contents: 770, 250, and 0 ppm vs. H_{24} contents: 764, 246, and 46 ppm, respectively).

Before data analyses, a calculated variable was added to the dataset: the mean instantaneous exposure to N_2O (in ppm), assuming there was no additional 'passive' exposure (no HCP followed over a full shift). The mean instantaneous exposure (MIE) is the time-averaged concentration over a relatively short period of time.

To investigate potential overexposures, the MIEs in the hospital units under study were compared with a threshold of 200 ppm over short periods[20].

N_2O measurements were stratified according to various criteria and compared between strata. Precisely, exposures to N_2O were compared between HCPs (senior vs. junior or trainee), treatment rooms (open vs. closed; i.e., with openable windows vs. absence of or hard-to-open windows), presumed durations of procedure (long vs. short, according to the authors' consensual opinion), real durations of procedure (<10 vs. >10 min and <15 vs. >15 min), and need for EMONO (Yes vs. No).

Poisson regression models adjusted on real exposure times were used to compare differences in MIEs to N_2O between the above-cited categories.

The variables submitted for analysis had no missing data. The analyses used Stata 13 programs (StataCorp. 2013. *Stata Statistical Software: Release 13*. College Station, TX, USA: StataCorp LP). In all comparisons, statistical significance was set at $p<0.05$.

The study was conducted during usual HCPs' activities without any interference with or change in patient care. It did not need then a previous approval from the competent institutional ethics committee. Informed consent on the objectives and interests of the study was obtained from each included participant.

Results

Table 1 shows an overview of the raw measurements carried out in the seven paediatric units. Its unprocessed data give an idea of HCP relative degrees of exposure between units but do not indicate under- or overexposure (for the latter, see Table 2).

HCPs were the most exposed in Emergency and DH for thoracic & abdominal diseases. However, in some units, the

Table 1. Overview of N_2O measurements (raw data) in various paediatric units

Paediatric unit	N	N_2O level (ppm)	Exposure time (min)
Emergency	38 [a]	234 (1; 1,352) [b]	13 (5; 50) [b]
DH thoracic & abdominal diseases	31 [c]	249 (2; 1,242)	10 (3; 32)
Unit of visceral & urologic surgery	8	80 (8.4; 767)	16 (10; 88)
DH nephrology	5	165 (102; 656)	9 (3; 10)
CH endocrinology	2	503 (325; 682)	6 (6; 6)
CH neurol., nephrol., & rheumatol.	2	322 (304; 340)	10 (10; 10)
CH thoracic & abdominal diseases	2	605 (304; 907)	10 (10; 10)

[a] of which 21 short exposures; [b] Median (min; max); [c] of which 22 short exposures; N, number of measurements; CH, conventional hospital; DH, Day hospital; HCPs, Health care providers.

number of measurements was not sufficient to provide very accurate comparisons. HCPs were the least exposed in the Unit of visceral & urologic surgery despite long procedures (up to 88 min). In Emergency, HCPs seemed equally exposed whatever the duration of the procedure (median 234 ppm for all 38 procedures vs. 257 ppm for 21 short procedures). On the contrary, in the DH for thoracic & abdominal diseases, the HCPs were unevenly exposed despite practically equivalent procedure durations (median 249 ppm for all 31 procedures vs. 80 ppm for 21 short procedures; duration range: 3 to 32 min in both sets).

In all seven units, some exposures could exceed the 200 ppm short-time exposure limit as defined by the Deutsche Forschungsgemeinschaft[20].

Table 2 shows the results of univariate analyses; i.e., the main indicators of exposure according to various circumstances of gas use.

Regarding HCP position, on average, the exposure was lower in senior than in junior HPCs (nurses vs. trainees). The average exposure time was lower in nurses than in trainees (14.9 vs. 17.3 min) but the difference was not statistically significant. There was a moderate but statistically significant difference in MIE (284 vs. 320 ppm; $p<0.001$).

Regarding treatment rooms, the average exposure time was nearly the double in open than in closed rooms but the difference was not statistically significant (27.8 vs 14.4 min; $p=0.22$). Interestingly, the MIE was nearly five times higher in closed than in open rooms (354 vs. 77 ppm; $p<0.001$).

Regarding presumed procedure duration, the average exposure time was lower in presumably short than in presumably long procedures (13.6 vs. 19.3) though the difference was not statistically significant. However, the MIE was significantly higher in presumably short than in presumably long procedures (327 vs. 271 ppm; $p<0.001$).

Regarding real procedure duration, the MIE was not much different between short and long procedures (295 vs 301 ppm).

Suspecting that the above definition of short procedure (<10 min) might not be universal and knowing that a number of studies have considered procedures shorter vs. longer than 15 minutes, the same above-mentioned analysis was rerun with threshold 15 minutes. The latter analysis showed a significantly higher MIE in <15-min vs. >15-min procedures.

In various instances, HCPs performed procedures in treatment rooms equipped with EMONO delivery units but without using the gas. The time spent on the procedures was shorter in case of EMONO use than without the need for EMONO (13.2 vs 19.4 min), but this difference was not statistically significant. However, the MIE to N_2O was two times higher in case of EMONO use than in case of no use (419 vs. 190 ppm), which is a statistically significant difference.

Among 88 N_2O measurements, 77 (87.5%) exceeded the 200 ppm threshold over 15 minutes. In Emergency, this excess was seen in 29 over 38 procedures (76.3%). More frequent excesses were seen in DHs (34 out of 36 measurements: 94.4%) and in the other units (100%). The latter alarming result should be taken with caution and not generalized to all procedures of these units because the number of monitored procedures was very small (only 6). These exceeding measurements did not seem to depend on the status of the HCP (senior vs. junior), on the room (open vs.

Table 2. Exposure to N_2O according to HCP position, space, and procedure duration

Exposure circumstances	Average exposure time (min)	Mean instantaneous exposure (ppm)
Health care provider		
Senior	14.91 (13.66) [a]	283.8 [282.6; 285.0] [b] *
Junior	17.33 (22.21)	319.9 [318.4; 321.3]
Treatment room		
Open	27.8 (31.9)	77.4 [76.4; 78.4] *
Closed	14.4 (14.5)	354.1 [353.0; 355.2]
Procedure duration		
Presumably short	13.58 (16.20)	327.4 [326.1; 328.7] *
Presumably long	19.28 (19.09)	271.0 [269.7; 272.2]
Procedure real duration		
≤15 min	9.37 (3.27) c	349.6 [348.2; 351.1] *
>15 min	33.54 (26.51) c	261.9 [260.8; 263.0]
Need for N_2O		
Yes	13.24 (15.6)	419.4 [417.8; 420.9] *
No	19.45 (19.76)	190.4 [189.4; 191.4]

[a] M (SD); [b] M [95% CI]; [c] Test not applicable; * Significant difference between the pair of superimposed values.

close), or on the expected duration of the procedure (short vs. long).

Discussion

In the present study, HCPs' exposures to N_2O varied widely according to various factors. Briefly, as expected, the MIE could be four times higher in closed than in open treatment rooms and two times higher in case of gas use vs. no gas use in treatment rooms equipped with EMONO delivery units. Junior HCPs were more exposed than senior HCPs (by nearly 12%) and, unexpectedly, the MIEs were higher during presumably short vs. presumably long procedures (by 20%).

The study showed that, in Emergency and DHs, the MIEs were higher than the recommended level. This calls for regular monitoring of N_2O use in these two units after taking appropriate corrective actions.

During the four-day observation period before measurements, the investigators noted several details of HCP practices that could have contributed to overexposure: i) incorrect use of the mask or lack of synchronization with gas release and shut-off (up to 15 seconds extra exposure time); ii) mask take-off to hear the child or move around the bed (up to 45 seconds extra exposure); iii) presence of parents in the treatment room; iv) failure to open malfunctioning or locked out of service windows. These details were somewhat controlled during the data collection period. Nevertheless, the main source of overexposure seemed to be clearly due to insufficient air exchange in the treatment rooms. Actually, most of these rooms were rather small (all <23 m²) and had low air exchange rates (all <2 m^3/h) vs. the current practices of EMONO use (rate of generation, concentration, and mixing factors).

Over the last decade, several studies have shown overexposures of HCPs in paediatric units. In an obstetrics unit, Mills *et al.*[27] found that exposure to >100 ppm (up to 1,638 ppm) as 8h-TWA concerned 24% of midwifes. In a paediatric dental care unit, Gilchrist *et al.*[28] reported that exposure to >100 ppm as 8h-TWA concerned 62% of the personnel

despite the presence of exhaust fans. In France, N_2O-measurement campaigns conducted between 2002 and 2016 have shown that: i) 53% of 263 measurements on HCPs in general hospitals were >25 ppm per day; ii) the highest overexposures occurred in emergency units (as in the present study); iii) overexposures concerned one midwife or nurse out of two and two physicians out of three[29].

In France, the regulation of exposure to N_2O has been increasingly tightened. According to a study by Vieira *et al.*[21], it is officially recommended not to exceed 1/100 of the NOAEL (no observed adverse effect level); that is, 10 ppm/day. However, since 2008, the Société Française de Médecine du Travail has set to 2.5 ppm/day the threshold of exposure of pregnant women or women of childbearing age[30]. Unfortunately, in most hospitals, especially children's hospitals, HCPs are mainly women of childbearing age whereas the exposures are often >2.5 ppm/day. This calls for specific training, regular measurements, regulatory inspections, and, mostly, much more efficient ventilation.

One strength of this study is the collection of a hundred samples of EMONO during various procedures in seven paediatric units over eight consecutive days and nights. Another strength is sample collection from the breathing zone, which ensured reliable measurements of inhaled gas. A third strength is sample collection in real practice conditions, which showed a wide variety of breaches to gas safety recommendations.

One shortcoming of the study was the assumption that each HCP was exposed only during the monitored procedures. In fact, a few whole-day measurements (results not shown) demonstrated that each participant was exposed to various additional levels of N_2O over the day. This means that MIEs considered in this study are most probably underestimated.

In addition, the analyses could only dichotomize some variables, essentially the exposure time, because the number of measurements did not allow considering more than two categories. Another limitation is the findings' generalizability. This criterion is very difficult to reach in such a study because of the very wide diversity of hospital settings and the diversity of medical and nursing practices within each specialty, not to mention conditions such as unexpectedly long procedures, inappropriate children's behaviour, unsupportive parents' involvement, etc. However, the protocol used for sample collection and data analysis proved feasible, reliable, and effective in revealing overexposure.

The present study has shown that specific paediatric care units and ways of EMONO use were sources of HCP overexposure and that overexposure was very frequent in Emergency and Day hospitals. A better planning of work shifts would avoid personnel multiple exposures and cumulative exposures >200 ppm (here, 77 cases out of 88).

Though the study has targeted the major users of EMONO (thus, N_2O) among hospital specialties, the identification of the settings and working conditions likely to cause HCP overexposure led to recommend taking immediate and delayed measures to reduce exposure down to safe or acceptable levels. Immediate measures consist in using N_2O scavenging systems and improving substantially air exchange in treatment rooms through installing or upgrading exhaust fans. Delayed measures consist of : i) raising HCP awareness of unsafe equipment, practices, and conditions; ii) improving staff training regarding the handling of difficult children; iii) using dedicated treatment rooms to improve exposure monitoring; and iv) checking regularly for constant reduction of exposure and health hazards of HCPs who work in paediatric treatment rooms.

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References

1) Torri G (2010) Inhalation anesthetics: a review. Minerva Anestesiol **76**, 215–28.
2) National Institute on Drug Abuse (NIDA) Inhalants. NIH Publication Number 12-3818. 2012. https://www.drugabuse.gov/sites/default/files/inhalantsrrs.pdf. Accessed September 16, 2021.
3) Center for Disease Control and Prevention (CDC) The National Institute for Occupational Safety and Health (NIOSH) Nitrous oxide. 2018. https://www.cdc.gov/niosh/topics/nitrousoxide/. Accessed September 2021.
4) Shoults K (2016) Case report: neurological complications of nitrous oxide abuse. BC Med J **58**, 192–4.
5) Integra. Material Safety Data Sheet. Nitrous oxide. http://docplayer.net/59522912-Material-safety-data-sheet-revised-reviewed-july-20-2011.html. 2011. Accessed September 16, 2021.
6) Oussalah A, Julien M, Levy J, Hajjar O, Franczak C, Stephan C, Laugel E, Wandzel M, Filhine-Tresarrieu P, Green R, Guéant JL (2019) Global burden related to nitrous oxide exposure in medical and recreational settings: a systematic review and individual patient data meta-analysis.

J Clin Med **8**, 551.
7) Sanders RD, Weimann J, Maze M (2008) Biologic effects of nitrous oxide: a mechanistic and toxicologic review. Anesthesiology **109**, 707–22.
8) Conseil National de l'Ordre des Médecins (CNOM). Atlas de la démographie médicale en France. 2016. https://www.conseil-national.medecin.fr/sites/default/files/external-package/analyse_etude/1j2jckd/atlas_de_la_demographie_medicale_2016.pdf (in French). Accessed September 16, 2021.
9) Lointier F, Gold F, Hascoet JM (2013) Éthique du care et masculinité : l'exemple des hommes qui ont choisi la profession de « puéricultrice » [Ethics of care and masculinity: the case of men who choose the nursing profession]. Rech Soins Infirm **115**, 85–91 (in French).
10) Rowland AS, Baird DD, Weinberg CR, Shore DL, Shy CM, Wilcox AJ (1992) Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide. N Engl J Med **327**, 993–7.
11) Rowland AS, Baird DD, Shore DL, Weinberg CR, Savitz DA, Wilcox AJ (1995) Nitrous oxide and spontaneous abortion in female dental assistants. Am J Epidemiol **141**, 531–8.
12) Ahlborg G Jr., Axelsson G, Bodin L (1996) Shift work, nitrous oxide exposure and subfertility among Swedish midwives. Int J Epidemiol **25**, 783–90.
13) Bodin L, Axelsson G, Ahlborg G Jr. (1999) The association of shift work and nitrous oxide exposure in pregnancy with birth weight and gestational age. Epidemiology **10**, 429–36.
14) Shirangi A, Fritschi L, Holman CD (2008) Maternal occupational exposures and risk of spontaneous abortion in veterinary practice. Occup Environ Med **65**, 719–25.
15) Shirangi A, Fritschi L, Holman CD (2009) Associations of unscavenged anesthetic gases and long working hours with preterm delivery in female veterinarians. Obstet Gynecol **113**, 1008–17.
16) Institut National de Recherche et de Sécurité (INRS). Fiche DEMETER (document pour l'évaluation médicale des produits toxiques vis-à-vis de la reproduction). DEM 076. Protoxyde d'azote. 2010. http://www.inrs.fr/dms/inrs/PDF/bdd-demeter/DEM-076/DEM%20076.pdf (in French). Accessed September 16, 2021.
17) Direction Générale de la Santé. Circulaire DGS/3A/667bis du 10 octobre 1985 relative à la distribution des gaz à usage médical et à la création d'une commission locale de surveillance de cette distribution. 1985. http://mtriay.free.fr/Textes_officiels/c_10_10_1985.PDF (in French). Accessed September 16, 2021.
18) SIAD. Safety Data Sheet. Nitrous oxide E942. 2017. https://www.siad.com/safety/material-safety-data-sheet?p_p_id=com_liferay_sheet_portlet_SecuritySheetPortlet_INSTANCE_T7lbJDQJQNxs&p_p_lifecycle=2&p_p_state=normal&p_p_mode=view&p_p_cacheability=cacheLevelPage&p_p_col_id=column-3&p_p_col_pos=1&p_p_col_count=2&_com_liferay_sheet_portlet_SecuritySheetPortlet_INSTANCE_T7lbJDQJQNxs_filename=00093_LIQ_ALI_EN.pdf. Accessed September 16, 2021.
19) National Institute for Occupational Safety and Health (NIOSH). Criteria for a recommended standard: occupational exposure to waste anesthetic gases and vapors. DHHS (NIOSH) Publication number 77-140. 1977. https://www.cdc.gov/niosh/nioshtic-2/00070002.html. Accessed September 16, 2021.
20) Messeri A, Amore E, Dugheri S, Bonari A, Pompilio I, Arcangeli G, Rizzo G (2016) Occupational exposure to nitrous oxide during procedural pain control in children: a comparison of different inhalation techniques and scavenging systems. Paediatr Anaesth **26**, 919–25.
21) Vieira E, Cleaton-Jones P, Moyes D (1983) Effects of low intermittent concentrations of nitrous oxide on the developing rat fetus. Br J Anaesth **55**, 67–9.
22) Henderson KA, Matthews IP (2000) Environmental monitoring of nitrous oxide during dental anaesthesia. Br Dent J **188**, 617–9.
23) Denis M-A, Cadot R, Bergeret A (2016) Exposition du personnel soignant au protoxyde d'azote. Archives des Maladies Professionnelles et de l'Environnement **77**, 640–9 (in French).
24) California Environmental Protection Agency Air Resources Board. Procedure for determination of nitrous oxide in automotive exhaust by Fourier transform infrared spectroscopy. Standard Operating Procedure No. MLD 136, Revision 2.0. 2004. https://www.arb.ca.gov/testmeth/slb/slb136_rev_2.pdf. Accessed September 16, 2021.
25) Zafonte L, Rieger PL, Fuentes M, Ling R (2010) A precise gas chromatographic method using ECD detection for the measurement of nitrous oxide in vehicle exhaust. EPA/AWMA Symposium on Air Quality Measurement Methods and Technology. Los Angles, California, November 2, 2010. http://lotusinstruments.com/wp/wp-content/uploads/A-Precise-Gas-Chromatographic-Method-Using-ECD-Detection-for-the-Measurement-of-Nitrous-Oxide-in-Vehicle-Exhaust.pdf. Accessed September 16, 2021.
26) Silva CM, Corrêa SM, Arbilla G (2016) Determination of CO2, CH4 and N2O: a case study for the city of Rio de Janeiro using a new sampling method. J Braz Chem Soc **27**, 778–86.
27) Mills GH, Singh D, Longan M, O'Sullivan J, Caunt JA (1996) Nitrous oxide exposure on the labour ward. Int J Obstet Anesth **5**, 160–4.
28) Gilchrist F, Whitters CJ, Cairns AM, Simpson M, Hosey MT (2007) Exposure to nitrous oxide in a paediatric dental unit. Int J Paediatr Dent **17**, 116–22.
29) Passeron J, Guilleux A, Guillemot M, Langlois E, Pillière F (2016) Protoxyde d'azote lors de l'utilisation du MEOPA en milieu de soins : toxicité, situations d'exposition, données métrologiques, pistes de prévention et rôle du médecin du travail. Références en santé au travail **148**, 105–15 (in French).
30) Lafon D (2008) Recommandations et guides pour les

médecins du travail dans le cadre de la surveillance liée à l'exposition aux reprotoxiques. Archives des Maladies Professionnelles et de l'Environnement **69**, 268–71 (in French).