BEST PRACTICE AND SAFE USE OF MEDICINAL NITROUS OXIDE

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Amendments to Doc 153/08

Section	Change
All	The entire document has been re-written and updated with latest scientific bibliographic publications.

1 Introduction

Nitrous oxide (N_2O) has been used as analgesic agent for more than 150 years; however, inappropriate use has jeopardized its use in clinical practice.

This document reviews the pharmacological properties of N_2O and its intended use in today's clinical practice.

The document provides recommendations for safe use of N_2O and risk minimization strategies that should be respected by all healthcare professionals that are in contact with N_2O.

The document is laid out as follows:

- Describes basic pharmacokinetic and pharmacodynamic characteristics of N_2O, i.e., uptake and elimination by the body and interaction with its biological targets; and
- Shows how these properties are linked to known safety issues of N_2O.

This knowledge provides the rationale for best practice recommendations of safe handling and use of N_2O.

In this document we take a novel approach in presenting safety rules by anchoring each recommendation to a scientific rationale. The goal is to increase knowledge and confidence in N_2O use by providing the logic behind the rules so that healthcare professionals can draw maximum benefit from N_2O use while mitigating risks for patients and healthcare professionals.

2 Scope and purpose

2.1 Scope

This document is intended for use by

- Healthcare professionals (hospitals and outside hospitals),
- Safety workers regulators,
- bioengineering personnel,
- scientific societies,
- EIGA members,
- National Gas Associations and
- national regulatory authorities,
- patients' associations,
- media

It focuses only in the understanding and presentation of clinical best practices of use to mitigate the potential safety risks related to the human exposure to N_2O and N_2O mixtures.

2.2 Purpose

This document aims to promote the safe use of medicinal N_2O and N_2O mixtures and to raise awareness on the misuse of these medicinal products.

3 Definitions

For the purpose of this publication, the following definitions apply.

3.1 Publication terminology

3.1.1 Shall

Indicates that the procedure is mandatory. It is used wherever the criterion for conformance to specific recommendations allows no deviation.

3.1.2 Should

Indicates that a procedure is recommended.

3.1.3 May

Indicates that the procedure is optional.

3.1.4 Will

Is used only to indicate the future, not a degree of requirement.

3.1.5 Can

Indicates a possibility or ability.

3.2 List of Abbreviations

CNS	Central nervous system
ED50	Effective dose leading to 50% of inhibition
EIGA	European Industrial Gases Association
EMONO	Equimolar mixture of oxygen nitrous oxide
GABA	Gamma-aminobutyric acid
N_2O	Nitrous oxide
NIOSH	National Institute for Occupational Safety and Health
NMDA	N-methyl-D-aspartate
NOAEL	No-observed-adverse-effect level
O_2	Oxygen
OEL	Occupational exposure limits
ppm	Parts per million
PONV	postoperative nausea and vomiting
SAM	S-adenosyl methionine
SmPC	Summary of product characteristics
TWA-8	Total weight average during 8 hours

4 Executive summary

N_2O has been in use for more than 150 years due to its analgesic and anaesthetic properties. The main advantage of nitrous oxide is its fast on/off effect, which makes it an attractive agent for rapid analgesia and sedation in paediatrics, dentistry, and obstetrics [1][2]. In these situations, equimolar mixtures of nitrous oxide and oxygen (EMONO) are sufficient to provide analgesic effect while patients are conscious and preserve their reflexes. In general anaesthesia, N_2O as single agent is prohibited due to its low potency as anaesthetic agent. Rather, N_2O is administered together with other anaesthetics to increase their partial alveolar pressure, thereby leading to faster induction of anaesthesia [2].

In recent years, the place of nitrous oxide in modern analgesia and anaesthesia has been questioned due to concerns about nitrous oxide-related toxicities [3]. Known risks of N_2O that are supported by the current evidence base include occupational exposure, diffusion hypoxia, increase in size or pressure of air-or gas-filled spaces, for example increase in intracranial pressure and intraocular pressure,

neurological and haematological toxicities, as well as postoperative nausea and vomiting (PONV) [2]. Given its long history of clinical use and active surveillance of N_2O -related reactions, the safety profile of N_2O is well characterized.

This document reviews the different mechanisms of action of N_2O and their relationship to toxic effects. These effects are then discussed within the context of relevant clinical situations. Finally, recommendations are presented for the safe use of nitrous oxide and procedures to mitigate safety risks (Figure 1).

The goal is to raise awareness of the mode of action of nitrous oxide among health care professionals to increase their confidence in the safe use of nitrous oxide with the aim to draw maximum benefit while minimizing toxicities for their patients and personnel.

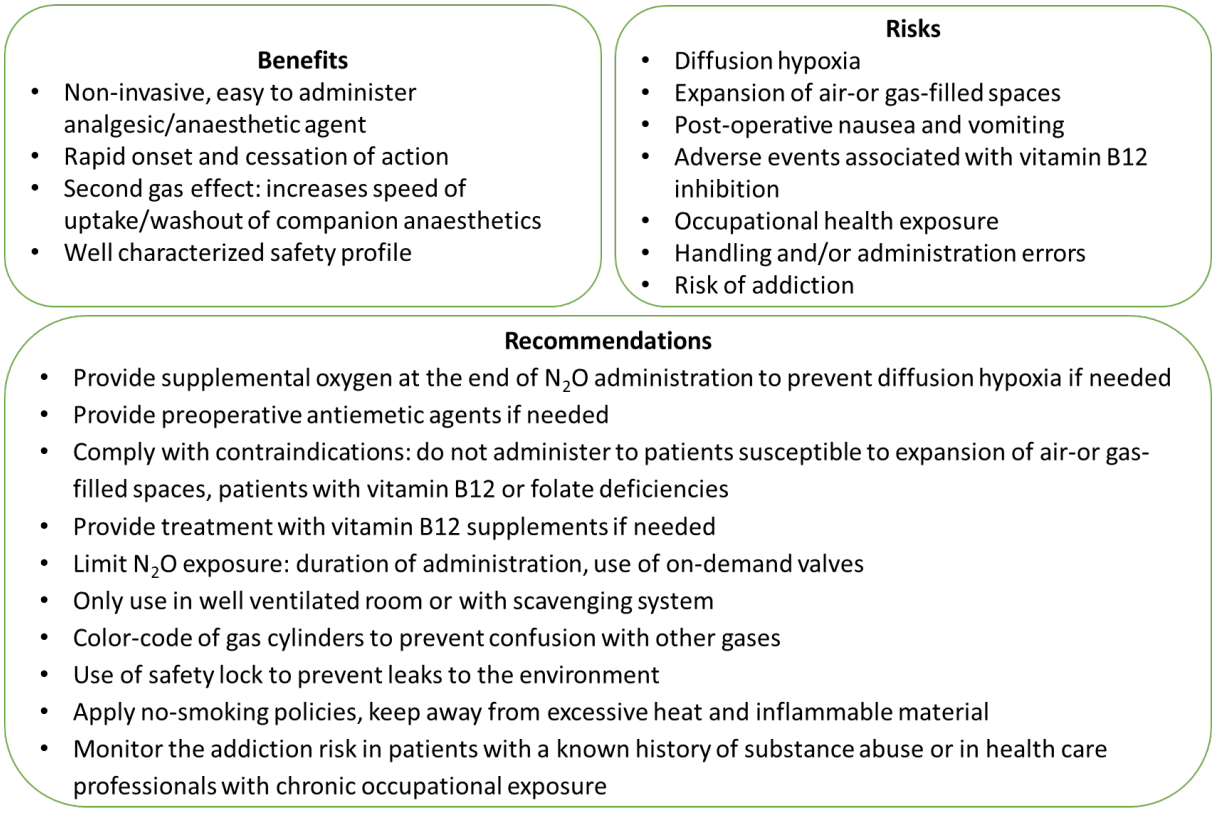


Figure 1 Overview of benefits, risks and recommendations for safe use of N_2O

5 Background

- Routine use of N_2O as analgesic and anaesthetic started in 1870, 100 years after its discovery.
- Reports of N_2O related toxicity and fatalities have emerged in the second half of the 20th century.
- Development of safe equipment and research into the mechanism of action of N_2O aimed at improving safety of N_2O use in clinical practice.

N_2O was discovered in 1772 by Joseph Priestly, an English cleric and chemist. However, it took almost a century before its analgesic and anaesthetic properties were recognized. Until then, N_2O was mostly known for inducing a state of euphoria, which led to becoming known as laughing gas and its use for entertainment at private events [2]. Eventually, dental surgeons became aware of the potential application of N_2O as analgesic during tooth extraction.

With the advance of high-pressure gas cylinders and ready-to-use mixtures of N_2O and oxygen (O_2), N_2O gained widespread use in dentistry, obstetrics and surgery, the latter in combination with other anaesthetics.

Towards the end of the 20th century, reports of N_2O related toxicities and fatalities emerged, leading to efforts to determine safe conditions and risk minimization strategies for the use of N_2O in clinical practice [4]–[6]

The reasons for N_2O related mortality and morbidity can broadly be attributed to:

1. Wrong handling of N_2O during storage and administration
2. Complications due to expansion of air-or gas-filled spaces in the body
3. The pharmacological effect of N_2O

Rare cases of administration errors have been reported, with the untoward consequence of asphyxia and diffusion hypoxia [4].

Complications related to the rapid diffusion of N_2O into air-filled spaces can lead to complications such as pneumothorax, intestinal distension and increased intracranial pressure [2].

Analgesic and anaesthetic effect is conveyed by nitrous oxide's action on several receptors of the central nervous system (CNS). However, N_2O also reacts with vitamin B12, and this off-target effect is associated with neurological and haematological toxicity [7].

The chemical reaction between N_2O and vitamin B12, which forms the basis of N_2O related toxicity, was reported in 1968 [8]; however, the clinical implications of this observation were not recognized for almost 10 years [9]. In 1978, several papers were published that linked prolonged exposures to N_2O with interference with B12 function, forming the basis for determination of safe limits of exposure to N_2O [10]–[12].

6 Pharmacokinetics

- N_2O has low solubility in blood and adipose tissue, leading to fast absorption and diffusion via the blood stream to the brain.
- Thanks to second gas effect, N_2O enhances uptake and elimination of associated volatile inhaled agents, thereby leading to faster induction and wakening in general anaesthesia.
- N_2O diffuses more rapidly into air- or gas-filled spaces compared with nitrogen and this can lead to changes in pressure and volume. A consequence is for example increased intracranial pressure.
- Upon cessation of N_2O intake, diffusion hypoxia can occur because of dilution of oxygen concentration in the alveolar compartment. Diffusion hypoxia can be handled through oxygen supply.

6.1 Pharmacokinetics background

Uptake of inhaled anaesthetics occurs at the alveoli and is governed by the solubility of the gas within blood and adipose tissue. N_2O has low solubility and equilibrium of gas concentrations between the air/alveoli interface is rapidly achieved, driving diffusion across the alveolar baseline membrane and uptake into the blood stream. Rapid absorption and distribution to the brain explains the fast onset of action of nitrous oxide [13]. Furthermore, because N_2O is quickly absorbed by alveoli, local concentration of other gases increases, which hastens their uptake, leading to the second gas effect. Conversely, once inhalation of N_2O ceases, N_2O exits rapidly the alveolar phase, which can lead to dilution of gaseous content in the alveoli and enhanced elimination of associated inhaled agents, resulting in fast emergence (wakening) [14], [15]. However, through the same mechanism, the relative oxygen content in the alveoli is diluted upon cessation of N_2O intake, leading to diffusion hypoxia [14]. In current N_2O delivery systems, an upper limit is set to the proportion of N_2O administered (70%), requiring at least 30% of O_2, which is above the ambient air O_2 content [16]. When using equimolar mixtures of N_2O and O_2, the risk of diffusion hypoxia is further mitigated given the high proportion of simultaneously inhaled O_2 [17].

Because of the difference in solubility between N_2O and nitrogen, there is a rapid expansion of air or gas filled spaces upon N_2O inhalation. This can lead to expansion of gas-filled spaces within the body and increase the risk of adverse effects in specific clinical situations [15].

A meta-analysis of clinical trial data showed that occurrence of PONV with N_2O is dependent on the duration of inhalation with exposure times less than 1 hour having a low risk for PONV [18].

6.2 Safety implications

The diffusion, absorption, and elimination characteristics of N_2O form the basis of a set of safety recommendations and contraindications.

People susceptible to expansion of air-or gas-filled spaces in the body should not receive N_2O, including people with signs of pneumothorax, pneumopericardium, severe head trauma, recent ocular surgery with intraocular injection of gas, and gastrointestinal extensions. Since N_2O diffuses more rapidly into these air-or gas-filled spaces compared to nitrogen, oxygen or other gases that are for example used in intraocular surgery, use of N_2O could lead to volume or pressure increase and related adverse effects (Table 1).

Diffusion hypoxia can occur after inhalation of N_2O due to dilution of oxygen in the alveolar space. N_2O should only be used when oxygen supplementation is available. In case of diffusion hypoxia, the patient should be given supplemental oxygen. The risk of diffusion hypoxia is mitigated when equimolar mixtures of N_2O and O_2 are used because of simultaneous inhalation of high O_2 content. After analgesia

with N_2O, patients should recover under medical surveillance for at least five minutes or until the patient has recovered to a sufficient level of alertness/consciousness [19].

Table 1 Clinical situations with N_2O associated risk

Risk factor	Adverse Effect
Pneumothorax, pneumopericardium, severe emphysema, gas emboli.	Rapid increase in size, leading to ventilatory and/or cardiovascular effects
Head injury	Increase in intracranial pressure
Severely dilated gastrointestinal tract	Increase in intra-abdominal pressure Difficult closure of the abdomen Intestinal rupture
Recent surgery using injections of intraocular gas (e.g., SF_6, C_3F_8)	Blindness Pain
After deep-sea diving with risk of decompression sickness	Rapid increase in symptoms Distal organ damage
Air embolism After air encephalograph	Rapid increase in size and effects
During middle ear, inner ear, and sinus surgery	Disruption of grafts Disruption of ossicular chain
If air has been injected into the epidural space (as part of epidural anaesthetic procedure)	Rapid increase in size and effects

Source: Peyton et al, 2011; Brown & Sneyd, 2016; Nitrous Oxide Summary of Product Characteristics, As Authorized by Health Authorities and Specified by Manufacturers.

7 Pharmacodynamics

7.1 Analgesia and anaesthesia

Key messages

- Concentrations between 30% to 60% of N_2O provide dose-dependent analgesia and sedation.
- Analgesic effect is mediated through the release of endogenous opioid peptides which trigger supraspinal inhibition of nociceptive signalling pathways.
- N_2O is a N-methyl-D-aspartate (NMDA) antagonist. At subanaesthetic concentrations, N_2O generates a moderate sedative effect. As NMDA antagonist, N_2O acts synergistically with other inhaled anaesthetic agents to increase the overall anaesthetic effect of both agents.
- The effect on the CNS requires caution when used in patients with a known history of substance abuse or in healthcare professionals with chronic occupational exposure

At concentrations between 30% and 60%, N_2O possesses dose-dependent analgesic and sedative properties. N_2O alleviates pain, acts as anxiolytic and reduces agitation without inhibiting reflexes or interfering with the ability to speak.

Antinociceptive action of N_2O is mediated by the release of endogenous opioid peptides and subsequent blockage of the inhibitory gamma-aminobutyric acid (GABA) ergic pathway [20]. Inhibition of GABA results in the release of norepinephrine through descendant pathways towards the spinal cord. Norepinephrine suppresses pain by blocking alpha-2-adrenoceptors both pre-and post-synaptically [21].

N_2O also acts as a non-competitive N-methyl-D-aspartate (NMDA) antagonist inhibiting excitatory neurotransmission [7], [22]. While N_2O potency is insufficient to induce anaesthesia, N_2O can provide moderate dose-dependent sedation [20].

In the context of anaesthesia or analgesia, N_2O may be given in combination with other agents that act as CNS depressants. N_2O has negligible effect on gamma-aminobutyric acid type A (GABAA) receptors [7], [22]. However, NMDA antagonist and GABAA modulators seem to act synergistically and combination of these agents increases the effect on the CNS of either agent. Attentive monitoring is required in patients taking CNS depressant drugs to mitigate hemodynamic and respiratory adverse effects risks [1], [23].

In relation with the CNS anxiolytic, analgesic and sedative effect of N_2O, repeated administration or exposure to N_2O can lead to addiction. Caution should be exercised in patients with a known history of substance abuse or in healthcare professionals with chronic occupational exposure to N_2O [24], [25].

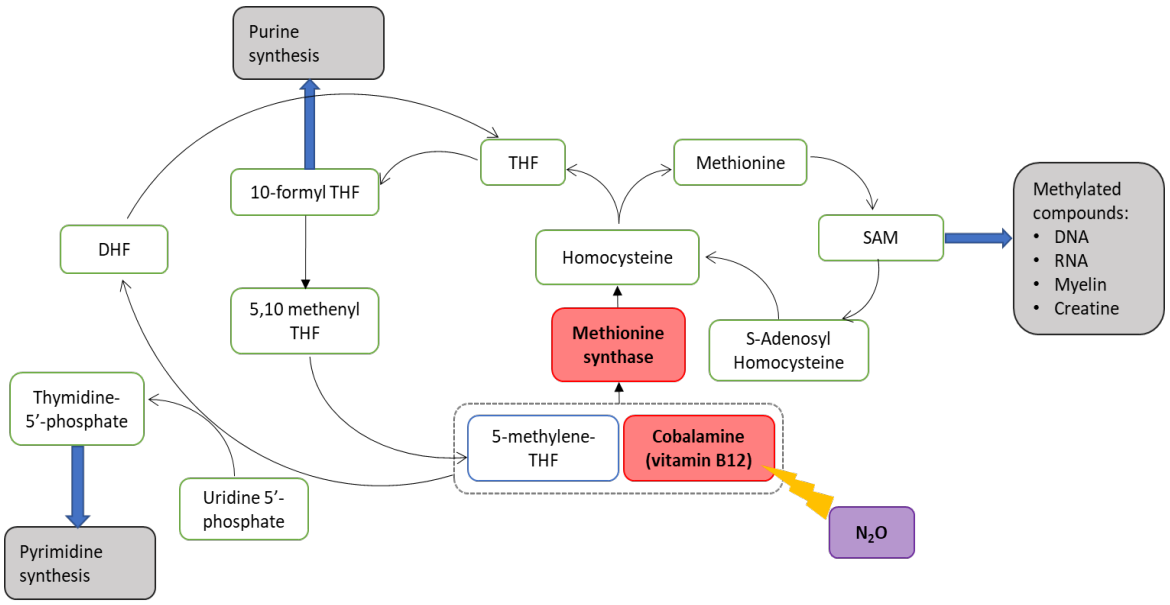
7.2 Methionine synthase inhibition

Key messages

- N_2O irreversibly oxidises cobalamin (vitamin B12) thereby inhibiting methionine synthase function.
- Inhibition of methionine synthase disrupts both the methionine and folate cycles.
- Disruption of the methionine cycle deprives the body from methylation agents, leading to a wide range of disorders, including spinal cord defects, neurological and neuropsychiatric disorders.
- Disruption of the folate cycle interferes with the production of blood cells in the bone marrow, resulting in megaloblastic anaemia.

- Inhibition of methionine synthase is dose and duration dependent with exposure of less than 6 hours deemed safe. Methionine synthase activity recovers slowly after 3 to 4 days.
- No inhibition of methionine synthase occurs at occupational exposures below 450 particles per million (ppm) for 24 hours.

N_2O reacts with vitamin B12, a cofactor of methionine synthase, thereby leading to inhibition of methionine synthase activity. Methionine synthase converts homocysteine to methionine, a reaction that requires two cofactors: vitamin B12 and 5-methyltetrahydrofolate [7], [26] (Figure 2).



DHF: dihydrofolate; SAM: S-Adenosyl Methionine; THF: tetrahydrofolate

Figure 2 Methionine and folate cycle and interaction with N_2O

Inhibition of methionine synthase has ramifications that go beyond methionine synthesis. Methionine is a precursor of S-adenosyl methionine (SAM), the single most important cellular methyl donor, involved in the synthesis of a wide range of methylated compounds, including DNA, RNA, histones, creatine and myelin [7], [26]. Disruption of transmethylation pathways results in psychiatric and neurological disorders as well as myelopathies. The posterior column of the spinal cord is the most common site of injury associated with N_2O intoxication [27]. Inhibition of methionine synthase by N_2O depletes internal methionine storage that is required for proper methylation of myelin sheath. In the absence of functioning methionine synthase, spinal cord damage can develop, leading to sensory disorders, limb weakness and poor balance [27]–[29]. Symptoms of spinal cord damage were most often reported in people with recreational N_2O use and correlated with the frequency of N_2O abuse [29]–[31]. Reports in patients of subacute spinal cord degeneration after N_2O exposure for analgesia or anaesthesia were usually limited to people with pre-existing vitamin B12 deficiency [27].

Methionine synthase inhibition has also a profound impact on the folate cycle. In case of methionine synthase deficiency, folates might get trapped in the 5-methyltetrahydrofolate form, leading to a shortage of other folates which are required in the synthesis of purines, pyrimidines and deoxythymidine monophosphate [26], [32], [33]. This has consequences on cell growth especially in quickly dividing cells, such as blood cells in the bone marrow. Disruption of the folate cycle because of vitamin B12 or folate deficiency can lead to megaloblastic anaemia, i.e., the bone marrow produces large immature blood cells (megaloblasts), that are functionally impaired, which are released to the blood stream but cannot exert their intended function, thereby leading to anaemia [34]. Megaloblastic anaemia is most

often observed during pregnancy due to the increased metabolic requirements and can be handled with folate and vitamin B12 supplementation.

In rats, after 30 minutes of N_2O exposure, methionine synthase activity decreased by 50% whereas virtually no activity was detected after 6 hours [6]. In humans, inactivation of methionine synthase is much slower. Analysis of liver biopsies in patients anaesthetized with N_2O (70%) indicated that methionine synthase activity was reduced by 50% within 45 minutes to 1.5 hours. After 200 minutes of N_2O inhalation, methionine synthase activity reached 0%. Typically, the enzymes' function will recover within 3 to 4 days. From a clinical perspective, inhalation of nitrous oxide for less than 6 hours during medical procedures was considered safe with no vitamin B12-related haematological toxicities [6], [28], [35]. In the absence of inborn errors or conditions leading to malabsorption, temporary folate and vitamin B12 deficiencies can be handled with nutritional supplements. Preoperative vitamin B12 treatment may be considered in patients undergoing procedures with N_2O use and that are thought at risk of vitamin B12 deficiency.

Analysis of inhibition of methionine synthase in Sprague Dawley rats exposed to varying concentrations of N_2O over prolonged periods of time (24 hours to 28 days) showed no significant effect at concentrations of up to 450 parts per million (ppm) [36]. The effective dose leading to 50% of inhibition (ED_{50}) was 5400 ppm and significant inhibition was observed at ≥ 1000 ppm. Direct extrapolation of rodents to humans is difficult; liver biopsy studies in humans suggest that the time course of inhibition is delayed in humans. Measurements of deoxyuridine concentrations, a product of DNA synthesis dependent on methionine synthase activity, indicate no effect of N_2O at concentrations up to 1000 ppm over 28 days, but 16 days of exposure to N_2O concentrations of 5000 ppm led to quantifiable inhibition of deoxyuridine [36].

Carcinogenicity and teratogenicity were analysed in rodents. Mice exposed to N_2O 10% or 50% for 4 hours a day, 5 days per week showed no increase in both neoplastic nonneoplastic findings after 78 weeks of treatment compared with controls [37]. In rats, exposure to 50 ppm and 500 ppm N_2O for 7 hours a day, 5 days per week, during 60 days prior to mating led to decreased ovulation and less efficient implantation. Foetal growth was slightly lower in N_2O exposed animals, but no major teratogenic effect was observed [38].

7.3 Safety Implications

Considering the CNS effects of N_2O, caution is mandatory in patients taking CNS depressant drugs as well as in patients with a known history of substance abuse or in healthcare professionals with chronic occupational exposure.

Because of N_2O interaction with vitamin B12, people with vitamin B12 or folic acid deficiency should not receive N_2O. Adverse effects related to vitamin B12 deficiency can be exacerbated by inhalation of N_2O.

In patients without contraindication to N_2O, vitamin B12-related toxicities can be minimized by limiting duration of N_2O inhalation. Clinical studies investigating haematological changes after N_2O exposure concluded that N_2O administration times of less than 6 hours were safe [28], [35].

8 Occupational exposure risk

- Environmental risk agencies recommend that N_2O concentrations averaged over 8 hours (total weight average during 8 hours; TWA-8h) do not exceed 25 ppm to 100 ppm.
- Ventilation and scavenging systems, on-demand valves and large rooms with at least one door or window decrease the risk of exceeding occupational exposure limits deemed safe.

8.1 Occupational exposure to N_2O

Because of the N_2O interference with methionine and folate cycle, concerns have been raised regarding a potential risk of neurotoxic, haematopoietic, and teratogenic side effects for healthcare professionals regularly exposed to nitrous oxide.

Based on experiments in rodents and studies in humans exposed to N_2O, recommendations of occupational exposure limits (OEL) to N_2O have been issued. In the UK and in Sweden an OEL of 100 ppm has been recommended, while the National Institute for Occupational Safety and Health (NIOSH) put forth an upper value of 25 ppm [7]. Early studies noticed that the OEL value of 25 ppm was based on detection limit rather than actual safety margins and constitutes an excessively stringent criterion [36].

N_2O at concentrations of 50% is commonly used in paediatric dentistry or other ambulatory care interventions in anxious children to induce conscious sedation, (i.e., a state characterized by central nervous system depression while preserving the patient's ability to respond to physical or verbal stimuli) [39]. N_2O at equimolar O_2 concentrations is also an option for pain relief during delivery, showing patient satisfaction [40].

However, repeated use of N_2O during practice hours can pose an occupational health risk to medical practitioners and personnel due to increased exposure to environmental concentrations of N_2O. Several studies have reported increased incidence of adverse events in health care professionals with regular N_2O exposure [5], [41], [42]. At the time the studies were reported these exposures were highly variable, depending on ventilation equipment and use of scavenging systems.

More recent studies continue to report a wide range of results in terms of N_2O exposure, emphasizing that occupational exposure to N_2O could remain a concern in the absence of ventilation or scavenging systems. In a study monitoring N_2O exposure in midwives at two UK hospitals, 70% of midwifes were exposed to environmental levels above the recommended 100 ppm [43]. The ventilation system in the monitored delivery units did not meet the recommended standards, though the authors did not specify the level of ventilation provided. On the other hand, Collins et al. reported N_2O exposures below the NIOSH limit of 25 ppm based on badge dosimetry results collected from midwives in two hospitals offering N_2O to parturient for pain relief [40]. The authors note that the USA Food and Drug Administration requirements necessitate both a blender and scavenging system and this could explain the low concentrations of contaminant N_2O. On-demand valves, large rooms with at least one door and sufficient time between procedures to refresh air can further help in minimizing environmental N_2O concentrations [19].

8.2 Safety implications

Health workers regularly exposed to low concentrations of N_2O could be at risk of vitamin B12-related toxicities. Nonclinical and clinical studies have determined occupational exposure limits (25 to 100 ppm) that are safe and do not entail a risk to healthcare professionals.

Every effort should be made to limit N_2O concentrations to nationally set limits [19].

N_2O should only be used in well-ventilated rooms or in the presence of scavenging systems. On demand-valves can be used to limit N_2O administration to patient's needs; this can also reduce the amount of N_2O released into the working environment.

9 Handling of Gas Cylinders

- Cylinders containing mixtures of N_2O and oxygen should not be stored at temperatures below - 5°C to avoid separation into two phases.
- N2O is non-flammable gas with oxidative properties and in EMONO oxygen is exothermic.
- Use and handling of N_2O and N_2O mixture containing cylinders should be avoided in the presence of sources that could initiate the decomposition reaction (smoking, electric sparks, excessive heat). The cylinders should be kept dry and free of grease.

N_2O is available as equimolar mixture of 50% N_2O and 50% O_2 or as 100% N_2O. The latter is intended for use with a blender to generate N_2O/O_2 mixtures with N_2O content varying between 30% and 60%.

Gas cylinder colour-code can assist the recognition of N_2O or equimolar mixture of 50% N_2O and 50% O_2 when compared with other gas cylinders. Medicinal nitrous oxide cylinders have a blue shoulder and a white cylinder body. The primary identification is the labelling.

When stored at low temperature there is a risk of separation of gaseous mixture product with separation into different phases. Separation of gases could lead to inhalation of pure N_2O, thereby leading to asphyxiation.

N_2O is non-flammable gas with oxidative properties. Even though N_2O is relatively stable, the decomposition reaction into molecular nitrogen and oxygen is exothermic, meaning that once the reaction is initiated it propagates without further energy requirement. N_2O decomposition can be initiated by several sources, including electric sparks, open flames, presence of flammable contaminants, shocks and welding/brazing. The presence of oxygen in EMONO-containing cylinders can aggravate combustion reactions and fires due to the additional oxidative power of oxygen [44].

When handling gas cylinders, health professionals should always check for leakage. Release of N_2O into the working environment and atmosphere is associated with the same risks of short and long-term exposures described in the previous sections.

9.1 Safety implications

If cylinders containing equimolar mixtures of N_2O/O_2 are stored at lower temperatures, they should be placed in a horizontal position at a temperature above +10°C for at least 48 hours before use. They should not be stored at temperature below -5°C to avoid separation into two phases.N_2O and N_2O mixture containing cylinders should be kept away from flammable material and should not be exposed to excessive heat to avoid initiation of decomposition reaction and open flames. No-smoking policy should be applied in all areas where N_2O and N_2O mixture is used or stored. The cylinders should be kept dry and free of grease, the latest could otherwise favour combustion reactions.

People handling gas cylinders should always check for leaks. Leaking cylinders should be emptied outside and returned to the supplier.

10 Summary of best practice and safe use recommendations

10.1 Contraindications

- Do not administer N_2O to subjects susceptible to expansion of air-or gas-filled spaces in the body because rapid N_2O diffusion can lead to volume or pressure increase and related adverse events.

- Do not administer N_2O to subjects with vitamin B12 or folic acid deficiency; N_2O interacts with vitamin B12 and can exacerbate adverse events related to vitamin B12 or folic acid deficiency.

10.2 Safe use recommendations for patients

- Only use pure N_2O in presence of oxygen supply in case of diffusion hypoxia.

- Limit duration of N_2O inhalation as specified in the product information provided by the manufacturer to mitigate the risk of adverse events related to vitamin B12 inhibition.

10.3 Safe use recommendations for healthcare professionals

- Only use in well-ventilated rooms or in presence of scavenging systems. Use inhalation systems with on-demand valve to reduce the amount of N_2O waste gas in the room.

10.4 Safe Handling of Gas Cylinders

- Verify proper storage and temperature of N_2O containing gas cylinders to avoid separation into two phases.

- Do not smoke and do not use N_2O and N_2O mixture containing cylinders in the presence of open flames to avoid initiation of decomposition reaction. N_2O should not be used in the presence of sources that could initiate the decomposition reaction (smoking, electric sparks, excessive heat). The cylinders should be kept dry and free of grease.

11 References

Unless otherwise specified, the latest edition shall apply.

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