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HEALTH TECHNOLOGY ASSESSMENT:

Effectiveness and safety of nitrous oxide as sedation regimen in children

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Hovedfunn

Lystgass (N_2O) har beroligende og smertedempende effekt ved inhalasjon. Lystgass blir i Norge brukt ved fødsler samt på tannlegekontor. I tillegg er det noen sykehus som bruker lystgass til sedering av barn ved forskjellige sykehusprosedyrer.

Formålet med denne metodevurderingen har vært å systematisk undersøke den kliniske effekten, samt sikkerhet for både pasient og behandler, ved bruk av lystgass for sedering av barn ved gjennomføring av små og smertefulle sykehusprosedyrer.

De viktigste funnene fra denne rapporten er:

- Lystgass kan brukes for sedering av barn uten å gi alvorlige bivirkninger
- Den tydeligste fordelen med lystgass er muligens den korte restitusjonstiden sammenlignet med alternative sederingsmetoder
- Helsepersonell (jordmødre og tannlegeassistenter) eksponert for lystgass versus ingen eksponering hadde ikke økt risiko for spontanabort
- Helsepersonell hadde ikke redusert fertilitet ved lav eksponering, men ved høy eksponering.
- Risikoen for misdannelser hos barn født av mødre eksponert for lystgass (konsentrasjon og eksponeringsgrad er ikke kjent) var høyere enn hos ikke-eksponerte mødre.
- Vi kan ikke si noe om lystgass har toksisk effekt på DNA eller andre cellulære mekanismer, da det ikke finnes gode resultat på dette.
- Vi fant ingen studier om negative helseeffekter for helsepersonell som bruker lystgass for sedering av barn som gjennomgår små sykehusprosedyrer.

Tilliten til sikkerhetsresultatene for helsepersonell er svært lav på grunn av studiedesign (retrospektive kohorter) samt at informasjon om nivå av eksponering av lystgass var meget mangelfull. For helsepersonell som arbeider med lystgass sedering av barn i forbindelse med små sykehusprosedyrer, vil vi forvente en betydelig lavere eksponeringsgrad enn i de studiene hvor toksiske effekter av lystgass er rapportert, av to grunner. For det første vil vi forvente en betydelig lavere konsentrasjon av lystgass på grunn av god ventilering og rensesystem for overskuddsgass. For det andre vil eksponeringstiden være betydelig lavere, både fordi hver prosedyre tar kortere tid (maksimalt 30 minutter) samt at antall prosedyrer per helsepersonell per uke vil være begrenset (personlig kommunikasjon).

Tittel:
Metodevurdering av sikkerhet og effekt ved bruk av lystgass for barn

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Publikasjonstype:

Fullstendig metodevurdering

En metodevurdering er resultatet av å
- innhente
- kritisk vurdere og
- sammenfatte relevante forskningsresultater ved hjelp av forhåndsdefinerte og eksplisitte metoder. Minst ett av følgende tillegg er også med: Helseøkonomisk evaluering, vurdering av konsekvenser for etikk, jus, organisasjon eller sosiale forhold

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Svarer ikke på alt:

- Ingen studier utenfor de eksplisitte inklusjonskriterient
- Ingen anbefalinger

Hvem står bak rapporten:

Folkehelseinstituttet har gjennomført oppdraget etter forespørsel fra Bestillerforum RHF

Når ble litteratursøket utført?

Søk etter studier ble avsluttet November 2017

Sammendrag

Bakgrunn

Barn (opp til 18 år) som gjennomgår smertefulle sykehusprosedyrer får tilbud om forskjellige smertestillende midler (analgesi), ofte i kombinasjon med avslappende midler (sedering). Det er ønskelig å finne frem til gode kombinasjoner av dette for å gjøre slike prosedyrer mer effektive.

Lystgass (dinitrogenoksid, N_2O) er en uorganisk, fargeløs og nesten luktløs gass. Lystgass har beroligende og smertedempende effekt ved inhalasjon. Lystgass tas effektivt opp i lungene og skilles raskt ut igjen. Flere internasjonale retningslinjer (1;2) nevner lystgass som mulig sedasjonsmetode til barn som gjennomgår små, men smertefulle sykehusprosedyrer. En systematisk oversikt av Pedersen *et al* (3) har oppsummert litteratur på sedasjon av barn med lystgass, og konkluderer med at dette ser ut til å være en effektiv metode som kan gjøre korte sykehusprosedyrer enklere. Denne artikkelen vurderer også med at metoden er sikker for barn som blir eksponert over kort tid og bare noen få ganger. Det som ikke er vurdert er effekten dette kan ha på helsearbeideren. Lystgass er antatt til å ha toksisk effekt på reproduksjon i tillegg til risikoen for hodepine, fatigue og irritabilitet, og dette har redusert bruken av lystgass i mange tilfeller.

Formål

Formålet har vært å systematisk undersøke den kliniske effekten, samt sikkerhet for både pasient og behandler, ved bruk av lystgass for sedering av barn ved gjennomføring av små og smertefulle sykehusprosedyrer.

Metode

Vi har gjennomført en metodevurdering på effekt og sikkerhet av lystgass for sedering av barn i henhold til håndboken "Slik oppsummerer vi forskning", av Folkehelseinstituttet.

Vi identifiserte litteratur som omhandlet både sykehus og tannlegekontor. Siden bestilleren vår, Bestillerforum RHF, representerer spesialisthelsetjenesten, besluttet vi å begrense rapporten til kun sykehus-setting. Men for vurdering av sikkerhet for helsepersonell inkluderte vi også personell fra tannlegekontor.

Resultat

Litteratursøk

Vi inkluderte 22 randomiserte, kontrollerte studier for vurdering av effekt og sikkerhet for barn. Vi inkluderte også 15 ikke-randomiserte studier for å dokumentere sikkerhetsaspektet for helsepersonell eksponert for lystgass som avfallsgass. I tillegg utarbeidet vi en tabell av ytterligere 58 ikke-randomiserte kontrollerte studier som rapporterte om sikkerhetsaspektet ved anestesigasser hvor lystgass sannsynligvis var en komponent av gassen.

Effekt av lystgass

Vi har vist at pasient og helsepersonell er mer fornøyd med lystgass enn placebogruppen og at pasienten er mindre stresset ved bruk av lystgass enn placebogruppen. Når disse utfallene ble sammenlignet med andre aktive legemidler, var det uklart om det var noen forskjell. Tilliten til resultatene var fra lav til moderat, mest på grunn av manglende blinding og utydelig presentasjon av data.

Den tydeligste forskjellen mellom lystgass og andre aktive legemidler, var restitusjonstiden hvor pasienten var restituert etter 0-30 minutter mens pasienter som fikk ketamin og/eller misazolam ble fulgt opp 21-83 minutter. Tilliten til dette resultatet resultatene ble vurdert som høy.

Sikkerhet ved bruk av lystgass

Femten studier rapporterte om bivirkninger. Blant 525 pasienter som ble sedert med lystgass, uavhengig av sykehusprosedyre eller kontrollgruppe, ble det ikke rapportert om noen alvorlige bivirkninger, definert ifølge FDA sine kriterier. Kvalme, oppkast, urolighet og eufori var de mest vanlige bivirkningen ved bruk av lystgass.

Helsepersonell med lystgass hadde ikke økt risiko for spontanabort ved noen av eksponeringsnivåene (lav eksponering (OR=0.89; 95%CI=0.67, 1.19), høy eksponering (OR=1.18; 95%CI=0.84, 1.66) og ukjent eksponering (OR=1.30; 95%CI=0.43, 3.88)).

Det var derimot en doseavhengig økning i risikoen for redusert fertilitet hos helseperonell eksponert for lystgass (lav ekspnering: OR=0.79; 95%CI=0.48, 1.30; høy eksponering: OR=3.48; 95%CI=1.99, 6.08). Videre, raten av misdannelser hos barn var høyere i eksponerte kvinner enn i kontrollgruppen (5.5±0.95, N=579 vs 3.6±0.34, N=2882). Tilliten til resultatene er veldig lav for alle resultatene.

"Sister chromatid exchange", mikronukleiformasjon, DNA-brudd og reaktive oksygenradikaler ble brukt for å studere genotoksisk effekt av lystgasseksponering. De fire inkluderte studiene presenterte ingen resultat som kunne belyse potensiell genotoksisk effekt av lystgass. Det samme gjalt de tre studiene som presenterte resultat på neurlogisk toksisitet av lystgass og de fire studiene som undersøkte effekten av lystgass på B12-metabolismen.

Diskusjon

Vi inkluderte 19 randomiserte kontrollerte studier i effekt- og sikkerhetsanalysene for barn. Studiene hadde forskjellige effektestimater og resultatene ble presentert forskjellig. Dette, i tillegg vide konfidensintervall, gjorde at det ikke var mulig å ha høy tillit til resultatene. Men resultatene tyder på at lystgass har samme effekt, eller er bedre enn, andre sederingsmetoder. Vi fant ingen alvorlige bivirkninger i noen av studiene.

Sikkerhet for helsepersonell som blir eksponert for overskuddsgass har lenge vært et spørsmål. Det er gjort mange studier på sikkerhet for helsepersonell i tannhelsetjenesten og i operasjonsrom, men de fleste av disse har sett på gasser generelt og ikke spesifikt på lystgass. De studiene som har sett spesifikt på lystgass, er fra situasjoner der vi forventer eksponering til gass gjennom hele arbeidsdagen, som i tannhelsetjenesten og på fødestuen. Helsepersonell som jobber med lystgass for sedering av barn for mindre sykehusprosedyrer vil sannsynligvis ha en mye lavere eksponeringsgrad enn i de studiene som viste toksiske effekter, både på grunn av kortere eksponering, men også på grunn av bedre ventilasjon og bedre masker som fjerner overskuddsgassen. Selv om det ikke er dokumentert, vil sannsynligvis "time-weighted average", TWA, for denne gruppen helsepersonell være under den norske terskelverdien på 50 ppm (4). I tillegg, ingen av de inkluderte studiene viste korrelasjon mellom alvorlige bivirkninger og enkeltstående høye verdier, men for langtids eksponering ved høy konsentrasjon.

Konklusjon

Resultatene viser at lystgass kan brukes for sedering av barn uten å gi alvorlige bivirkninger. Den tydeligste fordelen med lysgass fra resultatene er muligens den korte restitusjonstiden sammenlignet med alternative sederingsmetoder, noe som får hele prosedyren til å ta kortere tid og kan effektivisere sykehusprosedyrer på barn.

Vår metodevurdering viste at jordmødre og tannlegepersonell eksponert for lystgass versus ingen eksponering ikke hadde økt risiko for spontanabort, heller ikke redusert fertilitet ved lav eksponering. Ved høy eksponering var det sett redusert fertilitet. Risikoen for misdannelser hos barn født av mødre eksponert for lystgass (konsentrasjon og eksponeringsgrad er ikke kjent) var høyere enn hos ikke-eksponerte mødre. Det er viktig å forstå at alle studiene som ligger til grunn for disse resultatene er meget usikre siden de bygger på data fra retrospektive kohorter med egenrapportering. Informasjon om nivå av eksponering av lystgass var også meget mangelfull.

Vi kan ikke si noe om lystgass har toksisk effekt på DNA eller andre cellulære mekanismer, da det ikke finnes gode resultat på dette.

Vi fant ingen studier om negative reproduksjonseffekter for helsepersonell som bruker lystgass for sedering av barn som gjennomgår små sykehusprosedyrer. Alle studiene om reproduksjonseffekter for helsepersonell inkludert i denne metodevurderingen er fra tannleger, operasjonspersonell eller jordmødre, og er forventet å ha en daglig, mer eller mindre kontinuerlig eksponering av lystgass. For helsepersonell som arbeider med lystgass sedering av barn i forbindelse med små sykehusprosedyrer, vil vi forvente en betydelig lavere eksponeringsgrad enn i de studiene hvor toksiske effekter av lystgass er rapportert, av to grunner. For det første vil vi forvente en betydelig lavere konsentrasjon av lystgass på grunn av god ventilering og rensesystem for overskuddsgass. For det andre vil eksponeringstiden være betydelig lavere, både fordi hver prosedyre tar kortere tid (maksimalt 30 minutter) samt at antall prosedyrer per helsepersonell per uke vil være begrenset (personlig kommunikasjon).

Key Messages

Nitrous oxide, N_2O, has a sedative and analgesic effect by inhalation. N_2O is used at maternity wards and at dental offices in Norway. Additionally, a few hospitals use N_2O for sedation of children for minor hospital procedures.

The objective for the present report, is to systematically summarize published results on effectiveness using nitrous oxide in a paediatric setting for small, but painful hospital procedures. Safety issues for both the patients and health personnel exposed to nitrous oxide will also be reviewed.

The most important findings in this HTA is:

- N_2O can be used for sedation of children without serious adverse events
- The most prominent advantage with N_2O may be the short recovery time compared to other active drugs
- Health personnel (midwives and dental assistants) exposed to N_2O compared to no exposure did not increase the risk of spontaneous abortion
- Health personnel did not show reduced fertility at low exposure, but at high exposure
- The risk of congenital malfunctions in children was higher in N_2O exposed mothers than mothers with no exposure
- No conclusions can be drawn on the effect of N_2O on damage to DNA or other cellular mechanisms
- We did not find any studies on negative health effects in health personnel using N_2O as sedation of children for small hospital procedures

The evidence for safety for health personnel had very low certainty due to the study design (retrospective cohorts) and that information about exposure levels were scarce. For health personnel working with N_2O sedation of children we expect a significantly lower exposure than what was suggested in the cohorts because of present ventilation and scavenging systems of waste gas and since each procedure will be short (maximum 30 minutes) and the number of procedures per week will be minor (personal communication).

Title:
Effectiveness and safety of nitrous oxide as sedation regimen in children – an HTA

Type of publication:

Health technology assessment

Health technology assessment (HTA) is a multidisciplinary process that summarizes information about the medical, social, economic and ethical issues related to the use of a health technology in a systematic, transparent, unbiased, and robust manner. Its aim is to inform the development of safe, effective health policies that are patient-focused and that seek to achieve the best value

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Doesn't answer everything:

- Excludes studies that fall outside of the inclusion criteria
- No recommendations

Publisher:

Norwegian Institute of Public Health

Updated:

Last search for studies: November 20, 2017.

Executive summary

Background

Children (up to 18 years of age) who undergo painful procedures at hospitals are offered different kinds of pain relief (analgesics), often in combination with drugs for relaxation (sedatives). For successful procedures, as well as effective use of time and personnel, efforts are made to choose an efficient combination of analgesics and sedatives.

Nitrous oxide is an inorganic agent, administered by inhalation, colourless, odourless to sweet-smelling, and non-irritating to the tissues. It is an effective analgesic/anxiolytic/sedative agent causing central nervous system depression and euphoria with little effect on the respiratory system. Nitrous oxide has a rapid uptake, as it is being absorbed quickly from the alveoli, and is excreted quickly from the lungs. As nitrous oxide is 34 times more soluble than nitrogen in blood, diffusion hypoxia may occur (2).

Several guidelines (1;2) include nitrous oxide in their lists of alternative sedation methods in children. A systematic review by Pedersen *et al.* (3) summarize literature on nitrous oxide as a sedation method for minor paediatric procedures, suggesting it to be a safe and efficient sedation method which may ease the procedures.

Nitrous oxide has been considered safe for a patient who is exposed for a short time or only few times (3). However, adverse effects on health personnel is a greater concern (4). N2O is a suspected reproductive toxicants that may affect fertility, the rate of spontaneous abortion and congenital abnormalities. In addition, the risk of neurological effects and headache, fatigue and irritability, has limited the use of the gas in many settings. Also, damaging effects to DNA or to important metabolites in cellular or body function, as for example B12, has been studied with contradictory result.

Objective

The objective for the present report, is to systematically summarize published results on effectiveness using nitrous oxide in a paediatric setting for small, but painful hospital procedures. Safety issues for both the patients and health personnel exposed to nitrous oxide will also be reviewed.

Method

We performed a Health Technology Assessment on effectiveness and safety of nitrous oxide for sedation in children in accordance with the handbook "Slik oppsummerer vi forskning", by Norwegian Institute of Public Health (5).

We found literature from both hospital and dental settings. As our commissioner represents a hospital settings, we decided to narrow our report to only include efficiency assessment of literature covering a hospital setting. However, in the assessment of safety for health personnel, we included results also from dental setting.

Results

Literature search

We included 22 randomized controlled trials for the analyses of effect and safety of children. We also included 15 non-randomized controlled trials (19 articles) to document safety concerns of health personnel exposed to waste nitrous oxide. For the records only, we made a table of another 58 non-randomized controlled trials reporting results on safety of anaesthetic gases to health personnel, where nitrous oxide most likely is a part of the gas.

Effectiveness of nitrous oxide

We have shown that health personnel or patients had a higher satisfaction level, lower distress or anxiety, and higher success rate when N_2O was used compared to the placebo group. However, when other sedatives were used, N_2O showed no benefit. Further, the pain level was lower using N_2O compared to midazolam and/or ketamine, but not to EMLA or placebo.

The certainty of evidence were from low to moderate, mostly due to lack of blinding and imprecision of the results.

Most evident results was the reduced recovery time using N_2O over other active drugs, not surprisingly as N_2O has a very rapid onset and offset time.

The certainty of evidence were high due to the pronounced differences in time and the objectivity in the outcome.

Safety of nitrous oxide

Fifteen studies (19 articles) reported data on adverse events. Of 525 patients sedated with N_2O, independent of hospital procedure or control group, none of the adverse events reported met the U.S. Food and Drug Administration’s definition of a serious adverse events. In particular, none of the study participants experienced serious cardiac or respiratory events (including oxygen below saturation level). Nausea, vomiting, restlessness, and euphoria were the most common adverse events observed in the N_2O group.

Health personnel exposed to waste N_2O only, did not have an increased odds ratio for spontaneous abortion for none of the levels of N_2O exposure (low exposure (OR=0.89; 95%CI=0.67, 1.19), high exposure (OR=1.18; 95%CI=0.84, 1.66) and unknown exposure (OR=1.30; 95%CI=0.43, 3.88)).

However, there were a dose dependent increase in the odds ratio for reduced fertility in N_2O exposed health care personnel (low exposure: OR=0.79; 95%CI=0.48, 1.30; high exposure: OR=3.48; 95%CI=1.99, 6.08). Further, the adjusted rate of congenital abnormalities in children was higher in N_2O exposed women than in the control group (5.5±0.95, N=579 vs 3.6±0.34, N=2882). The certainty of the effect estimate was very low for all results.

Sister chromatid exchange, micronuclei formation, DNA breaks and reactive oxygen species were methods to study the genotoxic effect of N_2O exposure. The four included studies did not report evidence to reveal a potential genotoxic effect of N_2O in the given settings (both dental offices and operating rooms). This was also true for the three included studies of neurological toxicity of N_2O and for the four included studies of the effect of N_2O on B12 metabolism.

Discussion

We included 19 randomized controlled trials in the analyses for effectiveness and safety for children. However, the studies used different effect estimates and the data were presented differently. It was not possible to obtain high certainty of evidence for the outcomes analysed due to poor presentation of data as well as wide confidence intervals. However, the findings support that N_2O works similarly or better than existing sedation methods and that it also show an analgesic effect. Further, there were no serious adverse events reordered in any of the included studies.

Safety of health personnel exposed to N_2O has for long time been a greater concern. Numerous studies have been performed on safety issues for health personnel in dental setting or working in operating theatres, analysing the effect of anaesthetic gases in general rather than N_2O only. All studies on safety for health personnel included in this review are taken from either dental settings, operating theatres or maternity wards, suggesting an everyday, continuous exposure to N_2O. The expected levels in a paediatric setting, as the background for this commission, using modern masks, effective scavenging and ventilation systems, and without an everyday exposure, will most probably be lower than in the studies showing adverse toxic effects. Although not documented, the time-weighted average (TWA) for the subjects experiencing the adverse effects were probably exposed to levels far above the Norwegian TWA threshold of 50 ppm (4). Further, none of the adverse effects are correlated to peak values, but rather to long term exposure at high levels.

Conclusion

The results show that nitrous oxide can be used for sedation of children without serious adverse events. The most noticeable advantage by using N_2O is the short restitution compared to other sedation methods which shortens the whole procedure and may streamline hospital procedures in children.

The present technology assessment shows that midwives and dental personnel exposed to N_2O compared to no exposure, did not increase the risk of spontaneous abortion or, at low exposure, reduced fertility. High exposure showed reduced fertility. The risk for congenital abnormalities born by exposed mothers (concentration or exposure degree not known) was higher than in non-exposed mothers. It is important to understand that these results are generated from data based on self-reporting questionnaires. Also, information about level of exposure were inadequate.

No sufficient evidence were shown to draw conclusions of the toxic effect of N_2O on DNA or cellular mechanisms.

There were no studies on negative effects on reproductive health for health personnel in a setting where N_2O were used for sedation of children for small hospital procedures. The personnel included in the present studies, were expected to have a more or less continuous exposure to N_2O during their work hours. For personnel working with N_2O sedation of children for small hospital procedures the exposure is expected to be significantly lower than the health care workers in the studies where toxic effects were reported, justified by two reasons. First, the concentration of N_2O is expected to be lower because the access to better scavenging and ventilation systems; and second, the net exposure time would be lower as the procedure time (maximum 30 minutes per procedure) and the number for the hospital procedures per health worker per week would be relatively few (personal communication).

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Preface

RHF-Bestillerforum commissioned a Health Technology Assessment on the effectiveness and safety on the use of nitrous oxide sedation in children from the National Institute of Public Health (NIPH).

The project group consisted of:

- Tjelle, Torunn Elisabeth, Senior scientist, FHI
- Eva Pike, Senior consultant
- Hafstad, Elisabeth, Information specialist, FHI
- Bidonde, Julia, Senior scientist, FHI
- Harboe, Ingrid, Information specialist, FHI

The aim of this report is to support well-informed decisions in health care that lead to improved quality of services. The evidence should be considered together with other relevant issues, such as clinical experience and patient preference.

Kåre Birger Hagen *Director, Reviews and health technology assessment*	Lene K Juvet *Department director*	Torunn Elisabeth Tjelle *Project leader*

LOGG	
Forslag til metode innsendt/ metodevarsel publisert på nyemetoder.no	10.11.2015
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Start metodevurdering	15.06.2017
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Brukerrepresentant kontaktet første gang	Ikke aktuelt
Første møte med faggruppe	På epost, ikke felles. Møte med en fagfelle (Ketil Størdal) juni 2017
LIS/sykehusinnkjøp kontaktet for første gang	Ikke aktuelt
Dato for rapport sendt til eksterne fagfeller	04.05.2018, purret 30.05.2018, Svar: 13.06.2018
Dato for rapport sendt til interne fagfeller	26.06.2018
Dato for rapport sendt til ekstern produsent	Ikke aktuelt
Dato for rapport sendt til sekretariatet for Bestillerforum RHF	
TID	
Tid brukt til å innhente ytterligere dokumentasjon fra produsent	Ikke aktuelt.
Tid brukt til å innhente ytterligere dokumentasjon fra andre aktører	LMV lovet informasjon som aldri ble mottatt.
Totalt antall dager i påvente av dokumentasjon	Ingen
Totalt antall dager til metodevurdering	

Objective

The main objective for the present report, is to systematically summarize published results on effectiveness using nitrous oxide in a paediatric setting for small, but painful hospital procedures. Safety issues for the patients and health personnel exposed to nitrous oxide will also be reviewed.

Background

Children (up to 18 years of age) who undergo painful procedures at hospitals, for example suture laceration, orthopaedic manipulation, arthrocentesis, insertion of peripheral venous catheters or lumbar puncture, are offered different kinds of pain relief (analgesics), often in combination with drugs for relaxation (sedatives). For successful procedures, as well as effective use of time and personnel, efforts are made to choose an efficient combination of analgesics and sedatives.

Available sedatives for children

Drugs classified as sedatives may exert one or several effects. Common effects, in addition to the sedative effect are anxiolytic, amnestic, hypnotic and/or analgesic. The choice of sedatives depends on the procedures to be carried out, procedure duration, effect needed, available personnel and previous experience with the child's responsiveness to the procedure or sedative. The most commonly used sedative at paediatric departments in Norwegian hospitals is midazolam (6;7) which can be administered by several different routes (e.g. orally, intramuscular, buccal and nasal spray). Other drugs used for sedative purposes in children are ketamine, chloral hydrate, opioid drugs, propofol and sevoflurane and nitrous oxide gas. The use of these sedatives have been reviewed by the National Institute for Health and Care Excellence (NICE) guideline in 2010 (1). According to this guideline nitrous oxide or midazolam are the active drugs recommended for a minimal to moderate sedation, also known as "anxiolytic" or "conscious" sedation, respectively (defined by American Society of Anesthesiologists, ASA (8)).

Nitrous oxide

Nitrous oxide is an inorganic agent, administered by inhalation, colourless, odourless to sweet-smelling, and non-irritating to the tissues. It is an effective analgesic/anxiolytic/sedative agent causing central nervous system depression and euphoria with little effect on the respiratory system. Nitrous oxide has a rapid uptake, as it is being absorbed quickly from the alveoli, and is excreted quickly from the lungs. As nitrous oxide is 34 times more soluble than nitrogen in blood, diffusion hypoxia may occur (2).

Nitrous oxide is used as a sedative in dental care for both children and adults (2;9) and for women in labour (10;11). The gas is normally used with oxygen in different concentrations, the most common being 50-70% nitrous oxide (12). Administration is simple and painless and has a rapid onset and short duration of action. It has analgesic, anxiolytic and sedative effects. In Norway it is known as “Medisinsk lystgass” and a popular name in English is “laughing gas” or "gas and air".

Several studies have documented the use of nitrous oxide sedation in children in hospital setting, in particular in the emergency department (13;14). Several guidelines (1;2) include nitrous oxide in their lists of possible sedation methods in children. A systematic review by Pedersen *et al.* (3) summarizes literature on nitrous oxide as a sedation method for minor paediatric procedures for example under peripheral venous cannulations, lumbar punctures or intramuscular injections. The authors conclude that nitrous oxide is a safe and effective method to achieve analgesia and sedation during minor, but painful procedures. The authors therefore suggest that under the right conditions and with proper information to the child, the use of nitrous oxide can ease hospital procedures which otherwise would be performed using other sedatives that requires longer time, both onset and follow up time, more personnel, or even that it can substitute full anaesthesia.

Safety profile of nitrous oxide

Nitrous oxide is considered safe for the patient who is exposed for a short time or only few times. However, a debate about the adverse effects on health personnel is still a concern.

N_2O is a suspected reproductive toxicants that may affect fertility, the rate of spontaneous abortion and congenital abnormalities in health personnel who are highly exposed. In addition, the risk of neurological effects and headache, fatigue and irritability, has limited the use of the gas in many settings. Also, damaging effects to DNA or to important metabolites in cellular or body function, as for example B12, has been studied with contradictory result. Potential biological effects of N_2O and their mechanisms have been summarized by Sanders et al (4). Updated safety issues will be summarized in this report.

European countries have made regulations for the protection of workers against the gas and introduced gas exposure limits measured by time-weighted average (TWA) nitrous oxide concentration limits, which is based on an 8-hour workday and a 40-hour workweek. For Norway and Denmark the TWA is 50 ppm, for UK and Germany the level is 100 ppm and in US it is 25 ppm (4). The rational for the different thresholds are not readily available, as the research in this field is mainly based on large retrospective surveys, where no recordings of the level of gas exposure related to the adverse effects were available, as will be shown in this report.

Already in the seventies, scavenging systems for controlling N_2O concentration of in operating theatres, and thereby reducing the exposure level for health personnel,

were introduced. In an ad hoc study from 1972 it was shown that the mean concentration of N_2O in 14 operating theatres were reduced from 1080 ppm to 165 ppm without and with scavenging systems, respectively (15). A recent report (16) compared different inhalation techniques and scavenging systems. They showed that more important than an on-demand valve (the gas is only delivered when the child inhales), the scavenging system is crucial for keeping the concentration of waste gas in the room below reference values. A scavenging system can typically be a mask connected to an evacuation pump or effective ventilation system in the room.

Nitrous oxide in a Norwegian setting

In Norway, nitrous oxide is a registered drug used as an anaesthetic in combination with other inhalation anaesthetics or intravenous anaesthetics, and as an analgesic or sedation agent in all situations where instant pain relieve is needed (17). The contraindications for health personnel refers to studies showing increased risk of spontaneous abortion and congenital malfunctions to children born by exposed women when scavenging systems are not sufficiently used. However, in the summary of product leaflet these results are disputed due to low quality and limited transferability of the studies.

As internationally, the gas is routinely used in dental offices where the method has been established and room ventilation is properly dimensioned for evacuation of waste gases. Further, maternity wards in Norway are still offering women in labour N_2O sedation (18), but several hospitals have quit this service, mainly due to safety concerns for health personnel, explained by poor ventilation systems at the maternity wards (19).

Nitrous oxide sedation for use in children is not a standard sedation method in Norway, although it is used in some hospitals for minor hospital procedures (St. Olavs Hospital, Trondheim and Akershus University Hospital, Oslo, personal communication). In addition, there is one ongoing quality study investigating the effectiveness of this sedative (Østfold Hospital Trust, personal communication).

In the present Health Technology Assessment, we will systematically summarize published results on effectiveness and safety using nitrous oxide in a paediatric setting for small, but painful hospital procedures. In addition, we will systematically summarize published results on safety for health workers exposed to waste N_2O.

Method

We performed a Health Technology Assessment on effectiveness and safety of nitrous oxide for sedation in children in accordance with the handbook "Slik oppsummerer vi forskning", by the Norwegian Institute of Public Health (5).

Literature search and article selection

Search strategy for effectiveness and safety for the children

Inclusion and exclusion criteria

We used the population, intervention, comparison, outcome, and design (PICO) framework to evaluate the eligibility of evidence for inclusion of studies (*Table 1*).

Table 1. *PICO-S framework for effectiveness*

Population	Children up to 18 years of age undergoing painful hospital procedures that require minimal or moderate sedation
Intervention	a) Nitrous oxide only b) Nitrous oxide combined with other sedatives/analgesics/anaesthetics* Nitrous oxide/oxygen concentration: 50/50% – 70/30%
Comparator	a) Other pharmacological intervention (sedatives/analgesics/anaesthetics) b) Non-pharmacological intervention (e.g. psychological techniques) c) Control (treatment as usual)
Outcome	a) Hospital procedure satisfaction (e.g. ease, distress, anxiety) b) Hospital procedure characteristics (e.g. successful procedural completions, number of attempts, duration of procedure) c) Pain d) Safety of sedation - Number of acute adverse events (e.g. vomiting, oxygen desaturation, cardiac arrest) - Long term adverse effects (e.g. toxicity) due to repeated exposure - Parameters of gas concentration in the procedure room or body

	- Adverse events due to combination with other sedatives/ analgesics/ anaesthetics For each of the outcomes, data could be provided by the patient (child), caregiver (parent) or health personnel (medical staff).
Study design	Systematic reviews of randomized controlled trials, health technology assessments (HTA) or randomized controlled trials.

We excluded studies if:

- Study designs not covered in the inclusion criteria
- Patient groups scheduled for procedures only requiring the sleeping effect (for example imaging procedures) or for dental procedures.
- Nitrous oxide concentration was below 50%
- Nitrous oxide was used in combination with other drugs where the aim is to obtain or keep general anaesthesia

Search strategy

We performed a systematic search for literature to identify studies on the defined PICO. We searched the following databases 24. August 2017:

Systematic reviews & HTA

- CRD database, HTA (Centre for Reviews and Dissemination, University of York)
- Cochrane Library (Wiley):
    - Cochrane Database of Systematic Reviews
    - Database of Abstracts of Reviews of Effects
- Epistemonikos
- Embase (OVID)
- PubMed (NLM)

Randomized controlled trials (and non-randomized studies, if required)

- Cochrane Central Register of Controlled Trials (Wiley)
- PubMed (NLM)/MEDLINE (OVID)
- Embase (OVID)

Ongoing, completed or terminated (unpublished) trials

- Clinical Trials (National Institutes of Health, US)
- International Clinical Trials Registry Platform (WHO)

The provided strategy was reviewed by two experienced information specialists. The search strategies are found in Appendix 2.

The search strategies combined index terms and text words relating to population and intervention, adapting the search syntax to each database. We added filters for study design for the PubMed/MEDLINE and Embase databases.

Search strategy for safety of health personnel

Inclusion and exclusion criteria

To ensure retrieval of relevant safety data for health personnel, we performed a search with a different PICO-framework than for the effectiveness data, focusing on health personnel as the population (*Table 2*).

Table 2. *PICO-S framework for occupational safety*

Population	Health workers exposed to N_2O through their occupation
Intervention	Passive nitrous oxide exposure from sedation or general anaesthesia of patients
Comparator	No exposure or different levels of exposure to nitrous oxide
Outcome	Biological effects on health workers
Study design	Randomized controlled trials or non-randomized studies (Non-randomized controlled trials, Controlled before-and-after study, Prospective cohort study, Retrospective cohort study, Cross sectional studies, Case-control study (more than 50 participants), Case series (more than 100 participants)).

We excluded studies if biological effects were not reported.

Search strategy

We performed a supplementary search to identify studies on health personnel exposure to nitrous oxide. We searched the following databases 21. November 2017:

- Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
- Embase (OVID) 1974 to 2017 November 20

The search strategies combined index terms and text words (in the title and author keywords fields) relating to nitrous oxide and occupational exposure. We did not use a filter for study design in this search. The full search strategy is given in Appendix 2.

Article selection

Two reviewers independently assessed titles and abstracts to determine relevant full-texts to be examined. Subsequently, the same reviewers independently assessed the full-text publications to decide which studies we would include in the Health Technology Assessment.

Data extraction and analyses

One review author (TET) extracted data from the included studies and another review author (EP) verified the data. We extracted the following data:

- Information about the study (authors, year of publication, setting and study design)
- Participant characteristics (number of participants in the trial, age, procedure to be performed during intervention)
- Intervention and control characteristics (combination of drug, doses, length of exposure)
- Outcomes (endpoints examined, methods used to analyse outcome data, length of follow up and loss to follow up)

Statistical analyses and presentation of results

We analysed dichotomous data by calculating relative risk (RR) or odds ratio (OR) and the corresponding 95% confidence interval (CI). Continuous data were presented as standardized mean difference calculated from the mean value and standard deviation (SD) using RevMan 5.3. If mean values were presented with standard error of the mean (SEM), we calculated the standard deviation by the formula $SD=SEM*\sqrt{n}$, where n is the population.
For data presented by the investigators in a form where it was not possible to extract mean values with corresponding standard deviation, or absolute numbers, we presented the results in a narrative form.

Assessment of methodological risk of bias

Two review authors assessed the quality of the included studies independently by evaluating risk of bias of randomized controlled trials using the Cochrane Risk of Bias tool (http://training.cochrane.org/handbook, Chapter 8.5a). For surveys and other non randomised controlled trials we used a simplified form of the ROBINS-I tool (see Appendix 3). The Cochrane-tool classifies the risk of bias as low, uncertain or high while ROBINS-I uses low, moderate, serious, critical or no information. We resolved disagreements by discussions or, if required, by consulting one of the other review authors.

Certainty of the evidence

We assessed the certainty of the evidence for each selected outcome using the GRADE system (Grading of Recommendations Assessment, Development, and Evaluation, http://www.guidelinedevelopment.org/). We did this by ascertain the strength of the study design, possible risk of bias, imprecision and inconsistency of the estimates, and indirectness and magnitude of effect, dose response gradient and potential confounding factors. The GRADE system classifies the certainty of the evidence as high, moderate, low, or very low for each outcome.

Addendum to project plan

In the original plan, the population was identified as children undergoing short and painful hospital procedures. In the first search, no information about safety for the health personnel working with the procedure was found. Since the commissioner, as well as the external experts, stressed the importance of safety of health personnel, we extended the project plan to perform a separate search to identify studies concerning safety for health personnel, independent to setting. An addendum to the project plan was made (Appendix 10).

We also included cross sectional studies for analyses of safety of health personnel, which was not in the original project plan.

Stakeholder involvement

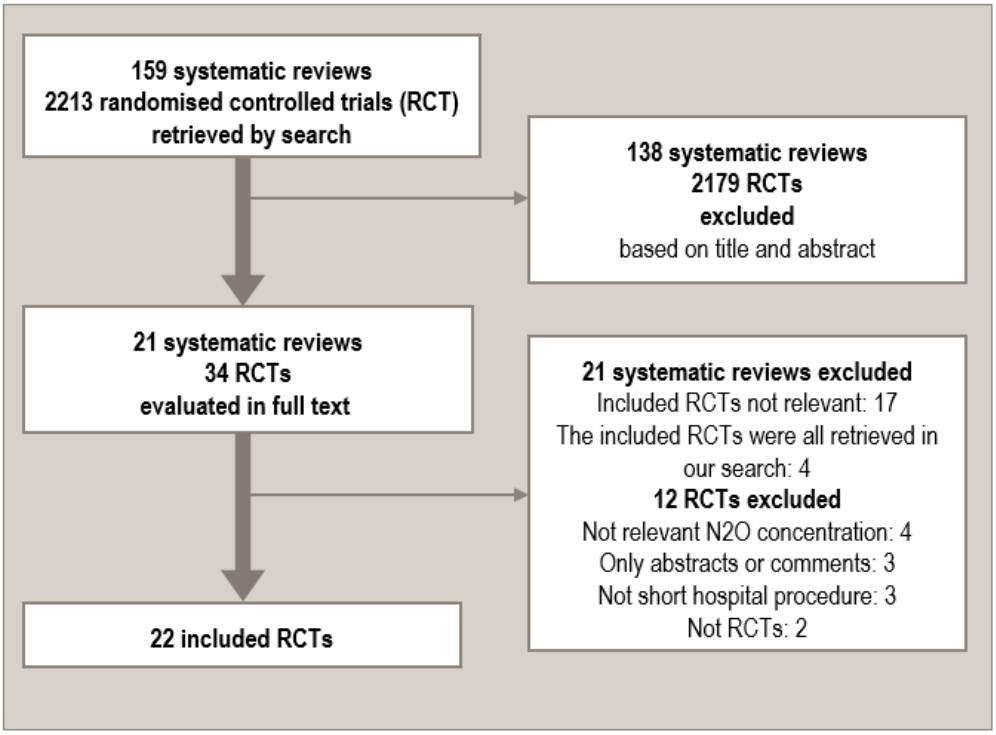
Two external clinical experts and two internal research directors were invited to review and give feedback on the project plan, including the inclusion and exclusion criteria, as well as to the report. We also collected personal experience with the method from hospitals in Norway. We contacted the producer of the device presently used for N_2O sedation of children in Norway, Livopan, provided by AGA to understand the method and differences from administration to other patient groups as women in labour.

Results – effectiveness and safety for patients

Literature search and article selection

The search results for randomized controlled trials and systematic reviews are presented in *Figure 1* and Appendix 2. There were 21 systematic reviews and 34 randomized controlled trials to be screened in full text. We found four systematic reviews which corresponded to our specifications and 22 randomised controlled trials (RCT) (*Table 3*). The excluded articles (21 systematic reviews and 12 RCTs) are listed in Appendix 4 with reasons for exclusion.

Figure 1. *Flow chart of article selection for randomized controlled trials and systematic reviews*



Review of systematic reviews

We reviewed four systematic reviews (see description of the studies in Appendix 5). Data on N_2O in the systematic reviews were presented narratively and three of the reviews concluded that there were insufficient data to draw any conclusions (20-22) while one review concluded a lower anterograde amnesia using N_2O compared to benzodiazepines (23). All of the RCTs included in the systematic reviews were included in our search. We did therefore not perform any analyses of the results from the systematic reviews.

Description of included randomized clinical trials

We included 22 randomized controlled trials, listed in *Table 3*.

The total number of patients were 1.692, ranging from 14 to 204 in the different trials. The age of the children were from premature babies to 18 years, and with both genders. All children were classified as normal healthy patients (ASA I), to patients with mild systemic disease (ASA II), according to the ASA (American Society of Anaesthesiologists) physical status classification system.

The trials were published from 1990-2015 and were performed in Europe (n=7), North America (n=7), South America (n=1), Australia (n=1), Asia (n=4), and Africa (n=2). One of the trials was a multicentre trial (Carbajal), the others performed at a single centre.

Eight of the trials compared N_2O with EMLA (a eutectic mixture of local anaesthetic cream with lidocaine and procaine, cutaneous application) (*Table 3*); 7 studies compared N_2O with placebo gas or standard care, and 6 studies compared N_2O with other analgesics. One trial compared N_2O with play therapy. Typically, face mask with O_2 or mixture of N2 and O_2 was used as the only control or together with the control drug in the blinded studies. The hospital procedures performed in the studies were venous cannulation and/or venepuncture (n=9), laceration repair (n=3), fracture reduction (n=2) and other procedures (n=8).

Sixteen of the trials were blinded of which twelve were double-blinded and four partly blinded. For the partly blinded, one of the trials the observer doing the assessments was blinded for all endpoints (24) and in three trials the observers were only blinded for some of the endpoints (13;25;26). Five of the trials were not blinded (27-31), and for one of the trials (32) it was unclear whether it was blinded or not (see *Table 3* for corresponding references).

Table 3. *Overview of the included randomized controlled trials sorted by comparator*

Study ID	Population*	Intervention**	Control	Procedure	Outcomes /Blinding
N_2O vs EMLA					
Vetter 1995 (29)	6-12 years	70% N_2O N=25	EMLA N=25	Venous cannulation	Pain Safety Not blinded
Mjahed 1997 (33)	3 months-5 years, 57% boys	N_2O and placebo cream N=25	EMLA and O_2 N=25	Venous cannulation	Procedure satisfaction Procedure characteristics Pain Double blinded
Udelsmann 1997 (34)	2-12 years, 78% boys	66% N_2O and placebo cream N=28	EMLA and O_2 N=27	Venepuncture	Procedure satisfaction Double blinded
Paut 2001 (7)	6-11 years	70% N_2O and placebo cream N=20	EMLA and O_2 N=20	Venous cannulation	Procedure satisfaction Procedure characteristics Pain Safety Double blinded
Belyamani 2003 (35)	6-12 years	70% N_2O and placebo cream N=40	EMLA and O_2 N=40	Venous cannulation	Procedure satisfaction Pain Safety Double blinded
Hee 2003 (25)	8-15 years, 90% boys	N_2O N=40	1: EMLA and O_2 N=40 2: EMLA and N_2O N=40	Venous cannulation	Procedure satisfaction Procedure characteristics Pain Safety Partly blinded
Mann 2007 (31)	3-15 years, 55% boys	70% N_2O N=57	EMLA N=46	Venous cannulation Venepuncture	Procedure satisfaction Procedure characteristics Pain Safety Not blinded
Carbajal 2008 (36)	Less than 2 years 31% boys	N_2O and placebo cream N=55 Cross-over	EMLA and air inhalation N=55 Cross-over	Palivizumab injection	Pain Safety Partly blinded, unclear if VAS-recording was blinded
N_2O vs other active drugs					
Keidan 2005 (30)	3-15 years, 19% boys	N_2O N=23	Midazolam (0.5 mg/kg) orally N=24	Voiding cystourethrography	Procedure satisfaction Procedure characteristics Pain Safety Not blinded
Luhmann 2006 (26)	5-17 years, 60% boys	N_2O Oxycodone were given at arrival. N=47	Ketamine (1 mg/kg) and midazolam (0.1 mg/kg), intravenous. Oxycodone were given at arrival. N=55	Fracture reduction	Procedure satisfaction Procedure characteristics Pain Safety Partly blinded, subjective outcomes were blinded
Ekbom 2011 (37)	5-18 years, (60 obese and 30 growth-retarded)	N_2O and lidocain-prilocain N=30	Midazolam (0.3 mg/kg), orally, lidocain-prilocain and O_2 N=30	Venous cannulation	Procedure satisfaction Procedure characteristics Pain Safety Double blinded

Study ID	Population*	Intervention**	Control	Procedure	Outcomes /Blinding
Lee 2012 (28)	3-10 years, 81% boys	50-70% N_2O N=18	Ketamine (2 mg/kg), intravenously N=14	Laceration repair	Procedure satisfaction Procedure characteristics Pain Safety Double blinded
Evans 1995 (27)	4-15 years, 63% boys	N_2O N=15	Intramuscular meperidine (2 mg/kg) and promethazine (1 mg/kg) N=15	Fracture reduction	Procedure satisfaction Procedure characteristics Pain Safety Not blinded
Bruce 2006, Study 3 only (38)	3.5 months-2.75 years	N_2O (Entonox) N=6	Morphine (0.1 mg/kg), intravenously N=6	Chest drain removal after cardiac surgery	Procedure satisfaction Pain Safety Double blinded
N_2O vs placebo gas or standard care					
Henderson 1990 (24)	3 weeks-18 years	N_2O N=39	O_2 N=44	Venous cannulation	Pain Safety Double blinded
Burton1998 (39)	2-7 years	N_2O and lidocaine N=17	O_2 and lidocaine N=13	Laceration repair	Procedure satisfaction Procedure characteristics Pain Safety Double blinded
Garcia 1998 (40)	3-60 months	N_2O and topical anaesthesia, midazolam and atropine N=16	O_2 and topical anaesthesia, midazolam and atropine N=16	Fiberoptic bronchoscopy	Procedure satisfaction Procedure characteristics Pain Safety Double blinded
Luhmann 2001 (13)	2-6 years, 66% boys	N_2O and standard care N=51	Standard care N=50	Laceration repair	Procedure satisfaction Procedure characteristics Safety Partly blinded, subjective outcomes were blinded
Fauroux 2004 (41)	1 months-18 years, 49% boys	N_2O N=53	50% O_2 and 50%N2 N=52	Fiberoptic bronchoscopy	Procedure satisfaction Procedure characteristics Pain Safety Double blinded
Reinoso-Barbero 2011 (42)	1-18 years, 58% boys	N_2O (EMONO) N=50 Pain relieve were given.	50% O_2 and 50%N2 N=50 Pain relieve were given.	Short diagnostic or therapeutic procedures on skin, muscles, or bones/joints	Procedure satisfaction Procedure characteristics Pain Safety Double blinded
Mandel 2012 (43)	Premature infants, birthweight < 1500 g or gestation of < 30 weeks, N=40	N_2O (EMONO) N=22	50% O_2 and 50%N2 N=18	Retinopathy screening	Pain Safety Double blinded
N_2O vs play therapy					
Mohan 2015 (32)	4-15 years	N_2O (Entonox) N=31	1: Play therapy, N=32 2: Standard intervention N=30	Short-term painful procedure	Pain Safety Blinding not described

* Where gender distribution is not given, this information was not available.

** Where no N_2O concentration is given, it is 50% N_2O in 50% oxygen.

EMONO and Entonox, standardized delivery systems for 50% N_2O and 50% O_2.

Data from four main categories of outcomes were analysed: procedure satisfaction, procedure characteristics, pain and safety. In the studies, the three first categories were recorded by different scales and recorded by different persons (i.e. patients, parents, health personnel, investigators). When the same outcome was reported by several different people in the same study, we only present one of the data sets, in the following prioritized order: patient, operator and parent. In a situation where recordings were performed by either patient or nurse, depending on the age group, the recordings including most patients were used.

Type of hospital procedure and which comparative drug used, were most often linked, as for venous cannulation the topical drug EMLA was used as a comparator and for fracture reduction and laceration repair most often midazolam or ketamine was used. In our analyses, we sub-grouped the comparators, not the hospital procedure or hospital setting.

Risk of bias

We used the RevMan risk of bias tool to analyse and visualize the risk of bias in the included trials. The results are shown under the analyses of each outcome.

Hospital procedure satisfaction and ease of use

We extracted data from the articles reporting on satisfaction by patients, parents or operators based on measures of satisfaction with the procedure and the ease of performing it. In *Table 4* we have presented the available data as no statistically significant difference (NS) or statistically significant difference (+) between N_2O sedation and the comparator in favour of N_2O.

In four of 11 studies, the procedure satisfaction was reported by the patient while the remaining was scored by observing the patient. The results show that when N_2O was compared to another active drug, there were no significant difference in procedure satisfaction between the two sedation methods in 7 of the 8 studies, representing a population of 444 patients, while 1 of the datasets, representing 60 patients, showed a statistical significant difference between the two groups. For the three studies (237 participants) where N_2O was compared with placebo or standard care, all showed statistical significant difference between the groups.

No studies showed that the sedation method changed the ease or effectiveness of performing the hospital procedure itself, according to the investigator or nurse. This is in line with the satisfaction results, indicating that the sedation method does not influence the performance of the actual procedure. The summary of findings are presented in *Table 5*.

Table 4. *Results on hospital procedure satisfaction*

Ref	Procedure	Comparator	Effect measure	Result, effect size		RoB
Satisfaction, higher score, higher satisfaction						
Evans 1995 N=30	Fracture reduction	Intramuscular meperidine	Scale 1-5, by patient	N_2O: 3.7 (0-5), N=15 Meperidine: 2.5 (0-5), N=15 p>0.05 Mean (range)	NS	High
Lee 2012 N=32	Laceration repair	Ketamine	VAS, by operator	No numbers, descriptive presentation of results N_2O: N=18 Ketamine: N=14	NS	High
Luhmann 2006 N=102	Fracture reduction	Ketamine/midazolam (K/M)	Choosing same sedation method next time, by patient, yes/no	N_2O: 88%, N=47 K/M: 86%, N=55 OR: 0.6 (95%CI, 0.2 to 2.3) Percent and Odd ratio	NS	High
Keidan 2005 N=47	Voiding cystourethrography	Midazolam	Scale 0-10, by operator	N_2O: -3±2, N=23 Midazolam: -4±2, N=24 p=0.09 Mean±SD (inverse numbers made by us)	NS	High
Ekbom 2011 N=60	Venous cannulation	Midazolam	Scale 1-5, by patient	No numbers, descriptive presentation of results Each group N=30	+	Low
Vetter 1995 N=50	Venous cannulation	EMLA	Listing, by operator	No numbers, descriptive presentation of results Each group: N=25	NS	High
Hee 2003 N=80	Venous cannulation	EMLA and O_2	Scale 0-100%, by patient	N_2O: 84±22.02, N=40 EMLA: 81.13±24.61, N=40 Mean±SD	NS	High
Mann 2007 N=103	Venous cannulation	EMLA	Scale 1-5, by parent	N_2O: 5 (4-5), N=57 EMLA: 5 (4-5), N=46 p=0.29 Median (interquartile range)	NS	High
Garcia 1998 N=32	Fiberoptic bronchoscopy	O_2	VAS, by operator	N_2O: 84.6±15.3, N=16 O_2: 9.1±30.2, N=16 p<0.05 Mean±SD	+	Low
Faroux 2004	Fiberoptic bronchoscopy	O_2 and N_2	Scale of 4 levels, by operator	N_2O: 3.173±0.89, N=53 O_2: 2.089±0.89, N=51 p=0.000001 Mean±SD (calculated by us)	+	Low
Luhmann 2001 N=101	Laceration repair	Standard care	VAS, by operator	N_2O: 8.2, N=51 O2: 6.6, N=50 p=0.02 Least square means	+	High
Ease/ effectiveness of procedure (by investigator/nurse), higher score, easier/more efficient						
Paut 2001 N=40	Venous cannulation	EMLA and O_2	Ease of procedure, scale 0-3	N_2O: 1.15±0.348, N=20 EMLA: 1.3±0.543, N=20 p=0.31 (calculated by us)	NS	Low
Belyamani 2003 N=80	Venous cannulation	EMLA and O_2	Scale 0-3	N_2O: 0 (0-1), N=40 EMLA: 0 (0-2), N=40 Mean of (range)	NS	Low
Hee 2003 N=80	Cannulation	EMLA and O_2	Scale 0-4	No numbers, descriptive presentation of results, Each group: N=40	NS	Low

Ref	Procedure	Comparator	Effect measure	Result, effect size		RoB
Reinoso-Barbero 2011 N=100	Short diagnostic procedures	O_2 and N2	Ease of use, yes/no	N_2O: 98.1%, N=50 O_2: 95.8%, N=50 Percentage of yes	NS	Low

RoB, Risk of Bias; NS, no statistical significant difference; +, statistical significance in favour of N_2O; VAS, Visual analogue pain scale; EMLA, eutectic mixture of local anaesthetics (lidokain-prilokain).

Certainty of effect estimate for satisfaction and ease of procedure

For each outcome and control intervention there were only one study which presented results with standard deviation. Several studies only presented their data in a narrative form concluding whether there were statistical or non-statistical differences between the groups. We therefore presented the results in a narrative form in the available GRADE-tool (*Table 5*). All studies were randomized controlled trials. However, we downgraded the certainty of evidence based on lack of blinding in some studies (limitation in design) and also due to unclear precision.

Table 5. *Summary of findings table for satisfaction and ease with hospital procedure under N_2O sedation*

Outcomes	Effect	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Satisfaction, N_2O vs active drug	It is uncertain whether there are differences between the groups. 7 of 8 studies did not show any differences between the groups but no meta analyses could be performed.	514 (8 RCTs)	⨁⨁◯◯ LOW	7 of 8 studies were not blinded (Limitation in design) 3 of 8 studies had only narrative data presentation (Imprecision)
Satisfaction, N_2O vs placebo	Higher score (from 1.2 to 9 times greater) in satisfaction during a painful hospital procedure in the N_2O group.	238 (3 RCTs)	⨁⨁⨁◯ MODERATE	1 of 3 studies was not blinded (Limitation in design). 1 of 3 studies presented data without variation. (Imprecision). But, the effect was significantly larger in the intervention group in all studies.
Ease/efficacy of procedure, N_2O vs active drug or placebo	It is uncertain whether there are differences between the groups.	300 (4 RCTs)	⨁⨁⨁◯ MODERATE	1 of 4 studies did not report numbers, only conclusions (imprecision).

Patient-experienced distress, anxiety or cooperativeness during the hospital procedure

The patients' experience of distress, anxiety or cooperativeness during the hospital procedure was reported by the patient (13) or observed by the operator (13;30;34;38;39;42). All five studies comparing N_2O with another active drug

showed no statistical significant difference between the groups, while all three studies showed statistical significant lower distress in the N_2O group compared to the placebo group (O_2 or standard care) (*Table 6*). The summary of findings are presented in *Table 7*.

Table 6. *Results on patient-experienced distress, anxiety or cooperativeness during the hospital procedure*

Distress/anxiety/cooperativeness, lower score, lower distress						
Ref	Procedure	Comparator	Effect measure	Result, effect size		RoB
Udelsmann 1997 N=55	Venepuncture	EMLA and O_2	Distress, scale 0-3, by observer	N_2O: 0.79±0.77, N=28 EMLA: 1.11±0.99, N=27 p=0.18 Mean±SD (calculated by us)	NS	Low
Luhmann 2001 N=101	Laceration repair	Midazolam	Distress, OSBD-R, by observer	No numbers, descriptive presentation of results N_2O: N=51 K/M: N=50	NS	Low
Luhmann 2006 N=102	Fracture reduction	Ketamine/midazolam	Anxiety, VAS, by patient	N_2O: 3.1, N=47 K/M: 3.2, N=55 Difference in mean: 0.2 (95%CI, -1.1 to 1.5)	NS	Low
Keidan2005 N=47	Voiding cystourethrography	Midazolam	Anxiety, OSBD, by observer	N_2O: 0.5±1.3, N=23 Midazolam: 0.5±1.7, N=24 p=0.68 Mean±SD	NS	High
Bruce 2006 N=14	Chest drain removal	Morphine	Anxiety, VAS, by observer	Figure p=0.268 Each group: N=6	NS	Low
Burton 1998 N=30	Laceration repair	O2	Anxiety, scale 1-4, by observer	N_2O: 1 (1-3), N=17 O_2: 3 (1-4), N=13 p<0.001 Median (range)	+	Low
Reinoso-Barbero2011 N=100	Short diagnostic procedures	O_2	Cooperativeness, scale 1-5, by observer	N_2O: 2.47±1.63, N=51 O_2: 4.29±1.171, N=48 (calculated by us) Figure p<0.05	+	Low
Luhmann 2001 N=101	Laceration repair	Standard care	Distress, OSBD-R, by observer	No numbers, descriptive presentation of results N_2O: N=51 K/M: N=50	+	Low

RoB, Risk of Bias; NS, no statistical significant difference; +, statistical significance in favour of N_2O; OSBD-R, Observational Scale of Behavioural Distress-Revised; VAS, Visual analogue pain scale.

Certainty of effect estimate for patient-experienced distress

We were not able to extract statistical analyses from all of the included articles and therefore presented the results in a narrative form in the available GRADE-tool (*Table 7*). All studies were randomized controlled trials. However, we downgraded the certainty of evidence based on lack of blinding in one study and also due to poor presentation of data in two of the studies (imprecision).

Table 7. *Summary of findings table for patient-experienced distress*

Outcomes	Impact	№ of partici-pants (studies)	Certainty of the evidence (GRADE)	Comments
Distress/ anxiety/ co-operative-ness, N_2O vs active drug	It is uncertain whether there are differ-ences between the groups.	317 (5 RCTs)	⊕⊕◯◯ LOW	Lack of blinding in one study (Limitation in de-sign). Poor presentation of data in 2 studies (Im-precision.
Distress/ anxiety/ co-operative-ness, N_2O vs placebo	Lower levels of distress/anxiety/coop-erativeness in the N_2O group.	230 (3 RCTs)	⊕⊕⊕◯ MODERATE	1 of 3 studies gave no data (Imprecision)

Hospital procedure characteristics

We analysed two main categories of hospital procedure characteristics: time of re-covery after the procedure and number of successful procedures. The results are pre-sented in *Table 8*. Further, the summary of findings are presented in *Table 9*.

All five studies with an active drug as a comparator showed shorter recovery time for the N_2O sedation regimen. The percentage of successful procedures were higher for sedation by N_2O than for other drugs or placebo in 4 of the 5 studies. Procedure time and total procedure time were also measured in several studies. However, as the procedures were different and the authors presented different start and end points of the timing, we did not make any summary of those results.

Table 8. *Results of hospital procedure characteristics*

Ref	Procedure	Comparator	Result, effect size		RoB
Outcome: Recovery time, minutes					
Evans 1995 N=30	Fracture reduction	Mepiridine	N_2O: 30 min (15-60) Mepiridine: 83 min (60-105) p<0.01 Mean (range)	+	Low
Luhmann 2006 N=102	Fracture reduction	Ketamine/mid-azolam	N_2O: 16 (14) min Ket/mid: 83 (85) min p<0.0001 Mean minutes (median)	+	Low
Lee 2012 N=32	Laceration repair	Ketamine	N_2O: 0.0 min (0.0-4.0) Ketamine: 21.5 (12.5-37.5) p<0.05 Median (interquartile range)	+	Low
Keidan 2005 N=47	Voiding cys-tourethrography	Midazolam	N_2O: 29±10 min G2-mid: 63±25 min p<0.001 Mean±SD	+	Low
Luhmann 2001 N=102	Laceration repair	Midazolam	N_2O: 21 min Midazolam: 30 min Mean, p-value only suggested in discussion to be <0.05	+	Low

Ref	Procedure	Comparator	Result, effect size		RoB
Luhmann 2001 N=101	Laceration repair	Standard care	N_2O: 21 min Standard care: 21 min p=0.90 Mean	NS	Low
Outcome: Successful procedures (percent)					
Ekbom 2011 N=90	Venous cannulation	Midazolam	N_2O: 67% Midazolam: 37% p=0.04	+	Low
Mjahed 1997 N=50	Venous cannulation	EMLA	No numbers, descriptive presentation of results	NS	Low
Fauroux 2004 N=105	Fiberoptic bronchoscopy	O_2 and N_2	N_2O: 79.2% O_2: 38.5%	+	Low
Reinoso-Barbero 2011 N=100	Short procedures	O_2 and N_2	N_2O: 81.8% O_2: 45.2% p=0.0208	+	Low

RoB, Risk of Bias; NS: no statistical significant difference; +: p-value statistical significant in favour of N_2O.

Certainty of effect estimate – procedure characteristics

We were not able to extract statistical analyses from all of the included articles and therefore presented the results in a narrative form in the available GRADE-tool (*Table 9*). All studies were randomized controlled trials. However, we downgraded the certainty of evidence based on lack of blinding and also due to poor presentation of data (imprecision).

Table 9. *Summary of findings table for procedure characteristics*

Outcomes	Effect	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Recovery time, N_2O vs active drugs	Shorter recovery time in the N_2O group.	313 (5 RCTs)	⊕⊕⊕⊕ HIGH	None of the studies were blinded but the outcome was objective. All studies showed large effects. 4 of 5 studies did not show overlap in time between the groups.
Recovery time, N_2O vs placebo (13)	No difference in recovery time.	101 (1 RCT)	⊕⊕◯◯ LOW	Low sample size. No variation given (imprecision).
Successful procedures, N_2O vs active drug	No conclusions can be given based on the two included studies.	140 (2 RCTs)	⊕⊕◯◯ LOW	The two studies gave contradictory results (inconsistency). Low sample size.
Successful procedures, N_2O vs placebo	Higher success rate in the N_2O group.	205 (2 RCTs)	⊕⊕⊕⊕ HIGH	

Patient experienced pain

Table 10 show the studies reporting pain. One of the included studies was premature infants (43). We considered this population to be too different from the children population as understood in the present report, and did not include it in the summary of results.

Table 10. *Summary table of results of pain*

Study ID	Procedure	Comparator	Effect measure	Result, effect size		RoB
N_2O vs active drug						
Vetter 1995 N=50	Venous cannulation	EMLA	VAS, by patient,	N_2O: 3.2±1.4, N=25 EMLA: 23±6.7, N=25 p=0.006 Mean±SEM	+*	High
Mjahed 1997 N=50	Venous cannulation	EMLA	CHEOPS, by observer	N_2O: 10.0±1.9, N=25 EMLA: 9.3±2.4, N=25 p=0.276 Mean±SD (results calculated by us)	NS*	Low
Paut 2001 N=40	Venous cannulation	EMLA and O_2	VAS, by patient	N_2O:3.9±9.3, N=20 EMLA: 4.4± 7.5, N=20 p=0.85 Mean±SD	NS*	Low

Study ID	Procedure	Comparator	Effect measure	Result, effect size		RoB
Belyamani 2003 N=80	Venous cannulation	EMLA and O_2	VAS, by patient	N_2O: 4.18±8.8, N=40 EMLA: 4.2±6.54, N=40 p=0.99 (p-value calculated by us) Mean±SD	NS*	Low
Hee 2003 N=80	Venous cannulation	EMLA and O_2	VAS, by patient	N_2O: 18.35±18.11, N=40 EMLA: 26.13±27.59, N=40 p=0.16 (p-value calculated by us) Mean±SD	NS*	Low
Mann 2007 N=103	Venous cannulation	EMLA	Wong-Baker FACES, by patient	N_2O: 1 (0-2), N=57 EMLA: 1 (1-2), N=46 p=0.85 Median pain score (interquartile range)	NS	High
Carbajal 2008 N=55 (cross over)	Palivizumab injection	EMLA	VAS, by operator	N_2O: 40.4±22.6, N=55 EMLA: 45.9±22.1, N=55 p=0.1997 (p-value calculated by us) Mean±SD	NS*	Low
Evans 1995 N=30	Fracture reduction	Meperidine, intramuscular	CHEOPS, by physician	N_2O: 9.6 (6-12), N=15 Meperidine: 9.3 (5-13), N=15 Mean (range)	NS	High
Keidan 2005 N=47	Voiding cystourethrography	Midazolam	FLACC, by nurse	N_2O: 0.2±1.0, N=23 Midazolam: 1.5±2.3, N=24 p=0.23 Mean±SD	NS*	High
Ekbom 2011 N=60	Venous cannulation	Midazolam and O_2	VAS, by patient	No numbers, descriptive presentation of results Each group N=30	+	Low
Luhmann 2006 N=102	Fracture reduction	Ketamine and midazolam (oxycodone given to both groups)	VAS, by patient	N_2O: 1.8, N=47 KM: 2.9, N=55 p=0.0335 (calculated by us) Mean 1.1 (95%CI, 0.0 to 2.1) Difference in mean (95% CI)	+*	High
Lee 2012 N=32	Laceration repair	Ketamine	CHEOPS, by observer	N_2O: 6.0 (5.8-6.8), N=18 Ketamine: 6.0 (6.0-6.0), N=14 p=1.00 median score above 4 (range)	NS	High
Bruce 2006 N=12	Chest drain removal after cardiac surgery	Morphine	CHEOPS, by researcher	Results presented as figure p=0.946 Each group N=6	NS	Low
N_2O vs placebo group						
Henderson 1990 N=83	Venous cannulation	O_2	CHEOPS, by observer	N_2O: 56%, N=39 O_2: 16%, N=44 p<0.05 Percentage patients ≤ 6	+	Low

Study ID	Procedure	Comparator	Effect measure	Result, effect size		RoB
Burton1998 N=30	Laceration repair	O_2 (lidocaine in both groups)	Modified CHEOPS, by observer	N_2O: 1 (0-6), N=17 O2: 8 (2-10), N=13 p<0.001 Median (range)	+	Low
Reinoso-Barbero 2011 N=100	Short procedures	O_2 and N2	LLANTO, by nurse	N_2O: 4.6±4.1, N=50 O_2: 6.8± 4.2, N=50 p=0.028 Mean±SEM	+*	Low
Fauroux 2004 N=105	Fiberoptic bronchoscopy	O_2 and N2	CHEOPS, by observer	N_2O: 4.8±1.3, N=53 O_2: 6.5±2.1, N=52 Mean±SE	+*	Low
Mohan 2015 N=61	Short procedures	Standard care	FLACC, by nurse or patient	N_2O: 2.87; 2 (1-5), N=31 Standard: 5.87; 6 (2-8.25), N=30 Mean score; median score (range)	+	Uncertain

** Data from these studies are also presented in a Forest plot.*
RoB, Risk of Bias; NS: no statistical significant difference; +: p-value statistical significant in favour of N_2O; VAS, Visual analogue pain scale; CHEOPS, Children's Hospital of Eastern Ontario Pain Scale; FLACC/LLANTO, Face, Legs, Activity, Cry, Consolability; PIPP, Premature Infant Pain Profile;. See Appendix 1 for details about scales used.

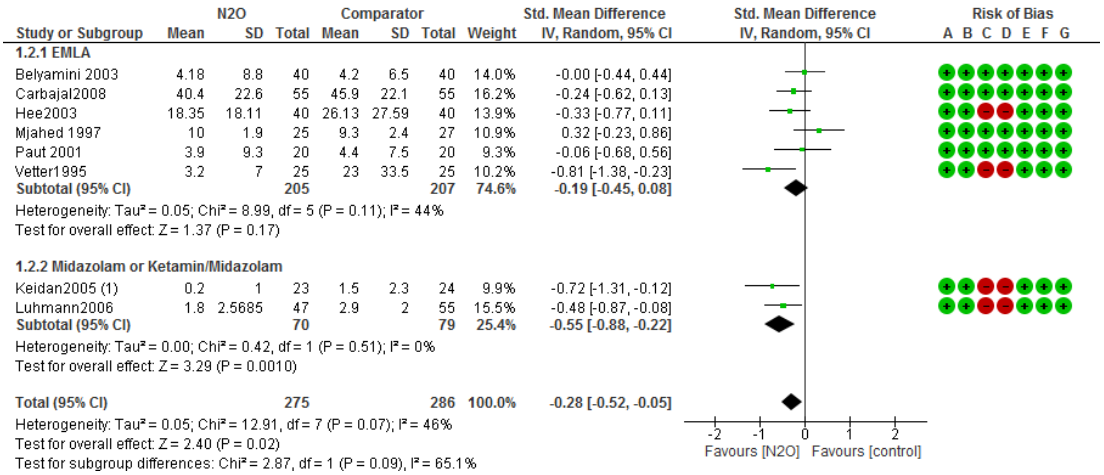
Meta-analyses of pain data

We extracted mean and standard deviation in 11 of the 19 studies that reported data on pain. The remaining 8 studies did not present data which was possible to extract for a meta-analyses (lack of numbers or variation). These were combined and analysed in forest plot and presented as standardized mean difference. The risk of bias for each study are shown in the plots. Of note is that we combined studies independent of which hospital procedure was used. Venous cannulation was the procedure for all but one (Palivizumab injection) study for the EMLA subgroup, while for the midazolam/ketamine subgroup three procedures were studies; venous cannulation, fracture reduction and voiding cystourethography.

The results showed that when the N_2O group was compared with the analgesic EMLA for venous cannulation, the standardised mean difference (SMD) in pain score were -0.19 (95%CI=-0.45, 0.08; p=0.11) (*Figure 2*). However, N_2O showed a statistically significant lower pain score when compared to the sedative midazolam or a combination of midazolam and ketamine (SMD=-0.55, 95%CI=-0.88,-0.22; p=0.001).

Compared to a placebo group, the N_2O group showed a standardized mean difference in pain score of -0.10 (95%CI=-0.38, 0.17) (*Figure 3*). This is in contrast with the vote counting from *Table 10* where sedation by N_2O seems to be associated with lower feeling of pain in all the 5 included studies when compared to placebo.

Figure 2. *Experienced pain by patients sedated with N_2O vs active drug*



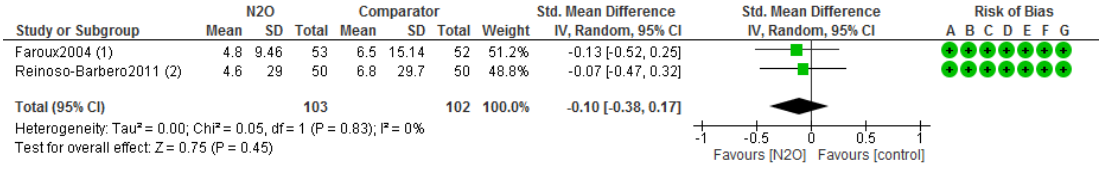
Footnotes

(1) The author report this to be a non-significant difference in the article, while it is significant in our meta-analyses. This is probably due to the different statistical tests being used.

For EMLA subgroup: One article from Table 10 was not included in this meta-analyses. The results from this article showed no difference between the groups, supporting the results in the meta-analyses.

For midazolam or ketamine/midazolam subgroup: Two articles from Table 10 were not included in this meta-analyses. The results from these articles showed no differences between the groups, which may cause a skewing of the results in the meta-analyses towards no difference.

Figure 3. *Experienced pain by patients sedated with N_2O vs placebo*



Footnotes

(1)(2) The authors report this to be a significant difference, while it is non-significant in our meta- analyses. This is probably due to the different statistical tests being used.

Three articles from Table 10 were not included in this meta-analyses. The results from these articles showed significant lower pain score in the N_2O group, which may cause a skewing of the results in the meta-analyses towards a significant difference between the groups.

Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias)
(D) Blinding of outcome assessment (detection bias)
(E) Incomplete outcome data (attrition bias)
(F) Selective reporting (reporting bias)
(G) Other bias

Certainty of effect estimate - pain

Summarizing the meta-analyses and the narrative presentation of the data in *Table 10*, the potential difference in pain between the groups in all cases are minor and probably not of clinical significance. The certainty of effect estimate presented in the meta-analyses is considered to be moderate (*Table 11*).

Table 11. *Summary of findings table for pain*

Outcomes	Effect	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
Pain, N_2O vs EMLA	SMD 0.19 SD lower for N_2O (0.45 lower to 0.08 higher)	412 (6 RCTs)	⊕⊕⊕◯ MODERATE	1 of the 6 studies were not blinded.
Pain, N_2O vs midazolam/ketamine	SMD 0.55 SD lower for N_2O (0.88 lower to 0.22 lower)	149 (2 RCTs)	⊕⊕◯◯ LOW	None of the studies were blinded.
Pain, N_2O vs placebo	SMD 0.1 SD lower for N_2O (0.38 lower to 0.17 higher)	205 (2 RCTs)	⊕⊕⊕◯ MODERATE	Wide confidence interval.

Safety for patients

Fifteen studies (19 articles) reported data on adverse events (7;13;25;28;30;31;35;37;39;41;42;44;45). We have presented the crude results of adverse events experienced by the use of N_2O across all studies and control groups, due to the limited information if analysed separately for each comparator and treatment.

Of 525 patients sedated with N_2O, independent of hospital procedure or control group, none of the adverse events reported met the U.S. Food and Drug Administration's definition of a serious adverse event (46). In particular, none of the study participants experienced serious cardiac or respiratory events (including oxygen below saturation level).

Agitation (13.4%), dysphoria (11.7%), euphoria (5.88%-22.5%), excessive crying (11%), headache (11.6%), nausea and vomiting (0%-13.2%) were the most frequent adverse events observed in the N_2O group. Of 47 patients undergoing fracture reduction, 4 patients suffered ataxia (26)).

Children receiving N_2O were more agitating (OR=3.35, CI95%=1.38, 8.14), experienced more often dysphoria (OR=9.07, CI95%=1.09,75.3) and euphoria (OR=24.4, CI95%=1.37,436) than in the EMLA group. Children receiving ketamine or midazolam experienced more hallucinations (OR=0.12, CI95%=0.03 to 0.5) and vasoconstriction (OR=0.01, CI95%=0.00, 0.1) than in the N_2O group. These were the only statistically significant differences. Appendix 6 presents results for all the adverse events in detail.

All reported adverse events occurred during or shortly after the procedure.

Certainty of effect estimate – safety

N_2O possibly does not lead to serious adverse events (low certainty evidence). This judgement is based on no serious adverse events being reported in the 15 randomized controlled trials included in this review with a relatively few number of patients (a total of 525).

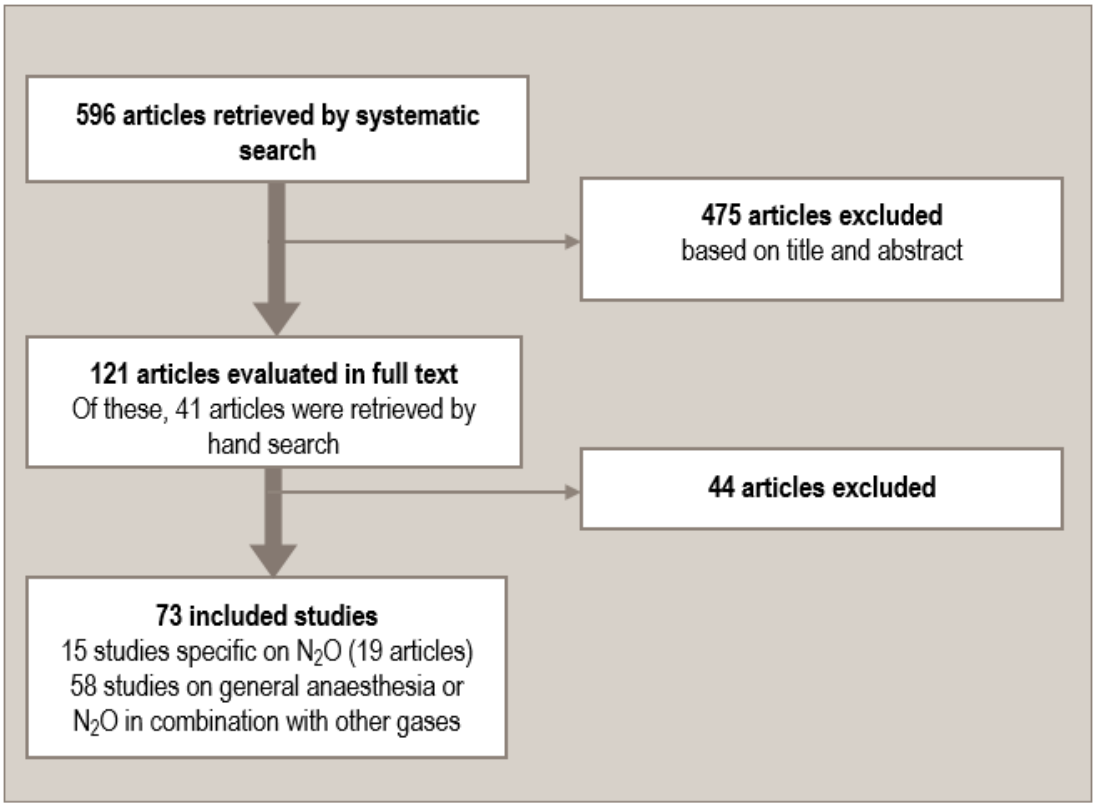
The results on frequency of experiencing certain adverse events under N_2O sedation is uncertain (low certainty evidence) due to the variation between the trials and the low number of events. Further, the risk of experiencing adverse events using N_2O compared to the control groups is also low certainty evidence due to the high confidence intervals.

Results – safety for health personnel

Literature search and article selection

After reading through the full text versions of the included articles in the efficacy studies we concluded that there were no data on safety for health personnel. We therefore performed a second systematic search, as described under Methods, with health personnel as the population of interest. We retrieved 557 articles by the systematic search. However, we realized that limiting the search to N_2O, we lost several studies on N_2O in combination with other gases or in general anaesthesia. We therefore also performed an extensive hand-search in the retrieved articles and found 41 articles for full text evaluation. We included 15 studies which investigated the effect of N_2O only (Appendix 7) and 58 studies with data on the effect of general anaesthesia or N_2O in combination with other gases on health personnel (Appendix 8). The excluded articles are listed in Appendix 4 with reasons for exclusion.

Figure 4. *Flow chart of article selection for occupational safety*



Description of included studies

All the studies were controlled, however none were randomized. Only fifteen studies (Appendix 7) reported N_2O exposure on sufficient level of detail to allow inclusion in the following analysis. The remaining 58 articles are only shown in Appendix 8.

The 15 studies were published in 19 articles from 1980 to 2016, see summary *Table 12*. Nine of the articles showed information about N_2O concentration in the air and six articles stated that a scavenging system was used (see *Table 13*).

The 15 studies were published in 19 articles. All of the 15 studies, except two (47;48) describe how they handled possible confounders, either by matching the control group to the exposed group with respect to these, or by adjusting their analyses for specific confounders. Confounding factors are given in the risk of bias table in **Feil! Fant ikke referansekilden.**.

Three large retrospective cross sectional studies presented data in seven articles:

> These were the only studies to present endpoints for spontaneous abortion, fertility, or congenital malformations of children born by exposed women. The inclusion/exclusion criteria or other reasons that reduced the numbers of eligible persons were well accounted for in all the three surveys and the response rates were from 69-84%.

- Epidemiological survey, USA, 1968-1978 (49;50): Questionnaires were sent to male dentist of the American Dental Association for the exposure period 1968 to 1978. About 15 000 male dentist and 15 000 female dental assistants were included in the analyses. The exposure was N_2O only. The endpoints were spontaneous abortion and congenital abnormalities in one publication (49), and neurological diseases in the other publication (50).
- Epidemiological survey, USA, 1987-1988 (51;52): Questionnaires were sent to female dental assistants in USA, more specific to the dental-assistant registry of California. The questionnaires were followed up by telephone interviews conducted in the period 1987-88. The exposure was N_2O alone. The endpoints were fertility, where 418 women were included in the analyses (51), and spontaneous abortion, were 1465 women were included in analyses (52). This was the only survey that gave information about use of scavenging system and compared the effect on fertility with and without the use of scavenging systems.
- Epidemiological survey, Sweden, (53-55): Questionnaires were sent to midwives, born 1940 and after, registered in the Swedish Midwives Association. The exposure was N_2O and shift work. This survey resulted in three publications; Ahlborg et al (53) presented fertility data were 1484 pregnancies of 751 women were included in the analyses; Axelsson et al (54) presented data on spontaneous abortion, including 1717 pregnancies (number of women not given); and Bodin et al (55) showed data for birth weight and gestational age, including 1781 pregnancies of 1302 women.

Nine controlled studies were controlled presenting exposure data from blood samples:

- Four trials presented data on potential toxic effect of N_2O on DNA. Different assays were used: sister chromatid exchange (56), micronuclei formation (57), comet assay (58;59), and reactive oxygen species (59). All trials included less than 150 participants. The study subjects were male and female dentists, chairside female dental assistants, or female nurses.
- Four trials presented data on the effect of N_2O on B12 through the analyses of different markers in the blood (48;60-62). All were small trials with 2-185 participants. One of the trials were from a paediatric emergency department (62), the others were from operating theatres.
- One trial measured the effect of N_2O on folate metabolism (63)

Three studies showed results on the neurological effect of N_2O:

- One study was a retrospective survey (50) (a part of the Epidemiological survey, USA, 1968-1978 described above) with questionnaires to identify neurological diseases/symptoms.
- Two were small controlled trials, with less than 100 participants showing neurobehavioral effects of N_2O using different test systems (47;64).

Table 12. *Outcomes, effect measures and study groups of included studies*

	Effect measure	Groups
Outcome: Spontaneous abortion		
Cohen 1980 (49)	Rate of spontaneous abortion/100 live births ± SE.	Female dental assistants, N=number of pregnancies No exposure, N= 3197 Exposure, N=701
Heidam 1984 (65)	Number abortions and odd ratio, 95%CI, both adjusted and crude	Dental assistants, N=number of pregnancies No exposure, N=97 Exposure, N=255
Rowland 1995 (52)	Relative risk, 95%CI and adjusted rate	Female dental assistants, N=number of pregnancies No exposure, N=684 Light exposure: Scavenged room, N=356 Heavy exposure: Unscavenged rooms, N=147
Axelsson 1996 (54)	Number abortions and odd ratio, 95%CI, both adjusted and crude	Swedish female midwives, N=number of pregnancies No exposure, N=598 Light exposure: ≤ 50% of the deliveries with N_2O, N=495 Heavy exposure: > 50% of the deliveries with N_2O, N=624
Outcome: Fertility		
Rowland 1992 (51)	Infertility rate and adjusted fertility ratio	Female dental assistants, N=number of women No exposure, N=203 Light exposure: Scavenged room, N=121 < 5h/week, N=85 ≥ 5h/week, N=36 Heavy exposure: unscavenged rooms, N=60 < 5h/week, N=41 ≥ 5h/week, N=19
Ahlborg 1996 (53)	Infertility rate and adjusted fertility ratio	Swedish female midwives, N=number of women No exposure, N=346 Low exposure: 1-10 deliveries per month: N=160 11-20 deliveries per month: N=136 21-30 deliveries per month: N=43 High Exposure: ≥ 30 deliveries per month: N=41
Outcome: Adverse events to children born by exposed women		
Cohen 1980 (49)	Adjusted rate for congenital abnormalities.	Female dental assistants, N=number of children No exposure, N= 2 882 Exposure, N=579
Bodin 1999 (55)	Birthweight as weight and rate of low birth weight (LBW). Gestational age as weeks and rate of preterm birth and rate of small for gestational age (SGA).	Swedish female midwives, N=number of children No exposure, N=931 Light exposure: ≤ 50% of deliveries with N_2O, N=357 Heavy exposure: > 50% of deliveries with N_2O, N=454
Outcome: Genetic toxicity		

	Effect measure	Groups
Husum 1986 (56)	Sister chromatid exchange per cell	Dentists and chairside assistants, N=number of female dentists and assistants, MN=number of male dentists 0 hour exposure per week, N=30, MN=20 < 1 hour exposure per week, N=26, MN=5 1-5 hour exposure per week, N=36 > 5 hour exposure per week, N=20 > 1 hour exposure per week, MN=5
Chang 1996 (57)	Micronuclei formation	Female paediatric anaesthetic nurses, N=female nurses No exposure, N=18 Exposure, N=18
Wronska – Nofer 2009 (66)	DNA damage (Comet assay), concentration of gases	Nurses and anaesthesiologists, N=number of subjects No exposure, N=52 Light exposure (97.44 (19.89-177.99) ppm), N=22 Heavy exposure (391.08 (248.54- 834.39 ppm)), N=33
Wronska – Nofer 2012 (59)	DNA damage (Comet assay), reactive oxygen species (ROS) in leucocytes, oxidative stress markers	Female nurses, N=number of subjects No exposure, N=36 Exposure: N=36
Outcome: Neurological and neurobehavioral effects		
Brodsky 1981 (50)	Neurologic disease rate, defined in four categories: Group 1: symptoms secondary to specific nerve irritation Group 2: nonspecific symptoms without a neurologic diagnosis Group 3: symptoms secondary to specific diseases Group 4: miscellaneous neurologic disease Group 5: no neurologic complaints	Male dentists and female dental assistants, DN=number of dentists, DAN=number of dental assistants No exposure, DN=7886, DAN=6593 Light exposure: < 6 hours per week, DN=6761, DAN=9311 Heavy exposure: ≥ 6 hours per week, DN=3206, DAN=2163
Isolani 1999 (47)	Neurobehavioral effect: Simple reaction time (ms), Colour Word Vigilance (ms) and Mood Rating Scale (score)	Anaesthetists, N=number of subjects No exposure: first day of working week (beginning and end), N=37 Exposure, defined as low: last day of working week (beginning and end), N=37 (same as no-exposure)
Scapellato 2008 (64)	Neurobehavioral effect: Euroquest, Block design, Mood scale, and Colour word vigilance test	Operating room nurses, N=number of subjects No exposure, N=23 Exposure, N=38 < 13 µg/l N_2O in urine 13-26 µg/l N_2O in urine ≥ 27 µg/l N_2O in urine
Outcome: B12 metabolism		
Nunn 1982 (60)	Serum methionine in urine	Operating staff, N=number of subjects No exposure, N=10 Exposure, N=10

	Effect measure	Groups
Armstrong 1991 (63)	Formaminoclutamic acid in urine	Anaesthetists, N=number of subjects No exposure, N=10 Exposure, N=10
Krajewski 2007 (61)	B12, homocysteine and folic acid	Operating theatre nurses, N=number of subjects No exposure, N=90 Light exposure (102.77 ppm), N=46 Heavy exposure (418.03 ppm), N=49
Ekbom 2008 (48)	Homocysteine	Nurses No exposure: samples from nurses after vacation, N=2 Exposure: hospital procedures, N=43
Staubli 2016 (62)	B12 and homocysteine	Emergency department personnel, N=number of subjects No exposure, N=29 Exposure, N=29

We also included 58 articles (Appendix 8) with uncertain exposure to N_2O, where N_2O was mentioned in combination with other gases, but with no specific data presented for N_2O (in 38 studies). In addition, we included studies where general anaesthesia (in 20 studies) were used, as N2O is one of several inhalation commonly used in general anaesthesia (67). We did not analyse data from these studies, but a summary of the results and study characteristics are presented in Appendix 8.

Risk of bias

We used a modified version of ROBINS-I to evaluate the risk of bias in the studies (see template in Appendix 3 and results in **Feil! Fant ikke referansekilden.**).

Level of exposure of N_2O in the studies

The studies span from 1980 to 2016 and the technology of delivering gases, as well as ventilation and scavenging systems has changed through the time. We have extracted information of N_2O concentration in the rooms as well as other measures of occupational exposure such as hours of exposure (*Table 13*). In addition, some studies mentioned whether the rooms were ventilated or had scavenging systems. Only one study mentioned that the mask used had an on-demand valve (62), meaning that gas only was delivered on the patient's inhalation and not continuous flow of gas.

Table 13. *Degree of N_2O exposure in the included studies*

ID	Concentration of N_2O in the air	Occupational exposure	Room ventilation	Scavenging system
Cohen 1980 (49)	-	-	-	-

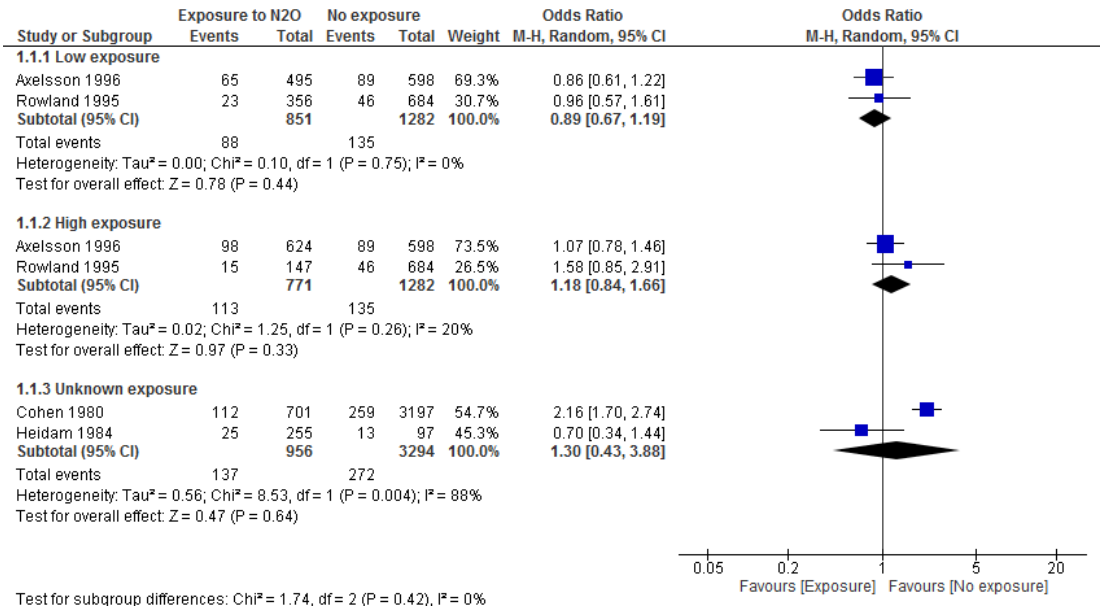
ID	Concentration of N_2O in the air	Occupational exposure	Room ventilation	Scavenging system
Brodsky 1981 (50)	-	Self-reported light exposure (< 6 hours per week) and high exposure (> 6 hours per week over a decade)	-	-
Nunn 1982 (60)	Range: 150-400 ppm	-	-	-
Heidam 1984 (65)	-	-	Many of the clinics were poorly ventilated	-
Husum 1986 (56)	Single measurements showed TWA above 100 ppm	Range: 1-40 years Hours of exposure per week:, <1, 1-5, >5	-	Yes
Armstrong 1991 (63)	Range: 53.4-159.2 ppm	≥ 6 months, full-time work Hours of exposure per week	-	-
Rowland 1992 (51)	-	More or less than 5 hours per week.	-	Scavenged vs unscavenged systems
Rowland 1995 (52)	-	Fulltime during pregnancy. Self-reported low (<3 hours of unscavenged exposure and scavenged nitrous oxide) and high exposure (≥3 hours per week, unscavenged exposure)	-	Scavenged vs unscavenged systems
Ahlborg 1996 (53)	-	More or less than 30 deliveries per month (midwives)	-	Both with and without scavenging systems
Axelsson 1996 (54)	-	More or less than 50% of the deliveries with exposure.	-	-
Chang 1996 (57)	-	At least 5 years employment with constant involvement in paediatric anaesthesia.	-	-
Bodin 1999 (55)	-	More or less than 50% of deliveries with exposure.	-	-
Isolani 1999 (47)	TLV-TWA: 50.83 ppm (indicated value calculated from urine concentration)	Mean: 13.9 years	-	-
Krajewski 2007 (61)	Range: 19.44-58.33 ppm	≥ 5 h per day	Yes	Yes
Ekbom 2008 (48)	≤ 500 ppm	-	Yes	Yes
Scapellato 2008 (64)	<50 ppm (indicated value calculated from urine concentration)	-	-	-
Wronska –Nofer 2009 (66)	Range: 19.89- 834.39 ppm	Range: 5-31 years.	Yes	-
Wronska –Nofer 2012 (59)	Range: 102.77-834.39 ppm	Range: 5-27 years	-	-

ID	Concentration of N_2O in the air	Occupational exposure	Room ventilation	Scavenging system
Staubli 2016 (62)	-	>50% exposure through the paediatric emergency department. The exposure to N_2O in the ED staff was very short and only a few times per day.	-	(On-demand valve)
- , No information given; TLV, Threshold Limit Values; TWA, time weighted averages				

Effect of N_2O on spontaneous abortion

Four articles showed data on the effect of N_2O exposure on spontaneous abortion, three from a dental setting (49;52;65) and one (53) from a maternity ward. The degree of N_2O exposure were divided into three categories (no exposure, light exposure and heavy exposure) in two of the studies: low exposure were defined as less than 50% of deliveries by included midwifes (54) or as working in rooms with scavenging systems (51); high exposure were defined as more than 50% of deliveries or working in rooms with no scavenging systems. The two other studies (49;65) only showed data on no exposure- and exposure groups. In *Figure 5* we show the effect of different levels of exposures of N_2O on spontaneous abortion. The results show that neither for low exposure (OR=0.89; 95%CI=0.67, 1.19), high exposure (OR=1.18; 95% CI=0.84, 1.66) nor unknown exposure (OR=1.30; 95% CI=0.43, 3.88), there were a statistical significant increased odds for spontaneous abortion in the N_2O exposed groups.

Figure 5. *Effect of exposure vs no exposure of N_2O on spontaneous abortion*



Certainty of evidence

The summary of findings are presented in *Table 14*. The results are taken from three large retrospective surveys, presented in 4 articles, with the risk of bias. The authors

adjusted for several confounding factors including age, smoking, shift work and history of spontaneous abortions in their analyses (**Feil! Fant ikke referansekilden.**). We do not know the concentrations of N_2O in the room as the low and high exposure only relates to time exposed to the gas. As a summary, mainly due to the study design (see risk of bias assessment in **Feil! Fant ikke referansekilden.**), the certainty of evidence is very low, implying that we are not sure that the given results represents the true effect of N_2O exposure.

Table 14. *Summary of findings table for rate of spontaneous abortion in women exposed to N_2O*

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of pregnancies (studies)	Certainty of the evidence (GRADE)
	Risk with no exposure	Risk with exposure			
Low exposure	105 per 1 000	95 per 1 000 (73 to 123)	OR 0.89 (0.67 to 1.19)	2135 (2 surveys)	⨁◯◯◯ VERY LOW
High exposure	105 per 1 000	122 per 1 000 (89 to 163)	OR 1.18 (0.83 to 1.66)	2053 (2 surveys)	⨁◯◯◯ VERY LOW
Unknown exposure	83 per 1 000	128 per 1 000 (70 to 225)	OR 1.63 (0.83 to 3.22)	4250 (2 surveys)	⨁◯◯◯ VERY LOW

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; OR: Odds ratio

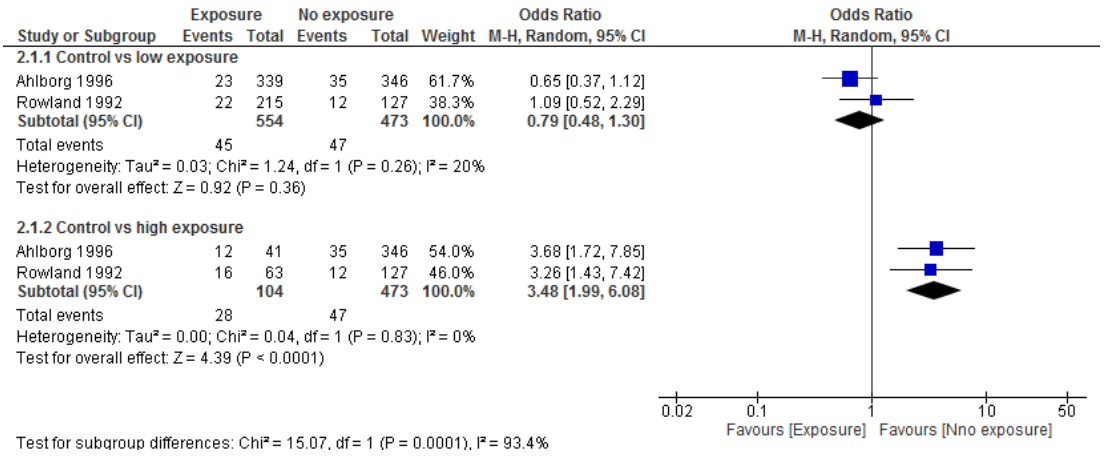
Effect on fertility

Two studies reported data on the effect of N_2O exposure on fertility (51;53) (*Table 12*). The data were presented as rate of fertility or cycles to conception. More than 13 cycles to pregnancy was considered as a threshold number for infertility.

We performed a meta-analyses on the percentage of infertility given in the papers, not adjusted for confounding factors. We defined low and high exposure for the two studies to be scavenged and unscavenged rooms for the dental assistants (51) or more or less than 30 deliveries per month for the midwives (53).

Women with high exposure to N_2O had an increased risk of infertility (OR=3.48; 95%CI=1.99, 6.08) in contrast to women with low exposure (OR=0.79; 95%CI=0.48, 1.30). The OR of the high and low exposure groups were statistically significantly different suggesting that the toxic effect of N_2O on fertility is concentration dependent.

Figure 6. *Effect of exposure vs no exposure of N_2O on fertility*



Certainty of evidence

The summary of findings are presented in *Table 15*. The results are taken from two large retrospective surveys based on questionnaires to a broad population, the same as described in the chapter of spontaneous abortion. Therefore, mainly due to the design, the certainty of the evidence is very low. However, for fertility, in contrast to spontaneous abortion, the effect of N_2O is suggested to be dose dependent with increased odds of infertility in a high exposure group.

Table 15. *Summary of findings table for fertility rate in women exposed to N_2O*

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
	Risk with no exposure	Risk with exposure			
Low exposure	99 per 1 000	80 per 1 000 (50 to 125)	OR 0.79 (0.48 to 1.30)	1027 (2 surveys)	⨁◯◯◯ VERY LOW
High exposure	99 per 1 000	277 per 1 000 (180 to 401)	OR 3.48 (1.99 to 6.08)	577 (2 surveys)	⨁◯◯◯ VERY LOW

*The risk in the intervention group (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
CI: Confidence interval; OR: Odds ratio

Effect on children born by exposed women

One study (49) showed results on the rate and nature of congenital abnormalities of children born to exposed parents. They found that the adjusted rate of abnormalities in the exposed group were higher compared to the non-exposed group (see *Table 16*). The degree of exposure was unknown.

The adjusted odds ratio for low birth weight (defined as birth weight < 2500 grams) was not affected by N_2O exposure to the mother (*Table 16*), although the exposure

lead to a minor reduction in birthweight of 77 g (95%CI=-129, -24) (55). The adjusted odds ratio of preterm birth were not affected by N_2O exposure (55).

Certainty of evidence

The data included in the analyses are taken from two retrospective surveys (49;55). They are large and well-designed surveys with clear outcome measures. Due to the study design as well as few studies, the certainty of evidence was found to be very low.

Table 16. *Summary of findings table for effect of N_2O on children born by exposed women*

Outcomes (ref)	Effect	№ of children (studies)	Certainty of the evidence (GRADE)
Congenital abnormalities (49)	The adjusted rate of congenital abnormalities in children born by N_2O exposed women is higher than in the control group (5.5±0.95, N=579 vs 3.6±0.34, N=2882, p=0.02).	3539 (1 Survey)	⊕◯◯◯ VERY LOW
Birth weight (55)	N_2O exposure did not affect the adjusted odds ratio of low birth weight (OR=1.5; 95%CI=0.7, 3.3)	4960 (1 Survey)	⊕◯◯◯ VERY LOW
Preterm birth (55)	N_2O exposure did not affect the adjusted odd ratio of preterm birth (OR=0.7; 95%CI=0.3, 1.4).	4960 (1 Survey)	⊕◯◯◯ VERY LOW

Genetic toxicity

Four of the included articles showed results on genetic toxicity of N_2O to exposed health personnel (56;57;59;66).

No mutagenic effect of N_2O exposure was found in female and male dentists and female dental assistants as measured by sister chromatid exchange (SCE) (statistics was not shown) (56). In this study, smoking was the only factor statistically significant leading to an increase of SCE. Mutagenic stresses to the cell, as measured by micronuclei formation, showed a statistically significant increase in lymphocytes of female nurses with more than 5 years of continuous employment in paediatric anaesthesia (57). However, the authors did not discuss the impact of the size of the difference.

Wronska-Nofer et al found a positive correlation between N_2O concentration and DNA damage in operating room personnel (both genders) (Wroska-Nofer 2009(66): r=0.56, P<0.001; Wroska-Nofer 2012(59): r=0.54; p<0.01). A similar correlation was found between N_2O and reactive oxygen species (59) (r=0.85, P<0.001). A causal relationship was also found between N_2O exposure and oxidative stress although the authors did not discuss the impact of the size of the difference (59). No correlation between sevoflurane or isoflurane concentrations and DNA damage was found in these studies.

Certainty of evidence

The results came from controlled, non-randomised studies. The population were small and for cellular and DNA damage or stress it was not possible to draw any conclusions due to inconsistent results. The certainty of evidence of an increased level of oxidative stress markers in N_2O exposed personnel, was considered low due to a small study population and only one study.

Neurological toxicity of N_2O

We included three articles that showed results on the effect of N_2O exposure on different neurological outcomes (47;50;64).

Brodsky et al (50) found a statistically significant higher rate of subjects experiencing numbness, tingling, and/or muscle weakness in the N_2O exposed groups compared to non-exposed subjects. While the rate for female dental assistants experiencing these side effects was statistically significant higher for both the light (0.83±0.10) and heavy exposures (1.46±0.24) compared to the non-exposed subjects (0.46±0.09), the rate for male dentist was only statistically significant higher in the heavy exposure group (1.53±0.24) compared to the control group (0.35±0.07) (all values are mean rate with standard error). The same tendency was seen for another group of side effects being symptoms secondary to specific diseases as for example multiple sclerosis, Guillian-Barré syndrome, pernicious anaemia. Such complaints were 4-fold greater for women and 3-fold greater for men in the high exposure groups. The baseline (the non-exposed group) were lower for these symptoms than the previous mentioned groups of symptoms (0.11±0.04 for men and 0.16±0.05 for women).

Isolani et al (47) were not able to show any correlation between reaction time, stress level or arousal levels with levels of N_2O in urine in anaesthetists (both gender). They reported, however, differences in neurobehavioral reactions between the beginning and end of a work day or work week. In contrast, Scarpellato et al (64) found an increased reaction time in nurses (both genders) and decreased learning effect with N_2O levels in the urine (≥27 µg/l) compared to non-exposed nurses.

Certainty of evidence

The certainty of evidence of the one retrospective survey reporting different neurological effects of N_2O, was considered very low due to the study design subjective outcomes. No conclusions can be drawn on neurobehavioral effects of N_2O due to contradictory results in the two included studies.

Effect of N_2O on B12 metabolism and other blood and urine markers

Four articles showed the effect of N_2O on B12 metabolism by analysing different markers in the B12 metabolism (48;60-62).

The levels of B12 or B12 metabolism markers in the study subjects were not statistically significant different between the exposed and non-exposed groups in three of the studies, N=82 (125 blood samples) (48;60;62). One study showed a decrease in the vitamin B12 concentration in the high exposure group (436.8 pmol/l (13.2) vs 372.8 pmol/l (12.1), p<0.001, N=185) (61).

These studies also analysed other blood and urine markers summarized below:

- Hepatic enzyme activity was found normal in exposed subjects (60)
- Haemoglobin was found normal in two studies (48;61), but slightly higher in one study (62)
- Markers for folate metabolism were normal in two studies (61;63)
- Other haematological parameters as red blood counts and haematocrit were not affected by N_2O exposure in one study (61)

Certainty of evidence

We were not able to draw any conclusions on the effect of N_2O on B12 metabolism or blood or urine markers studied in the included trials. This was due to the discrepancies in the results and the few studies of each parameter measured.

Budget impact

We have not been asked to make any cost effectiveness or budget impact analyses in this report. However, the cost of the device and disposable parts are listed below. Note that the prices are list prices from AGA, with the understanding that hospitals in Norway have agreements with AGA for specific discounts.

Fixed parts		
321593	DEMANDVENTIL LIVOPAN	NOK 4.554,00
301589	Chart	NOK 5.875,00
335930	Bag	NOK 1.375,00
334156	MS 32/33 EVACUATION EJECTOR	NOK 2.530,80
335931	LIVOPAN SCENT KIT (STRAW, CHOCO,VANIL)	NOK 1.230,00
112115	LIVOPAN 5 L	NOK 4.894,00
Disposables		
332850	SCAVENGING SYSTEM LIVOPAN/ENTONOX (25 pieces)	NOK 4.503,00
329113	ENGANGSPASIENTFILTER AGSS AVLEDER (50 pieces)	NOK 1.965,00
330336	ECOMASKE STØRRELSE 2 BARN (25 pieces)	NOK 709,00
333874	ECOMASKE STØRRELSE 3 (35 pieces)	NOK 1.348,00
332361	ECOMASKE STØRRELSE 4 VOKSEN (35 pieces)	NOK 1.018,00

Estimated cost per patient for one treatment, by AGA: 400 NOK

Discussion

Summary of results

In this report we systematically reviewed:

- Randomized controlled trials on effectiveness and safety of nitrous oxide sedation in children
- Cross sectional studies on safety for health personnel exposed to nitrous oxide through their work

Our findings from 22 randomized controlled trials on effectiveness and safety for children were:

- Satisfaction level were higher using N_2O when compared to placebo sedation (certainty: moderate), but there were no difference when compared to other active drugs (certainty: low)
- Distress/anxiety was lower and cooperativeness higher, using N_2O when compared to placebo group (certainty: moderate), but not compared to other active drugs (certainty: low)
- Recovery time was shorter using N_2O compared to other active drugs (certainty: high) but not to placebo (certainty: low)
- Success rate for the hospital procedures was higher when using N_2O compared to placebo (certainty: high), but no conclusions could be drawn when compared to other active drugs
- Pain level is the same using N_2O when compared to EMLA or placebo, but not compared to midazolam and/or ketamine
- There were no serious adverse events reported from the studies. The most frequent non-serious adverse events in the N_2O group were agitation, dysphoria, euphoria, excessive crying, headache and nausea and vomiting.

Our findings from 15 cross sectional studies (19 articles) on safety for health personnel exposed to N_2O were:

- The risk of spontaneous abortion were not increased in persons exposed to N_2O.
- At low exposure of N_2O, no increased risk of reduced fertility was seen. The risk was however increased in health care personnel with high exposure to N_2O.

- The rate of congenital abnormalities in children born by exposed women was higher than in the control group. No information of exposure level was given.
- No conclusions of the effect of N_2O exposure on DNA damage could be drawn based on the different measures taken together (sister chromatid exchange, Comet assay, micronuclei formation)
- The level of oxidative stress markers in N_2O exposed subjects was increased
- The rate of subjects exposed to N_2O who experience numbness, tingling, and/or muscle weakness were higher than non-exposed subjects
- The rate of subjects exposed to N_2O who experience symptoms specific to neurological diseases were higher than non-exposed subjects
- No conclusions could be drawn on neurobehavioral effects of N_2O
- No conclusions could be drawn on the effect of N_2O on B12 metabolism
- Scavenging systems is important to reduce the level of waste gas exposure

Certainty of effect estimates for all findings were considered very low due to the study design, few studies or contradictory results.

Included studies on nitrous oxide sedation in children

Population and setting

We defined children undergoing painful hospital procedures in need of conscious pain relive and sedation as the population of interest. We did not include dental patients as the commission was specific for hospital setting and procedures. Also, procedures, length of procedures and equipment for delivery of the gas are different between the hospital and dental setting. We also excluded neonates from our analyses, both because N_2O is not widely used for this group of patients, but also since the tools for monitoring relevant outcomes are not as established as for the older children. The results presented is therefore only applicable for children from 1 year, and for a hospital setting. In Norway the method is used in the paediatric department (Akershus University Hospital) for venous cannulation and other small hospital procedures and emergency department (St. Olavs Hospital) for fracture reduction and suturing. In addition, Østfold Hospital Trust uses the method in medical procedures as lumbar punctures, enemas, change of gastrostomy devices, venous cannulation and botulinum toxin injections, as well as surgical or orthopaedic procedures as wound stitching, fracture reduction, removal of osteosynthetic materials and foreign bodies.

Intervention – N_2O sedation

Most commonly, N_2O is used in an equimolar concentration with oxygen. We included studies with both 50% and 70% N_2O with oxygen. We did not systematically analyse the effectiveness of other concentrations of N_2O, but most available literature used 50% N_2O, which has been established as the common concentration for such procedures. A study comparing 50% and 70% showed that both concentrations

was safe for children (68). In Norway, Livopan (AGA), an equimolar delivery system including on-demand mask with scavenging system, is used in several hospitals where this method is in use (Østfold Hospital Trust, Akershus University Hospital). The principle behind the sedation method is that the child should hold the mask itself to ensure that the child keeps conscious.

Outcomes

The studies used a wide variety of outcome measures as well as performed the trials in different settings as emergency departments, paediatric department and outpatient departments. The hospital procedures also differed between the studies, including venous cannulation, laceration repair, fiberoptic bronchoscopy, and for two studies, the procedures were not described. In addition, different score systems were used for the outcomes. Further, many studies reported the results in a narrative form, not leaving actual numbers to the reader. It was therefore challenging to perform meta-analyses and to summarize the results in a consistent way.

Study design

All study designs were randomized controlled trials. However, not all were blinded (16 of 22). When blinded, typically O2 were given through the mask in the control group.

Included studies on health personnel exposed to only N_2O

Population and setting

The aim was to assess the effect of N_2O exposure to health personnel as such, not limited to hospital workers, and included study subjects were therefore both health personnel working in a hospital setting (13 articles) or a dental setting (6 articles).

It is important to note, though, that N_2O levels tend to be higher in dental offices than in hospital operating rooms (52), often explained by that in dental offices only a nose mask can be used.

Professions as operating room nurses, anaesthetists, emergency department personnel, midwives, dental assistants and dentists were included in the studies. For all types of outcomes (Appendix 7) both genders were included. However, if exposed males were included for outcomes related to offspring, their spouses were also included in the analyses.

Intervention – waste N_2O exposure

For occupational exposure of N_2O there were numerous studies on the exposure of anaesthetic gases where N_2O was a potential constituent. We decided to perform a systematic analyses of the studies presenting results on N_2O exposure only, leaving exposure to general anaesthetics or combinations of N_2O with other gases to only a summarising table.

There are several ways of estimating N_2O exposure; one is to count the amount of time being exposed to the gas, another is to determine the gas concentration in the room and a third way is to measure N_2O in the urine. All studies presenting data on spontaneous abortion and fertility were retrospective surveys, exposure to the gas was self-reported exposure time, and the exposure concentration of N_2O was therefore not available. It has been suggested that at the time the population in Cohen et al's study was exposed (in the seventies), the one larger study showing an increased odds ratio for spontaneous abortion, room concentrations of nitrous oxide were routinely 1000-2000 ppm (69). We assume, supported by the information given in several of the older articles we included, that necessary ventilation of operating rooms or effective scavenging systems of waste gas was not common at that time (*Table 13*). For the newer studies (1999-2016) included in our report, showing neurobehavioral effects and blood-sample based outcomes, the exposure concentration of N_2O ranged from 20 to 800 ppm.

Neither the Swedish survey (53;54) nor Rowlands two surveys (51;52), studying spontaneous abortion and fertility, measured the exposure concentration of N_2O. However, Rowland et al (52) highlighted the significance of scavenging systems showing that the risk of spontaneous abortion increased by only a 3 hours N_2O exposure per week in dental offices without scavenging systems, compared to the crude population working in a scavenged office. A recent report (16) compared different inhalation techniques and scavenging systems for use in children. They introduce two technical details which may contribute to reduce the level of waste gas: an on-demand mask, where there is no continuous flow of gas, but the delivery is controlled by a valve to only release the gas when the child inhales; and a scavenging system which consists of a tube leading the exhaled gas from the mask and outside the room. An effective scavenging system will include a pump to actively evacuate the waste gas from the mask system. Messeri et al (16) showed that more than an on-demand valve, the scavenging system is important for the concentration of waste gas in the room. While an on-demand valve used in connection with a Mapelson B respiratory circuit (for drawing, see http://www.creaghbrown.co.uk/anae/bc.htm) reduced the TWA of N_2O from 74.5 to 59.7 ppm, a double face mask, allowing a more effective scavenging system, reduced the TWA from 59.7 to 2.3 ppm (both latter systems used an on-demand valve). The mask and scavenging system used for children in Norway are more similar to the less effective scavenging system with on-demand valve (personal communication with AGA).

Outcomes

The included studies showed data on spontaneous abortion, infertility, effect on children born by exposed women, genetic toxicity, neurological or neurobehavioral effects or effects on B12 metabolism. As none of the studies were randomized, it was important to identify confounding factors. The most relevant factors that the authors had adjusted for, were age, smoking, shift-work, diseases, other toxins or drugs, as well as response rate for questionnaires. Meta-analyses was possible only for spontaneous abortion and infertility, but mainly non-adjusted numbers were used in our

analyses. The blood-based outcomes were small and for several, gave contradictory results.

Study design

Studies were either large retrospective surveys among dental personnel or midwives, or controlled studies from hospital or dental setting. None of the trials were blinded. For the studies reporting on the effect of N_2O on reproductive health, all collected data came from questionnaires, and all confounding factors were self-reported. This was the main reason why we assessed all the surveys based on retrospective questionnaires to have serious risk of bias, according to the ROBIN-I-tool.

Discussion of results

We found four systematic reviews analysing the effect of N_2O sedation in children where three of them concluded that there were insufficient data to draw any conclusions (20-22) while one review concluded a lower anterograde amnesia using N_2O compared to benzodiazepines (23). Our Health Technology Assessment had a broader perspective as we did not limit the searches to specific hospital procedures or comparative drugs. We were therefore able to include more studies in our analyses.

N_2O as an analgesic

We presented evidence that the patients experienced lower pain when N_2O was used as sedation method compared to other active drugs or no drugs. This suggests that although N_2O is mainly used as a sedation, it has also to some extent analgesic effects. The mechanism for this has been summarized by Sanders et al (4). However, we cannot conclude that the pain is considerably reduced compared to other standard analgesics as EMLA for small procedures where topical pain reduction is sufficient. The available evidence therefore suggests that N_2O can be used interchangeably with other relevant analgesics for short and painful hospital procedures for children, depending on the available resources.

N_2O for specific hospital procedures

The included studies mostly reported on ordinary and short lasting hospital procedures as venepuncture/venous cannulation, fracture reduction and laceration repair. We decided not to perform subgroup-analyses for the different hospital procedures covered by the studies due to that few results were reported as numbers with variation. In a systematic review by Pedersen et al (3) focusing on using N_2O for peripheral venous cannulation, lumbar puncture and intramuscular injection, N_2O were found to be suitable for all of them.

Safety for the children

Numerous adverse events were reported in 15 studies. Due to the low total number of both events (83 events divided on about thirty different types of events) and patients (525 patients) we were not able to draw any certain conclusion of which types of side effects were the most frequent using N_2O, or the odds ratio of the events using N_2O compared to the control group. The results show that N_2O can be used for sedation of children without serious adverse events.

Safety for health personnel exposed to N_2O as the only gas

N_2O effect on reproductive health

The most serious adverse effects that N_2O exposure has been suspected to cause, are spontaneous abortion, infertility or congenital abnormalities in children born by exposed women. These effects suggest damages to DNA although the mechanism and level is not known.

In our health technology assessment we found four articles with data on the effect of N_2O exposure on spontaneous abortion, three from a dental setting (49;51;70) and one from a maternity ward (54). The results show that the odds ratio for spontaneous abortion in women were not significantly different in any of the exposure groups compared to the unexposed group. None of the papers measured the concentration of N_2O in the room, but Rowland et al (52) suggested that in dental offices without scavenging equipment, exposure during administration of N_2O often exceeded 1000 ppm while the concentration may be lower in hospital operating rooms due to better mask systems and air exchange. Only one of the four studies on reproductive health (49) showed a significant increase in the odds ratio for both spontaneous abortions and congenital abnormalities in children born by exposed women. This study was a retrospective survey from a dental setting in the seventies, most probably without scavenging systems and poor room-ventilation. Further, a statistically significant decrease in fertility was shown (51;70), but only at high exposure of N_2O. All the studies used data collected by interviews or questionnaires mailed to women, implying a high risk of reporting bias. The certainty of the effect measure was therefore considered to be very low for both spontaneous abortion and congenital abnormalities in children. There was a dose-response for the fertility outcome and we upgraded this result to be of low certainty.

To understand the relevance of these results in a Norwegian paediatric setting, it is important to translate the difference between high and low exposures to N_2O concentrations in the room. This is challenging as none of the surveys presented data on actual concentrations. According to the information outlined previously (*Intervention – waste N2O exposure*), we suggest that working in a none-scavenging environment may will give N_2O concentrations from 1000-2000 ppm while with using scavenging systems the concentration may range from 20-800 ppm. However, for all practical purposes, level of exposure is related to the time exposed to a given concentration, shown by the international standard TWA, which relates to an 8 hour workday. For two of the studies, the number of deliveries using N_2O defined the high and

low exposure groups, while in other studies exposure hours per week was used to define the groups (*Table 12*). Estimating the TWA based on exposure time in a non-scavenged room when exposed 50% of the work day, will be 500-1000 ppm TWA, while with a scavenging system a similar calculation would suggest a TWA of 10-400 ppm. A nurse using N_2O for sedation in a paediatric setting in a Norwegian hospital where scavenging systems are used, will probably only be exposed maximally 2 hours per day suggesting a TWA of maximally 25 ppm, which is below the Norwegian TWA threshold level of 50 ppm. Using a more effective scavenging system as described in Messeri et al (16), may further reduce the exposure.

Neurological effects of N_2O

Only one of the included studies (50) showed data on neurological effects, and N_2O was shown to increase subjects experiencing numbness, tingling or muscle weakness. This study was from 1981, in a dental setting, and no information about scavenging systems were given. We therefore assume that also here the level of exposure will be far above the TWA threshold for Norway, and no results relevant in a Norwegian setting can be presented.

Blood-sample based outcomes

The included articles approaching the mutagenic effect of N_2O did not have comparable outcomes and conclusions were therefore difficult to draw. One study showed statistically significant increased micronuclei formation (57) but did not discuss the impact of the difference, or the level of N_2O exposure. Another study found a positive correlation between N_2O concentration and DNA damage (59;66), reactive oxygen species and oxidative stress (59). These studies showed the presence of other gases in the operating room, but we included them as the results were correlated to N_2O only. However, a synergistic or additive effect of the other gases could not be ruled out. The impact or downstream effect for the mutagenic effects, were not discussed.

In one study, B12 was decreased in operating theatre nurses exposed to a mean of 419 ppm at minimum 5 hours per day (61), which gives a TWA of 260 ppm. However, in three other studies, no differences in B12 metabolism markers were found. Although for some of the articles the concentration of N_2O was given, the exposure time was unclear and no dose-correlation could be made.

Hence, for none of the blood-sample based outcomes we were able to extract relevant conclusions to a paediatric setting in Norway.

Safety for health personnel exposed to anaesthetic gases where N_2O is a component

We decided to briefly look at the effect of anaesthetic gases or mixture of gases where N_2O was a constituent. All the data are presented in Appendix 8.

Wiesner et al (71) raises the problem of studying the isolated genotoxic effects of N2O in an anaesthetic setting, as the effect of other volatile anaesthetics, the challenge of comparing data from different combinations of anaesthetics as well as other

potential genotoxic agents in a hospital setting. This was our rational for not including all these studies in our data analyses. Rather we wanted to show the numerous articles often referred to as evidence for N_2O toxicity. Not surprisingly, without any evaluation of the quality of the studies or the certainty of the results, all six retrospective surveys from 1971-1975, show an increased odds ratio of spontaneous abortion in women exposed to waste gases. However, only two of ten of the studies from 1977-2015 showed the same effect. We suggests this to be due to increased awareness of the toxicity of anaesthetic waste gases and hence, also better ventilation or other types of reduction of waste gases, as for example mask design.

For blood-sample based tests, new and emerging methods have given the possibility to test genotoxicity and it will be interesting to see more studies to reveal the mechanism behind the toxicity of waste anaesthetic gases to understand potential long-term effects.

N_2O, a better choice?

We were not able to present solid results favouring N_2O over other active drugs or even placebo for neither satisfaction nor pain although, based on the presented results, we have reason to believe that N_2O is as good as the established analgesics. However, the results (from 5 studies) showed that the patients in the N_2O group needed shorter recovery time than when other active drugs were used. Further, although not documented in this report, shorter preparation time is expected in that the onset of effect is immediate, compared to for example EMLA which needs an onset time of 30 minutes. Total sedation time may therefore be the most important single advantage of N_2O. In accordance with the results shown in this report that personnel or patients were more satisfied with N_2O sedation than no sedation, nurses using N_2O for short procedures in Norway reports that the method is well appreciated by children who come repetitively for treatments which are painful. Happy children and parents also reduces the stress of health care personnel and should not be underestimated. Also, all studies on safety for health personnel included in this review are taken from either dental settings, operating theatres or maternity wards, suggesting an everyday, continuous exposure to N_2O. Using N_2O as sedation in children for small hospital procedures, the exposure will probably be a few times a week, each lasting for a maximum of 30 minutes (personal communication). This level of exposure will be far below any of the studies reporting adverse effects of N_2O.

Conclusion

The results show that nitrous oxide can be used for sedation of children without serious adverse events. The most noticeable advantage by using N_2O is the short restitution compared to other sedation methods which shortens the whole procedure and may streamline hospital procedures in children.

The present Health Technology Assessment shows that midwives and dental personnel exposed to N_2O compared to no exposure, did not increase the risk of spontaneous abortion or, at low exposure, reduced fertility. High exposure showed reduced fertility. The risk for congenital abnormalities born by exposed mothers (concentration or exposure degree not known) was higher than in non-exposed mothers. It is important to understand that these results are generated from data based on self-reporting questionnaires. Also, information about level of exposure was inadequate.

No sufficient evidence was shown to draw conclusions of the toxic effect of N_2O on DNA or cellular mechanisms.

There were no studies on negative effects on reproductive health for health personnel in a setting where N_2O was used for sedation of children for small hospital procedures. The personnel included in the present studies, were expected to have a more or less continuous exposure to N_2O during their work hours. For personnel working with N_2O sedation of children for small hospital procedures the exposure is expected to be significantly lower than the health care workers in the studies where toxic effects were reported, justified by two reasons. First, the concentration of N_2O is expected to be lower because the access to better scavenging and ventilation systems; and second, the net exposure time would be lower as the procedure time (maximum 30 minutes per procedure) and the number for the hospital procedures per health worker per week would be relatively few (personal communication).

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Appendix

Appendix 1. Glossary

ASA	American Society of Anaesthesiologists
EMLA	Eutectic mixture of local anaesthetic cream with lidocaine and procaine, cutaneous application
EMONO	Equimolecular mixture of oxygen and nitrous oxide
FDA	U.S. Food and Drug Administration

Methods and scales used for different outcomes

Scale	Explanation	Reference
For pain		
VAS	Visual analogue pain scale. Score: 0-10 cm or 0-100 mm, where 10/100 is the highest pain.	Original reference not found (72)
CHEOPS	Children's Hospital of Eastern Ontario Pain Scale. The scale includes behavioural and verbal measures of pain. Score: 1-13, where 13 is the most intense pain. In some papers 4< is considered without pain, while others use <6 as the limit.	(73)
FLACC/ LLANTO	FLACC: Face, Legs, Activity, Cry, Consolability. A measurement used to assess pain for children between the ages of 2 months and 7 years or individuals that are unable to communicate their pain. LLANTO: Spanish version of an observational pain scale using observation of crying, attitude, respiratory pattern, muscle tone and facial expression. Score for each of the criteria: 0–2, giving a total of 10 points. Higher score, higher distress/pain.	(74)

Wong Baker Faces Pain Scale	Pain severity. Scale: 0-10: 10=worst pain; 7-9=severe pain; 4-6=moderate pain; 1-3=mild pain; 0=no pain	(75)
PIPP	Premature Infant Pain Profile. A multidimensional composite pain score developed and validated in clinical settings used for evaluating acute procedural pain in preterm neonates. It measures seven different elements including physiological parameters, facial expression, behaviour and gestational age. Scale for each elements: 0-3 giving a total of 21 points, where 21 is the maximum pain.	(76)
For procedure satisfaction		
OSBD-R	Observational Scale of Behavioural Distress-Revised. The scale includes 8 behaviours (information seeking, cry, scream, restraint, verbal resistance, emotional support, verbal pain, and flail). Score: each behaviour is scored from 0 to 23. Higher score, higher distress.	(77)
Other scales		

Appendix 2. Search strategy and result

Search for:	2015_049 Nitrous oxide for sedation of children: search strategies and log
Date run:	24. August, 2017 (for nitrous oxide for sedation of children) 20. November, 2017 (for occupational safety)
Databases:	Paediatric sedation: Cochrane Library, Centre for Reviews and Dissemination, Embase, Epistomonikos, MEDLINE, PubMed Occpuational safety: Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present, Embase 1974 to 2017 November 20
Other sources:	Paediatric sedation: SveMed+, Clinical Trials, Inernational Clinical Trials Registry Platform
Total unique hits:	Paediatric sedation: 2509 Occupational safety: 557
Searched by:	Elisabeth Hafstad

Summary of search

Search source	Hits
Systematic reviews and HTA – paediatric sedation	
Cochrane Database of Systematic Reviews	11
Database of Abstracts of Reviews of Effect (via Cochrane Library)	19
Centre for Reviews and Dissemination - HTA	1
Embase	85
Epistemonikos	27
MEDLINE	60
PubMed	3
Total	206
Total unique hits, systematic reviews and HTA	**159**
RCTs – paediatric sedation	
Cochrane Central Register of Controlled Trials	1814
Embase	622
MEDLINE	1406
PubMed	31
SveMed+	11
Total	3884
Total unique hits, RCTs	**2213**

Ongoing, completed and terminated trials – paediatric sedation	
Clinical Trials (National Institute of Health)	75
International Clinical Trials Registry Platform (ICTRP)	62
Total unique hits, clinical trials	**137**
Primary studies – occupational safety	
Databases (see below)	557
Hand search	39
Total hits, occupational safety	**596**

* MEDLINE and Embase hits after deduplication in OVID. (Federated search)

Search strategies for paediatric sedation

Cochrane Library

Hits: 30 (Cochrane Reviews: 11; Database of abstracts of reviews of effect: 19)
1814 (Trials)
Search strategy:

Cochrane Database of Systematic Reviews (Reviews), Trials:
(((([mh ^"Nitrous Oxide"]) OR (Livopan OR Entonox OR Kalinox OR Nitronox OR Anesoxyn-50 OR Eutonal OR Nitralgin OR ALnox OR Liqui-Med OR EMONO OR nitrous-oxide OR nitrious-oxide OR (dinitrogen NEXT (monoxide OR oxide)) OR hyponitrous-acid-anhydride OR laughing-gas OR (nitrogen NEXT (hypoxide OR monoxide OR oxide OR protoxide)) OR N2O OR "N(2)O"):ab,kw,ti) AND (([mh Infant] OR [mh Child] OR [mh ^Adolescent] OR [mh Pediatrics] OR [mh ^"Child Health"] OR [mh ^"Child Health Services"]) OR (infant* OR infancy OR newborn* OR new-born* OR baby* OR babies OR neonat* OR neo-nat* OR preterm* OR pre-term* OR prematur* OR pre-matur* OR postmatur* OR post-matur* OR toddler* OR child* OR kid or kids OR boy OR boys OR girl* OR adolesc* OR teen* OR pubert* OR pubescen* OR prepubescen* OR pre-pubescen* OR youngster* OR young-person* OR young-people* OR youth OR schoolchild* OR school age* OR schoolage* OR preschool* OR pre-school* OR schooler* OR nursery-school* OR kindergar* OR primary-school* OR secondary-school* OR elementary-school* OR middle-school* OR high-school* OR highschool* OR paediatric* OR pediatric* OR juvenile* OR minors OR under-age* OR underage*):ab,kw,ti)))
Other Reviews:
(((([mh ^"Nitrous Oxide"]) OR (Livopan OR Entonox OR Kalinox OR Nitronox OR Anesoxyn-50 OR Eutonal OR Nitralgin OR ALnox OR Liqui-Med OR EMONO OR nitrous-oxide OR nitrious-oxide OR (dinitrogen NEXT (monoxide OR oxide)) OR hyponitrous-acid-anhydride OR laughing-gas OR (nitrogen NEXT (hypoxide OR monoxide OR oxide OR protoxide)) OR N2O OR "N(2)O")) AND (([mh Infant] OR [mh Child] OR [mh ^Adolescent] OR [mh Pediatrics] OR [mh ^"Child Health"] OR [mh ^"Child Health Services"]) OR (infant* OR infancy OR newborn* OR new-born* OR baby* OR babies OR neonat* OR neo-nat* OR preterm* OR pre-term* OR prematur* OR pre-matur*

OR postmatur* OR post-matur* OR toddler* OR child* OR kid or kids OR boy OR boys OR girl* OR adolesc* OR teen* OR pubert* OR pubescen* OR prepubescen* OR pre-pubescen* OR youngster* OR young-person* OR young-people* OR youth OR schoolchild* OR school age* OR schoolage* OR preschool* OR pre-school* OR schooler* OR nursery-school* OR kindergar* OR primary-school* OR secondary-school* OR elementary-school* OR middle-school* OR high-school* OR highschool* OR paediatric* OR pediatric* OR juvenile* OR minors OR under-age* OR underage*))))

Centre for Reviews and Dissemination (University of York)

Hits: 1

Search strategy:

(((MeSH DESCRIPTOR Nitrous Oxide) OR (Livopan OR Entonox OR Kalinox OR Nitronox OR Anesoxyn-50 OR Eutonal OR Nitralgin OR ALnox OR Liqui-Med OR EMONO OR nitrous-oxide OR nitrious-oxide OR (dinitrogen AND (monoxide OR oxide)) OR hyponitrous-acid-anhydride OR laughing-gas OR (nitrogen AND (hypoxide OR monoxide OR oxide OR protoxide)) OR N2O)) AND (((MeSH DESCRIPTOR Infant EXPLODE ALL TREES) OR (MeSH DESCRIPTOR Child EXPLODE ALL TREES) OR (MeSH DESCRIPTOR Adolescent) OR (MeSH DESCRIPTOR Pediatrics EXPLODE ALL TREES) OR (MeSH DESCRIPTOR Child Health) OR (MeSH DESCRIPTOR Child Health Services)) OR (infant* OR infancy OR newborn* OR newborn* OR baby* OR babies OR neonat* OR neo-nat* OR preterm* OR pre-term OR prematur* OR pre-matur* OR postmatur* post-matur* OR toddler* OR child OR children* OR kid OR kids OR boy OR boys OR girl* OR adolesc* OR teen* OR pubert* OR pubescen* OR prepubescen* OR pre-pubescen* OR youngster* OR young person* OR young people* OR youth OR schoolchild* OR school-age* OR school-age* OR preschool* OR pre-school* OR schooler* OR nursery school* OR kindergar* OR primary school* OR secondary school* OR elementary school* OR middle school* OR high-school* OR highschool* OR paediatric* OR pediatric* OR juvenile* OR minors OR under-age* OR underage*))) IN HTA

Embase

Hits: 85 – Systematic reviews and HTA
622 – RCTs

Search strategy:

Embase 1974 to August 24, 2017

1	Nitrous Oxide/
2	(Livopan or Entonox or Kalinox or Nitronox or Anesoxyn-50 or Eutonal or Nitralgin or ALnox or Liqui-Med).tw,kw.
3	EMONO.tw,kw.
4	(nitrous oxide or nitrious oxide).tw,kw.

5	(dinitrogen adj (monoxide or oxide)).tw,kw
6	hyponitrous acid anhydride.tw,kw.
7	laughing gas.tw,kw.
8	(nitrogen adj (hypoxide or monoxide or oxide or protoxide)).tw,kw
9	(N2O or "N(2)O").tw,kw.
10	10024-97-2.rn.
11	exp Child/
12	exp Adolescent/
13	exp Pediatrics/
14	exp Child Health/
15	exp Child Health Care/
16	Juvenile/
17	(infant* or infancy or newborn* or new-born* or baby* or babies or neonat* or neo-nat*).tw,kw.
18	(preterm* or pre-term* or prematur* or pre-matur* or postmatur* or post-matur*).tw,kw.
19	(toddler* or child or children* or kid or kids).tw,kw.
20	(boy or boys or girl*).tw,kw.
21	(adolesc* or teen* or pubert* or pubescen* or prepubescen* or pre-pubescen*).tw,kw.
22	(youngster* or young person* or young people* or youth).tw,kw.
23	(schoolchild* or school age* or schoolage* or schooler*).tw,kw.
24	(preschool*or pre-school* or nursery school* or kindergar* or primary school* or secondary school* or elementary school* or middle school* or high-school* or highschool*).tw,kw.
25	(paediatric* or pediatric*).tw,kw.
26	juvenile*.tw,kw.
27	(minors or under-age* or underage*).tw,kw.
28	(or/1-10) and (or/11-27)
29	Meta-Analysis/ or Systematic Review/ or "Meta Analysis (topic)"/ or "Systematic Review (topic)"/ or Biomedical Technology Assessment/ or ((systematic* adj3 (review* or overview*)) or (methodologic* adj3 (review* or overview*))).ti,ab,kw. or ((quantitative adj3 (review* or overview* or synthes*))

	or (research adj3 (integrati* or overview*))).ti,ab,kw. or ((integrative adj3 (review* or overview*)) or (collaborative adj3 (review* or overview*)) or (pool* adj3 analy*)).ti,ab,kw. or (data synthes* or data extraction* or data abstraction*).ti,ab,kw. or (handsearch* or hand search*).ti,ab,kw. or (mantel haenszel or peto or der simonian or dersimonian or fixed effect* or latin square*).ti,ab,kw. or (met analy* or metanaly* or technology assessment* or HTA or HTAs or technology overview* or technology appraisal*).ti,ab,kw. or (meta regression* or metaregression*).ti,ab,kw. or (meta-analy* or metaanaly* or systematic review* or biomedical technology assessment* or biomedical technology assessment*).mp,hw. or (medline or cochrane or pubmed or medlars or embase or cinahl).ti,ab,hw. or (cochrane or (health adj2 technology assessment) or evidence repORt).jx. or (comparative adj3 (efficacy or effectiveness)).ti,ab,kw. or (outcomes research or relative effectiveness).ti,ab,kw. or ((indirect or indirect treatment or mixed-treatment) adj comparison*).ti,ab,kw. use oemezd [CADTH filter for systemic reviews and HTA in Embase]
30	Controlled Clincal Trial/ or "Randomized Controlled Trial (topic)"/ or Randomized Controlled Trial/ or Randomization/ or Double Blind Procedure/ or Single Blind Procedure/ or Placebo/ or (random* or sham or placebo*).ti,ab,hw,kw. or ((singl* or doubl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw. or ((tripl* or trebl*) adj (blind* or dumm* or mask*)).ti,ab,hw,kw. use oemezd [CADTH filter for randomized controlled studies in Embase]
31	28 and 29 [SR/HTA]
32	28 and 30 [RCT]

Epistemonikos

Hits: 27 (Broad Synthesis: 0; Structured summary: 2; Systematic review: 25)

Search strategy:

[Advanced Search - Title/Abstract:]
((Livopan OR Entonox OR Kalinox OR Nitronox OR "Anesoxyn-50" OR Eutonal OR Nitralgin OR ALnox OR Liqui-Med OR EMONO OR "nitrous oxide" OR "nitrious oxide" OR "dinitrogen monoxide" OR "dinitrogen oxide" OR "hyponitrous acid anhydride" OR "laughing gas" OR "nitrogen hypoxide" OR "nitrogen monoxide" OR "nitrogen oxide" OR "nitrogen protoxide" OR N2O OR "N(2)O") AND (infant* OR infancy OR newborn* OR new-born* OR baby* OR babies OR neonat* OR neo-nat* OR preterm* OR pre-term OR prematur* OR pre-matur* OR postmatur* post-matur* OR toddler* OR child OR children* OR kid OR kids OR boy OR boys OR girl* OR adolesc* OR teen* OR pubert*

OR pubescen* OR prepubescen* OR pre-pubescen* OR youngster* OR "young person" OR "young persons" OR "young people" OR youth OR schoolchild* OR school-age* OR schoolage* OR preschool* OR pre-school* OR schooler* OR "nursery school" OR "nursery schools" OR kindergar* OR "primary school" OR "primary schools" OR "secondary school" OR "secondary schools" OR "elementary school" OR "elementary schools" OR "middle school" OR "middle schools" OR "high school "OR "high schools" OR highschool* OR high-school* OR paediatric* OR pediatric* OR juvenile* OR minors OR under-age* OR underage*))

MEDLINE

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present

Hits: 60 – Systematic Review/HTA
1406 – RCT
Search strategy:

1. ((((Nitrous Oxide/) OR (Livopan OR Entonox OR Kalinox OR Nitronox OR Anesoxyn-50 OR Eutonal OR Nitralgin OR ALnox OR Liqui-Med OR EMONO OR nitrous oxide OR nitrious oxide OR (dinitrogen ADJ (monoxide OR oxide)) OR hyponitrous acid anhydride OR laughing gas OR (nitrogen ADJ (hypoxide OR monoxide OR oxide OR protoxide)) OR N2O OR "N(2)O").tw,kf OR (K50XQU1029 OR N01A X13 OR 10024-97-2 OR 233-032-0).rn) AND ((exp Infant/ OR exp Child/ OR Adolescent/ OR exp Pediatrics/ OR Child Health/ OR Child Health Services/) OR (infant* OR infancy OR newborn* OR new-born* OR baby* OR babies OR neonat* OR neo-nat* OR preterm* OR pre-term* OR prematur* OR pre-matur* OR postmatur* OR post-matur* OR toddler* OR child OR children* OR kid or kids OR boy OR boys OR girl* OR adolesc* OR teen* OR pubert* OR pubescen* OR prepubescen* OR pre-pubescen* OR youngster* OR young person* OR young people* OR youth OR schoolchild* OR school age* OR schoolage* OR preschool* OR pre-school* OR schooler* OR nursery school* OR kindergar* OR primary school* OR secondary school* OR elementary school* OR middle school* OR high-school* OR highschool* OR paediatric* OR pediatric* OR juvenile* OR minors OR under-age* OR underage*).tw,kf))) use ppez
2. ((exp "Meta-Analysis as Topic"/ OR Technology Assessment, Biomedical/) OR meta-analysis.pt OR ((systematic* ADJ3 (review* OR overview*)) OR (methodologic* ADJ3 (review* OR overview*))).ti,ab,kf,kw. OR ((quantitative ADJ3 (review* OR overview* OR synthes*)) OR (research ADJ3 (integrati* OR overview*))).ti,ab,kf,kw. OR ((integrative ADJ3 (review* OR overview*)) OR (collaborative ADJ3 (review* OR overview*)) OR (pool* ADJ3 analy*)).ti,ab,kf,kw. OR (data synthes* OR data extraction* OR data abstraction*).ti,ab,kf,kw. OR (handsearch* OR hand search*).ti,ab,kf,kw. OR (mantel haenszel OR peto OR der simonian OR dersimonian OR fixed effect* OR

latin square*).ti,ab,kf,kw. OR (met analy* OR metanaly* OR technology assessment* OR HTA OR HTAs OR technology overview* OR technology appraisal*).ti,ab,kf,kw. OR (meta regression* OR metaregression*).ti,ab,kf,kw. OR (meta-analy* OR metaanaly* OR systematic review* OR biomedical technology assessment* OR bio-medical technology assessment*).mp,hw. OR (medline OR cochrane OR pubmed OR medlars OR embase OR cinahl).ti,ab,hw. OR (cochrane OR (health ADJ2 technology assessment) OR evidence report).jw. OR (comparative ADJ3 (efficacy OR effectiveness)).ti,ab,kf,kw OR (outcomes research OR relative effectiveness).ti,ab,kf,kw. OR ((indirect OR indirect treatment OR mixed-treatment) ADJ comparison*).ti,ab,kf,kw.) use ppez [CADTH filter for systematic reviews and HTA in MEDLINE]

3. (Randomized Controlled Trial.pt OR Pragmatic Clinical Trial.pt OR Controlled Clinical Trial.pt OR (exp "Randomized Controlled Trials as Topic"/ OR Random allocation/ OR Double-Blind Method/ OR Single-Blind Method/ OR Placebos/) OR (random* OR sham OR placebo*).ti,ab,kf,kw. OR ((singl* OR doubl*) ADJ (blind* OR dumm* OR mask*)).ti,ab,kf,kw. OR ((tripl* OR trebl*) ADJ (blind* OR dumm* OR mask*)).ti,ab,kf,kw.) use ppez [CADTH filter for randomized controlled trials in MEDLINE]
4. 1 and 2 [SR/HTA in MEDLINE]
5. 1 and 3 [RCT in MEDLINE]

PubMed

Hits: 3 – Systematic reviews and HTA
31 – RCT

Search strategy:

#1 ((((("Nitrous Oxide"[mh:noexp]) OR (Livopan[tiab] OR Entonox[tiab] OR Kalinox[tiab] OR Nitronox[tiab] OR Anesoxyn-50[tiab] OR Eutonal[tiab] OR Nitralgin[tiab] OR ALnox[tiab] OR Liqui-Med[tiab] OR EMONO[tiab] OR nitrous-oxide[tiab] OR nitrious-oxide[tiab] OR dinitrogen-monoxide[tiab] OR dinitrogen-oxide[tiab] OR hyponitrous-acid-anhydride[tiab] OR laughing-gas[tiab] OR nitrogen hypoxide[tiab] OR nitrogen-monoxide[tiab] OR nitrogen-oxide[tiab] OR nitrogen-protoxide[tiab] OR N2O[tiab] OR "N(2)O"[tiab])) AND (("Infant"[mh] OR "Child"[mh] OR "Adolescent"[mh:noexp] OR "Pediatrics"[mh] OR "Child Health"[mh:noexp] OR "Child Health Services"[mh:noexp]) OR (infant*[tiab] OR infancy[tiab] OR newborn*[tiab] OR new-born*[tiab] OR baby*[tiab] OR babies[tiab] OR neonat*[tiab] OR neo-nat*[tiab] OR preterm*[tiab] OR pre-term[tiab] OR prematur*[tiab] OR pre-matur*[tiab] OR postmatur*[tiab] post-matur*[tiab] OR toddler*[tiab] OR child[tiab] OR children*[tiab] OR kid[tiab] OR kids[tiab] OR boy[tiab] OR boys[tiab] OR girl*[tiab] OR adolesc*[tiab] OR teen*[tiab] OR pubert*[tiab] OR pubescen*[tiab] OR prepubescen*[tiab] OR pre-pubescen*[tiab] OR youngster*[tiab] OR young-person*[tiab] OR young-people*[tiab] OR youth[tiab] OR schoolchild*[tiab] OR school-age*[tiab] OR schoolage*[tiab]

OR preschool*[tiab] OR pre-school*[tiab] OR schooler*[tiab] OR nursery-school*[tiab] OR kindergar*[tiab] OR primary-school*[tiab] OR secondary-school*[tiab] OR elementary-school*[tiab] OR middle-school*[tiab] OR high-school*[tiab] OR highschool*[tiab] OR paediatric*[tiab] OR pediatric*[tiab] OR juvenile*[tiab] OR minors[tiab] OR under-age*[tiab] OR under-age*[tiab]))) AND (publisher[sb] OR pubmednotmedline[sb]))
#2 systematic[sb] OR meta-analysis[pt] OR "meta-analysis as topic"[mh] OR "meta-analysis"[mh] OR meta analy*[tw] OR metanaly*[tw] OR metaanaly*[tw] OR met-analy*[tw] OR integrative-research[tiab] OR integrative-review*[tiab] OR integrative-overview*[tiab] OR research-integration*[tiab] OR research-overview*[tiab] OR collaborative-review*[tiab] OR collaborative-overview*[tiab] OR systematic-review*[tiab] OR technology-assessment*[tiab] OR technology-overview*[tiab] OR "Technology Assessment, Biomedical"[mh] OR HTA[tiab] OR HTAs[tiab] OR comparative-efficacy[tiab] OR comparative-effectiveness[tiab] OR outcomes-research[tiab] OR indirect-comparison*[tiab] OR ((indirect-treatment[tiab] OR mixed-treatment[tiab]) AND comparison*[tiab]) OR Embase*[tiab] OR Cinahl*[tiab] OR systematic-overview*[tiab] OR methodological-overview*[tiab] OR methodologic-overview*[tiab] OR methodological-review*[tiab] OR methodologic-review*[tiab] OR quantitative-review*[tiab] OR quantitative-overview*[tiab] OR quantitative-synthes*[tiab] OR pooled-analy*[tiab] OR Cochrane[tiab] OR Medline[tiab] OR Pubmed[tiab] OR Medlars[tiab] OR handsearch*[tiab] OR hand-search*[tiab] OR meta-regression*[tiab] OR metaregression*[tiab] OR data-synthes*[tiab] OR data-extraction[tiab] OR data-abstraction*[tiab] OR mantel-haenszel[tiab] OR peto[tiab] OR der-simonian[tiab] OR dersimonian[tiab] OR fixed-effect*[tiab] OR "Cochrane Database Syst Rev"[Journal] OR "health technology assessment winchester, england"[Journal] OR "Evid Rep Technol Assess (Full Rep)"[Journal] OR "Evid Rep Technol Assess (Summ)"[Journal] OR "Int J Technol Assess Health Care"[Journal] OR "GMS Health Technol Assess"[Journal] OR "Health Technol Assess (Rockv)"[Journal] OR "Health Technol Assess Rep"[Journal]
#3 (randomized controlled trial[pt] OR controlled clinical trial[pt] OR "randomized controlled trials as topic"[mh] OR "random allocation"[mh] OR "double-blind method"[mh] OR "single-blind method"[mh] OR random*[tw] OR "Placebos"[mh] OR placebo[tiab] OR ((singl*[tw] OR doubl*[tw] OR trebl*[tw] OR tripl*[tw]) AND (mask*[tw] OR blind*[tw] OR dumm*[tw])))
#4 #1 and #2
#5 #1 and #3

SveMed+

Hits: 11
Search strategy:

noexp:"Nitrous Oxide" AND (exp:"Children" OR exp: "Infant" OR noexp:"Adolescent" OR exp:"Pediatrics" OR noexp:"Child Health" OR noexp:"Child Health Services")

Clinical Trials (US)

Hits: 75
Search strategy:

(10024-97-2 OR Livopan OR Entonox OR Kalinox OR Nitronox OR Anesoxyn-50 OR Eutonal OR Nitralgin OR ALnox OR Liqui-Med OR EMONO OR nitrous oxide OR laughing gas)
Filters:
Group: Children (birth – 17)

International Clinical Trials Registry Platform

Hits: 62
Search strategy:

10024-97-2 AND newborn OR Livopan AND newborn OR Entonox AND newborn OR Kalinox AND newborn OR EMONO AND newborn OR nitrous oxide AND newborn OR N2O AND newborn OR laughing gas AND newborn OR 10024-97-2 AND infan* OR Livopan AND infan* OR Entonox AND infan* OR Kalinox AND infan* OR EMONO AND infan* OR nitrous oxide AND infan* OR N2O AND infan* OR laughing gas AND infan* OR 10024-97-2 AND child* OR Livopan AND child* OR Entonox AND child* OR Kalinox AND child* OR EMONO AND child* OR nitrous oxide AND child* OR N2O AND child* OR laughing gas AND child* OR 10024-97-2 AND adolescen* OR Livopan AND adolescen* OR Entonox AND adolescen* OR Kalinox AND adolescen* OR EMONO AND adolescen* OR nitrous oxide AND adolescen* OR N2O AND adolescen* OR laughing gas AND adolescen* OR 10024-97-2 AND pediatric* OR Livopan AND pediatric* OR Entonox AND pediatric* OR Kalinox AND pediatric* OR EMONO AND pediatric* OR nitrous oxide AND pediatric* OR N2O AND pediatric* OR laughing gas AND pediatric* OR 10024-97-2 AND paediatric* OR Livopan AND paediatric* OR Entonox AND paediatric* OR Kalinox AND paediatric* OR EMONO AND paediatric* OR nitrous oxide AND paediatric* OR N2O AND paediatric* OR laughing gas AND paediatric* OR Nitronox OR Anesoxyn-50 OR Eutonal OR Nitralgin OR ALnox OR Liqui-Med

Search strategy for occupational exposure

Databases

Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present,
Embase 1974 to 2017 November 20

Hits: 557
Search strategy:

1	Nitrous Oxide/ or (Livopan or Entonox or Kalinox or Nitronox or Anesoxyn-50 or Eutonal or Nitralgin or ALnox or Liqui-Med).ti,kw,kf. or EMONO.ti,kw,kf. or (nitrous oxide or N2O or "N(2)O").ti,kw,kf.
2	Occupational exposure/ or ((occupation* or work* or personnel or professional* or long term or staff or practitioner* or provider* or anesthesist* or anaesthesist* or anesthetist* or anaesthetist* or anesthesiologist* or anaesthesiologist* or physician* or nurse* or midwife or midwives or dentist*) and (expos* or hazard*)).ti,kw,kf.
3	1 and 2
4	remove duplicates from 3

Hand search

Hits: 39
We searched for literature also concerning exposure to general anaesthetics in the retrieved papers.

Appendix 3. Simplified template for ROBINS-I risk of bias assessment tool

Simplified version of ROBINS-I assessment tool (The Risk Of Bias In Non-randomized Studies – of Interventions) (version for cohort-type studies)

By Torunn E Tjelle, March 2018

Instruction

This template for assessing risk of bias of non-randomized studies is based on the ROBINS-I-tool (The Risk Of Bias In Non-randomized Studies – of Interventions, https://sites.google.com/site/riskofbiastool//welcome/home). The introducing description of the studies are not included in this template as it is expected that a table of characteristic already have been made at this stage.

Compared to the original tool, instead of spelling out all questions and asking for yes and no answers, this template only gives a guide to which questions should be considered. All headings from the ROBINS-I tool are covered.

As for the ROBINS-I tool, each heading should conclude with *Low, Moderate, Serious* or *Critical* risk of bias. If further support for the decision is needed (other than the table of characteristics), use the *result* field.

When answering the questions, a yes to green questions will favour **low** bias, while a yes to red questions will favour **critical** bias.

Template

Type of tool	Simplified version of ROBINS-I assessment tool (The Risk Of Bias In Non-randomized Studies – of Interventions) (version for cohort-type studies)
Paper ID	
Reviewer	

Bias due to confounding	**Result**
Is there potential for confounding of the effect of intervention in this study? Consider: - Is it mentioned in the analyses whether the confounding factors are corrected for, and was it an appropriate analyses method?*	Low / Moderate / Serious / Critical / No information
Optional, if more help is needed on confounding:	
If the analysis was based on splitting participants' follow up time according to intervention received (baseline confounding), consider: - Did the authors use an appropriate analysis method that controlled for all the important confounding domains? - Did the authors control for any post-intervention variables that could have been affected by the intervention?	Low / Moderate / Serious / Critical / No information
If the intervention discontinues or switches and this is likely to be related to factors that are prognostic for the outcome (baseline and time-varying confounding), consider: - Did the authors use an appropriate analysis method that controlled for all the important confounding domains and for time-varying confounding? - Were confounding domains that were controlled for measured validly and reliably by the variables available in this study?	Low / Moderate / Serious / Critical / No information
Optional: What is the predicted direction of bias due to confounding?	Favours experimental / Favours comparator / Unpredictable
Bias in selection of participants into the study	**Result**
Was selection of participants into the study (or into the analysis) based on participant characteristics observed after the start of intervention? Consider: - Were the post-intervention variables that influenced selection likely to be associated with intervention? - Were the post-intervention variables that influenced selection likely to be influenced by the outcome or a cause of the outcome? - Do start of follow-up and start of intervention coincide for most participants? - Were adjustment techniques used that are likely to correct for the presence of selection biases?	Low / Moderate / Serious / Critical / No information
Optional: What is the predicted direction of bias due to selection of participants into the study?	Favours experimental / Favours comparator / Towards

	null /Away from null / Unpredictable
Bias in classification of interventions	**Result**
Consider: - Were intervention groups clearly defined? - Was the information used to define intervention groups recorded at the start of the intervention? - Could classification of intervention status have been affected by knowledge of the outcome or risk of the outcome?	Low / Moderate / Serious / Critical / No information
Optional: What is the predicted direction of bias due to classification of interventions?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Bias due to deviations from intended interventions	**Result**
If the aim for this study is to assess the effect of assignment to intervention, consider: - Were there deviations from the intended intervention beyond what would be expected in usual practice? - If yes, were these deviations from intended intervention unbalanced between groups *and* likely to have affected the outcome?	Low / Moderate / Serious / Critical / No information
If the aim for this study is to assess the effect of starting and adhering to intervention, consider: - Were important co-interventions balanced across intervention groups? - Was the intervention implemented successfully for most participants - Did study participants adhere to the assigned intervention regimen? If no: - Was an appropriate analysis used to estimate the effect of starting and adhering to the intervention?	Low / Moderate / Serious / Critical / No information
Optional: What is the predicted direction of bias due to deviations from the intended interventions?	Favours experimental / Favours comparator / Unpredictable
Bias due to missing data	**Result**
Consider: - Were outcome data available for all, or nearly all, participants? - Were participants excluded due to missing data on intervention status? - Were participants excluded due to missing data on other variables needed for the analysis? If no: - Are the proportion of participants and reasons for missing data similar across interventions? - Is there evidence that results were robust to the presence of missing data?	Low / Moderate / Serious / Critical / No information
Optional: What is the predicted direction of bias due to missing data?	Favours experimental / Favours comparator / Towards

	null /Away from null / Unpredictable
Bias in measurement of outcomes	**Result**
Consider: - Could the outcome measure have been influenced by knowledge of the intervention received? - Were outcome assessors aware of the intervention received by study participants? - Were the methods of outcome assessment comparable across intervention groups? - Were any systematic errors in measurement of the outcome related to intervention received?	Low / Moderate / Serious / Critical / No information
Optional: What is the predicted direction of bias due to measurement of outcomes?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Bias in selection of the reported results	**Result**
Consider: - Is the reported effect estimate likely to be selected, on the basis of the results, from o multiple outcome *measurements* within the outcome domain o multiple *analyses* of the intervention-outcome relationship? o different *subgroups*?	Low / Moderate / Serious / Critical / No information
Optional: What is the predicted direction of bias due to selection of the reported result?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable
Overall risk of bias	Low / Moderate / Serious / Critical / No information
Optional: What is the overall predicted direction of bias for this outcome?	Favours experimental / Favours comparator / Towards null /Away from null / Unpredictable

Appendix 4. Excluded articles

Excluded randomized controlled trials for N_2O sedation in children

	Excluded randomized controlled trials	Rational for exclusion
1.	Gregory P, Sullivan J. Nitrous oxide compared with intravenous regional anesthesia in pediatric forearm fracture manipulation. Journal of pediatric orthopedics 1996;16(2):187-91.	Concentration of N_2O is not given.
2.	Lembert N, Wodey E, Geslot D, Ecoffey C. Prevention of pain on injection with propofol in children: comparison of nitrous oxide with lidocaine. Annales francaises d'anesthesie ET de reanimation 2002;21(4):263-70.	The children will undergo surgery procedures and the N_2O sedation is only pain relieve to achieve general anaesthesia.
3.	Ekbom K, Jakobsson J, Marcus C. Nitrous oxide inhalation is a safe and effective way to facilitate procedures in paediatric outpatient departments. Archives of disease in childhood 2005;90(10):1073-6.	Titration of N_2O, from 33% and up.
4.	Zier J, Rivard P, Krach L, Wendorf H. Effectiveness of sedation using nitrous oxide compared with enteral midazolam for botulinum toxin A injections in children. Developmental medicine and child neurology 2008;50(11):854-8.	Titration of N_2O. Not possible to say which concentration is effective.
5.	Reinoso-Barbero F, Pascual SI, Garcia S, De Lucas R, Billoet C. Pain relief management by 50% nitrous oxide/oxygen (KalinoxTM) for short-time painful procedures in paediatrics patients. European Journal of Pain 2009;13:S42.	Abstract only.
6.	Kwak H-J, Chae Y, Lee S, Kim Y, Kim J-Y. Combination of nitrous oxide and lidocaine to prevent withdrawal after rocuronium in children. Korean journal of anesthesiology 2010;58(5):446-9.	Preparation for general anaesthesia (Rocuronium injection) and forced mask. Probably also loss of consciousness.
7.	Ben-Meir D, Livne P, Feigin E, Djerassi R, Efrat R. Meatotomy using local anesthesia and sedation or general anesthesia with or without penile block in children: a prospective randomized study. Journal of urology 2011;185(2):654-7.	Comparator is general anaesthesia.
8.	Gutierrez B, Casero T, Vallejo R, Garcia I, Morcillo J. Valuation of the effectiveness of the nitrous oxide administration to the paediatric patient during channelling a peripheral venous [sic] [Spanish]. Nure investigacion 2011;(50).	Describes a design of a study, no results.
9.	Johnston C. Equimolar nitrous oxide/oxygen versus placebo for procedural pain in children: A randomized trial: Reinoso-Barbero F, Pascual-Pascual SI, de Lucal R, et al. Pediatrics 2011;127:e1464-70. Journal of emergency medicine 2011;41(3):344-5.	Abstract only. Comment to Reinoso-Barbero F, Pediatrics 2011;127(6):e1464-70.

	Excluded randomized controlled trials	Rational for exclusion
10.	Ekbom K, Kalman S, Jakobsson J, Marcus C. Effects of midazolam and nitrous oxide on endocrine and metabolic measurements in children. Hormone research in paediatrics 2012;77(5):309-19.	Control group not part of the study.
11.	Kehar M, Yadav S, Sachdeva A, Gupta S. Nitrous oxide is as effective as ketamine-midazolam sedation for procedure related pain in children with cancer. Pediatric blood & cancer 2012;59(6):1117.	Abstract only.
12.	Duchicela SI, Meltzer JA, Cunningham SJ. A randomized controlled study in reducing procedural pain and anxiety using high concentration nitrous oxide. American Journal of Emergency Medicine 2017;1:01.	Titrated N_2O from 30-70%.

Excluded systematic reviews for N2O sedation in children

	Excluded systematic reviews	Rational for exclusion
1.	Tobias JD. Tolerance, withdrawal, and physical dependency after long-term sedation and analgesia of children in the pediatric intensive care unit. Critical Care Medicine 2000;28(6):2122-32.	Full text is not read, as it is not found. However, only one person cannot write a systematic review.
2.	Faddy SC, Garlick SR. A systematic review of the safety of analgesia with 50% nitrous oxide: can lay responders use analgesic gases in the prehospital setting? Emergency medicine journal : EMJ 2005;22(12):901-8.	Only three of the studies includes children. Uncertain hospital setting and personnel.
3.	Agarwal A. Neonatal pain in surgical neonate. Journal of Neonatology 2006;20(4):363-76.	Full text is not read, as it is not found. However, only one person cannot write a systematic review.
4.	Migita RT, Klein EJ, Garrison MM. Sedation and analgesia for pediatric fracture reduction in the emergency department: a systematic review. Archives of pediatrics & adolescent medicine 2006;160(1):46-51.	The two relevant RCT in this review are included in our RCT-search.
5.	Leroy PL, Schipper DM, Knape HJ. Professional skills and competence for safe and effective procedural sedation in children: recommendations based on a systematic review of the literature. International journal of pediatrics 2010;2010:934298.	Mixture of study designs. (Interesting for safety data.)
6.	Victorri-Vigneau C, Gerardin M, Wainstein L, Guerlais M, Rousselet M, Jolliet P. MEOPA dependence potential: French data. Fundamental and Clinical Pharmacology 2011;25:31.	Not a systematic review, only abstract.
7.	Apfel CC, Heidrich FM, Jukar-Rao S, Jalota L, Hornuss C, Whelan RP, et al. Evidence-based analysis of risk factors for postoperative nausea and vomiting. British Journal of Anaesthesia 2012;109(5):742-53.	Systematic review of post-operative side effects, after general anaesthesia. Mixture of RTCs and epidemiological observational data
8.	Jones R. Weak evidence that oral midazolam is an effective sedative agent for children undergoing dental treatment. Evidence-based dentistry 2012;13(3):76-7.	Commentary only (to Liege LM).

	Excluded systematic reviews	Rational for exclusion
9.	Liege LM, Paul FA, Susan F. Sedation of children undergoing dental treatment. Cochrane Database of Systematic Reviews 2012;3(3):CD003877.	Wrong concentration.
10.	Young A, Ismail M, Papatsoris AG, Barua JM, Calleary JG, Masood J. Entonox® inhalation to reduce pain in common diagnostic and therapeutic outpatient urological procedures: a review of the evidence. Annals of the Royal College of Surgeons of England 2012;94(1):8-11.	Excluded. Only adult populations.
11.	Rao J, Kennedy SE, Cohen S, Rosenberg AR. A systematic review of interventions for reducing pain and distress in children undergoing voiding cystourethrography. Acta paediatrica (Oslo, Norway : 1992) 2012;101(3):224-9.	The one relevant RCT with nitrous oxide in the review are included in our RCT-search.
12.	Pedersen RS, Bayat A, Steen NP, Jacobsson ML. Nitrous oxide provides safe and effective analgesia for minor paediatric procedures--a systematic review. Danish medical journal 2013;60(6):A4627.	Observational studies included. Can be used for safety data.
13.	Wong GTC, Yu CKY, Yuen VMY, Irwin MG. The effects of anaesthesia on the developing brain: A summary of the clinical evidence. F1000Research 2013;2(166).	Intervention mostly general anesthesia.
14.	Ana CO, Álvaro NA, Delcio M, Edina MKdS. Intravenous versus inhalational anaesthesia for paediatric outpatient surgery. Cochrane Database of Systematic Reviews 2014;2(2):CD009015.	Nitrous oxide was not the main study drug and was only in combination for other drugs to be compared. One study comparing halothane with propofol had nitrous oxide in the halothane group.
15.	Friesen RH. Anesthetic drugs in congenital heart disease. Seminars in Cardiothoracic and Vascular Anesthesia 2014;18(4):363-70.	Not a systematic review. Population is patients with heart disease. May be interesting for discussion for sub-population.
16.	Sun L, Guo R, Sun L. Dexmedetomidine for preventing sevoflurane-related emergence agitation in children: a meta-analysis of randomized controlled trials. Acta anaesthesiologica Scandinavica 2014;58(6):642-50.	Not our focus. Side effects after general anesthesia. Most studies included do not include nitrous oxide or it is in both groups being compared.
17.	Wang M, Zhang JH, Applegate RL. Adverse effect of inhalational anesthetics on the developing brain. Medical Gas Research 2014;4(2).	Animal studies for the articles handling nitrous oxide.
18.	Mittal N, Goyal A, Jain K, Gauba K. Pediatric Dental Sedation Research: Where Do We Stand Today? Journal of Clinical Pediatric Dentistry 2015;39(3):284-91.	Discussion paper.

	Excluded systematic reviews	Rational for exclusion
19.	Araújo CM, Oliveira BMd, Silva YPe. Nitrous oxide 50% in oxygen for painful pediatric procedures used by non-anestesiologists: a systematic review of the literature. Rev méd Minas Gerais 2015;25.	The two relevant RCT (Bruce 2006 and Carbajal 2008) are included in the RCT-search.
20.	Hartling L, Milne A, Foisy M, Lang ES, Sinclair D, Klassen TP, et al. What Works and What's Safe in Pediatric Emergency Procedural Sedation: An Overview of Reviews. Academic Emergency Medicine 2016;23(5):519-30.	Overview of systematic reviews. All the included papers about nitrous oxide is captured by our search of SRs.
21.	Viana KA, Daher A, Maia LC, Costa PS, De Castro Martins C, Paiva SM, et al. What is the level of evidence for the amnestic effects of sedatives in pediatric patients? A systematic review and meta-analyses. PLoS ONE 2017;12.	All included studies are RCTs but only two of them corresponds to our inclusion criteria (Evans 1995 and Lembert 2002).

Excluded titles on safety for health personnel

	Excluded titles on safety for health personnel	Rational for exclusion
1.	Sweeney B, Bingham RM, Amos RJ, Petty AC, Cole PV. Toxicity of bone marrow in dentists exposed to nitrous oxide. British Medical Journal Clinical Research Ed 1985;291(6495):567-9.	No control, only case series
2.	Schuyt HC, Brakel K, Oostendorp SG, Schiphorst BJ. Abortions among dental personnel exposed to nitrous oxide. Anaesthesia 1986;41(1):82-3.	A comment on that the author experienced alarming high abortion rate in his clinic.
3.	Ahlborg G. [Irregular working hours, exposure to laughing gas and pregnancy complications among midwives]. Jordemodern 1989;102(11):415-7.	Description of study.
4.	Karakaya A, Tuncel N, Yucesoy B, Akin M, Cuhruk H, Sardas OS, et al. The effects of volatile anaesthetic agents on human immune system function via occupational exposure. Immunopharmacology & Immunotoxicology 1992;14(1):251-9.	Specifically mentioned that N_2O is not a major part in the intervention.
5.	Marraccini P, Vittadini G, Ghittori S, Giorgi I, Bonelli S, Buonocore M, et al. [Evaluation of several neuropsychological parameters in subjects occupationally exposed to anesthetics]. Giornale Italiano di Medicina del Lavoro 1992;14(1):75-8.	Italian, we only include the larger languages.
6.	Brodsky JB. Nitrous oxide and fertility. New England Journal of Medicine 1993;328(4):284-5.	Not a study, only comment.
7.	Gray RH. Nitrous oxide and fertility. New England Journal of Medicine 1993;328(4):284.	Not a study, only comment.
8.	Wynn RL. Nitrous oxide and fertility. Part II. General Dentistry 1993;41(3):212, 4.	Review

	Excluded titles on safety for health personnel	Rational for exclusion
9.	Wynn RL. Nitrous oxide and fertility, Part I. General Dentistry 1993;41(2):122-3.	Review
10.	Sungu YS, Kunt N, Cinar Z, Dogan A. The effect of voletile anaesthetic on the sister chromatid exchange in operation room personnel. [Turkish]. Turk Anesteziyoloji ve Reanimasyon 2000;28(4):193-5.	Turkish, we only include the larger languages.
11.	Rosen MA. Nitrous oxide for relief of labor pain: a systematic review. American Journal of Obstetrics & Gynecology 2002;186(5):S110-26.	Systematic review and no occupational safety.
12.	Proietti L, Longo B, Gulino S, Duscio D. [Techniques for administering inhalation anesthetic agents, professional exposure, and early neurobehavioral effects]. Medicina del Lavoro 2003;94(4):374-9.	Italian, we only include the larger languages.
13.	Zanetti C, Fiorio S, Moretto A, Foresto F, Baggio R, Gardin F, et al. Longitudinal study (16 years) of the reproductive health of 61 female workers exposed to known levels of volatile anaesthetics. [Italian]. Giornale Italiano di Medicina del Lavoro ed Ergonomia 2004;26(4):362-4.	Italian, we only include the larger languages.
14.	Zanetti C, Fiorio S, Moretto J, Foresto F, Baggio R, Gardin F, et al. Longitudinal study (16 years) of the health status of 119 workers exposed to known concentrations of volatile anaesthetics. [Italian]. Giornale Italiano di Medicina del Lavoro ed Ergonomia 2004;26(4):364-5.	Italian, we only include the larger languages.
15.	Fodale V, Mondello S, Aloisi C, Schifilliti D, Santamaria L. Genotoxic effects of anesthetic agents. Expert Opinion on Drug Safety 2008;7(4):447-58.	Systematic review.
16.	Schifilliti D, Mondello S, D'Arrigo MG, Chill G, Fodale V. Genotoxic effects of anesthetic agents: An update. Expert Opinion on Drug Safety 2011;10(6):891-9.	Systematic review.
17.	Ferner RE, Mackenzie AA, Aronson JK. The adverse effects of nitrous oxide. Adverse Drug Reaction Bulletin 2014;(285):1099-102.	Review.
18.	Likis FE, Andrews JC, Collins MR, Lewis RM, Seroogy JJ, Starr SA, et al. Nitrous oxide for the management of labor pain: A systematic review. Anesthesia and Analgesia 2014;118(1):153-67.	Systematic review.
19.	Edling C. Anesthetic gases as an occupational hazard. A review. Scandinavian Journal of Work, Environment and Health 1980;6(2):85-93.	Review.
20.	Vessey MP, Nunn JF. Occupational hazards of anaesthesia. British Medical Journal 1980;281(6242):696-8.	Review.
21.	Rogo EJ, Lupovici EM. Nitrous oxide. An occupational hazard for dental professionals. Dental Hygiene 1986;60(11):508-14.	Review.
22.	Kestenberg SH, Young ER. Potential problems associated with occupational exposure to nitrous oxide. Journal (Canadian Dental Association) 1988;54(4):277-86.	Review.

	Excluded titles on safety for health personnel	Rational for exclusion
23.	Unceta-Barrenechea Orue B, Vicinay Pinedo S, Garran Sabando B, Serna de Andres A, Seoane de Lucas A. [Occupational exposure of the anesthesiologist to nitrous oxide and halothane. Control measures]. Revista Espanola de Anestesiologia y Reanimacion 1989;36(5):267-75.	No biological effects reported.
24.	Sardas S. The significance of sister chromatid exchange as indicator of occupational exposure. Gazi Universitesi Eczacilik Fakultesi Dergisi 1992;9(2):69-74.	Turkish, we only include the larger languages.
25.	Cope KA, Merritt WT, Krenzischek DA, Schaefer J, Bukowski J, Foster WM, et al. Phase II collaborative pilot study: preliminary analysis of central neural effects from exposure to volatile anesthetics in the PACU. Journal of PeriAnesthesia Nursing 2002;17(4):240-50.	Pilot study with few subjects
26.	Levine J, Chengappa KN. Exposure to nitrous oxide may be associated with high homocysteine plasma levels and a risk for clinical depression. Journal of Clinical Psychopharmacology 2007;27(2):238-9.	A one-case case study.
27.	Cordier PY, Michel F, Pellegrini L, Lando A, Martin C. Occupational exposure to anaesthetic gases: Risk perception and reported practices by anaesthesiologists and nurse anaesthetists. European Journal of Anaesthesiology 2012;29:22.	Abstract only.
28.	Marahem M, Farzin H, Seyedghodraty M, Hamdi BA. Occupational exposures to anesthetic gases in operating room. Crescent Journal of Medical and Biological Sciences 2017;4(3):90-1.	Review.
29.	Lane, G. A., Nahrwold, M. L., & Tait, A. R. (1979). Nitrous oxide is teratogenic: xenon is not! Anesthesiology 1979;51(3 SUPPL).	Pre-clinical study.
30.	Sanders RD1, Weimann J, Maze M. Biologic effects of nitrous oxide: a mechanistic and toxicologic review. Anesthesiology 2008; 109(4):707-22.	Review.
31.	Myles PS, Leslie K, Chan MT, Forbes A, Paech MJ, Peyton P, Silbert BS, Pascoe E, ENIGMA Trial Group: Avoidance of nitrous oxide for patients undergoing major surgery: A randomized controlled trial. Anesthesiology 2007; 107: 221–31	Population is patients, not personnel.
32.	Quansah R, Jaakkola JJ. Occupational exposures and adverse pregnancy outcomes among nurses: A systematic review and meta-analysis. Journal of Women's Health 2010;19(10):1851-62.	Systematic review.
33.	Uzun S, Saricaoglu F, Ayhan B, Topatan B, Akinci SB, Aypar U. Homocysteine levels and bad obstetric outcome among female operating room personnel occupationally exposed to nitrous oxide. Bratislavske Lekarske Listy 2014;115(6):372-6.	Study setup not appropriate to our purpose as there were no control group.
34.	Messeri A, Amore E, Dugheri S, Bonari A, Pompilio I, Arcangeli G, Rizzo G. Occupational exposure to nitrous oxide during procedural pain control in children: a comparison of different inhalation techniques and scavenging systems. Paediatr Anaesth. 2016; 26(9):919-25.	No data on safety for personnel, only describing scavenging system.

	Excluded titles on safety for health personnel	Rational for exclusion
35.	Vessey MP and Nunn, JF, Occupational hazards of anesthesia. Br Med J. 1980; 281(6242): 696–698.	Review.
36.	Matte TD, Mulinare J, Erickson JD. Case-control study of congenital defects and parental employment in health care. Am J Ind Med 1993;24(1):11-23.	General exposure in health care personnel.
37.	Spence AA, Cohen EN, Brown Jr BW, Knill-Jones RP, Himmelberger DU. Occupational Hazards for Operating Room-Based Physicians. JAMA 1977;238:4.	General exposure in health care personnel.
38.	Knill-Jones RP, Newman BJ, Spence AA. Anesthetic practice and pregnancy. Controlled survey of male anaesthetists in the United Kingdom. Lancet (London, England) 1975;2(7939):807-9.	The groups are not properly described to understand the data.
39.	Vessey 79 Vessey MP. Health problems of anaesthetists and their families. Br Med J 1979;1(6170):1078-9.	Comment.
40.	Yilmaz S, Calbayram NC. Exposure to anesthetic gases among operating room personnel and risk of genotoxicity: A systematic review of the human biomonitoring studies. J Clin Anesth 2016;35:326-31.	Review.
41.	McDonald AD, Armstrong B, Cherry NM, Delorme C, Diodati-Nolin A, McDonald JC, et al. Spontaneous abortion and occupation. Journal of occupational medicine : official publication of the Industrial Medical Association 1986;28(12):1232-8.	General exposure in health care personnel.
42.	McDonald AD, McDonald JC, Armstrong B, Cherry NM, Cote R, Lavoie J, et al. Fetal death and work in pregnancy. British journal of industrial medicine 1988;45(3):148-57.	60 different working groups and no numbers of how the expected outcome (the control) is estimated.
43.	Rozgaj R, Kasuba V, Peric M. Chromosome aberrations in operating room personnel. Am J Ind Med 1999;35(6):642-6.	General exposure in health care personnel.
44.	Tomlin PJ. Health problems of anaesthetists and their families in the West Midlands. Br Med J 1979;1(6166):779-84.	No control groups.

Appendix 5. Description of systematic reviews on children undergoing N_2O sedation

Study	Description
Migita 2006 (20)	The objective was to assess the safety and efficacy of various forms of analgesia and sedation for fracture reduction in paediatric patients in the emergency department. Two of the eight randomised controlled trials included in the systematic review presented data on N_2O. Results on N_2O were judged too limited to support effectiveness or safety.
Rao 2012 (78)	The objective was to assess reduction of distress, pain or anxiety for children undergoing voiding cystourethrograhy using various forms of interventions. One of the eight randomised controlled trials included in the systematic review presented data on N_2O and only a narrative presented the data concluding that further evidence for the efficiency of N_2O is needed.
Araújo 2015 (22)	The objective was to assess the use of N_2O to decrease pain intensity during hospital procedures in children. Two randomized controlled trials were included in the systematic review and a narrative presented the data concluding that there were insufficient amount of data to conclude about the efficacy of N_2O to reduce pain.
Viana 2017 (23)	The objective was to assess the evidence for the amnestic effects of various sedatives in children. Seven of the 54 included studies presented data on N_2O. A narrative presentation of benzodiazepines compared to, among others, N_2O, showed that anterograde amnesia was likely with benzodiazepines than with N_2O (one study).

Appendix 6. Safety of patients undergoing N2O sedation

Adverse event	Studies	Intervention events	Control events	OR (95% CI)	Studies	Intervention events	Control events	OR (95% CI)	Studies	Intervention events	Control events	OR (95% CI)
	N_2O vs EMLA				N_2O vs ketamine or midazolam				N_2O vs placebo			
Agitation	4	21 of 157 (13.4%)	7 of 146 (4.79%)	3.35 (1.38 to 8.14)	0				0			
Ataxia	0				1	4.23 of 47 (9%)	13.2 of 55 (24%)	0.313 (0.0967 to 1.01)	0			
Cardiac or respiratory events	0				2	0 of 65 (0%)	5.85 of 69 (8.48%)	0.13 (0.0152 to 1.11)	2	0 of 103 (0%)	0 of 102 (0%)	
Carpopedal spasm/paraesthesia	1	2 of 57 (3.51%)	0 of 46 (0%)	4.19 (0.196 to 89.5)	0				0			
Dizziness	1	1 of 40 (2.5%)	0 of 40 (0%)	3.08 (0.122 to 77.8)	3	1 of 63 (1.59%)	3 of 59 (5.08%)	0.448 (0.0744 to 2.7)	0			
Drowsiness or lethargy	1	3 of 57 (5.26%)	0 of 46 (0%)	5.97 (0.301 to 119)	1	0 of 47 (0%)	0 of 55 (0%)		0			
Dysphoria	2	7 of 60 (11.7%)	0 of 60 (0%)	9.07 (1.09 to 75.3)	0				0			
Ear ache	0				1	0.94 of 47 (2%)	0 of 55 (0%)	3.43 (0.134 to 87.7)	0			

Adverse event	Stud-ies	Interven-tion events	Control events	OR (95% CI)	Stud-ies	Interven-tion events	Control events	OR (95% CI)	Stud-ies	Intervention events	Control events	OR (95% CI)
Erythema	1	0 of 40 (0%)	4 of 40 (10%)	0.1 (0.00521 to 1.92)	0				0			
Euphoria	1	9 of 40 (22.5%)	0 of 40 (0%)	24.4 (1.37 to 436)	0				1	1 of 17 (5.88%)	0 of 13 (0%)	2.45 (0.0923 to 65.3)
Excessive crying	0				1	5.17 of 47 (11%)	13.2 of 55 (24%)	0.391 (0.13 to 1.18)	0			
Hallucination	0				2	1.88 of 65 (2.89%)	16.95 of 69 (24.6%)	0.12 (0.0291 to 0.495)	0			
Headache	0				2	8.11 of 70 (11.6%)	7.05 of 79 (8.92%)	1.35 (0.46 to 3.98)	0			
Loss of consciousness	0				0				1	0 of 39 (0%)	0 of 44 (0%)	
Nausea or vomiting	3	4 of 117 (3.42%)	0 of 106 (0%)	3.5 (0.558 to 22)	3	13.22 of 95 (13.9%)	16.2 of 99 (16.4%)	0.824 (0.182 to 3.72)	2	0 of 103 (0%)	2 of 102 (1.96%)	0.189 (0.00885 to 4.03)
Nightmare	1	1 of 40 (2.5%)	0 of 40 (0%)	3.08 (0.122 to 77.8)	1	3.29 of 47 (7%)	11 of 55 (20%)	0.301 (0.082 to 1.11)	1	1 of 53 (1.89%)	1 of 52 (1.92%)	0.981 (0.0597 to 16.1)
Other	1	2 of 20 (10%)	1 of 20 (5%)	2.11 (0.176 to 25.3)	0				0			
Oxygen saturation	1	0 of 20 (0%)	0 of 20 (0%)		0				3	0 of 105 (0%)	0 of 111 (0%)	

Adverse event	Stud-ies	Interven-tion events	Control events	OR (95% CI)	Stud-ies	Interven-tion events	Control events	OR (95% CI)	Stud-ies	Intervention events	Control events	OR (95% CI)
Pain	0				1	0 of 15 (0%)	1 of 15 (6.67%)	0.312 (0.0117 to 8.28)	0			
Persistent cough after procedure	0				0				1	1 of 53 (1.89%)	1 of 52 (1.92%)	0.981 (0.0597 to 16.1)
Post-tussive emesis	1	0 of 57 (0%)	1 of 46 (2.17%)	0.264 (0.0105 to 6.63)	0				0			
Unacceptance of mask	2	2 of 60 (3.33%)	6 of 60 (10%)	0.307 (0.0591 to 1.6)	0				0			
Unpleasant sensation	0				0				1	2 of 50 (4%)	0 of 50 (0%)	5.21 (0.244 to 111)
Vasoconstriction	1	0 of 40 (0%)	28 of 40 (70%)	0.00541 (0.000308 to 0.0952)	0				0			

Appendix 7. Characteristics and outcomes of the included studies on health personnel exposed to N_2O

See Appendix 8. Summary of occupational safety with uncertain exposure to N_2O

N_2O is a common component in general anaesthesia and many of the included studies on our search for occupational exposure to N_2O (58 articles) were from hospital setting where the health personnel were exposed to anaesthetic waste gases through their work in operation theatres. In these studies, the role of N_2O was unclear and not analysed separately. We here show a short summary for the effect of anaesthetic gases on selected outcomes.

- *Reproducibility:* We found 20 articles with effect of anaesthetic waste gases on different aspects of reproducibility (*Table 17*). Of these, only 3 articles mentioned N_2O as a possible part of the anaesthetic gases.
- *DNA damage and cellular functions:* We found 20 articles with effect of anaesthetic waste gases on DNA damage and cellular functions (*Table 18*). All mentioned N_2O as a part of the gases exposed to the personnel.
- *Neurobehaviour:* We found 6 articles studying the neurobehavioral effect of anaesthetic gases (*Table 19*). Five of them mentioned N_2O as one of the gases.
- *Liver and kidney function:* We found 7 articles that studied the effect of anaesthetic gases on organ (liver and kidney) function (*Table 20*). All but two of these mentioned N_2O as a part of the gases exposed to the personnel.
- *Haematological and inflammatory parameters:* We found 4 articles studying haematological and inflammatory parameters (*Table 21*). All of these mentioned N_2O as a part of the gases exposed to the personnel.
- *Other outcomes than these mention above:* There were 5 articles presenting data on other outcomes from those mentioned above (*Table 22*). Two of them mentioned N_2O as a part of the exposure gases and the three others only mentioned exposure to anaesthetic gases.

The studies which mentioned N_2O did not present any specific data on this gas.

Table 17*. The effect* of anaesthetic gases on selected reproducibility outcomes*

References	Setting, N	Effect on spontaneous abortion	Effect on congenital abnormalities	Effect on infertility	Effect on birth weight	Effect on still birth/perinatal death
Cohen 1971	Hospital, N=290	Increased				

References	Setting, N	Effect on spontaneous abortion	Effect on congenital abnormali-ties	Effect on infertility	Effect on birth weight	Effect on still birth/perinatal death
Knill-Jones 1972	Hospital, N=1391	Working anaesthetists vs control: Increased Working vs non-working anaesthetists: Increased	Working anaesthetists vs control: No difference Working vs non-working anaesthetists: Increased			
Rosenberg 1973	Hospital, N= 302	Increased (no causality was drawn)				
ASA 1974	Hospital, N= 40 044	In female op-erating room personnel: Increased In wives of exposed males: Little evidence (no causality was drawn)	In female ex-posed group and in the wives of ex-posed males: Increased (no causality was drawn			
Corbett 1974	Hospital, N=695	No data	Increased (no causality was drawn)			
Cohen 1975	Dental operating rooms and dental office N=3328	In spouses of exposed sub-jects: Increased	No difference			
Mirakhur 1975	Hospital, N=280	Increased	No difference			No difference (stillbirth)
Pharoah 1977	Hospital, N=3387	No difference	Increased		Lower	Increased (still-birth)
Ericson 1979	Hospital, N=494 exposed plus an undefined number of controls	-	No difference		No difference	No difference (perinatal death)

References	Setting, N	Effect on spontaneous abortion	Effect on congenital abnormalities	Effect on infertility	Effect on birth weight	Effect on still birth/perinatal death
Lauwerys 1981	Hospital, N=1027	Exposed females and spouses to exposed males: No difference	Exposed females and spouses to exposed males: No difference			Exposed females and spouses to exposed males: No difference (stillbirths)
Wyrobek 1981	Hospital, N=72	-		No difference (sperm quality)		
Axelsson 1982	Hospital, N=610	No difference				
Hemminki 1985	Hospital, N=962	No difference	No difference			
Ericson 1985	Hospital, N=2705	No difference	Compared to expected nationwide data: Lower Compared to control nurses: No difference		No difference	No difference (perinatal death)
Ericson 1989	Different cohorts, see Appendix 8	No difference	No difference		No difference	Lower (perinatal death)
Guirguis 1990	Hospital, N=8538	Exposed females and spouses to exposed males: Increased	Exposed mothers: Increased			
Saurel-Cubizolles 1994	Hospital, N= 1367	Increased	No difference			
Roeleveld 2002	Hospital, N=1437	No difference	Increased		No difference	
Lawson 2012	Hospital, N=7482	No difference				
Sharifi 2015	Hospital, N=80	No difference	No difference			

*N=Number of all subjects in the study; *All the effects are the effect of exposure of anaesthetic gases versus no exposure*

Table 18. *Selected outcomes for the effect of anaesthetic waste gases on DNA and cellular functions*

DNA outcomes	Setting, N	Chromosome aberration	DNA damage	Sister chromatid exchange	Micronuclei formation
Bigatti 1985	Hospital, N=39	Increased		No difference	
Lamberti 1989	Hospital, N=30	No difference		No difference	
Karelova 1992	Hospital, N=54	Increased		Increased	
Sardas 1992	Hospital, N=117			Increased	
Sardas 1998	Hospital, N=107		Increased		
Hoerauf 1999 genetic damage	Hospital, N=20			Increased, dose dependent	No difference
Hoerauf 1999 Chromatide exchange	Hospital, N=54			Increased, in whole group, No difference in women	
Goto 2000*	Hospital, N=30				
Pasquini 2001	Hospital, N=112			Decreased	Increased in female exposed group, but not in male
Rozgaj 2001	Hospital, N=69	Increased		No difference	
Wiesner 2001	Hospital, N=75				Increased in high exposure No difference in low exposure
Lewinska 2005	Hospital, N=74				Increased
Eroglu 2006	Hospital, N=50			Increased	
Costa Paes 2014	Hospital, N=30		Increased		
Souza 2016	Hospital, N= 57		No difference		
Szyfter 2016	Hospital, N=200	No difference			
Chandrasekhar 2006	Hospital, N=90	Increased	Increased		
Baysal 2009	Hospital, N=60		Increased		
Izdes 2010	Hospital, N=80		Increased		
El-Elbiary 2013	Hospital, N=80		Increased		

** Presented none of the selected outcomes*

Table 19. *Neurobehavioral effects of anaesthetic waste gas exposure*

Reference	Population	Reaction time	Neurobehavioral effect
Korttila 1978	Hospital, N=30		No difference

Stollery 1988	Hospital, N=22		No difference
Tran 1994*	Hospital, N=281		
Lucchini 1995	Hospital, N=108	Increased	No difference
Lucchini 1996	Hospital, N=50	Increased	
Lucchini 1997	Hospital, N=247		No difference

** Presented none of the selected outcomes*

Table 20. *Selected outcomes for the effect of anaesthetic waste gases on organ function*

Reference	Population	Organ function
Dossing 1982	Hospital, N=26	Liver: No difference
De Zotti 1983	Hospital, N=217	Liver: No difference
Franco 1991	Hospital, N=34	Liver: Unfavourable effect (increased UDGa values)
Franco 1992	Hospital, N=48	Liver: No difference
Cohen 1975	Dentist, N=3328	Liver: Unfavourable effect Kidney: No difference
Trevisan 2003	Hospital, N=104	Kidney: No difference
ASA 1974	Hospital, N=40 044	Liver: Unfavourable effect Kidney: Female: Unfavourable effect Kidney: Male: No difference

Table 21. *Selected outcomes for the effect of anaesthetic waste gases on haematological parameters and inflammatory markers*

Reference	Population	Outcome
Peric 1991	Hospital, N=56	Red cell count, haemoglobin, haematocrit, T lymphocyte count: No difference Basophils: Disappeared during exposure CD2, CD4: Increased B cell: Decreased, and did not recover after holidays NK cells: Decreased, but recovered
Peric 1994	Hospital, N=77	Blood count, IgX, cell activity with mitogens: No effect
Bargellini 2001	Hospital, N=71	Immune cell parameters: Unfavourable effect (Derangements in lymphocyte subpopulations where T-lymphocytes were more affected than B cells).
Chaoul 2015	Hospital, N= 30	Pro-inflammatory cytokines: Unfavourable effect (Increase in IL-8, in high exposure group)

Table 22. *Selected outcomes for the effect of anaesthetic waste gases on other biological outcomes*

Reference	Population	Outcome
Corbett 1973	Hospital, N=525 + control cohort	Cancer frequency: Increased
Pasquini 1989	Hospital, N=101	Urinary thioethers: Increased Urinary mutagenicity, D-Dlucaric acid: No difference
Hedstrom 2013	Hospital, N=15 621	Occurrence of multiple sclerosis (MS): No association
ASA 1974	Hospital, N=40 044	Cancer incidences: Female exposed group: Increased Male exposed group: No difference
Cohen 1975	Hospital, N=3328	Cancer: No difference

Characteristics of the studies

The following table lists the trials where general anaesthetics or N_2O in combination with other gases were used, and where no specific N_2O data were presented.

Reproductive health

We found 20 articles with effect of anaesthetic gases on different aspects of reproducibility. Of these, only 3 articles mentioned N_2O as a part of the anaesthetic gases.

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
Cohen 1971 (79)	Operating room female nurses, N=67 Female anaesthetists, N=50 Control: General duty female nurses, N=92 Female physicians, N=81	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. Mean years in the operating room: 3.9 N_2O not mentioned	Spontaneous abortion: Higher rate in the exposed groups compared to the control groups.	Age slightly higher in the exposed groups compared to controls. This was not adjusted for in the analyses. All information were self-reported with the risk of influence the results.	Survey with interviews and questionnaires respectively. Time of data collection: 1966-1970. USA
Knill-Jones 1972 (80)	Female anaesthetists, N=563 (sub-grouped based on whether they worked during the first 6 months of pregnancy or not)	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Working anaesthetists vs control: - Higher spontaneous abortion in the working group - No difference in children with congenital abnormalities	No confounders discussed. All information were self-reported with the risk of influence the results.	Survey among hospital health personnel. 80% response rate for both groups.

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
	Control: Female doctors, N=828			Working vs non-working anaesthetists: - Higher rate of spontaneous abortion in the working group - Increased rate of children with congenital abnormalities in the working group Crude group of anaesthetists vs control: - No difference in spontaneous abortion - No difference in stillbirth - No difference in children with congenital abnormalities - Higher unknown cause of infertility in the anaesthetists - No difference in infertility		Time of data collection: 1970 UK
Rosenberg 1973 (81)	Operating room female nurses, N=182 (anaesthesia nurses, N=58, scrub nurses, N=124) Control: Other female nurses, N=120 (from causality department, N=75, from intensive care, N=45)	Anaesthetic gas exposure and/or stress	Working in operating room. Additional information about radiation and halothane exposure. No information about scavenging systems. Mean length of continuous employment prior to conception in women with miscarriages: About 20 months in the exposed groups, and about 19 months in the control groups. N_2O not mentioned.	Spontaneous abortion: Higher rate of spontaneous abortions in the operating room nurses as compared to the control groups. The authors suggest that this was due to excessive workloads rather than anaesthetic gases.	Excessive workload and stress. The nurses working in operating rooms often had a hard irregular workload, as well as night duty. In the present study, it was tempting for the nurses to blame x-ray and halothane for their miscarriages, but there were no differences between the mean exposure to these two pollutants in the nurses having miscarriages and in the corresponding groups having full-time pregnancies. All information were self-reported with the risk of influence the results.	Questionnaire to 300 female health workers working as anaesthetists, scrub, causality and intensive care unit nurses from 16 Central hospitals and 4 University hospitals. Time of data collection: 1965-1973 Finland
ASA 1974 (82)	ASA, AANA, AORN/T, both genders, responders, N=29 810	Anaesthetic gas exposure	No information about gas exposure, only based on type of work.	Spontaneous abortion: In the female members of the operating room-exposed group:	The rates were standardized for both age and smoking habit at time of pregnancy.	National survey. The exposed group: Questionnaires

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
	Control: AAP, ANA, both genders, responders, N=10 234		N_2O not mentioned.	Higher rate of spontaneous abortion than in the control group. In the wives of exposed males: Little evidence that male exposure gave higher rate of abortion in their spouse. Congenital abnormalities: In female exposed group and in the wives of exposed males: Higher rate than in the control groups, but no causality was drawn.	All information were self-reported with the risk of influence the results.	mailed to 49 585 members of American Society of Anesthesiologis (ASA), American Association of Nurse Anesthesists (AANA) and Associations of Operating Room Nurses and Technicians (AORN/T). The control (unexposed group): Questionnaires mailed to 23 911 members of American Academy of Pediatrics (AAP) and the American Nursing Association (ANA). Mean response rate of 55%. Time of data collection: 1973 USA
Corbett 1974 (83)	Working female nurse anaesthetists, N=434 Control: Not working female nurse, N=261	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Birth defects: Higher rate in exposed group compared to control group	Mothers age at birth similar in exposed and unexposed group. Possible effects due to viruses and radiations were not handled in the analyses. All information were self-reported with the risk of influence the results.	Survey. Questionnaires to 621 female nurse anaesthetists. Time of data collection: Not mentioned. USA
Cohen 1975 (84)	Exposed male oral surgeons and male dentists, N=1668	Exposure to anaesthesia gases at dental office	Unscavenged rooms. At least 3 h exposure per week.	Spouse spontaneous abortion: Higher rate in the spouses of the surgeons with higher exposure	Age, smoking, adjusted for.	Survey. Questionnaires to male members of

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
	Control: Males in the same cohort who has less than 3h exposure per week, N=1660.		Refer to general concentrations at that time: Halothane: Exceed 73 ppm N_2O: 500-6000 ppm	than spouses of surgeons with less than 3 h exposure per week. Congenital abnormalities: No difference between the groups	All information were self-reported with the risk of influence the results.	American Society of Oral Surgeons (ASOS), N=2642, response rate of 64.5%; and American Dental Association) ADA, N=4797, response rate of 38.9%. Time of data collection: Not mentioned. USA
Knill-Jones 1975 (85)	Not possible to identify the population.	Anaesthetic gas exposure				
Mirakhur 1975 (86)	1) Exposed female anaesthetists, working more than 5 years, N=47 2) Non-medical wives of exposed male anaesthetists, N=136 Controls: 1) Female non-exposed physician, N=50 2) Wives of unexposed male physicians, N=47	Anaesthetic gas exposure	On average, the anaesthetists had been working for 36.9 hours per week over a period of 9.5 years. N_2O not mentioned.	Spontaneous abortion: Higher rate in the exposed group than in the non-exposed group Premature labour, stillbirth: No difference between the groups Congenital anomalies: No difference between the groups	The mean age of anaesthetists was lower than that of the physicians: not adjusted for in the analyses. All information were self-reported with the risk of influence the results.	Survey. Questionnaires, N=425, sent to members of the Indian Society of Anaesthetists. 281 returned. Response rate 66.1% Time of data collection: Not mentioned. India
Pharoah 1977 (87)	Female doctors working with anaesthetics. Control: Female doctors not working with anaesthetics. Total in both groups: 3387	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Spontaneous abortion: No difference between the groups Stillbirth: Higher rate in the exposed group than in the non-exposed group Birth weight: Lower birth weight in the exposed group than in the non-exposed group	Analyses were performed for different age groups. All information were self-reported with the risk of influence the results.	Survey. Questionnaires to all women on the Medical Registry for 1975, N=7992. 72% response rate. Time of data collection: 1975 England and Wales

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
				Congenital abnormalities: higher rate in the exposed group than in the non-exposed group		
Ericson 1979 (88)	Female working in operating rooms during pregnancy, N=494 Control: A reference population composed of all females employed in medical work in Sweden, who had delivered during last 2 years. Number not given.	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Threatened abortion: No difference between the groups Birth weight: No difference between the groups Perinatal death rate: No difference between the groups Congenital malformations: No difference between the groups	Age was adjusted for in the analyses.	Register study of women working in operating rooms during pregnancy Controlled. Time of data collection: 1973-75. Sweden
Lauwerys 1981 (89)	Anaesthetics and operating theatre nurses. Control: Dermatologists, and intensive care unit nurses and social nurses. Total in both groups: 1027 persons with 1910 pregnancies. Both genders (588 male, 435 female and 4 unknown).	Anaesthetic gas exposure (nitrous oxide, ether, trichloroethylene, cyclopropane, halothane, methoxyflurane, enflurane)	No other information about gas exposure, only based on type of work. N_2O mentioned.	For all results: the exposed group consists of both female anaesthetics and operating theatre nurses as well as spouses to male anaesthetics and operating theatre nurses Spontaneous abortions: No difference between the groups Stillbirths: No difference between the groups Premature births: No difference between the groups Congenital malformations: No difference between the groups	Low response rate, but similar response rate of the exposed and control groups. No significant difference in smoking habits of the mothers between the different exposure groups. Some of the exposed groups had higher prevalence of radiographic examination, more use of contraceptives in the 12 months preceding pregnancy, and higher occurrence of illnesses of the mother during pregnancy than in the control group. These differences were not adjusted for. The results were given for the total exposed group (exposed mothers or/and exposed fathers) versus control. All information were self-reported with the risk of influence the results.	Survey. For exposed group: Questionnaire to members in Belgian Society of Anaesthetics, and to operating theatre nurses. For unexposed group: members of Belgian Society of Dermatologists and Belgian Society of Occupational Physicians, and to nurses in intensive care unit and social Nurses. Response rate: 47% Time of data collection: Not mentioned. Belgium

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
Wyrobek 1981 (90)	Male anaesthesiologist working for minimum 1 year in hospital operating rooms, N=46 Control: Beginning residents in anaesthesiology, N=26	Anaesthetic gas exposure	Ventilated rooms with modern scavenging devices. N_2O not mentioned.	Concentration of sperm with abnormal head: No difference between the groups	Age: The anaesthesiologists were slightly older than the beginning residents, but this was not associated with any difference in sperm morphology. Results did not change when the analyses were limited to men having no confounding factors (varicocele, recent illness or urogenital tract infection, medications, heavy smoking, or frequent sauna use). The proportion of men with confounding factors in the control and exposed populations did not differ significantly. All information were self-reported with the risk of influence the results.	Non-randomized, controlled study. From Three San Francisco Bay Area Hospitals Time of data collection: Not mentioned USA
Axelsson 1982 (91)	Exposed female hospital workers, N=288 Control: Non-exposed workers from medical wards without exposure, N=322	Anaesthetic gas exposure	High level exposure areas (operating and anaesthesia departments). Low exposure areas (Intensive care, recovery, ear, nose and throat out-patient clinic). N_2O not mentioned.	Spontaneous abortion: No difference between groups.	Results were evaluated in relation to age, smoking habits, work site at the first trimester of pregnancy All information were self-reported with the risk of influence the results.	Survey. A cohort of exposed female hospital workers, not physicians, at Uddevalla Hospital. The information given in the questionnaire concerning miscarriages was individually compared to data from hospital records. Time of data collection: Pregnancies from 1970-1979 Sweden
Hemminki 1985 (92)	Case female nurses were selected who had had a spontaneous abortion or a malformed child between the years 1973 and 1979:	Exposure to anaesthetic gases, sterilising agents, cytostatic drugs and x-rays (grouped).	No information about gas exposure, only based on type of work. N_2O exposure mentioned.	Spontaneous abortion: No difference in exposure to anaesthetic gases between nurses with spontaneous abortion or normal births	A case control study using individual matching. More permanent night work among the cases (2.5% vs 1.7%). Information about exposure from the head nurse may be biased.	A case control study, using the Hospital Discharge Register and the Register of Congenital Malformations.

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
	1: Nurses with spontaneous abortion, N=217 2: Nurses with malformed child, N=46 Control: Controls consisted of three female nurses who had had a normal birth per case nurse. The control nurses were matched for age and hospital of employment. 1: Matched female nurses to the nurses with spontaneous abortion, N=571 2: Matched nurses to the nurses with malformed child, N=128			Congenital malformations: No difference in exposure to anaesthetic gases between nurses with malformed child or normal child	No adjustments were done.	Questionnaire for exposure to head nurses at general hospitals. 81% response rate. Time of data collection: Pregnancies from 1973-1979 Finland
Ericson 1985 (93)	Operating room female nurses, N=1323 Control: Expected values based on nationwide data.	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Spontaneous abortion: No difference between exposed group and nationwide average. Perinatal death rate: No difference between exposed group and nationwide average. Malformations: Lower rate when compared to nationwide average. Preterm birth: No difference between exposed group and control groups. Birth weight: No difference between exposed group and control groups.	Confounding factors raised by the authors: "It is possible that the conclusions drawn from questionnaire studies with sometimes rather high non-responder rates are false due to shortcomings in the material analysed, and that the registry data used in the present study are more likely to give correct estimates of the risks involved."	Register data and questionnaires. Information from Nurse Registry, Medical Birth Registry and Registry of Abortions were used to obtain the population. Time of data collection: 1973-1978. Sweden
Ericson 1989 (94)	Cohort 1. The 1976-1986 birth cohort: Infants born by dentists, dental assistants,	Exposure not clearly stated. Both mercury	No information about gas exposure, only based on type of work.	Cohort 1: Perinatal death: Lower rate in the exposed group than in the control	Mercury: The actual exposure may be low.	Register study: Central Health Registries, Medical Birth Registry, Hospital

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
	dental technicians in 1976 or 1982-86, N=8157 Cohort 2. The 1980-1981 birth cohort, spontaneous abortions, number of hospitalized spontaneous abortions, N=175 Cohort 3. The 1960s cohort, N=78 pregnancies with 7 spontaneous abortions Cohort 4. The 1965-1967 cohort: 220 infants born with neural tube defect. Control: Expected values based on number of births from all women with gainful occupation, after standardization for maternal age, in 1981.	and N_2O mentioned.	N_2O not mentioned.	Malformations: No difference between the groups Low birthweight: No difference between the groups Cohort 2: Spontaneous abortions: No difference between the groups Cohort 3: Spontaneous abortions: No difference between the groups Cohort 4: Congenital malformation, Neural tube defect: No difference between groups.	Cohort 1: Do not know that the women actually worked in early pregnancy in the professions stated. Cohort 2: Spontaneous abortions were identified from a Hospital Discharge Registry. Women who were not hospitalized and had an abortion, were not identified. No adjustments were done.	Discharge Register, and Registry of Congenital Malformations. Controlled. Time of data collection: See population. Sweden
Guirguis 1990 (95)	Exposed hospital female personnel, N=6336 Control: Non-exposed hospital female staff, N=2202	Anaesthetic gas exposure.	Chronically exposed: Spending at least two hours a week in the operating room. N_2O not mentioned.	Spontaneous abortion: Increased rate in both female workers and in spouses of exposed male workers. Congenital abnormalities: Increased risk for children born by exposed mothers.	*Confounders adjusted for in the analyses for spontaneous abortion*: Birth order, previous spontaneous abortion, age of mother at pregnancy, smoking during pregnancy, alcohol consumption during pregnancy, occupation. *Confounders adjusted for in the analyses for congenital abnormality*: As above with the exception of previous spontaneous abortion. *For both:* All information were self-reported with the risk of influence the results.	Retrospective study by questionnaires send to 75 hospitals in Ontario, Canada. 78.8% response rate for exposed personnel and 87.2% response rate for non-exposed staff. Time of data collection: 1981-1985 Canada
Saurel-Cubizolles 1994 (96)	Operating room female nurses, N=489 (268 in anal-	Anaesthetic gas exposure	No information about gas exposure, only based on type of work.	Spontaneous abortion: Higher rate in the exposed group.	Odds ratios for spontaneous abortions were adjusted for:	Survey among 17 hospitals in Paris in 1987-1989.

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
	yses for spontaneous abortions, and 221 in analyses for birth defects) Control: Female nurses in other departments, N=878 (458 in analyses for spontaneous abortions, and 420 in analyses for birth defects)		N_2O not mentioned.	Congenital abnormalities: No difference between the groups.	Work in operating room at time of pregnancy, exposure to antineoplastic drugs, age, number and outcomes of previous pregnancies, smokers. Odd ratios for birth defects adjusted for: Work in operating room at time of pregnancy, exposure to antineoplastic drugs, age, pregnancy order. All information were self-reported with the risk of influence the results.	Nurses interviewed by the occupational practitioners at time of yearly visit. Time of data collection: 1987-1989 France
Roeleveld 2002 (97)	Operating room female nurses, N=427 Control: Non-exposed female nurses from same hospitals, N=1010	Exposure through operating rooms during first month of the last pregnancy	No information about gas exposure, only based on type of work. N_2O not mentioned.	Spontaneous abortion: No difference between the groups. Low birth weight: No difference between the groups. Congenital malformations: Increased rate in the exposed group. Premature birth: No difference between the groups.	Operating room personnel consumed more alcohol, were more frequently exposed to disinfectants, ionising radiation, carrying heavy loads, standing longer than the control group. Reference nurses were more often exposed to antibiotics and experienced more time pressure. These differences were adjusted for during the analyses. All information were self-reported with the risk of influencing the results.	Survey. 83 of 121 Dutch hospitals. 4393 responded, 79% response rate. Of these: 1437 eligible. Time of data collection: 1990-1997. Netherlands
Lawson 2012 (98)	Female nurses from the Nurses' Health Study II, N=7482, with 775 spontaneous abortions. Abortions separated into categories of mother's exposure. Exposure of <1 hour/day is the reference (control)	Different occupational exposures: Antineoplastic, anaesthetic gases, antiviral drugs, sterilization agents, and x-rays. Exposure ≥ 1 h per day during first trimester.	N_2O mentioned.	Spontaneous abortion: No difference between the different anaesthetic exposure groups. (Higher odds ratio for nurses exposed to antineoplastic agents and sterilising agents.)	Other work exposures Parity, shift work and hours worked per week. All these confounders were adjusted for in sub-analysis. All information were self-reported with the risk of influencing the results.	Survey. Nurses taken from The Nurses' Health Study II, a prospective cohort study of 116 430 US nurses, aged 25-42, in 14 states. Pregnancy and occupational exposures were collected retrospectively from 8461

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
						participants of this study. 7842 eligible for analysis, based on at least 1 pregnancy from 1993-2001. USA
Afshari 2015 (99)	Operating room female personnel, N=40 Control: Non-exposed hospital female personnel, N=40	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Spontaneous abortion: No difference between the groups Congenital malformations: No difference between the groups	The groups matched for age, education, consanguinity, gender, work experience, number of children and hours of work. All information were self-reported with the risk of influencing the results.	Case control. Personnel selected from 6 hospitals in Ahvaz. Time of data collection: Not mentioned. Iran

Effect of anaesthetic gases on DNA and cellular functions

We found 20 articles that studied the effect of anaesthetic gases on DNA and cellular functions. All of these mentioned N_2O as a part of the gases exposed to the personnel.

DNA outcomes	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design / Country
Bigatti 1985 (100)	Operating room personnel, N=17 Control: 1: X-ray exposed, N=12 2: Non-exposed control group, N=10	N_2O and enflurane (anaesthetic gases) exposure	No information	Chromosome aberration (CA): Increased frequency in the exposed group Sister chromatid exchanges (SCE) frequency in lymphocytes: No difference between the groups	Smoking, but no correlation to smoking was found	Non-randomized, controlled study Italy
Lamberti 1989 (101)	Hospital workers exposed to anaesthetic gases, N=15 Control: Hospital workers not exposed, N=15	N_2O, enflurane, halothane and isoflurane exposure	No information	Chromosomal aberration: No difference between the groups SCE: No difference between the groups	Smoking, but no statistically significant effect was found.	Non-randomized, controlled study. In hospital setting. Italy

DNA outcomes	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design / Country
Karelova 1992 (102)	Anaesthesiologists and nurses, N=24 Control: Healthy blood donors, N=30	N_2O and halothane exposure, with focus on halothane.	Only halothane were measured (9-450 mg/m3).	Aberrant cells: Increased frequency in the exposed group SCE: Increased frequency in the exposed group	Data on drug intake, contraception, viral or other diseases and vaccination during the preceding 3 months, smoking habits, alcohol intake, coffee drinking and X-ray diagnostics and therapy were collected via interviews, and may influence the results. However, no significant exposure to any genotoxic factor, other than anaesthetic gases, was found. No adjustments were done.	Non-randomized, controlled study. Departments of anaesthesiology and resuscitation. Czechoslovakia
Sardas 1992 (103)	Operating theatre personnel, N=67 Control: Unexposed healthy controls, N=50	Exposure to anaesthetic gases such as halothane, N_2O and isoflurane	No information	SCE: Increased frequency in the exposed group	Self-reported information, that may influence the results, were collected. Smoking, an increase in SCEs was found in smoking operating room personnel as compared to non-smoking controls.	Case-control. In hospital setting. Turkey
Sardas 1998 (104)	Anaesthetists, N=66 Control: Unexposed healthy controls, N=41	N_2O, halothane and isoflurane exposure	No information	Single strand DNA break: increased Also in smoke group	Self-reported information, that may influence the results, were collected. Smoking: an increase in DNA damage in exposed smokers were significantly higher than exposed non-smokers.	Non-randomized, controlled study. Turkey
Hoerauf 1999 genetic damage (105)	Non-smoking surgeons, N=10 Control: Matched non-smoking veterinary surgeons, N=10	N_2O and isoflurane exposure	TWA N_2O: 12.8 ppm TWA isoflurane: 5.3 ppm	SCE: Increased frequency in a dose-dependent matter Micronuclei (micronuclei/500 binucleated cells): No difference between groups	Self-reported information, that may influence the results, were collected. Smoking was not an issue, since both the exposed and the non-exposed group were non-smokers. No adjustments were done.	Non-randomized, controlled study. Operating theatre Germany
Hoerauf 1999 Chromatide exchange (106)	Non-smoking operating room workers, N=27 Control: Non-smoking matched personnel, N=27	N_2O and isoflurane exposure	N_2O TWA: 11.8 ppm Isoflurane TWA: 0.5 ppm	SCE: Increased frequency in the in whole exposed group, but no difference in exposed women	Gender: More females in the exposed group than in the control group. Self-reported information, that may influence the results, were collected. Smoking was not an issue, since both the exposed and the non-exposed group were non-smokers. No adjustments were done.	Non-randomized, controlled study. Operating theatre Germany
Goto 2000 (107)	Health care workers, N=20 Control: Non-exposed volunteers, N=10	N_2O, sevoflurane and isoflurane exposure	Scavenged / unscavenged theatres. Respective concentrations: N_2O: 39.5+-37.2 ppm/ 26+-16.1 ppm	Cell culture apoptosis: Inhibited at 24 h cell culture but not 1 h and 12 h in the exposed group	Gender: Fewer males in the exposed group than in the control group. No adjustments were done.	Non-randomized, controlled study. Ireland

DNA outcomes	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design / Country
			Isoflurane: 0.2+-0.3 ppm/ 0.3+-0.2 ppm Sevoflurane: 1.1+-0.7ppm/ 0.8+-1.5 ppm			
Pasquini 2001 (108)	Anaesthesiologists, N=46 Controls: persons living in same area, N=66	Mostly N_2O and enflurane exposure	No information	SCE: Decreased in the exposed group Micronuclei: Increased in female, but not male, exposed group	Self-reported information, that may influence the results, were collected. Gender, smoking, age were adjusted for.	Non-randomized, controlled study. Department of anaesthesiology in hospital, 19 operating rooms Italy
Rozgaj 2001 (109)	Health workers exposed to anaesthetic gases, N=43 Control: Non-exposed health workers, N=26	Exposure to N_2O and halothane, most commonly used	No ventilation	SCE: No difference between the groups Chromosome aberration: Increased in the exposed group	Self-reported information, that may influence the results, were collected. The ratio between smokers and non-smokers was not comparable between the groups. None worked with radiation. Adjusted for adjusted for gender, age, smoking and years of exposure.	Non-randomized, controlled study. Croatia
Wiesner 2001 (110)	1: High level exposure personnel, N=25 2: Low level exposure personnel, N=25 Control: Matched controls, 2 x N=25 (from the same two hospitals)	N_2O, halothane and isoflurane exposure	High level N_2O: 170 ppm Low level N_2O: 12 ppm	Micronuclei: Increased in the high exposure group, but not in the low exposure group	Self-reported information, that may influence the results, were collected. There were no differences between exposed and control groups regarding age, gender, and smoking habits. No one suffered from significant acute or chronic disease, and no one had former or continuing radiotherapy or chemotherapy.	Non-randomized, controlled study. Eastern European (high exposure group) and Germany (low exposure group. Poland and Austria
Lewinska 2005 (111)	Female nurses at surgical department, N=46 Control: Female nurses, non-exposed, N=28	N_2O, sevoflurane and isoflurane exposure through surgical department.	N_2O concentration: 36-2803 mg/m3 Sevoflurane and isoflurane below threshold limit (18 mg/m3)	Micronuclei: Increased rate in a dose dependent matter	Self-reported information, that may influence the results, were collected. Smoking; 46% in intervention group, 25% in control group. Multiple regression analysis was used to assess the effects of smoking, as well as other confounding factors as age, duration of exposure and exposure status on the induction of cytogenetic effects.	Non-randomized, controlled study. Surgical department at hospital in Lodz Poland

DNA outcomes	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design / Country
Eroglu 2006 (112)	Anaesthesiologists at end of working week, N=25 Control: 1: Same anaesthesiologists, but after 2 months outside operating theatre 2: Non-anaesthesiologists, N=25	N_2O and sevoflurane exposure	Air-conditioned operating theatre. N_2O: 119 ppm Sevoflurane: 8.9 ppm	SCE: Increased in the exposed group but full recovery after 2 months absence from exposure	Self-reported information, that may influence the results, were collected. There were no significant differences in subject characteristics (age, weight, height, gender, intake of alcohol, and duration of work in the hospital) between groups. Smokers were excluded from the study. No adjustments done.	Non-randomized, controlled study. Before-after. Hospital setting Turkey
Costa Paes 2014 (113)	Medical residents from anaesthesia and surgery areas, N=15. Both genders, age 27.9±2.3 years Control: 15 non exposed Both genders, age 26.8±1.9 years	Mainly isoflurane, to a lesser degree to sevoflurane and N_2O From eight months to 22 months of exposure.	No active scavenging system.	DNA damage (comet assay): Increased damage in the exposed group. Antioxidant defence: Increased level in the exposed group	Subjects with any disease, smokers, and alcoholics, those recently exposed to radiation, under medication or vitamin supplements/antioxidants, and those with any kind of occupational exposure other than waste anaesthetic gases (exposed group) were excluded from the study. There were no significant differences between the groups in age, gender, weight, height or body mass index ($p>0.05$). Self-reported information, that may influence the results, were collected. No adjustments were done.	Non-randomized, controlled study. Seven anaesthesiology and Surgery areas, UFAM Hospital in Manaus Brazil
Souza 2016 (114)	Anaesthesiologists, N= 30 Control: Matched, unexposed health workers, N=27	N_2O, isoflurane, sevoflurane and desfluran exposure	7 operating theatres, one with air-condition without scavenging; 6 with central scavenging systems and 6-8 air changes per h. Gas flow: 10 l/min. TWA N_2O: 178 ppm N_2O: 159 ppm (range 61-350 ppm) Isoflurane: 5.5 ppm Sevoflurane: 7.7 ppm Desfluran: 16.4 ppm	DNA damage: No difference between the groups Genomic instability, cytotoxicity, proliferative changes: Increased levels in the exposed group	Self-reported information, that may influence the results, were collected. The outcomes and their association with potential confounding variables (age, gender, duration of exposure) were analysed using a Poisson regression model.	Non-randomized, controlled study. Sao Paulo university hospital Brazil
Szyfter 2016 (115)	Exposed personnel from operating theatres, N=100	N_2O, halothane, isoflurane and sevoflurane exposure	Possible scavenging system	DNA lesions in lymphocytes: No difference between the groups	Time period of exposure. DNA fragmentation given in relation to exposure period.	Non-randomized, controlled study. Operating theatre

DNA outcomes	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design / Country
	Control: Non-exposed, N=100					personnel at University and local hospital in the Central Poland Poland
Chandrasekhar 2006 (116)	Operating room personnel, N=45 Both gender Mean age: 38.76 ± 8.66 Control: Matched, non-exposed, N=45 Both gender Age: 35.93 ± 11.43 (matched by age, gender, alcohol consumption, smoking habits)	Halothane, isoflurane, sevoflurane, sodium pentothal, N_2O, desfluran and enflurane exposure.	Air was conditioned by a laminar flow system producing an air exchange rate of 2000 cubic ft. air turnovers an hour without recirculation. The exhaust outlets of the anaesthetic machines of the operating room were connected to the hospital's central scavenging system with suction flow of 45 l/min. Definition of exposure: work for 6 days/week. The average duration of their employment in the operation theatre was 10.47 years (range 1–23 years).	DNA damage: Increased damage in the exposed group Chromosome aberrations, micronuclei frequency: Increased levels in the exposed group	Self-reported information, that may influence the results, were collected. Analysis of variance showed that smoking had a significant effect on DNA mean tail length, whereas alcohol consumption, duration of exposure to anaesthetic agents, age and gender had no significant effect. All the confounding factors had significant effect by the micronucleus test. However, smoking, alcohol consumption, age, gender and years of exposure showed no significant effect by the chromosome aberrations test.	Non-randomized, controlled study Questionnaire Operating room personnel India
Baysal 2009 (117)	Operating room personnel, N=30 Both gender 33±5 years Control: Non-exposed, N=30 Both gender 32±5 years	Halothane, isoflurane, sevoflurane, N_2O and desfluran exposure	The operating rooms have air conditioning and central high-flow scavenging system.	DNA damage: increased level in the exposed group	Self-reported information, that may influence the results, were collected Control group matched by age and gender. Persons with conditions that affect the determination of their oxidative stress status and DNA damage, such as autoimmune diseases, liver or pulmonary disease, or acute or chronic inflammation were excluded. Those taking any medications, vitamin supplements, or antioxidants or who smoked or drank alcohol on a regular basis were also excluded. No adjustments were done.	Non-randomized, controlled study Questionnaire Operating room personnel Turkey
Izdes 2010 (118)	Nurses, N=40 (31 female, 9 male) Mean age: 36.8±5.7 years Control:	Exposure to anaesthetic gases as N_2O, isoflurane, sevoflurane, and desfluran	Duration of exposure mean: 14.5±6.6 years. No scavenging system.	DNA damage: Increased level in the exposed group Total antioxidant capacity and	Self-reported information, that may influence the results, were collected. DNA damage was negatively correlated with the duration of exposure and age while smoking had no effect.	Controlled, not randomised. Questionnaires. Blood samples at the end of the last day of a workweek.

DNA outcomes	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design / Country
	Healthy non-exposed, N=40 (30 female , 10 male) Mean age: 34.4±6.5 years			glutathione levels: Lower levels, meaning unfavourable effect, in the exposed group		Nurses working in 0perating theatres. No history of infections and with no exposure to radiation. Turkey
El-Ebiary 2013 (119)	Operating room personnel, N=40 Both gender 26-56 years Years of exposure: 1-35 years Non-exposed, N=40 Both gender 27-55 years	A mixture of anaesthetic gases: Most commonly were New-Flotan1 (halothane stabilized with thymol), Isoflurane1, Ultane1 (sevoflurane containing no additives), and nitrous oxide.	Air conditioning systems but not central high-flow scavenging systems.	DNA damage: Increased damage in the exposed group	Self-reported information, that may influence the results, were collected Significant difference between smoker and non-smoker OR personnel in mean comet tail length. No difference due to age, gender, or duration of exposure.	Non-randomized, controlled study. Questionnaire. Operating room personnel University Hospital Egypt

SCE, Sister chromatid exchanges; CA, Chromosome aberration;

Neurobehavioral effects of anaesthesia exposure

We found 6 articles studying the neurobehavioral effect of anaesthetic gases. Four of them mentioned N_2O as one of the gases.

Neurobehavioral effects	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
Korttila 1978 (120)	Operating nurses, N=19 Control: Nurses from another ward at the same clinic, N=11	Exposure to: 1: N_2O relaxant-analgesic combination anaesthesia, N= 9 2: Halotane- N_2O anaesthesia, N=6 3: Halotane- N_2O anaesthesia, N=4	1: Engstrøm; semi-closed system; intubated patients; room-ventilation (10x per h) 2: Reise; Semi-open; intubated children; water tap suction of waste gases; no room ventilation 3: Reose; semi-open system; face mask; water tap suction, no room ventilation N_2O in room, mean (range): 1: 721 (470-1200) ppm 2: 397 (245-550) ppm 3: 265 (100-490) ppm	Neurobehavioral tests*: No difference between groups *- Driving skills - Psychomotor test - Hand coordination - Tapping speed - Reaction skills - Driving simulator	Age: Higher in operating nurses than in ward nurses. Linear correlation coefficients between age and various test parameters within the whole group was used.	Non-randomized, controlled study. Three operating rooms in Helsinki University Central Hospital Finland

Neurobehavioral effects	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
Stollery 1988 (121)	Anaesthetists, N=22 The population worked 1 day in reference facility and 1 day in a scavenged operating theatre	N_2O and halothane exposure	Anaesthetic machines with active, non-recirculating scavenging circuits with closed receiving systems (Howorth). Room-ventilation (15x per h). N_2O: 50.5-65.6 ppm (TWA) Halothane: 1.4 ppm	Neurobehavioral tests*: No difference between groups *- Psychological tasks - Syntactic reasoning - Serial reaction time - Category-search and free-recall - Visual-spatial memory	Self-reported information, that may influence the results, were collected. The same persons worked in operating theatre and in reference facility. The effect of carry-over effects was tested by including the order-of-exposure factor (group A *v.* group B) as the only between-subject factor in a repeated measures analysis. Other factors that were shown to have influence: Performance of the task was sensitive to self-reports of work demands, work autonomy, stress and arousal.	Cross-over. Operating theatre. UK
Tran 1994 (122)	Operating room staff, N=99 (73% responded to questionnaire) Control: Non-exposed staff, N=182 (91% responded to questionnaire)	Exposure of waste anaesthetic gases through work, with dosimetry, all operating rooms used scavenging systems	Operating rooms with scavenging systems. N_2O levels exceeded the current TLV of 50 ppm in 4 of 12 operating rooms.	Fatigue, headache, irritation: No difference between groups (increased headache for CO2 exposure)	Self-reported information, that may influence the results, were collected. Carbon dioxide, but in both groups. The poor association between nitrous oxide levels and acute symptoms remained after controlling for potential confounders, such as age, occupation, smoking habits, history of allergy, and carbon dioxide levels.	Cross sectional study (questionnaires and measurements). Operating theatre. USA
Lucchini 1995 (123)	Operating theatre staff, N=62 Control: Nurses from other departments, N=46	N_2O and ethrane (enflurane).	- Refer to historic values (N_2O during 1980's: above 300 ppm; early 1990's: below 100 ppm) - In Urine: First day a week: 20.7; last day: 26.8.	"Simple reaction time": Increased reaction time in the exposed group Other acute neurobehavioral effects*: No difference between groups (*psychomotoric test battery, profile of mood state, visual digit span for mechanical memory, Benton visual retention for visual memory, digit serial for visual learning ability, digit symbol for coding speed, aiming pursuit for motor speed and steadiness)	Self-reported information, that may influence the results, were collected. The subjects were neither currently nor previously exposed to neurotoxic agents such as metals, organic solvents or pesticides. The subjects were screened for any neurological and neuropsychiatric illness and consumption of medication that might have influenced their performance in psychometric tests. Stress and work organization were suggested as possible confounders. No adjustments was done.	Non-randomized, controlled study. 32 operating theatres at Spedali Civili of Brescia (hospital). Italy

Neurobehavioral effects	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
Lucchini 1996 (124)	Operating room workers, N=30 Control: Other hospital workers not exposed, N=20	Gaseous anaesthesia, including N2O	N_2O: 50.9 ppm	Neurobehavioral effect at relative low exposure level: Slower reaction time in the exposed group	Self-reported information, that may influence the results, were collected. The effect of stress was tested as a possible confounder However, the same group were tested during gaseous and nongaseous anaesthesia to ensure same stress level but different gas exposure levels.	Controlled trial, blinded. Cardiac Surgery Department of Brescian General Hospital Italy
Lucchini 1997 (125)	Operating theatre personnel, N=112 Control: Non-exposed personnel, N=135	Low levels of anaesthetic gases	N_2O: 20-23 ppm Halogenated gases: 0.3-0.4	Neurobehavioral effect at low exposure level: No difference between the groups	Self-reported information, that may influence the results, were collected. Bias due to confounding factors was reduced by the following exclusion criteria: daily alcohol intake exceeding 80g; daily coffee consumption exceeding 5 cups; assumption of CNS medication; neurological or psychiatric disorders; age ≥60 years; occupational or non-occupational exposure to other neurotoxic agents as metals and organic solvents. Stress level same for both groups. No adjustments done.	Non-randomized, controlled multicentre study. Several hospitals in northern Italy. Italy

Effect of anaesthetic gases on organ function

We found 7 articles that reported the effect of anaesthetic gases on organ function. All but one mentioned N_2O as a part of the gases exposed to the personnel.

Organ function	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
Dossing 1982 (126)	Technicians for control of anaesthesiology equipment, N=6 Anaesthesiologists, N=7 Control: Matched controls, N=13	N_2O and halothane	Technicians: exposure repair and control of equipment in room without ventilation. Anaesthesiologists: variation of nonbreeding systems without scavenging to closed systems with effective scavenging. N_2O: 55-75 ppm Halothane: 2-7 ppm	Hepatic microsomal activity: No difference between the groups	Self-reported information, that may influence the results, were collected. Bias due to confounding factors was reduced since the persons did not take drugs on a regular basis, and none of them had taken any drugs 14 d prior to the study All had an average daily alcohol consumption of less than five drinks (i e. < 50 g of ethanol) None suffered from allergic disorders, previous or present liver or kidney diseases. The exposed and the control groups were matched according to age, gender,	Non-randomized, controlled study. Surgery at Rigshospitalet, Copenhagen. Denmark.

Organ function	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
					educational level, and daily consumption of tobacco and alcohol. No adjustments was done.	
De Zotti 1983 (127)	A1: Anaesthetists, N=32 A2: Surgeons, nurses, N=29 Control: B: No exposure to anaesthetics but sharing infection and noxious chemical risks, N=87 C: Exposure to ionizing radiation, N=69	N_2O and enflurane, with and without scavenging	Three theatres has scavenging systems from the patients mask (non-rebreathing system used). Gas concentration was 3-8 times lower in the theatres with scavenging. N_2O: 500-1275 ppm Enflurane: 17.3-22.6 ppm (Enflurane: Recommended 2 ppm/ h, Wikipedia. Not used anymore)	Hepatic function*, renal function, haematological function**: No difference * Serum glutamic transaminase, serum glutamic ozaloacetic transaminase, alkaline phosphatase, bilirubin, prothrombin. ** Haemoglobin, haematocrit, red cell count, white and differential counts, platelet counts, IgG, IgA, IgM, IgD	No use of self-reporting information. No other confounding factors mentioned. No adjustments were done,	Non-randomized, controlled study. Seven operating theatres. Italy.
Franco 1991 (128)	Workers from anaesthesiology and ICU department, N=18 Control: Non-exposed, N=16	N_2O and isoflurane	N_2O concentration: <900 ppm Isoflurane concentration: <10 ppm Exposure defined as working 35 h/week for a period of 7-16 years.	Hepatic function*: Unfavourable effect in exposed subjects (short term effect only: after a workday, not before) * Determined by UDGA (urinary D-glucaric acid) excretion)	Self-reported information, that may influence the results, were collected. The exposed group and the control group had different exclusion criteria for smoking and alcohol, both higher for the exposed group. No adjustments were done,	Non-randomized, controlled study. Single centre. Italy.
Franco 1992 (129)	Anaesthesia staff, N=24 Control: Matched controls, N=24	N_2O and isoflurane	Mixture: N_2O concentration: <100 ppm Isoflurane concentration: <1 ppm	Hepatic function* No effect of N_2O but dose dependent effect of isoflurane * Determinesexd by UDGA (urinary D-glucaric acid) excretion)	Self-reported information, that may influence the results, were collected. Each subject was matched with an unexposed control by sex and age. No adjustments were done.	Non-randomized, controlled study. Anaesthesia unit. Italy
Cohen 1975 (84)	Exposed male oral surgeons and male dentists, N=1668 Control: Males in the same cohort who has	Exposure to anaesthesia gases at dental office	Unscavenged rooms. At least 3 h exposure per week. Refer to general concentrations at that time: Halothane: Exceed 73 ppm N_2O: 500-6000 ppm	Hepatic disease: Increased rate in exposed group Kidney disease: No difference between the groups	Self-reported information, that may influence the results, were collected. The incidence of liver disease was calculated after excluding cases of serum hepatitis to eliminate possible differences in exposure to blood and blood products.	Survey. Questionnaires to male members of American Society of Oral Surgeons (ASOS), N=2642, response rate of

Organ function	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
	less than 3h exposure per week, N=1660.					64.5%; and American Dental Association) ADA, N=4797, response rate of 38.9%. USA
Trevisan 2003 (130)	1: Personnel in surgical area using open circuits, N=25 2: Personnel in surgical area using closed circuit, N=36 Control: Non-exposed controls, N=43	N_2O and sevoflurane exposure	Open and closed circuits. N_2O: 0.9-111.6 ppm Sevoflurane: 0-1.88 ppm	Kidney function*: No difference between the groups * glucosaminidase, glutamine synthase, total protein	No self-reported data. No obvious confounders	Non-randomized, controlled study. Italy
ASA 1974 (82)	ASA, AANA, AORN/T, both genders, responders, N=29 810 Control: AAP, ANA, both genders, responders, N=10 234	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Hepatic disease: Higher rate in both female and male exposed groups compared to control groups. Renal disease: Female exposed group: Higher rate as compared to the control group. Male exposed group: No increase rate as compared to control group. In all cases: A cause-effect relationship could not be drawn.	Self-reported information, that may influence the results, were collected. The rates were standardized for age in the case of the disease rates.	National survey. The exposed group: Questionnaires mailed to 49 585 members of American Society of Anesthesiologis (ASA), American Association of Nurse Anesthesists (AANA) and Associations of Operating Room Nurses and Technicians (AORN/T). The control (unexposed group): Questionnaires mailed to 23 911 members of American Academy of Pediatrics (AAP)

Organ function	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
						and the American Nursing Association (ANA). Mean response rate of 55%. USA

Effect of anaesthetic gases on haematological and inflammatory parameters

We found 4 articles on the effect of anaesthetic gases on different haematological inflammatory parameters. All of these mentioned N_2O as a part of the gases exposed to the personnel.

Blood parameters	Population	Intervention	Gas delivery	Outcomes and short conclusion	Confounders	Study design
Peric 1991 (131)	Anaesthesiology staff, N=21 Control: 1: Baseline of the same staff (after holiday and after weekend) 2: Healthy controls, N=35	N_2O and halothane exposure	No scavenging. TWA N_2O: 85-1500 ppm	Red cell count, haemoglobin, haematocrit, T lymphocyte count: No difference between the groups Basophils: Disappeared in the exposed group CD2, CD4: Increased in the exposed group B cell decreased, and did not recover after holidays NK cells: decreased, but recovered	Self-reporting not mentioned. To avoid the influence of X rays on the immune system they had chosen personnel who did not work in an X-ray area. No adjustments done.	Non-randomized, controlled study. Before-after. Four operating theatres, Department of Anaesthesiology and Intensive Therapy Yugoslavia.
Peric 1994 (132)	Anaesthetic staff during peak working season, N=21 Control: 1: Same staff as intervention but after 3 weeks vacation, N=21 2: Matched heathy controls N=35	N_2O and halothane exposure.	Not available. Results analysed towards length (years) of exposure.	Blood count, IgX, Cell activity with mitogens: Correlation between higher recovery of erythrocyte count and increased age. Correlation between younger staff and stable monocyte, and T and B cell counts.	Self-reporting not mentioned. The results were age dependent. No adjustments done.	Non-randomized, controlled study. Before-after. Croatia.

Bargellini 2001 (133)	Physicians, N=51 Control: Matched controls, N=20	Exposure to anaesthetic gases (N_2O and isoflurane)	No concentrations are given. Short term: Activity in operating room during the last 15 days, yes/no Long term: Number of days in operating rooms during last semester: low: <40 days medium: 40-80 days high: >80 days	Immune cell parameters: Derangements in lymphocyte subpopulations where T-lymphocytes were more affected than B cells.	Self-reported information, that may influence the results, were collected. The analyses for T-cells (CD3) and for total T and T helper (CD4) were corrected for age, gender, coffee intake, physical activity, children at home. The analysis for natural killer cells (NK) was corrected for age, gender and coffee intake.	Cross-sectional survey. Three hospitals in Modena. Italy.
Chaoul 2015 (134)	Operating room medical personnel, minimum 3 years, N=15 Control: Unexposed medical personnel, N=15	Exposure to mixture of gases for 3 years (N_2O, isoflurane, sevoflurane)	N_2O concentration> 100 ppm Isoflurane and sevoflurane concentrations > 7 ppm	Pro-inflammatory cytokines: Increase in IL-8, in high exposure group	Self-reported information, that may influence the results, were collected. Obese individuals, pregnant women, smokers, alcoholics, and those who had any disease or history of occupational exposure to substances other than the anaesthetic gases under investigation, were excluded from the study. Subjects who had any type of infection or inflammation within the preceding 30 days, those who had taken medication or antioxidant supplements, and those who had recently received radiation, were also excluded from the study to avoid bias. Demographic data did not significantly differ between groups	Non-randomized, controlled study. Operating theatre. Brazil

Anaesthetic gases effect on other biological outcomes

There were 5 articles presenting data on other outcomes from those mentioned above. Two of them mentioned N_2O as a part of the exposure gases and the three others only mentioned exposure to anaesthetic gases.

Other outcomes	Population	Intervention	Gas delivery	Outcomes and short conclusion	Confounders	Study design
Corbett 1973 (135)	Nurse-anaesthetist, N=525 Control: Expected incidence, matched for five-year age groups, , based on statistics from the Connecticut Tumor Registry (1966-1969)	Exposure to anaesthetic gases	No information.	Cancer frequency: increased in the exposed group	Self-reported information, that may influence the results, were collected. Possible confounders as suggested by the authors: genetic influences and personal habits. No adjustments were done	Survey. Send to all the female nurse-anaesthetists in Michigan (N=621). 525 responded, 84,5% response rate. USA
Pasquini 1989 (136)	Exposed staff, N=64 Control: Unexposed staff, N=37	N_2O and enflurane	Operating rooms had different facilities: air-scavenging system and/or air-conditioning system.	Urinary thioethers: Increased in the exposed group Urinary mutagenicity, D-Dlucaric acid: No difference between groups	Self-reported information, that may influence the results, were collected. No adjustments were done.	Non-randomized, controlled study. Five operating rooms. Italy.
Hedstrom 2013 (137)	1798 incident cases 5216 with prevalent cases of multiple sclerosis Control: For each case, two controls were randomly selected from the national population register. For the Incident cases: 3906 controls. For the prevalence cases: 4701 controls.	Anaesthetic gases including N_2O	No information.	Occurrence of multiple sclerosis (MS): No association to N_2O exposure	Self-reported information, that may influence the results, were collected. All analyses were adjusted for age, gender, residential area, ancestry, smoking and BMI at age 20 years. The analysis of nitric oxide and MS risk, based on EIMS, was also adjusted for parity.	Two population-based, case-control studies: EIMS (Epidemiological Investigation of Multiple Sclerosis; and GEMS (Gene and Environment in Multiple Sclerosis) respectively. Info regarding exposure etc. from questionnaire. Cases recruited from 40 study centres, including all university hospitals in Sweden. Sweden.
ASA 1974 (82)	Operating room personnel, both genders, N=29 810 Control: Non-exposed health care workers, both genders, N=10 234	Anaesthetic gas exposure	No information about gas exposure, only based on type of work.	Cancer incidences: Female exposed group: Higher rate as compared to the control group.	Self-reported information, that may influence the results, were collected. The rates were standardized for age.	National survey. The exposed group: Questionnaires mailed to 49 585 members of American Society of Anesthesiologis (ASA), American

			N_2O not mentioned separately.	Male exposed group: No increased rate as compared to control group. In all cases: A cause-effect relationship could not be drawn.		Association of Nurse Anesthesists (AANA) and Associations of Operating Room Nurses and Technicians (AORN/T). The control (unexposed group): Questionnaires mailed to 23 911 members of American Academy of Pediatrics (AAP) and the American Nursing Association (ANA). Mean response rate of 55%. Time of data collection: 1973 USA
Cohen 1975 (84)	Exposed male oral surgeons and male dentists, N=1668 Control: Males in the same cohort who has less than 3h exposure per week, N=1660.	Exposure to anaesthesia gases at dental office	Unscavenged rooms. At least 3 h exposure per week. Refer to general concentrations at that time: Halothane: Exceed 73 ppm N_2O: 500-6000 ppm	Cancer frequency: No difference between the groups	Self-reported information, that may influence the results, were collected. Age, smoking, adjusted for	Survey. Questionnaires to male members of American Society of Oral Surgeons (ASOS), N=2642, response rate of 64.5%; and American Dental Association) ADA, N=4797, response rate of 38.9%. Time of data collection: Not mentioned. USA

Appendix 9. Risk of Bias (according to Robins) for included studies on health

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
N2O effect on reproductive health									
Cohen 1980 (49)	Moderate Confounding factors are mentioned and adjusted for. However, all of them were self-reported.	Rates of congenital abnormality and spontaneous abortions in chairside assistants exposed to N2O alone were adjusted for age, smoking, and pregnancy history.	Low Participants were selected based on their profession.	Low	Serious Self-reported adherence to intervention (exposure)	Moderate The total number of participants is not clearly described. We therefore do not know if there are any missing data.	Moderate Self-reported outcomes.	Low No observed selection bias of reported results.	Serious
Heidam 1984 (65)	Moderate Self-reported confounding factors. Not adjusted for.	Possible confounders: - other toxins in dental practice - age - gravidity and pregnancy order Age, gravidity, pregnancy order were all adjusted for in the odds ratio analyses. Possible exposure to mercury was not adjusted for.	Low Participants were all dental assistants from 24 (all) clinics for the dental school service and 186 (of 194) private clinics. Their control group were employees less exposed (not exposed) to chemicals at work and included physiotherapists, occupational therapists, office workers, and technical assistants and designers. The study group and the controls were comparable with respect both to work postures and movements during a day.	Low	Serious Self-reported adherence to intervention (exposure)	Low The response rate was 91%.	Moderate Self-reported outcomes.	Low No observed selection bias of reported results.	Serious
Rowland 1992 (51)	Moderate Confounding factors are mentioned	Following confounders were considered and adjusted for: - recent use of oral contraceptives	Low Participants were selected based on their profession.	Low Good descriptions given, no	Serious Self-reported ad-	Low No observed missing data.	Moderate Self-reported outcomes.	Low No observed selection bias	Serious

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
	and adjusted for. However, all of them were self-reported.	- number of cigarettes per day - age - history of pelvic inflammatory disease - number of sexual partners, frequency of intercourse - race Confounding by other unmeasured factors potentially related to subfertility was minimized because they compared exposed dental assistants with unexposed dental assistants who were demographically similar. Mercury and amalgam are potential confounders but were not adjusted for as both groups were suggested to have the same potential exposure.		reason to suspect bias.	herence to intervention (exposure)			of reported results.	
Rowland 1995 (52)	Moderate Confounding factors are mentioned and adjusted for. However, all of them were self-reported.	As Rowland 1992	Low Participants were selected based on their profession.	Low Good descriptions given, no reason to suspect bias.	Serious Self-reported adherence to intervention (exposure)	Low No observed missing data.	Moderate Self-reported outcomes.	Low No observed selection bias of reported results.	Serious
Ahlborg 1996 (53)	Moderate Confounding factors are mentioned and adjusted for. However, all of them were self-reported.	The analysis was adjusted for shift work, cycle order, age, pregnancy order, previous fertility problem, oral contraceptive use, smoking and tea consumption.	Low Participants were selected based on their profession.	Low Good descriptions given, no reason to suspect bias.	Serious Self-reported adherence to intervention (exposure)	Low No observed missing data.	Moderate Self-reported outcomes.	Low No observed selection bias of reported results.	Serious

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
Axelsson 1996 (54)	Moderate Confounding factors are mentioned and adjusted for. However, all of them were self-reported.	The analysis was adjusted for shift work, cycle order, age, pregnancy order, previous fertility problem, oral contraceptive use, smoking and tea consumption.	Low Participants were selected based on their profession.	Low Good descriptions given, no reason to suspect bias.	Serious Self-reported adherence to intervention (exposure)	Low No observed missing data.	Moderate Self-reported outcomes.	Low Objective outcomes.	Serious
Bodin 1999 (55)	Moderate Confounding factors are mentioned and adjusted for. However, all of them were self-reported.	The analyses were adjusted for maternal age, parity, employment and work schedule.	Low Participants were selected based on their profession.	Low Interventions were shift work and N_2Oexposure. Both were described in detailed, both degree of shift work and amount of exposure with N_2O.	Serious Self-reported adherence to intervention (exposure)	Low No observed missing data.	Moderate Self-reported outcomes.	Low No observed selection bias of reported results.	Serious
Genetic toxicity of N_2O									
Husum 1986 (56)	Moderate Self-reported confounding factors. Not adjusted for.	Potential confounding factors: - other toxins in dental practice - smoking - age Smoking and age were adjusted for. The potential toxic effect of other toxins in dental practice was not mentioned.	Low Participants were selected based on their profession.	Low Intervention groups, which is level of exposure were clearly asked in the questionnaire (number of exposure hours per week).	Serious Self-reported adherence to intervention (exposure)	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Serious
Chang 1996 (57)	Low	Potential confounders: - other gases - age The analyses were adjusted for age. Smoking, chemotherapeutics, significant medical illnesses, chemotherapy, radiotherapy	Moderate Low number of participants.	Moderate Mean years of exposure given was shown with standard deviation. However, there were no information on how	Low Exposure related to the presence in the room.	Low No observed missing data.	Low Objective outcomes.	Low Objective outcomes.	Moderate

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
		were not possible confounders, since only non-smokers who were not involved with chemotherapeutics on the job and did not have significant medical illnesses, previous chemotherapy, or previous radiotherapy were included.		these data were selected.					
Wronska –Nofer 2009 (66)	Low	Smoking, age, gender, hospital locations were included as independent variables in a multiple linear regression model, without changing the results.	Low The control group was matched with the exposed group for age, gender, smoking habit and employment duration.	Low Intervention groups clearly defined and method for analyses and concentrations in operating rooms given.	Low Concentration of N_2O was measured.	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Low
Wronska-Nofer 2012 (59)	Low	Smoking, age, gender, hospital locations were included as independent variables in a multiple linear regression model, without changing the results.	Low The control group was matched with the exposed group for age, gender, smoking habit and employment duration.	Low Intervention groups clearly defined and method for analyses and concentrations in operating rooms given.	Low Concentration of N_2O was measured.	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Low
Neurological toxicity of N_2O									
Brodsky 1981 (50)	Moderate Confounding factors are mentioned and adjusted for. However, all of them were self-reported.	Following factors were considered: - age - smoking history - mercury exposure - whether the questionnaire was returned promptly or the respondent required prompting - response rate (70%) - exposure to halogenated anaesthetics - medical records	Low The questionnaires were send to aesthetic users and nonusers during the same time frame (1968-1978). A strength of the present study was availability of a control group of dentists and chair-side assistants who worked in the dental operatory under essentially similar operative conditions, but who	Low Intervention groups clearly defined: The level of aesthetic exposure was calculated by cumulative exposure hours.	Serious Self-reported adherence to intervention (exposure).	Low	Low Objective outcomes.	Low Pre-defined subsets of outcomes were described in methods.	Serious

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
		Problems of responder bias, inaccurate recall of events, and incomplete return rates were reduced due to the study design of this study, since the control group of dentists and chair-side assistants worked in the dental operatory under essentially similar operative conditions, but without using inhalation anaesthetics.	did not use inhalation anaesthetics in their practice.						
Isolani 1999 (47)	Low	None as the study subjects were their own control, analysed in the beginning and end of working week.	Low The population was their own control, analysed in the beginning and end of working week.	Low Urinary concentrations of N_2O was measured and thereby confirmed the intervention.	Low No reason to suspect bias.	Low No observed missing data.	Moderate The methods of outcome assessment were similar for the exposed and the non-exposed groups. The outcomes were subjective.	Low No observed selection bias of reported results.	Low (despite one moderate bias, due to the potential low effect of this bias on the results)
Scapellato 2008 (64)	Moderate Possible influence of isoflurane.	Alcohol intake and gender tested for with no influence. Subjects were excluded in the event of - alcohol intake exceeding 80 g/day; - coffee intake >5 cups/day - intake of drugs affecting the CNS - neurological or psychiatric disorders - age above 60 years - occupational or non-occupational exposure to other neurotoxic agents.	Low No reason to suspect bias.	Low Intervention groups clearly defined.	Low	Low No observed missing data.	Moderate Subjective outcomes.	Low No observed selection bias of reported results.	Moderate
N_2O effect on B12 metabolism and liver function									

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
Nunn 1982 (60)	Moderate	Possible confounders: - dietary intake of methionine - exposure to other gases in the operating theatre No confounding factors were discussed.	Moderate The selection of the exposed population were only 10 members of the operating theatre staff. Control subjects were sampled simultaneously and comprised of hospital staff who did not work in an environment where anaesthetics were used. No information for the two groups about diets rich in methionine.	Low. Classified based on exposure.	Low Gas concentration was measured.	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Moderate
Armstrong 1991 (63)	Moderate No confounding factors were discussed.	No information were given about possible variations between the exposed group and the control group.	Moderate There were no description on how the exposed subjects were selected.	Low The intervention groups were clearly defined (exposure through full-time work for at least 6 months).	Low The study was carried out through 5 consecutive days and the participants were followed during the week.	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Moderate
Krajewski 2007 (61)	Low	To avoid inclusion of confounding factors, subjects with haematological diseases, serious symptoms of neurological deterioration or heart failure were excluded. Self-reporting on alcohol, coffee and medications.	Low Participants were selected based on their profession.	Low Good description of type and concentrations of interventions. Exposure and control groups properly described.	Low The level of N_2O exposure were defined as below and above a given Occupational Exposure Limits (OEL).	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Low
Ekbom 2008 (48)	Low	No information about confounding factors but only two subjects which gave their blood samples at different time points.	Low Only two nurses, each serving as their own control.	Low Good description of exposure levels.	Low	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Low

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
Staubli 2016 (62)	Low	The analysis for B12 was adjusted for age. The control group (working in ICU) was assumed to have the same level of stress as the exposed group. No difference in distribution for gender.	Low Subjects had the same working background. Two of the included subjects did not continue the study (one refused to sign the written informed consent, and the other met the exclusion criteria of the study).	Low Intervention groups clearly defined.	Low Concentration of N_2O was measured.	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Low

for confounding factors.

	Population	Intervention	Gas exposure details	Outcome	Study design	Country
N_2O effect on reproductive health						
Cohen 1980 (49)	Groups compared for the outcomes in our report: Pregnancies/live births among exposed female dental assistants, N=701 / 579 Control: Pregnancies/live births among non-exposed female dental assistants, N=3197 / 2882	N_2O exposure in dental setting.	Self-reported use of anaesthetics and information about N_2O exposure per week. No information about scavenging of gases.	For dental assistants with specific data for N_2O - Spontaneous abortion - Congenital abnormalities The number exposed to only N_2O are not given.	Epidemiologic survey, controlled For recruiting dentists: Postcard to members of the American Dental Association (138 278). A stratified systematic sampling of the responders (107 771, 73% response rate) was subsequently used to establish two groups of equal size representing approximately 15 000 users and 15 000 non-users of inhalation anaesthetics. For recruiting chairside assistants: Dentists were asked to give names on their assisting personnel.	USA
Heidam 1984 (65)	Dental assistants: Questionnaires sent: 772 Replies: 728 Control: Reference group, N=1431 (physiotherapists, occupational therapists, office workers, technical assistants, designers)	Exposure of potential toxic agents through 10 different occupations. For dental workers: N_2O	Self-reported exposure. N_2O is mentioned separately.	Spontaneous abortion	Survey and hospital records. Dental assistants, factory workers, painters, gardening workers. Dental assistants: from 24 (all) clinics for the dental school service and 186 of 194 private clinics.	Denmark
Rowland 1992 (51)	Female dental assistants who was pregnant during a given period and completed telephone interview, N=418 Age range: 18-39 years	N_2O exposure in dental setting	No concentrations given. Scavenged vs non-scavenged gas and hours of N_2O exposure per week (catego-	- Fertility (infertility defined as more than 30 cycles without conception)	Epidemiologic survey, controlled. Female dental assistants from the dental-assistant	USA

	Population	Intervention	Gas exposure details	Outcome	Study design	Country
	The population was divided into exposure groups (see results chapter).		rized to more or less than 5 hours (Rowland 1992), or 3 hours (Rowland 1995) per week).		registry of the California Department of Consumer Affairs were mailed a questionnaire for eligibility (N=7000). 69% response rate.	
Rowland 1995 (52)	Female dental assistants, who provided information when they conceived their most recent pregnancy, and was working full time, N=1465 Age 18-39 years The population was divided into exposure groups (see results chapter).			- Spontaneous abortion		
Ahlborg 1996 (53)	Pregnancies, N=1484 in 751 female midwives The population was divided into exposure groups (see results chapter).	N_2O exposure as the only gas. Shift work.	Number of deliveries with N_2O exposure (more or less than 30 deliveries per month), no concentration given. In the questionnaire, the subjects were asked about whether scavenging systems were used on their work place, but due to high uncertainty in the replies, this was not used in the analyses.	- Fertility	Epidemiologic survey, controlled Midwives from the Swedish Midwives Association, born 1940 and after, were mailed a questionnaire (N=3985). 84.3% response rate.	Sweden
Axelsson 1996 (54)	Pregnancies, N=1717 (the number of midwives is not mentioned but criteria included: pregnancies of women working as midwives, and working more than half time during first trimester) The population was divided into exposure groups (see results chapter).		As above, but level of exposure were more or less than 50% of deliveries with exposure.	- Spontaneous abortion		
Bodin 1999 (55)	Pregnancies, N=1781 pregnancies in 1302 women (inclusion criteria: working more than half time during the second trimester of pregnancy) The population was divided into exposure groups (see results chapter).		As Ahlborg 1996, but no sub-grouping of exposure.	- Birth weight - Gestational age		

	Population	Intervention	Gas exposure details	Outcome	Study design	Country
Genetic toxicity of N_2O						
Husum 1986 (56)	Female dentists, N=38 Female chairside assistants, N=74 Male dentists, N=30 Age range: 18-67 years The population was divided into the degree of exposure (see results chapter details).	N_2O exposure in dental setting.	N_2O exposure groups defined by hours of exposure per week. Only single measurements of the concentration of N_2O were done, revealing concentrations significantly above 100 ppm. The duration of working in the dental operatory ranged from 1-40 years. Scavenging system.	- Sister chromatid exchange	Non-randomized controlled trial. Multicentre, Public Child Dental Service and private practices.	Denmark
Chang 1996 (57)	Female paediatric anaesthetic nurses, N=18 Control: Other nurses, N=18	N_2O and negligible concentrations of halothane and isoflurane	At least 5 years employment with constant involvement in paediatric anaesthesia.	- Micronuclei formation	Non-randomized, controlled study. Paediatric anaesthesia.	Taiwan.
Wronska – Nofer 2009 (66)	Female nurses, n=55 Male anaesthesiologists, N= 29 Control: Matched unexposed female nurses, n=52 Matched unexposed male doctors, N=31 Matched for age, gender, smoking habits and employment duration.	N_2O and halogenated hydrocarbon exposure.	Concentration of gases (mean, range): - N_2O: 244.4 ppm (19.86-834.39) - Isoflurane: 0.69 (0.066-1.86) ppm - Sevoflurane: 0.57 (0.049-1.83) ppm The operating rooms had 1 of 3 different ventilation systems with respect to number of air changes/h and efficiency in removing exhaust gases. Employment duration, mean (range): Women: 15 (5-26) years Men: 18 (5-31) years This study is included despite hydrocarbon exposure were present since results were presented in a dose-dependent matter for N_2O and not for other gases.	- DNA damage (Comet assay) - Concentration of gases	Cross-sectional, controlled. Included questionnaires about demographic data, place of residence, smoking habit, and working activities in the past. Blood samples were collected simultaneously from medical personnel of operating rooms and other wards. Multicentre (10 hospitals, 24 operating rooms).	Poland
Wronska-Nofer 2012 (59)	Female nurses, N=36 Control: Matched unexposed female health care workers, N=36.	N_2O and halogenated hydrocarbon exposure.	Concentration if gases (range): - N_2O: 102.77- 834.39 ppm - Isoflurane: 0.053-1.99 ppm - Sevoflurane: 0.061-1.71 ppm No information about ventilation or scavenging systems.	- DNA damage (Comet assay) - Reactive oxygen species (ROS) in leucocytes - Oxidative stress markers	Cross-sectional, controlled Included questionnaires about demographic data, place of residence, smoking habit, and working activities in the past.	Poland

	Population	Intervention	Gas exposure details	Outcome	Study design	Country
	Matched for age and employment duration. Smokers, past-smokers and subjects with history of occupational exposure to X-rays were excluded.		Employment duration: 5-27 years. Reason for inclusion despite presence of other gases, as Wronska-Nofer 2009.		Blood samples were collected simultaneously from medical personnel of operating rooms and other wards. Multicentre.	
Neurological toxicity of N_2O						
Brodsky 1981 (50)	Male dentists: Non-exposed, N=7886 Light exposure, N=6761 Heavy exposure, N=3206 Female dental assistants: Non-exposed, N=6593 Light exposure, N=9311 Heavy exposure, N=2163 Age were not reported, but assume same as in Cohen 1980. The population was divided into outcome groups.	N_2O exposure in dental setting	Self-reported use of anaesthetics and information about N_2O exposure alone. No information about scavenging of gases.	Neurologic disease: Group 1: symptoms secondary to specific nerve irritation Group 2: nonspecific symptoms without a neurologic diagnosis Group 3: symptoms secondary to specific diseases Group 4: miscellaneous neurologic disease Group 5: no neurologic complaints Study participants were categorized accordingly.	Epidemiologic survey. Same as *Cohen 1980.*	USA
Isolani 1999 (47)	Anaesthetists, N=37 (20 men, 17 women) Mean age: 42.7±5.8 years. The anaesthetists were their own control, tests taken on the first and on the last day of the working week.	Low N_2O exposure in operating theatre setting	Mean occupational exposure to N_2O:13.9±7.1 years. No information about scavenging of gases.	Neurobehavioral effect: - SRT (simple reaction time) - CWV (colour word vigilance) - Stress and arousal by MRS (mood rating scale) - Concentration of N_2O in urine	Non-randomized controlled trial. Single centre.	Italy
Scapellato 2008 (64)	Operating room nurses, N=38 Population divided according to N2O exposure. For the highest exposure: Both gender, more female Mean age: 33.75±7.72 years Control: Unexposed nurses, N=23 Both gender, mostly female: Mean age: 32.09±7.23 years	N_2O and isoflurane exposure in operating theatre setting.	The highest urinary value of N_2O ≥27 µg/l, this correspond to environmental concentration of 50 ppm. No information about scavenging of gases. The study is included despite trace amounts of other gases are found in the blood, argued by the authors that the levels are "below biological exposure limits".	- Euroquest - Block Design test - Stress and arousal (Mood Scale) - Complex reaction time (CWV, Colour Word Vigilance) - Urinary N_2O Tests/samples taken on Monday and Friday of a working week, before and after work shift	Non-randomized controlled trial. Single centre.	Italy
N_2O effect on B12 metabolism and liver function						

	Population	Intervention	Gas exposure details	Outcome	Study design	Country
Nunn 1982 (60)	Exposed operating staff, N=10 Both gender Age: 20-60 years Control: Non-exposed hospital staff, N=10 Both gender Age: 24-46 years	N_2O exposure in operating theatre	Concentration of N_2O: 150-400 ppm. No scavenging of gases.	- Serum concentration of methionine, leucine, isoleucine and valine (indicators for B12) - Hepatic enzymes Blood samples were taken between 1.30 and 3.30 pm on Thursday a typical working week.	Non-randomized controlled trial, from two hospitals. Multicentre.	England
Armstrong 1991 (63)	Anaesthetists, N=10 Gender and age not given Control: Healthy subjects, N=10 Both gender Age: 30.1±7.5 years	N_2O (70%) exposure in operating theatre	Concentration of N_2O: 53.4-159.2 ppm. The anaesthetists had been working full-time for at least 6 months. No information about scavenging of gases.	- Folate metabolism through the measurement of forminoglutamic acid excretion in urine Blood samples were taken over 5 or 7 consecutive days, for the controls and the anaesthetics, respectively.	Non-randomized controlled trial. Single centre.	Scotland
Krajewski 2007 (61)	Operating theatre nurses, N=95 Age: 25-56 years Control: Unexposed counterparts, N=90	N_2O and halogenated hydrocarbon exposure.	Concentration of gases: - N_2O: 19.44-58.33 ppm - Sevoflurane: 0.024-2.59 ppm - Isoflurane: 0.046-3.05 ppm - Halothane: 0.05-5.2 ppm Low exposure of N_2O: 102.77 ppm High exposure of N_2O: 417.75 ppm Exposure defined as above 5 h per week. Different scavenging system in different operating rooms. Fifteen of 26 operating theatres used anaesthetic gas scavenging devices. Reason for inclusion despite presence of other gases, as Wronska-Nofer 2009.	- B12 status (total homocysteine) - Haematological parameters - Folic acid	Non-randomized, controlled study. Multicentre.	Poland
Ekbom 2008 (48)	Nurses, N=2, performing 43 procedural pain management in children. Procedures last from 9-39 minutes	N_2O exposure in operating theatre	Concentration of N_2O: below 500 ppm. Scavenging mask and room ventilation for 2-3 air changes per hour. Scavenger not working in 9 of 43 procedures.	- Homocysteine - Haemoglobin - Macrocytosis - N_2O concentration	Non-randomized controlled trial. Single centre.	Germany

	Population	Intervention	Gas exposure details	Outcome	Study design	Country
	Control: Same nurses after vacation				Blood samples were taken before and after a nitrous oxide-free vacation.	
Staubli 2016 (62)	Physicians, N=7 Nurses, N=22 Both gender Age, mean: 41.3 years Control: Unexposed counterparts, N=31 Both gender Age, mean: 34.6 years	N_2O exposure in paediatric emergency department	On-demand valve or blender where exhaled gas goes into the room. No measurements of N_2O concentrations, but typically long- and short term maximum workplace concentration value of 200 ppm during 8 h/d and 800 ppm during 15 min/d, respectively.	- B12 - Homocysteine - Haematological parameters	Cross-sectional with control. Single centre.	Switzerland

Appendix 8. Summary of occupational safety with uncertain exposure to N_2O

N_2O is a common component in general anaesthesia and many of the included studies on our search for occupational exposure to N_2O (58 articles) were from hospital setting where the health personnel were exposed to anaesthetic waste gases through their work in operation theatres. In these studies, the role of N_2O was unclear and not analysed separately. We here show a short summary for the effect of anaesthetic gases on selected outcomes.

- *Reproducibility:* We found 20 articles with effect of anaesthetic waste gases on different aspects of reproducibility (*Table 17*). Of these, only 3 articles mentioned N_2O as a possible part of the anaesthetic gases.
- *DNA damage and cellular functions:* We found 20 articles with effect of anaesthetic waste gases on DNA damage and cellular functions (*Table 18*). All mentioned N_2O as a part of the gases exposed to the personnel.
- *Neurobehaviour:* We found 6 articles studying the neurobehavioral effect of anaesthetic gases (*Table 19*). Five of them mentioned N_2O as one of the gases.
- *Liver and kidney function:* We found 7 articles that studied the effect of anaesthetic gases on organ (liver and kidney) function (*Table 20*). All but two of these mentioned N_2O as a part of the gases exposed to the personnel.
- *Haematological and inflammatory parameters:* We found 4 articles studying haematological and inflammatory parameters (*Table 21*). All of these mentioned N_2O as a part of the gases exposed to the personnel.
- *Other outcomes than these mention above:* There were 5 articles presenting data on other outcomes from those mentioned above (*Table 22*). Two of them mentioned N_2O as a part of the exposure gases and the three others only mentioned exposure to anaesthetic gases.

The studies which mentioned N_2O did not present any specific data on this gas.

Table 17*. The effect* of anaesthetic gases on selected reproducibility outcomes*

References	Setting, N	Effect on spontaneous abortion	Effect on congenital abnormalities	Effect on infertility	Effect on birth weight	Effect on still birth/perinatal death
Cohen 1971	Hospital, N=290	Increased				

References	Setting, N	Effect on spontaneous abortion	Effect on congenital abnormali-ties	Effect on infertility	Effect on birth weight	Effect on still birth/perinatal death
Knill-Jones 1972	Hospital, N=1391	Working anaesthetists vs control: Increased Working vs non-working anaesthetists: Increased	Working anaesthetists vs control: No difference Working vs non-working anaesthetists: Increased			
Rosenberg 1973	Hospital, N= 302	Increased (no causality was drawn)				
ASA 1974	Hospital, N= 40 044	In female op-erating room personnel: Increased In wives of exposed males: Little evidence (no causality was drawn)	In female ex-posed group and in the wives of ex-posed males: Increased (no causality was drawn			
Corbett 1974	Hospital, N=695	No data	Increased (no causality was drawn)			
Cohen 1975	Dental operating rooms and dental office N=3328	In spouses of exposed sub-jects: Increased	No difference			
Mirakhur 1975	Hospital, N=280	Increased	No difference			No difference (stillbirth)
Pharoah 1977	Hospital, N=3387	No difference	Increased		Lower	Increased (still-birth)
Ericson 1979	Hospital, N=494 exposed plus an undefined number of controls	-	No difference		No difference	No difference (perinatal death)

References	Setting, N	Effect on spontaneous abortion	Effect on congenital abnormalities	Effect on infertility	Effect on birth weight	Effect on still birth/perinatal death
Lauwerys 1981	Hospital, N=1027	Exposed females and spouses to exposed males: No difference	Exposed females and spouses to exposed males: No difference			Exposed females and spouses to exposed males: No difference (stillbirths)
Wyrobek 1981	Hospital, N=72	-		No difference (sperm quality)		
Axelsson 1982	Hospital, N=610	No difference				
Hemminki 1985	Hospital, N=962	No difference	No difference			
Ericson 1985	Hospital, N=2705	No difference	Compared to expected nationwide data: Lower Compared to control nurses: No difference		No difference	No difference (perinatal death)
Ericson 1989	Different cohorts, see Appendix 8	No difference	No difference		No difference	Lower (perinatal death)
Guirguis 1990	Hospital, N=8538	Exposed females and spouses to exposed males: Increased	Exposed mothers: Increased			
Saurel-Cubizolles 1994	Hospital, N= 1367	Increased	No difference			
Roeleveld 2002	Hospital, N=1437	No difference	Increased		No difference	
Lawson 2012	Hospital, N=7482	No difference				
Sharifi 2015	Hospital, N=80	No difference	No difference			

*N=Number of all subjects in the study; *All the effects are the effect of exposure of anaesthetic gases versus no exposure*

Table 18. *Selected outcomes for the effect of anaesthetic waste gases on DNA and cellular functions*

DNA outcomes	Setting, N	Chromosome aberration	DNA damage	Sister chromatid exchange	Micronuclei formation
Bigatti 1985	Hospital, N=39	Increased		No difference	
Lamberti 1989	Hospital, N=30	No difference		No difference	
Karelova 1992	Hospital, N=54	Increased		Increased	
Sardas 1992	Hospital, N=117			Increased	
Sardas 1998	Hospital, N=107		Increased		
Hoerauf 1999 genetic damage	Hospital, N=20			Increased, dose dependent	No difference
Hoerauf 1999 Chromatide exchange	Hospital, N=54			Increased, in whole group, No difference in women	
Goto 2000*	Hospital, N=30				
Pasquini 2001	Hospital, N=112			Decreased	Increased in female exposed group, but not in male
Rozgaj 2001	Hospital, N=69	Increased		No difference	
Wiesner 2001	Hospital, N=75				Increased in high exposure No difference in low exposure
Lewinska 2005	Hospital, N=74				Increased
Eroglu 2006	Hospital, N=50			Increased	
Costa Paes 2014	Hospital, N=30		Increased		
Souza 2016	Hospital, N= 57		No difference		
Szyfter 2016	Hospital, N=200	No difference			
Chandrasekhar 2006	Hospital, N=90	Increased	Increased		
Baysal 2009	Hospital, N=60		Increased		
Izdes 2010	Hospital, N=80		Increased		
El-Elbiary 2013	Hospital, N=80		Increased		

** Presented none of the selected outcomes*

Table 19. *Neurobehavioral effects of anaesthetic waste gas exposure*

Reference	Population	Reaction time	Neurobehavioral effect
Korttila 1978	Hospital, N=30		No difference

Stollery 1988	Hospital, N=22		No difference
Tran 1994*	Hospital, N=281		
Lucchini 1995	Hospital, N=108	Increased	No difference
Lucchini 1996	Hospital, N=50	Increased	
Lucchini 1997	Hospital, N=247		No difference

** Presented none of the selected outcomes*

Table 20. *Selected outcomes for the effect of anaesthetic waste gases on organ function*

Reference	Population	Organ function
Dossing 1982	Hospital, N=26	Liver: No difference
De Zotti 1983	Hospital, N=217	Liver: No difference
Franco 1991	Hospital, N=34	Liver: Unfavourable effect (increased UDGa values)
Franco 1992	Hospital, N=48	Liver: No difference
Cohen 1975	Dentist, N=3328	Liver: Unfavourable effect Kidney: No difference
Trevisan 2003	Hospital, N=104	Kidney: No difference
ASA 1974	Hospital, N=40 044	Liver: Unfavourable effect Kidney: Female: Unfavourable effect Kidney: Male: No difference

Table 21. *Selected outcomes for the effect of anaesthetic waste gases on haematological parameters and inflammatory markers*

Reference	Population	Outcome
Peric 1991	Hospital, N=56	Red cell count, haemoglobin, haematocrit, T lymphocyte count: No difference Basophils: Disappeared during exposure CD2, CD4: Increased B cell: Decreased, and did not recover after holidays NK cells: Decreased, but recovered
Peric 1994	Hospital, N=77	Blood count, IgX, cell activity with mitogens: No effect
Bargellini 2001	Hospital, N=71	Immune cell parameters: Unfavourable effect (Derangements in lymphocyte subpopulations where T-lymphocytes were more affected than B cells).
Chaoul 2015	Hospital, N= 30	Pro-inflammatory cytokines: Unfavourable effect (Increase in IL-8, in high exposure group)

Table 22. *Selected outcomes for the effect of anaesthetic waste gases on other biological outcomes*

Reference	Population	Outcome
Corbett 1973	Hospital, N=525 + control cohort	Cancer frequency: Increased
Pasquini 1989	Hospital, N=101	Urinary thioethers: Increased Urinary mutagenicity, D-Dlucaric acid: No difference
Hedstrom 2013	Hospital, N=15 621	Occurrence of multiple sclerosis (MS): No association
ASA 1974	Hospital, N=40 044	Cancer incidences: Female exposed group: Increased Male exposed group: No difference
Cohen 1975	Hospital, N=3328	Cancer: No difference

Characteristics of the studies

The following table lists the trials where general anaesthetics or N_2O in combination with other gases were used, and where no specific N_2O data were presented.

Reproductive health

We found 20 articles with effect of anaesthetic gases on different aspects of reproducibility. Of these, only 3 articles mentioned N_2O as a part of the anaesthetic gases.

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
Cohen 1971 (79)	Operating room female nurses, N=67 Female anaesthetists, N=50 Control: General duty female nurses, N=92 Female physicians, N=81	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. Mean years in the operating room: 3.9 N_2O not mentioned	Spontaneous abortion: Higher rate in the exposed groups compared to the control groups.	Age slightly higher in the exposed groups compared to controls. This was not adjusted for in the analyses. All information were self-reported with the risk of influence the results.	Survey with interviews and questionnaires respectively. Time of data collection: 1966-1970. USA
Knill-Jones 1972 (80)	Female anaesthetists, N=563 (sub-grouped based on whether they worked during the first 6 months of pregnancy or not)	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Working anaesthetists vs control: - Higher spontaneous abortion in the working group - No difference in children with congenital abnormalities	No confounders discussed. All information were self-reported with the risk of influence the results.	Survey among hospital health personnel. 80% response rate for both groups.

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
	Control: Female doctors, N=828			Working vs non-working anaesthetists: - Higher rate of spontaneous abortion in the working group - Increased rate of children with congenital abnormalities in the working group Crude group of anaesthetists vs control: - No difference in spontaneous abortion - No difference in stillbirth - No difference in children with congenital abnormalities - Higher unknown cause of infertility in the anaesthetists - No difference in infertility		Time of data collection: 1970 UK
Rosenberg 1973 (81)	Operating room female nurses, N=182 (anaesthesia nurses, N=58, scrub nurses, N=124) Control: Other female nurses, N=120 (from causality department, N=75, from intensive care, N=45)	Anaesthetic gas exposure and/or stress	Working in operating room. Additional information about radiation and halothane exposure. No information about scavenging systems. Mean length of continuous employment prior to conception in women with miscarriages: About 20 months in the exposed groups, and about 19 months in the control groups. N_2O not mentioned.	Spontaneous abortion: Higher rate of spontaneous abortions in the operating room nurses as compared to the control groups. The authors suggest that this was due to excessive workloads rather than anaesthetic gases.	Excessive workload and stress. The nurses working in operating rooms often had a hard irregular workload, as well as night duty. In the present study, it was tempting for the nurses to blame x-ray and halothane for their miscarriages, but there were no differences between the mean exposure to these two pollutants in the nurses having miscarriages and in the corresponding groups having full-time pregnancies. All information were self-reported with the risk of influence the results.	Questionnaire to 300 female health workers working as anaesthetists, scrub, causality and intensive care unit nurses from 16 Central hospitals and 4 University hospitals. Time of data collection: 1965-1973 Finland
ASA 1974 (82)	ASA, AANA, AORN/T, both genders, responders, N=29 810	Anaesthetic gas exposure	No information about gas exposure, only based on type of work.	Spontaneous abortion: In the female members of the operating room-exposed group:	The rates were standardized for both age and smoking habit at time of pregnancy.	National survey. The exposed group: Questionnaires

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
	Control: AAP, ANA, both genders, responders, N=10 234		N_2O not mentioned.	Higher rate of spontaneous abortion than in the control group. In the wives of exposed males: Little evidence that male exposure gave higher rate of abortion in their spouse. Congenital abnormalities: In female exposed group and in the wives of exposed males: Higher rate than in the control groups, but no causality was drawn.	All information were self-reported with the risk of influence the results.	mailed to 49 585 members of American Society of Anesthesiologis (ASA), American Association of Nurse Anesthesists (AANA) and Associations of Operating Room Nurses and Technicians (AORN/T). The control (unexposed group): Questionnaires mailed to 23 911 members of American Academy of Pediatrics (AAP) and the American Nursing Association (ANA). Mean response rate of 55%. Time of data collection: 1973 USA
Corbett 1974 (83)	Working female nurse anaesthetists, N=434 Control: Not working female nurse, N=261	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Birth defects: Higher rate in exposed group compared to control group	Mothers age at birth similar in exposed and unexposed group. Possible effects due to viruses and radiations were not handled in the analyses. All information were self-reported with the risk of influence the results.	Survey. Questionnaires to 621 female nurse anaesthetists. Time of data collection: Not mentioned. USA
Cohen 1975 (84)	Exposed male oral surgeons and male dentists, N=1668	Exposure to anaesthesia gases at dental office	Unscavenged rooms. At least 3 h exposure per week.	Spouse spontaneous abortion: Higher rate in the spouses of the surgeons with higher exposure	Age, smoking, adjusted for.	Survey. Questionnaires to male members of

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
	Control: Males in the same cohort who has less than 3h exposure per week, N=1660.		Refer to general concentrations at that time: Halothane: Exceed 73 ppm N_2O: 500-6000 ppm	than spouses of surgeons with less than 3 h exposure per week. Congenital abnormalities: No difference between the groups	All information were self-reported with the risk of influence the results.	American Society of Oral Surgeons (ASOS), N=2642, response rate of 64.5%; and American Dental Association) ADA, N=4797, response rate of 38.9%. Time of data collection: Not mentioned. USA
Knill-Jones 1975 (85)	Not possible to identify the population.	Anaesthetic gas exposure				
Mirakhur 1975 (86)	1) Exposed female anaesthetists, working more than 5 years, N=47 2) Non-medical wives of exposed male anaesthetists, N=136 Controls: 1) Female non-exposed physician, N=50 2) Wives of unexposed male physicians, N=47	Anaesthetic gas exposure	On average, the anaesthetists had been working for 36.9 hours per week over a period of 9.5 years. N_2O not mentioned.	Spontaneous abortion: Higher rate in the exposed group than in the non-exposed group Premature labour, stillbirth: No difference between the groups Congenital anomalies: No difference between the groups	The mean age of anaesthetists was lower than that of the physicians: not adjusted for in the analyses. All information were self-reported with the risk of influence the results.	Survey. Questionnaires, N=425, sent to members of the Indian Society of Anaesthetists. 281 returned. Response rate 66.1% Time of data collection: Not mentioned. India
Pharoah 1977 (87)	Female doctors working with anaesthetics. Control: Female doctors not working with anaesthetics. Total in both groups: 3387	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Spontaneous abortion: No difference between the groups Stillbirth: Higher rate in the exposed group than in the non-exposed group Birth weight: Lower birth weight in the exposed group than in the non-exposed group	Analyses were performed for different age groups. All information were self-reported with the risk of influence the results.	Survey. Questionnaires to all women on the Medical Registry for 1975, N=7992. 72% response rate. Time of data collection: 1975 England and Wales

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
				Congenital abnormalities: higher rate in the exposed group than in the non-exposed group		
Ericson 1979 (88)	Female working in operating rooms during pregnancy, N=494 Control: A reference population composed of all females employed in medical work in Sweden, who had delivered during last 2 years. Number not given.	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Threatened abortion: No difference between the groups Birth weight: No difference between the groups Perinatal death rate: No difference between the groups Congenital malformations: No difference between the groups	Age was adjusted for in the analyses.	Register study of women working in operating rooms during pregnancy Controlled. Time of data collection: 1973-75. Sweden
Lauwerys 1981 (89)	Anaesthetics and operating theatre nurses. Control: Dermatologists, and intensive care unit nurses and social nurses. Total in both groups: 1027 persons with 1910 pregnancies. Both genders (588 male, 435 female and 4 unknown).	Anaesthetic gas exposure (nitrous oxide, ether, trichloroethylene, cyclopropane, halothane, methoxyflurane, enflurane)	No other information about gas exposure, only based on type of work. N_2O mentioned.	For all results: the exposed group consists of both female anaesthetics and operating theatre nurses as well as spouses to male anaesthetics and operating theatre nurses Spontaneous abortions: No difference between the groups Stillbirths: No difference between the groups Premature births: No difference between the groups Congenital malformations: No difference between the groups	Low response rate, but similar response rate of the exposed and control groups. No significant difference in smoking habits of the mothers between the different exposure groups. Some of the exposed groups had higher prevalence of radiographic examination, more use of contraceptives in the 12 months preceding pregnancy, and higher occurrence of illnesses of the mother during pregnancy than in the control group. These differences were not adjusted for. The results were given for the total exposed group (exposed mothers or/and exposed fathers) versus control. All information were self-reported with the risk of influence the results.	Survey. For exposed group: Questionnaire to members in Belgian Society of Anaesthetics, and to operating theatre nurses. For unexposed group: members of Belgian Society of Dermatologists and Belgian Society of Occupational Physicians, and to nurses in intensive care unit and social Nurses. Response rate: 47% Time of data collection: Not mentioned. Belgium

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
Wyrobek 1981 (90)	Male anaesthesiologist working for minimum 1 year in hospital operating rooms, N=46 Control: Beginning residents in anaesthesiology, N=26	Anaesthetic gas exposure	Ventilated rooms with modern scavenging devices. N_2O not mentioned.	Concentration of sperm with abnormal head: No difference between the groups	Age: The anaesthesiologists were slightly older than the beginning residents, but this was not associated with any difference in sperm morphology. Results did not change when the analyses were limited to men having no confounding factors (varicocele, recent illness or urogenital tract infection, medications, heavy smoking, or frequent sauna use). The proportion of men with confounding factors in the control and exposed populations did not differ significantly. All information were self-reported with the risk of influence the results.	Non-randomized, controlled study. From Three San Francisco Bay Area Hospitals Time of data collection: Not mentioned USA
Axelsson 1982 (91)	Exposed female hospital workers, N=288 Control: Non-exposed workers from medical wards without exposure, N=322	Anaesthetic gas exposure	High level exposure areas (operating and anaesthesia departments). Low exposure areas (Intensive care, recovery, ear, nose and throat out-patient clinic). N_2O not mentioned.	Spontaneous abortion: No difference between groups.	Results were evaluated in relation to age, smoking habits, work site at the first trimester of pregnancy All information were self-reported with the risk of influence the results.	Survey. A cohort of exposed female hospital workers, not physicians, at Uddevalla Hospital. The information given in the questionnaire concerning miscarriages was individually compared to data from hospital records. Time of data collection: Pregnancies from 1970-1979 Sweden
Hemminki 1985 (92)	Case female nurses were selected who had had a spontaneous abortion or a malformed child between the years 1973 and 1979:	Exposure to anaesthetic gases, sterilising agents, cytostatic drugs and x-rays (grouped).	No information about gas exposure, only based on type of work. N_2O exposure mentioned.	Spontaneous abortion: No difference in exposure to anaesthetic gases between nurses with spontaneous abortion or normal births	A case control study using individual matching. More permanent night work among the cases (2.5% vs 1.7%). Information about exposure from the head nurse may be biased.	A case control study, using the Hospital Discharge Register and the Register of Congenital Malformations.

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
	1: Nurses with spontaneous abortion, N=217 2: Nurses with malformed child, N=46 Control: Controls consisted of three female nurses who had had a normal birth per case nurse. The control nurses were matched for age and hospital of employment. 1: Matched female nurses to the nurses with spontaneous abortion, N=571 2: Matched nurses to the nurses with malformed child, N=128			Congenital malformations: No difference in exposure to anaesthetic gases between nurses with malformed child or normal child	No adjustments were done.	Questionnaire for exposure to head nurses at general hospitals. 81% response rate. Time of data collection: Pregnancies from 1973-1979 Finland
Ericson 1985 (93)	Operating room female nurses, N=1323 Control: Expected values based on nationwide data.	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Spontaneous abortion: No difference between exposed group and nationwide average. Perinatal death rate: No difference between exposed group and nationwide average. Malformations: Lower rate when compared to nationwide average. Preterm birth: No difference between exposed group and control groups. Birth weight: No difference between exposed group and control groups.	Confounding factors raised by the authors: "It is possible that the conclusions drawn from questionnaire studies with sometimes rather high non-responder rates are false due to shortcomings in the material analysed, and that the registry data used in the present study are more likely to give correct estimates of the risks involved."	Register data and questionnaires. Information from Nurse Registry, Medical Birth Registry and Registry of Abortions were used to obtain the population. Time of data collection: 1973-1978. Sweden
Ericson 1989 (94)	Cohort 1. The 1976-1986 birth cohort: Infants born by dentists, dental assistants,	Exposure not clearly stated. Both mercury	No information about gas exposure, only based on type of work.	Cohort 1: Perinatal death: Lower rate in the exposed group than in the control	Mercury: The actual exposure may be low.	Register study: Central Health Registries, Medical Birth Registry, Hospital

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
	dental technicians in 1976 or 1982-86, N=8157 Cohort 2. The 1980-1981 birth cohort, spontaneous abortions, number of hospitalized spontaneous abortions, N=175 Cohort 3. The 1960s cohort, N=78 pregnancies with 7 spontaneous abortions Cohort 4. The 1965-1967 cohort: 220 infants born with neural tube defect. Control: Expected values based on number of births from all women with gainful occupation, after standardization for maternal age, in 1981.	and N_2O mentioned.	N_2O not mentioned.	Malformations: No difference between the groups Low birthweight: No difference between the groups Cohort 2: Spontaneous abortions: No difference between the groups Cohort 3: Spontaneous abortions: No difference between the groups Cohort 4: Congenital malformation, Neural tube defect: No difference between groups.	Cohort 1: Do not know that the women actually worked in early pregnancy in the professions stated. Cohort 2: Spontaneous abortions were identified from a Hospital Discharge Registry. Women who were not hospitalized and had an abortion, were not identified. No adjustments were done.	Discharge Register, and Registry of Congenital Malformations. Controlled. Time of data collection: See population. Sweden
Guirguis 1990 (95)	Exposed hospital female personnel, N=6336 Control: Non-exposed hospital female staff, N=2202	Anaesthetic gas exposure.	Chronically exposed: Spending at least two hours a week in the operating room. N_2O not mentioned.	Spontaneous abortion: Increased rate in both female workers and in spouses of exposed male workers. Congenital abnormalities: Increased risk for children born by exposed mothers.	*Confounders adjusted for in the analyses for spontaneous abortion*: Birth order, previous spontaneous abortion, age of mother at pregnancy, smoking during pregnancy, alcohol consumption during pregnancy, occupation. *Confounders adjusted for in the analyses for congenital abnormality*: As above with the exception of previous spontaneous abortion. *For both:* All information were self-reported with the risk of influence the results.	Retrospective study by questionnaires send to 75 hospitals in Ontario, Canada. 78.8% response rate for exposed personnel and 87.2% response rate for non-exposed staff. Time of data collection: 1981-1985 Canada
Saurel-Cubizolles 1994 (96)	Operating room female nurses, N=489 (268 in anal-	Anaesthetic gas exposure	No information about gas exposure, only based on type of work.	Spontaneous abortion: Higher rate in the exposed group.	Odds ratios for spontaneous abortions were adjusted for:	Survey among 17 hospitals in Paris in 1987-1989.

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
	yses for spontaneous abortions, and 221 in analyses for birth defects) Control: Female nurses in other departments, N=878 (458 in analyses for spontaneous abortions, and 420 in analyses for birth defects)		N_2O not mentioned.	Congenital abnormalities: No difference between the groups.	Work in operating room at time of pregnancy, exposure to antineoplastic drugs, age, number and outcomes of previous pregnancies, smokers. Odd ratios for birth defects adjusted for: Work in operating room at time of pregnancy, exposure to antineoplastic drugs, age, pregnancy order. All information were self-reported with the risk of influence the results.	Nurses interviewed by the occupational practitioners at time of yearly visit. Time of data collection: 1987-1989 France
Roeleveld 2002 (97)	Operating room female nurses, N=427 Control: Non-exposed female nurses from same hospitals, N=1010	Exposure through operating rooms during first month of the last pregnancy	No information about gas exposure, only based on type of work. N_2O not mentioned.	Spontaneous abortion: No difference between the groups. Low birth weight: No difference between the groups. Congenital malformations: Increased rate in the exposed group. Premature birth: No difference between the groups.	Operating room personnel consumed more alcohol, were more frequently exposed to disinfectants, ionising radiation, carrying heavy loads, standing longer than the control group. Reference nurses were more often exposed to antibiotics and experienced more time pressure. These differences were adjusted for during the analyses. All information were self-reported with the risk of influencing the results.	Survey. 83 of 121 Dutch hospitals. 4393 responded, 79% response rate. Of these: 1437 eligible. Time of data collection: 1990-1997. Netherlands
Lawson 2012 (98)	Female nurses from the Nurses' Health Study II, N=7482, with 775 spontaneous abortions. Abortions separated into categories of mother's exposure. Exposure of <1 hour/day is the reference (control)	Different occupational exposures: Antineoplastic, anaesthetic gases, antiviral drugs, sterilization agents, and x-rays. Exposure ≥ 1 h per day during first trimester.	N_2O mentioned.	Spontaneous abortion: No difference between the different anaesthetic exposure groups. (Higher odds ratio for nurses exposed to antineoplastic agents and sterilising agents.)	Other work exposures Parity, shift work and hours worked per week. All these confounders were adjusted for in sub-analysis. All information were self-reported with the risk of influencing the results.	Survey. Nurses taken from The Nurses' Health Study II, a prospective cohort study of 116 430 US nurses, aged 25-42, in 14 states. Pregnancy and occupational exposures were collected retrospectively from 8461

References	Population (Exposed and Control group)	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design /Country
						participants of this study. 7842 eligible for analysis, based on at least 1 pregnancy from 1993-2001. USA
Afshari 2015 (99)	Operating room female personnel, N=40 Control: Non-exposed hospital female personnel, N=40	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Spontaneous abortion: No difference between the groups Congenital malformations: No difference between the groups	The groups matched for age, education, consanguinity, gender, work experience, number of children and hours of work. All information were self-reported with the risk of influencing the results.	Case control. Personnel selected from 6 hospitals in Ahvaz. Time of data collection: Not mentioned. Iran

Effect of anaesthetic gases on DNA and cellular functions

We found 20 articles that studied the effect of anaesthetic gases on DNA and cellular functions. All of these mentioned N_2O as a part of the gases exposed to the personnel.

DNA outcomes	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design / Country
Bigatti 1985 (100)	Operating room personnel, N=17 Control: 1: X-ray exposed, N=12 2: Non-exposed control group, N=10	N_2O and enflurane (anaesthetic gases) exposure	No information	Chromosome aberration (CA): Increased frequency in the exposed group Sister chromatid exchanges (SCE) frequency in lymphocytes: No difference between the groups	Smoking, but no correlation to smoking was found	Non-randomized, controlled study Italy
Lamberti 1989 (101)	Hospital workers exposed to anaesthetic gases, N=15 Control: Hospital workers not exposed, N=15	N_2O, enflurane, halothane and isoflurane exposure	No information	Chromosomal aberration: No difference between the groups SCE: No difference between the groups	Smoking, but no statistically significant effect was found.	Non-randomized, controlled study. In hospital setting. Italy

DNA outcomes	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design / Country
Karelova 1992 (102)	Anaesthesiologists and nurses, N=24 Control: Healthy blood donors, N=30	N_2O and halothane exposure, with focus on halothane.	Only halothane were measured (9-450 mg/m3).	Aberrant cells: Increased frequency in the exposed group SCE: Increased frequency in the exposed group	Data on drug intake, contraception, viral or other diseases and vaccination during the preceding 3 months, smoking habits, alcohol intake, coffee drinking and X-ray diagnostics and therapy were collected via interviews, and may influence the results. However, no significant exposure to any genotoxic factor, other than anaesthetic gases, was found. No adjustments were done.	Non-randomized, controlled study. Departments of anaesthesiology and resuscitation. Czechoslovakia
Sardas 1992 (103)	Operating theatre personnel, N=67 Control: Unexposed healthy controls, N=50	Exposure to anaesthetic gases such as halothane, N_2O and isoflurane	No information	SCE: Increased frequency in the exposed group	Self-reported information, that may influence the results, were collected. Smoking, an increase in SCEs was found in smoking operating room personnel as compared to non-smoking controls.	Case-control. In hospital setting. Turkey
Sardas 1998 (104)	Anaesthetists, N=66 Control: Unexposed healthy controls, N=41	N_2O, halothane and isoflurane exposure	No information	Single strand DNA break: increased Also in smoke group	Self-reported information, that may influence the results, were collected. Smoking: an increase in DNA damage in exposed smokers were significantly higher than exposed non-smokers.	Non-randomized, controlled study. Turkey
Hoerauf 1999 genetic damage (105)	Non-smoking surgeons, N=10 Control: Matched non-smoking veterinary surgeons, N=10	N_2O and isoflurane exposure	TWA N_2O: 12.8 ppm TWA isoflurane: 5.3 ppm	SCE: Increased frequency in a dose-dependent matter Micronuclei (micronuclei/500 binucleated cells): No difference between groups	Self-reported information, that may influence the results, were collected. Smoking was not an issue, since both the exposed and the non-exposed group were non-smokers. No adjustments were done.	Non-randomized, controlled study. Operating theatre Germany
Hoerauf 1999 Chromatide exchange (106)	Non-smoking operating room workers, N=27 Control: Non-smoking matched personnel, N=27	N_2O and isoflurane exposure	N_2O TWA: 11.8 ppm Isoflurane TWA: 0.5 ppm	SCE: Increased frequency in the in whole exposed group, but no difference in exposed women	Gender: More females in the exposed group than in the control group. Self-reported information, that may influence the results, were collected. Smoking was not an issue, since both the exposed and the non-exposed group were non-smokers. No adjustments were done.	Non-randomized, controlled study. Operating theatre Germany
Goto 2000 (107)	Health care workers, N=20 Control: Non-exposed volunteers, N=10	N_2O, sevoflurane and isoflurane exposure	Scavenged / unscavenged theatres. Respective concentrations: N_2O: 39.5+-37.2 ppm/ 26+-16.1 ppm	Cell culture apoptosis: Inhibited at 24 h cell culture but not 1 h and 12 h in the exposed group	Gender: Fewer males in the exposed group than in the control group. No adjustments were done.	Non-randomized, controlled study. Ireland

DNA outcomes	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design / Country
			Isoflurane: 0.2+-0.3 ppm/ 0.3+-0.2 ppm Sevoflurane: 1.1+-0.7ppm/ 0.8+-1.5 ppm			
Pasquini 2001 (108)	Anaesthesiologists, N=46 Controls: persons living in same area, N=66	Mostly N_2O and enflurane exposure	No information	SCE: Decreased in the exposed group Micronuclei: Increased in female, but not male, exposed group	Self-reported information, that may influence the results, were collected. Gender, smoking, age were adjusted for.	Non-randomized, controlled study. Department of anaesthesiology in hospital, 19 operating rooms Italy
Rozgaj 2001 (109)	Health workers exposed to anaesthetic gases, N=43 Control: Non-exposed health workers, N=26	Exposure to N_2O and halothane, most commonly used	No ventilation	SCE: No difference between the groups Chromosome aberration: Increased in the exposed group	Self-reported information, that may influence the results, were collected. The ratio between smokers and non-smokers was not comparable between the groups. None worked with radiation. Adjusted for adjusted for gender, age, smoking and years of exposure.	Non-randomized, controlled study. Croatia
Wiesner 2001 (110)	1: High level exposure personnel, N=25 2: Low level exposure personnel, N=25 Control: Matched controls, 2 x N=25 (from the same two hospitals)	N_2O, halothane and isoflurane exposure	High level N_2O: 170 ppm Low level N_2O: 12 ppm	Micronuclei: Increased in the high exposure group, but not in the low exposure group	Self-reported information, that may influence the results, were collected. There were no differences between exposed and control groups regarding age, gender, and smoking habits. No one suffered from significant acute or chronic disease, and no one had former or continuing radiotherapy or chemotherapy.	Non-randomized, controlled study. Eastern European (high exposure group) and Germany (low exposure group. Poland and Austria
Lewinska 2005 (111)	Female nurses at surgical department, N=46 Control: Female nurses, non-exposed, N=28	N_2O, sevoflurane and isoflurane exposure through surgical department.	N_2O concentration: 36-2803 mg/m3 Sevoflurane and isoflurane below threshold limit (18 mg/m3)	Micronuclei: Increased rate in a dose dependent matter	Self-reported information, that may influence the results, were collected. Smoking; 46% in intervention group, 25% in control group. Multiple regression analysis was used to assess the effects of smoking, as well as other confounding factors as age, duration of exposure and exposure status on the induction of cytogenetic effects.	Non-randomized, controlled study. Surgical department at hospital in Lodz Poland

DNA outcomes	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design / Country
Eroglu 2006 (112)	Anaesthesiologists at end of working week, N=25 Control: 1: Same anaesthesiologists, but after 2 months outside operating theatre 2: Non-anaesthesiologists, N=25	N_2O and sevoflurane exposure	Air-conditioned operating theatre. N_2O: 119 ppm Sevoflurane: 8.9 ppm	SCE: Increased in the exposed group but full recovery after 2 months absence from exposure	Self-reported information, that may influence the results, were collected. There were no significant differences in subject characteristics (age, weight, height, gender, intake of alcohol, and duration of work in the hospital) between groups. Smokers were excluded from the study. No adjustments done.	Non-randomized, controlled study. Before-after. Hospital setting Turkey
Costa Paes 2014 (113)	Medical residents from anaesthesia and surgery areas, N=15. Both genders, age 27.9±2.3 years Control: 15 non exposed Both genders, age 26.8±1.9 years	Mainly isoflurane, to a lesser degree to sevoflurane and N_2O From eight months to 22 months of exposure.	No active scavenging system.	DNA damage (comet assay): Increased damage in the exposed group. Antioxidant defence: Increased level in the exposed group	Subjects with any disease, smokers, and alcoholics, those recently exposed to radiation, under medication or vitamin supplements/antioxidants, and those with any kind of occupational exposure other than waste anaesthetic gases (exposed group) were excluded from the study. There were no significant differences between the groups in age, gender, weight, height or body mass index ($p>0.05$). Self-reported information, that may influence the results, were collected. No adjustments were done.	Non-randomized, controlled study. Seven anaesthesiology and Surgery areas, UFAM Hospital in Manaus Brazil
Souza 2016 (114)	Anaesthesiologists, N= 30 Control: Matched, unexposed health workers, N=27	N_2O, isoflurane, sevoflurane and desfluran exposure	7 operating theatres, one with air-condition without scavenging; 6 with central scavenging systems and 6-8 air changes per h. Gas flow: 10 l/min. TWA N_2O: 178 ppm N_2O: 159 ppm (range 61-350 ppm) Isoflurane: 5.5 ppm Sevoflurane: 7.7 ppm Desfluran: 16.4 ppm	DNA damage: No difference between the groups Genomic instability, cytotoxicity, proliferative changes: Increased levels in the exposed group	Self-reported information, that may influence the results, were collected. The outcomes and their association with potential confounding variables (age, gender, duration of exposure) were analysed using a Poisson regression model.	Non-randomized, controlled study. Sao Paulo university hospital Brazil
Szyfter 2016 (115)	Exposed personnel from operating theatres, N=100	N_2O, halothane, isoflurane and sevoflurane exposure	Possible scavenging system	DNA lesions in lymphocytes: No difference between the groups	Time period of exposure. DNA fragmentation given in relation to exposure period.	Non-randomized, controlled study. Operating theatre

DNA outcomes	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design / Country
	Control: Non-exposed, N=100					personnel at University and local hospital in the Central Poland Poland
Chandrasekhar 2006 (116)	Operating room personnel, N=45 Both gender Mean age: 38.76 ± 8.66 Control: Matched, non-exposed, N=45 Both gender Age: 35.93 ± 11.43 (matched by age, gender, alcohol consumption, smoking habits)	Halothane, isoflurane, sevoflurane, sodium pentothal, N_2O, desfluran and enflurane exposure.	Air was conditioned by a laminar flow system producing an air exchange rate of 2000 cubic ft. air turnovers an hour without recirculation. The exhaust outlets of the anaesthetic machines of the operating room were connected to the hospital's central scavenging system with suction flow of 45 l/min. Definition of exposure: work for 6 days/week. The average duration of their employment in the operation theatre was 10.47 years (range 1–23 years).	DNA damage: Increased damage in the exposed group Chromosome aberrations, micronuclei frequency: Increased levels in the exposed group	Self-reported information, that may influence the results, were collected. Analysis of variance showed that smoking had a significant effect on DNA mean tail length, whereas alcohol consumption, duration of exposure to anaesthetic agents, age and gender had no significant effect. All the confounding factors had significant effect by the micronucleus test. However, smoking, alcohol consumption, age, gender and years of exposure showed no significant effect by the chromosome aberrations test.	Non-randomized, controlled study Questionnaire Operating room personnel India
Baysal 2009 (117)	Operating room personnel, N=30 Both gender 33±5 years Control: Non-exposed, N=30 Both gender 32±5 years	Halothane, isoflurane, sevoflurane, N_2O and desfluran exposure	The operating rooms have air conditioning and central high-flow scavenging system.	DNA damage: increased level in the exposed group	Self-reported information, that may influence the results, were collected Control group matched by age and gender. Persons with conditions that affect the determination of their oxidative stress status and DNA damage, such as autoimmune diseases, liver or pulmonary disease, or acute or chronic inflammation were excluded. Those taking any medications, vitamin supplements, or antioxidants or who smoked or drank alcohol on a regular basis were also excluded. No adjustments were done.	Non-randomized, controlled study Questionnaire Operating room personnel Turkey
Izdes 2010 (118)	Nurses, N=40 (31 female, 9 male) Mean age: 36.8±5.7 years Control:	Exposure to anaesthetic gases as N_2O, isoflurane, sevoflurane, and desfluran	Duration of exposure mean: 14.5±6.6 years. No scavenging system.	DNA damage: Increased level in the exposed group Total antioxidant capacity and	Self-reported information, that may influence the results, were collected. DNA damage was negatively correlated with the duration of exposure and age while smoking had no effect.	Controlled, not randomised. Questionnaires. Blood samples at the end of the last day of a workweek.

DNA outcomes	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design / Country
	Healthy non-exposed, N=40 (30 female , 10 male) Mean age: 34.4±6.5 years			glutathione levels: Lower levels, meaning unfavourable effect, in the exposed group		Nurses working in 0perating theatres. No history of infections and with no exposure to radiation. Turkey
El-Ebiary 2013 (119)	Operating room personnel, N=40 Both gender 26-56 years Years of exposure: 1-35 years Non-exposed, N=40 Both gender 27-55 years	A mixture of anaesthetic gases: Most commonly were New-Flotan1 (halothane stabilized with thymol), Isoflurane1, Ultane1 (sevoflurane containing no additives), and nitrous oxide.	Air conditioning systems but not central high-flow scavenging systems.	DNA damage: Increased damage in the exposed group	Self-reported information, that may influence the results, were collected Significant difference between smoker and non-smoker OR personnel in mean comet tail length. No difference due to age, gender, or duration of exposure.	Non-randomized, controlled study. Questionnaire. Operating room personnel University Hospital Egypt

SCE, Sister chromatid exchanges; CA, Chromosome aberration;

Neurobehavioral effects of anaesthesia exposure

We found 6 articles studying the neurobehavioral effect of anaesthetic gases. Four of them mentioned N_2O as one of the gases.

Neurobehavioral effects	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
Korttila 1978 (120)	Operating nurses, N=19 Control: Nurses from another ward at the same clinic, N=11	Exposure to: 1: N_2O relaxant-analgesic combination anaesthesia, N= 9 2: Halotane- N_2O anaesthesia, N=6 3: Halotane- N_2O anaesthesia, N=4	1: Engstrøm; semi-closed system; intubated patients; room-ventilation (10x per h) 2: Reise; Semi-open; intubated children; water tap suction of waste gases; no room ventilation 3: Reose; semi-open system; face mask; water tap suction, no room ventilation N_2O in room, mean (range): 1: 721 (470-1200) ppm 2: 397 (245-550) ppm 3: 265 (100-490) ppm	Neurobehavioral tests*: No difference between groups *- Driving skills - Psychomotor test - Hand coordination - Tapping speed - Reaction skills - Driving simulator	Age: Higher in operating nurses than in ward nurses. Linear correlation coefficients between age and various test parameters within the whole group was used.	Non-randomized, controlled study. Three operating rooms in Helsinki University Central Hospital Finland

Neurobehavioral effects	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
Stollery 1988 (121)	Anaesthetists, N=22 The population worked 1 day in reference facility and 1 day in a scavenged operating theatre	N_2O and halothane exposure	Anaesthetic machines with active, non-recirculating scavenging circuits with closed receiving systems (Howorth). Room-ventilation (15x per h). N_2O: 50.5-65.6 ppm (TWA) Halothane: 1.4 ppm	Neurobehavioral tests*: No difference between groups *- Psychological tasks - Syntactic reasoning - Serial reaction time - Category-search and free-recall - Visual-spatial memory	Self-reported information, that may influence the results, were collected. The same persons worked in operating theatre and in reference facility. The effect of carry-over effects was tested by including the order-of-exposure factor (group A *v.* group B) as the only between-subject factor in a repeated measures analysis. Other factors that were shown to have influence: Performance of the task was sensitive to self-reports of work demands, work autonomy, stress and arousal.	Cross-over. Operating theatre. UK
Tran 1994 (122)	Operating room staff, N=99 (73% responded to questionnaire) Control: Non-exposed staff, N=182 (91% responded to questionnaire)	Exposure of waste anaesthetic gases through work, with dosimetry, all operating rooms used scavenging systems	Operating rooms with scavenging systems. N_2O levels exceeded the current TLV of 50 ppm in 4 of 12 operating rooms.	Fatigue, headache, irritation: No difference between groups (increased headache for CO2 exposure)	Self-reported information, that may influence the results, were collected. Carbon dioxide, but in both groups. The poor association between nitrous oxide levels and acute symptoms remained after controlling for potential confounders, such as age, occupation, smoking habits, history of allergy, and carbon dioxide levels.	Cross sectional study (questionnaires and measurements). Operating theatre. USA
Lucchini 1995 (123)	Operating theatre staff, N=62 Control: Nurses from other departments, N=46	N_2O and ethrane (enflurane).	- Refer to historic values (N_2O during 1980's: above 300 ppm; early 1990's: below 100 ppm) - In Urine: First day a week: 20.7; last day: 26.8.	"Simple reaction time": Increased reaction time in the exposed group Other acute neurobehavioral effects*: No difference between groups (*psychomotoric test battery, profile of mood state, visual digit span for mechanical memory, Benton visual retention for visual memory, digit serial for visual learning ability, digit symbol for coding speed, aiming pursuit for motor speed and steadiness)	Self-reported information, that may influence the results, were collected. The subjects were neither currently nor previously exposed to neurotoxic agents such as metals, organic solvents or pesticides. The subjects were screened for any neurological and neuropsychiatric illness and consumption of medication that might have influenced their performance in psychometric tests. Stress and work organization were suggested as possible confounders. No adjustments was done.	Non-randomized, controlled study. 32 operating theatres at Spedali Civili of Brescia (hospital). Italy

Neurobehavioral effects	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
Lucchini 1996 (124)	Operating room workers, N=30 Control: Other hospital workers not exposed, N=20	Gaseous anaesthesia, including N2O	N_2O: 50.9 ppm	Neurobehavioral effect at relative low exposure level: Slower reaction time in the exposed group	Self-reported information, that may influence the results, were collected. The effect of stress was tested as a possible confounder However, the same group were tested during gaseous and nongaseous anaesthesia to ensure same stress level but different gas exposure levels.	Controlled trial, blinded. Cardiac Surgery Department of Brescian General Hospital Italy
Lucchini 1997 (125)	Operating theatre personnel, N=112 Control: Non-exposed personnel, N=135	Low levels of anaesthetic gases	N_2O: 20-23 ppm Halogenated gases: 0.3-0.4	Neurobehavioral effect at low exposure level: No difference between the groups	Self-reported information, that may influence the results, were collected. Bias due to confounding factors was reduced by the following exclusion criteria: daily alcohol intake exceeding 80g; daily coffee consumption exceeding 5 cups; assumption of CNS medication; neurological or psychiatric disorders; age ≥60 years; occupational or non-occupational exposure to other neurotoxic agents as metals and organic solvents. Stress level same for both groups. No adjustments done.	Non-randomized, controlled multicentre study. Several hospitals in northern Italy. Italy

Effect of anaesthetic gases on organ function

We found 7 articles that reported the effect of anaesthetic gases on organ function. All but one mentioned N_2O as a part of the gases exposed to the personnel.

Organ function	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
Dossing 1982 (126)	Technicians for control of anaesthesiology equipment, N=6 Anaesthesiologists, N=7 Control: Matched controls, N=13	N_2O and halothane	Technicians: exposure repair and control of equipment in room without ventilation. Anaesthesiologists: variation of nonbreeding systems without scavenging to closed systems with effective scavenging. N_2O: 55-75 ppm Halothane: 2-7 ppm	Hepatic microsomal activity: No difference between the groups	Self-reported information, that may influence the results, were collected. Bias due to confounding factors was reduced since the persons did not take drugs on a regular basis, and none of them had taken any drugs 14 d prior to the study All had an average daily alcohol consumption of less than five drinks (i e. < 50 g of ethanol) None suffered from allergic disorders, previous or present liver or kidney diseases. The exposed and the control groups were matched according to age, gender,	Non-randomized, controlled study. Surgery at Rigshospitalet, Copenhagen. Denmark.

Organ function	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
					educational level, and daily consumption of tobacco and alcohol. No adjustments was done.	
De Zotti 1983 (127)	A1: Anaesthetists, N=32 A2: Surgeons, nurses, N=29 Control: B: No exposure to anaesthetics but sharing infection and noxious chemical risks, N=87 C: Exposure to ionizing radiation, N=69	N_2O and enflurane, with and without scavenging	Three theatres has scavenging systems from the patients mask (non-rebreathing system used). Gas concentration was 3-8 times lower in the theatres with scavenging. N_2O: 500-1275 ppm Enflurane: 17.3-22.6 ppm (Enflurane: Recommended 2 ppm/ h, Wikipedia. Not used anymore)	Hepatic function*, renal function, haematological function**: No difference * Serum glutamic transaminase, serum glutamic ozaloacetic transaminase, alkaline phosphatase, bilirubin, prothrombin. ** Haemoglobin, haematocrit, red cell count, white and differential counts, platelet counts, IgG, IgA, IgM, IgD	No use of self-reporting information. No other confounding factors mentioned. No adjustments were done,	Non-randomized, controlled study. Seven operating theatres. Italy.
Franco 1991 (128)	Workers from anaesthesiology and ICU department, N=18 Control: Non-exposed, N=16	N_2O and isoflurane	N_2O concentration: <900 ppm Isoflurane concentration: <10 ppm Exposure defined as working 35 h/week for a period of 7-16 years.	Hepatic function*: Unfavourable effect in exposed subjects (short term effect only: after a workday, not before) * Determined by UDGA (urinary D-glucaric acid) excretion)	Self-reported information, that may influence the results, were collected. The exposed group and the control group had different exclusion criteria for smoking and alcohol, both higher for the exposed group. No adjustments were done,	Non-randomized, controlled study. Single centre. Italy.
Franco 1992 (129)	Anaesthesia staff, N=24 Control: Matched controls, N=24	N_2O and isoflurane	Mixture: N_2O concentration: <100 ppm Isoflurane concentration: <1 ppm	Hepatic function* No effect of N_2O but dose dependent effect of isoflurane * Determinesexd by UDGA (urinary D-glucaric acid) excretion)	Self-reported information, that may influence the results, were collected. Each subject was matched with an unexposed control by sex and age. No adjustments were done.	Non-randomized, controlled study. Anaesthesia unit. Italy
Cohen 1975 (84)	Exposed male oral surgeons and male dentists, N=1668 Control: Males in the same cohort who has	Exposure to anaesthesia gases at dental office	Unscavenged rooms. At least 3 h exposure per week. Refer to general concentrations at that time: Halothane: Exceed 73 ppm N_2O: 500-6000 ppm	Hepatic disease: Increased rate in exposed group Kidney disease: No difference between the groups	Self-reported information, that may influence the results, were collected. The incidence of liver disease was calculated after excluding cases of serum hepatitis to eliminate possible differences in exposure to blood and blood products.	Survey. Questionnaires to male members of American Society of Oral Surgeons (ASOS), N=2642, response rate of

Organ function	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
	less than 3h exposure per week, N=1660.					64.5%; and American Dental Association) ADA, N=4797, response rate of 38.9%. USA
Trevisan 2003 (130)	1: Personnel in surgical area using open circuits, N=25 2: Personnel in surgical area using closed circuit, N=36 Control: Non-exposed controls, N=43	N_2O and sevoflurane exposure	Open and closed circuits. N_2O: 0.9-111.6 ppm Sevoflurane: 0-1.88 ppm	Kidney function*: No difference between the groups * glucosaminidase, glutamine synthase, total protein	No self-reported data. No obvious confounders	Non-randomized, controlled study. Italy
ASA 1974 (82)	ASA, AANA, AORN/T, both genders, responders, N=29 810 Control: AAP, ANA, both genders, responders, N=10 234	Anaesthetic gas exposure	No information about gas exposure, only based on type of work. N_2O not mentioned.	Hepatic disease: Higher rate in both female and male exposed groups compared to control groups. Renal disease: Female exposed group: Higher rate as compared to the control group. Male exposed group: No increase rate as compared to control group. In all cases: A cause-effect relationship could not be drawn.	Self-reported information, that may influence the results, were collected. The rates were standardized for age in the case of the disease rates.	National survey. The exposed group: Questionnaires mailed to 49 585 members of American Society of Anesthesiologis (ASA), American Association of Nurse Anesthesists (AANA) and Associations of Operating Room Nurses and Technicians (AORN/T). The control (unexposed group): Questionnaires mailed to 23 911 members of American Academy of Pediatrics (AAP)

Organ function	Population	Intervention	Gas exposure details	Outcomes and short conclusion	Confounders	Study design
						and the American Nursing Association (ANA). Mean response rate of 55%. USA

Effect of anaesthetic gases on haematological and inflammatory parameters

We found 4 articles on the effect of anaesthetic gases on different haematological inflammatory parameters. All of these mentioned N_2O as a part of the gases exposed to the personnel.

Blood parameters	Population	Intervention	Gas delivery	Outcomes and short conclusion	Confounders	Study design
Peric 1991 (131)	Anaesthesiology staff, N=21 Control: 1: Baseline of the same staff (after holiday and after weekend) 2: Healthy controls, N=35	N_2O and halothane exposure	No scavenging. TWA N_2O: 85-1500 ppm	Red cell count, haemoglobin, haematocrit, T lymphocyte count: No difference between the groups Basophils: Disappeared in the exposed group CD2, CD4: Increased in the exposed group B cell decreased, and did not recover after holidays NK cells: decreased, but recovered	Self-reporting not mentioned. To avoid the influence of X rays on the immune system they had chosen personnel who did not work in an X-ray area. No adjustments done.	Non-randomized, controlled study. Before-after. Four operating theatres, Department of Anaesthesiology and Intensive Therapy Yugoslavia.
Peric 1994 (132)	Anaesthetic staff during peak working season, N=21 Control: 1: Same staff as intervention but after 3 weeks vacation, N=21 2: Matched heathy controls N=35	N_2O and halothane exposure.	Not available. Results analysed towards length (years) of exposure.	Blood count, IgX, Cell activity with mitogens: Correlation between higher recovery of erythrocyte count and increased age. Correlation between younger staff and stable monocyte, and T and B cell counts.	Self-reporting not mentioned. The results were age dependent. No adjustments done.	Non-randomized, controlled study. Before-after. Croatia.

Bargellini 2001 (133)	Physicians, N=51 Control: Matched controls, N=20	Exposure to anaesthetic gases (N_2O and isoflurane)	No concentrations are given. Short term: Activity in operating room during the last 15 days, yes/no Long term: Number of days in operating rooms during last semester: low: <40 days medium: 40-80 days high: >80 days	Immune cell parameters: Derangements in lymphocyte subpopulations where T-lymphocytes were more affected than B cells.	Self-reported information, that may influence the results, were collected. The analyses for T-cells (CD3) and for total T and T helper (CD4) were corrected for age, gender, coffee intake, physical activity, children at home. The analysis for natural killer cells (NK) was corrected for age, gender and coffee intake.	Cross-sectional survey. Three hospitals in Modena. Italy.
Chaoul 2015 (134)	Operating room medical personnel, minimum 3 years, N=15 Control: Unexposed medical personnel, N=15	Exposure to mixture of gases for 3 years (N_2O, isoflurane, sevoflurane)	N_2O concentration> 100 ppm Isoflurane and sevoflurane concentrations > 7 ppm	Pro-inflammatory cytokines: Increase in IL-8, in high exposure group	Self-reported information, that may influence the results, were collected. Obese individuals, pregnant women, smokers, alcoholics, and those who had any disease or history of occupational exposure to substances other than the anaesthetic gases under investigation, were excluded from the study. Subjects who had any type of infection or inflammation within the preceding 30 days, those who had taken medication or antioxidant supplements, and those who had recently received radiation, were also excluded from the study to avoid bias. Demographic data did not significantly differ between groups	Non-randomized, controlled study. Operating theatre. Brazil

Anaesthetic gases effect on other biological outcomes

There were 5 articles presenting data on other outcomes from those mentioned above. Two of them mentioned N_2O as a part of the exposure gases and the three others only mentioned exposure to anaesthetic gases.

Other outcomes	Population	Intervention	Gas delivery	Outcomes and short conclusion	Confounders	Study design
Corbett 1973 (135)	Nurse-anaesthetist, N=525 Control: Expected incidence, matched for five-year age groups, , based on statistics from the Connecticut Tumor Registry (1966-1969)	Exposure to anaesthetic gases	No information.	Cancer frequency: increased in the exposed group	Self-reported information, that may influence the results, were collected. Possible confounders as suggested by the authors: genetic influences and personal habits. No adjustments were done	Survey. Send to all the female nurse-anaesthetists in Michigan (N=621). 525 responded, 84,5% response rate. USA
Pasquini 1989 (136)	Exposed staff, N=64 Control: Unexposed staff, N=37	N_2O and enflurane	Operating rooms had different facilities: air-scavenging system and/or air-conditioning system.	Urinary thioethers: Increased in the exposed group Urinary mutagenicity, D-Dlucaric acid: No difference between groups	Self-reported information, that may influence the results, were collected. No adjustments were done.	Non-randomized, controlled study. Five operating rooms. Italy.
Hedstrom 2013 (137)	1798 incident cases 5216 with prevalent cases of multiple sclerosis Control: For each case, two controls were randomly selected from the national population register. For the Incident cases: 3906 controls. For the prevalence cases: 4701 controls.	Anaesthetic gases including N_2O	No information.	Occurrence of multiple sclerosis (MS): No association to N_2O exposure	Self-reported information, that may influence the results, were collected. All analyses were adjusted for age, gender, residential area, ancestry, smoking and BMI at age 20 years. The analysis of nitric oxide and MS risk, based on EIMS, was also adjusted for parity.	Two population-based, case-control studies: EIMS (Epidemiological Investigation of Multiple Sclerosis; and GEMS (Gene and Environment in Multiple Sclerosis) respectively. Info regarding exposure etc. from questionnaire. Cases recruited from 40 study centres, including all university hospitals in Sweden. Sweden.
ASA 1974 (82)	Operating room personnel, both genders, N=29 810 Control: Non-exposed health care workers, both genders, N=10 234	Anaesthetic gas exposure	No information about gas exposure, only based on type of work.	Cancer incidences: Female exposed group: Higher rate as compared to the control group.	Self-reported information, that may influence the results, were collected. The rates were standardized for age.	National survey. The exposed group: Questionnaires mailed to 49 585 members of American Society of Anesthesiologis (ASA), American

			N_2O not mentioned separately.	Male exposed group: No increased rate as compared to control group. In all cases: A cause-effect relationship could not be drawn.		Association of Nurse Anesthesists (AANA) and Associations of Operating Room Nurses and Technicians (AORN/T). The control (unexposed group): Questionnaires mailed to 23 911 members of American Academy of Pediatrics (AAP) and the American Nursing Association (ANA). Mean response rate of 55%. Time of data collection: 1973 USA
Cohen 1975 (84)	Exposed male oral surgeons and male dentists, N=1668 Control: Males in the same cohort who has less than 3h exposure per week, N=1660.	Exposure to anaesthesia gases at dental office	Unscavenged rooms. At least 3 h exposure per week. Refer to general concentrations at that time: Halothane: Exceed 73 ppm N_2O: 500-6000 ppm	Cancer frequency: No difference between the groups	Self-reported information, that may influence the results, were collected. Age, smoking, adjusted for	Survey. Questionnaires to male members of American Society of Oral Surgeons (ASOS), N=2642, response rate of 64.5%; and American Dental Association) ADA, N=4797, response rate of 38.9%. Time of data collection: Not mentioned. USA

Appendix 9. Risk of Bias (according to Robins) for included studies on health

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
N2O effect on reproductive health									
Cohen 1980 (49)	Moderate Confounding factors are mentioned and adjusted for. However, all of them were self-reported.	Rates of congenital abnormality and spontaneous abortions in chairside assistants exposed to N2O alone were adjusted for age, smoking, and pregnancy history.	Low Participants were selected based on their profession.	Low	Serious Self-reported adherence to intervention (exposure)	Moderate The total number of participants is not clearly described. We therefore do not know if there are any missing data.	Moderate Self-reported outcomes.	Low No observed selection bias of reported results.	Serious
Heidam 1984 (65)	Moderate Self-reported confounding factors. Not adjusted for.	Possible confounders: - other toxins in dental practice - age - gravidity and pregnancy order Age, gravidity, pregnancy order were all adjusted for in the odds ratio analyses. Possible exposure to mercury was not adjusted for.	Low Participants were all dental assistants from 24 (all) clinics for the dental school service and 186 (of 194) private clinics. Their control group were employees less exposed (not exposed) to chemicals at work and included physiotherapists, occupational therapists, office workers, and technical assistants and designers. The study group and the controls were comparable with respect both to work postures and movements during a day.	Low	Serious Self-reported adherence to intervention (exposure)	Low The response rate was 91%.	Moderate Self-reported outcomes.	Low No observed selection bias of reported results.	Serious
Rowland 1992 (51)	Moderate Confounding factors are mentioned	Following confounders were considered and adjusted for: - recent use of oral contraceptives	Low Participants were selected based on their profession.	Low Good descriptions given, no	Serious Self-reported ad-	Low No observed missing data.	Moderate Self-reported outcomes.	Low No observed selection bias	Serious

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
	and adjusted for. However, all of them were self-reported.	- number of cigarettes per day - age - history of pelvic inflammatory disease - number of sexual partners, frequency of intercourse - race Confounding by other unmeasured factors potentially related to subfertility was minimized because they compared exposed dental assistants with unexposed dental assistants who were demographically similar. Mercury and amalgam are potential confounders but were not adjusted for as both groups were suggested to have the same potential exposure.		reason to suspect bias.	herence to intervention (exposure)			of reported results.	
Rowland 1995 (52)	Moderate Confounding factors are mentioned and adjusted for. However, all of them were self-reported.	As Rowland 1992	Low Participants were selected based on their profession.	Low Good descriptions given, no reason to suspect bias.	Serious Self-reported adherence to intervention (exposure)	Low No observed missing data.	Moderate Self-reported outcomes.	Low No observed selection bias of reported results.	Serious
Ahlborg 1996 (53)	Moderate Confounding factors are mentioned and adjusted for. However, all of them were self-reported.	The analysis was adjusted for shift work, cycle order, age, pregnancy order, previous fertility problem, oral contraceptive use, smoking and tea consumption.	Low Participants were selected based on their profession.	Low Good descriptions given, no reason to suspect bias.	Serious Self-reported adherence to intervention (exposure)	Low No observed missing data.	Moderate Self-reported outcomes.	Low No observed selection bias of reported results.	Serious

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
Axelsson 1996 (54)	Moderate Confounding factors are mentioned and adjusted for. However, all of them were self-reported.	The analysis was adjusted for shift work, cycle order, age, pregnancy order, previous fertility problem, oral contraceptive use, smoking and tea consumption.	Low Participants were selected based on their profession.	Low Good descriptions given, no reason to suspect bias.	Serious Self-reported adherence to intervention (exposure)	Low No observed missing data.	Moderate Self-reported outcomes.	Low Objective outcomes.	Serious
Bodin 1999 (55)	Moderate Confounding factors are mentioned and adjusted for. However, all of them were self-reported.	The analyses were adjusted for maternal age, parity, employment and work schedule.	Low Participants were selected based on their profession.	Low Interventions were shift work and N_2Oexposure. Both were described in detailed, both degree of shift work and amount of exposure with N_2O.	Serious Self-reported adherence to intervention (exposure)	Low No observed missing data.	Moderate Self-reported outcomes.	Low No observed selection bias of reported results.	Serious
Genetic toxicity of N_2O									
Husum 1986 (56)	Moderate Self-reported confounding factors. Not adjusted for.	Potential confounding factors: - other toxins in dental practice - smoking - age Smoking and age were adjusted for. The potential toxic effect of other toxins in dental practice was not mentioned.	Low Participants were selected based on their profession.	Low Intervention groups, which is level of exposure were clearly asked in the questionnaire (number of exposure hours per week).	Serious Self-reported adherence to intervention (exposure)	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Serious
Chang 1996 (57)	Low	Potential confounders: - other gases - age The analyses were adjusted for age. Smoking, chemotherapeutics, significant medical illnesses, chemotherapy, radiotherapy	Moderate Low number of participants.	Moderate Mean years of exposure given was shown with standard deviation. However, there were no information on how	Low Exposure related to the presence in the room.	Low No observed missing data.	Low Objective outcomes.	Low Objective outcomes.	Moderate

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
		were not possible confounders, since only non-smokers who were not involved with chemotherapeutics on the job and did not have significant medical illnesses, previous chemotherapy, or previous radiotherapy were included.		these data were selected.					
Wronska –Nofer 2009 (66)	Low	Smoking, age, gender, hospital locations were included as independent variables in a multiple linear regression model, without changing the results.	Low The control group was matched with the exposed group for age, gender, smoking habit and employment duration.	Low Intervention groups clearly defined and method for analyses and concentrations in operating rooms given.	Low Concentration of N_2O was measured.	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Low
Wronska-Nofer 2012 (59)	Low	Smoking, age, gender, hospital locations were included as independent variables in a multiple linear regression model, without changing the results.	Low The control group was matched with the exposed group for age, gender, smoking habit and employment duration.	Low Intervention groups clearly defined and method for analyses and concentrations in operating rooms given.	Low Concentration of N_2O was measured.	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Low
Neurological toxicity of N_2O									
Brodsky 1981 (50)	Moderate Confounding factors are mentioned and adjusted for. However, all of them were self-reported.	Following factors were considered: - age - smoking history - mercury exposure - whether the questionnaire was returned promptly or the respondent required prompting - response rate (70%) - exposure to halogenated anaesthetics - medical records	Low The questionnaires were send to aesthetic users and nonusers during the same time frame (1968-1978). A strength of the present study was availability of a control group of dentists and chair-side assistants who worked in the dental operatory under essentially similar operative conditions, but who	Low Intervention groups clearly defined: The level of aesthetic exposure was calculated by cumulative exposure hours.	Serious Self-reported adherence to intervention (exposure).	Low	Low Objective outcomes.	Low Pre-defined subsets of outcomes were described in methods.	Serious

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
		Problems of responder bias, inaccurate recall of events, and incomplete return rates were reduced due to the study design of this study, since the control group of dentists and chair-side assistants worked in the dental operatory under essentially similar operative conditions, but without using inhalation anaesthetics.	did not use inhalation anaesthetics in their practice.						
Isolani 1999 (47)	Low	None as the study subjects were their own control, analysed in the beginning and end of working week.	Low The population was their own control, analysed in the beginning and end of working week.	Low Urinary concentrations of N_2O was measured and thereby confirmed the intervention.	Low No reason to suspect bias.	Low No observed missing data.	Moderate The methods of outcome assessment were similar for the exposed and the non-exposed groups. The outcomes were subjective.	Low No observed selection bias of reported results.	Low (despite one moderate bias, due to the potential low effect of this bias on the results)
Scapellato 2008 (64)	Moderate Possible influence of isoflurane.	Alcohol intake and gender tested for with no influence. Subjects were excluded in the event of - alcohol intake exceeding 80 g/day; - coffee intake >5 cups/day - intake of drugs affecting the CNS - neurological or psychiatric disorders - age above 60 years - occupational or non-occupational exposure to other neurotoxic agents.	Low No reason to suspect bias.	Low Intervention groups clearly defined.	Low	Low No observed missing data.	Moderate Subjective outcomes.	Low No observed selection bias of reported results.	Moderate
N_2O effect on B12 metabolism and liver function									

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
Nunn 1982 (60)	Moderate	Possible confounders: - dietary intake of methionine - exposure to other gases in the operating theatre No confounding factors were discussed.	Moderate The selection of the exposed population were only 10 members of the operating theatre staff. Control subjects were sampled simultaneously and comprised of hospital staff who did not work in an environment where anaesthetics were used. No information for the two groups about diets rich in methionine.	Low. Classified based on exposure.	Low Gas concentration was measured.	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Moderate
Armstrong 1991 (63)	Moderate No confounding factors were discussed.	No information were given about possible variations between the exposed group and the control group.	Moderate There were no description on how the exposed subjects were selected.	Low The intervention groups were clearly defined (exposure through full-time work for at least 6 months).	Low The study was carried out through 5 consecutive days and the participants were followed during the week.	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Moderate
Krajewski 2007 (61)	Low	To avoid inclusion of confounding factors, subjects with haematological diseases, serious symptoms of neurological deterioration or heart failure were excluded. Self-reporting on alcohol, coffee and medications.	Low Participants were selected based on their profession.	Low Good description of type and concentrations of interventions. Exposure and control groups properly described.	Low The level of N_2O exposure were defined as below and above a given Occupational Exposure Limits (OEL).	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Low
Ekbom 2008 (48)	Low	No information about confounding factors but only two subjects which gave their blood samples at different time points.	Low Only two nurses, each serving as their own control.	Low Good description of exposure levels.	Low	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Low

Ref	Bias due to confounding	Confounding factors, or other comments	Bias in selection of participants into the study	Bias in classification of interventions	Bias due to deviations from intended interventions	Bias due to missing data	Bias in measurement of outcomes	Bias in selection of the reported results	Overall
Staubli 2016 (62)	Low	The analysis for B12 was adjusted for age. The control group (working in ICU) was assumed to have the same level of stress as the exposed group. No difference in distribution for gender.	Low Subjects had the same working background. Two of the included subjects did not continue the study (one refused to sign the written informed consent, and the other met the exclusion criteria of the study).	Low Intervention groups clearly defined.	Low Concentration of N_2O was measured.	Low No observed missing data.	Low Objective outcomes.	Low No observed selection bias of reported results.	Low

Appendix 10. Project plan

folkehelseinstituttet

Project plan:

Effectiveness and safety of nitrous oxide alone, c combination with other drugs, as sedation regime children

Project number	2015_049
Plan prepared (dd.mm.åååå):	30.08.2017

Short description and summary

Children (up to 18 years of age) who undergo painful procedures at hospitals, for suture laceration, orthopaedic manipulation, arthrocentesis, insertion of peripheral catheters or lumbar puncture, are given different kinds of pain relief (analgesics), combination with drugs for relaxation (sedatives). Several drugs are available and depending on procedure, procedure time, effect needed (anxiolytic, sedative or analgesi available personnel and previous experience with the child's responsiveness. Nitro (N_2O) (lystgass) is a drug administered for pain relief and relaxation, it is applied by in and its effects are analgesic, anxiolytic and sedative. It is widely used in maternity Norway for sedation during labour. Our aim is to evaluate the effectiveness and safet sedation regimen in children.

Kort beskrivelse/sammendrag

Barn (opp til 18 år) som gjennomgår smertefulle sykehusprosedyrer, for eksempel sut ortopediske manipulasjoner, leddpunksjoner, innsetting av veneflon og spinalpunks forskjellige smertestillende midler, ofte i kombinasjon med avslappende midler (se Flere legemidler er tilgjengelige og blir valgt ut fra hvilken prosedyre som skal gjøres, h tid prosedyren er forventet å ta, hvilken effekt man trenger (angstdempende, avsla smertestillende eller total bedøvelse), tilgang på personell, samt erfaring med hvordan før har respondert på behandlingen og sedasjonen. Lystgass gis ved inhalasjon og h smertestillende, angstdempende og beroligende effekt. Det er i etablert bruk på fødeavd Norge. Vårt mål er å evaluere effekt og sikkerhet av lystgass som sedasjonsmetode for b

Short title

Nitrous oxide sedation in children

Project category and commissioner	
Product (program area)	Health Technology Assessment
Thematic areas	Procedure Anaesthetics Sedation Health Technology Assessment
Commissioner:	The Regional Health Authorities F Forum) (RHF-Bestillerforum) (An Ordering Forum, Bestillerforum RH of the four medical directors (one for e health authority) and two delegate Norwegian Directorate of Health, has th prioritize the STAs and HTAs to be cond basis of submitted proposals and horiz reports.)
Project management and participants	
Project manager	Torunn Elisabeth Tjelle
Responsible for the project	Ingvil Sæterdal von Mehren
Internal project participants	Julia Bidonde Elisabeth Hafstad
External project participants	Karin Tylleskär, Helse Bergen HF, Universitetssjukehus Ketil Stordal, Sykehuset Østfold HF
Plan for replacement by project participants' absence	The person responsible for the project the project participants when needed
Internal reviewers	Brynjar Fure, Liv Merete Reinar
External reviewers	To be determined

Glossary

Anaesthetics	Drug to induce insensitivity to pain*
Amnesiacs	Drug to induce memory loss*
Analgesics	Drug for pain relieve without loss of consciousne
Anxiolytics	Drug to reduce anxiety*
Diffusion hypoxia	Decrease in alveolar oxygen tension caused b nitrous oxygen which diffuses out of the blood alveolar oxygen.
Hypnotics	Drug to induce sleep*
Minimal sedation (anxiolytic)	"A drug-induced state during which patients calm, and respond normally to verbal comma cognitive function and coordination may ventilatory and cardiovascular functions are unaf
Moderate sedation (conscious sedation)	"Drug-induced depression of consciousness patients are sleepy but respond purposefu commands or light tactile stimulation. No int required to maintain a patent airway. Spontane is adequate. Cardiovascular function is usually m
Sedative	Drug for calming or sleep-inducing effect*

** Definitions are taken from Oxford Dictionary (https://en.oxforddictionaries.com/defi*

Mandate

The Regional Health Authorities Forum (RHA Forum) in the national system fo introduction of new health technologies within the specialist health service RHF) has requested a health technology assessment (HTA) to evaluate safety ar of nitrous oxide sedation in children. In the note to Bestillerforum-RHF it was cost effectiveness was not important for the assessment and therefore this is here.

Goal

To evaluate effectiveness and safety of nitrous oxide sedation regimen in childre

Background

Children (up to 18 years of age) who undergo painful procedures at hospital suture laceration, orthopaedic manipulation, arthrocentesis, insertion of per catheters or lumbar puncture, are offered different kinds of pain relief (analg combination with drugs for relaxation (sedatives). For successful procedur effective use of time and personnel, efforts are made to choose an efficient analgesics and sedatives.

Drugs classified as sedatives may exert one or several effects. Common the sedative effect, are anxiolytic, amnestic, hypnotic and/or analgesic. T depends on the procedures to be carried out, procedure duration, eff personnel and previous experience with the child's responsiveness to the The most commonly used sedative at paediatric departments in No Midazolam (2) which can be administered by several different routes (e.g. buccal and nasal spray). Other drugs used for sedative purposes in ch Chloral hydrate, opioid drugs, Propofol and Sevofluorane and nitrous these sedatives have been reviewed by the National Institute for Healtl (NICE) guideline in 2010 (3). This guideline recommends to use Midazolam for sedation in children during painful hospital procedures w sedation is "minimal" or "moderate", also known as "anxiolysis" or respectively (the definition is established by American Society of Anesthes

Nitrous oxide is an inorganic agent, administered by inhalation, colorle smelling, and non-irritating to the tissues. It is an effective analgesic/anx causing central nervous system depression and euphoria with little eff system. Nitrous oxide has a rapid uptake, as it is being absorbed quickly fi excreted quickly from the lungs. As nitrous oxide is 34 times more sol blood, diffusion hypoxia may occur (4).

Nitrous oxide is used as a sedative in dental care for both children an women in labour (6;7). The gas is normally used with oxygen in differe most commonly being 50-70% nitrous oxide (8). Administration is simple a rapid onset and short duration of action. It has analgesic, anxiolytic a Norway it is known as "lystgass" and a popular name in English is "laug air".

Several studies have documented the use of nitrous oxide sedation in chi the emergency department (9;10). Several guidelines (3;4) include nitrou alternative sedation methods in children. A systematic review by Pedersen literature on nitrous oxide as a sedation method for minor paediatric pr under peripheral venous cannulations, lumbar punctures or intramus authors concludes that nitrous oxide is a safe and effective method to sedation during minor, but painful procedures. The authors therefore su right conditions, the use of nitrous oxide will ease hospital procedures w be performed using other sedatives that requires longer time, both onse more personnel, or even that it can substitute full anaesthesia.

In Norway, nitrous oxide sedation in children is not a standard sedation used in some hospitals for minor hospital procedures (St. Olavs Hospital, our knowledge, there is an ongoing (non-randomized) clinical tr effectiveness of this sedative (Sykehuset Østfold HF).

This project aims to evaluate and/or synthetize data on effectiveness and safety o sedation in children, alone or in combination with other sedatives or analgesics.

Methods

We will perform a systematic review on effectiveness and safety of nitrous oxide children in accordance with the handbook "Slik oppsummerer vi forskning" Institute of Public Health (12). The final report will be written as a systemati overview over systematic reviews, depending on available literature.

We will follow a population, intervention, comparator, outcome and study framework to set parameters for our literature search and study selection. Furth process are search for literature, select studies, assess the methodological quality retrieve data, combine data (if possible) and finally assess the certainty of evidenc

Study inclusion and exclusion criteria

Our PICO framework helps the inclusion criteria to evaluate the suitability of stud

Inclusion criteria

Population	Children up to 18 years of age undergoing painful hospital procedure minimal or moderate sedation
Intervention	a) Nitrous oxide only b) Nitrous oxide in combination with other sedatives/analgesics/an Nitrous oxygen/oxygen concentration: 50/50% – 70/30%
Control	a) Other pharmacological intervention (sedatives/analgesics/anaes b) Non-pharmacological intervention (e.g. psychological techniques c) Control (wait list, treatment as usual) (For safety outcomes we will accept studies without any control grou
Outcome	a) Hospital procedure satisfaction (e.g. easiness, distress, anxiety) b) Hospital procedure characteristics (e.g. successful procedural number of attempts, duration of procedure) c) Pain d) Safety of sedation - Number of acute adverse events (e.g. vomiting, oxygen cardiac arrest) - Long term adverse effects (e.g. toxicity) due to repeated expos - Parameters of gas concentration in the procedure room or bod - Adverse events due to combination with other sedatives anaesthetics For each of the outcomes, we will extract data provided either b (child), caregiver (parent) or health personnel (medical staff).
Study design	Systematic reviews, of high methodological quality, of randomiz trials, health technology assessments (HTA) or randomized contr

required, non-randomized studies (Non-randomized contr before-and-after study, Prospective cohort study, Retros Case-control study (more than 50 participants), Case rep than 100 participants) will be included for data on safety. published studies that assessed any of the predefined outcon

** For data on nitrous oxide in combination with other drugs we will only present it as s or safety of the individual drug.*

Exclusion criteria

We will exclude studies based on:

- Patient groups using nitrous oxide for sleeping disorders
- Imaging procedures or procedures only requiring the sleeping effe
- Procedures where the aim is to obtain general anaesthesia
- Animal studies

Search strategy

We will primarily search for systematic reviews and HTAs. If this is systematic reviews are older than 5 years, randomized controlled trials wi or to supplement the systematic reviews. If necessary for acquiring eno will conduct separate searches for non-randomized studies. The relevant da are listed below.

Systematic reviews & HTA

- CRD database, HTA (Centre for Reviews and Dissemination, Univ
- Cochrane Library (Wiley):
  - Cochrane Database of Systematic Reviews
  - Database of Abstracts of Reviews of Effects
- Epistemonikos
- Embase (OVID)
- PubMed (NLM)

Randomized controlled trials (and non-randomized studies, if required)

- Cochrane Central Register of Controlled Trials (Wiley)
- PubMed (NLM)/MEDLINE (OVID)
- Embase (OVID)

Ongoing, completed or terminated (unpublished) trials

- Clinical Trials (National Institutes of Health, US)
- International Clinical Trials Registry Platform (WHO)

An information specialist, in collaboration with the research team, will searches. The search strategies will combine index terms and text words and intervention, adapting the search syntax to each database. Filters fo added for databases PubMed/MEDLINE and Embase.

The research team will examine the bibliographies of included articles for relev identified by the searches.

Selection of studies

The team will select articles following a two-step strategy. Both steps will b considering inclusion and exclusion criteria detailed above. Disagreement at eithe settled by discussion or consultation with a third person.

Selection strategy:

1. Two reviewers will independently assess title and abstracts of retrieved article relevant full-text articles to be examined
2. Subsequently, two reviewers will independently assess the full-text articles to articles will be included in the systematic review.

Assessment of methodological quality and risk of bias

We will evaluate the quality (risk of bias) of the identified trials using the ((http://training.cochrane.org/handbook, Chapter 8.5a). For non-randomized st use the checklists given in our handbook (12). Two review authors will assess the included studies independently. We will resolve disagreements by discussions or, consulting one of the other review authors.

Data extraction and analyses

One review author will extract data from the included studies and another revie verify the data. We will extract the following data:

- Information about the study (authors, year of publication, setting, study d trial identification number and funding source)
- Participant characteristics (number of participants in the trial, age, pr performed during intervention)
- Intervention and control characteristics (combination of drug, dos exposure, frequency of intervention per patient)
- Outcomes (endpoints examined, methods used to analyse outcome data, le up and loss to follow up)

Statistical analyses

We will synthetize the outcomes depending upon the research design.

For all outcomes, we will present the results in summary of finding tables.

For Randomized Controlled Trials: If homogenous randomized controlled tri effect sizes will be combined in meta-analyses. Continuous data will be expressed mean difference (MD) or standardized mean difference (SMD) and 95% confi (CI), and Dichotomous data will be analysed by calculating relative risk (

corresponding 95% CI. Outcomes which cannot be combined, will be pr form.

If relevant or if possible, we will divide the data in groups and analyse the the setting (which department, which personnel), age of patient, hospital and if nitrous oxide is used in combination with other sedatives/ analgesi

Grading the certainty of evidence

Two review authors will independently assess the certainty of the evid outcome using the GRADE system (Grading of Recommendations Asse and Evaluation, http://www.guidelinedevelopment.org/). We will do strength of the study design, possible risk of bias, imprecision and estimates, and indirectness and magnitude of effect, dose response g confounding factors. The GRADE system classifies the certainty of moderate, low, or very low for each outcome, described in the table below

Table: Definition of each category for GRADE

Grade	Definition
High	We are very confident that the true effect lies close to t effect
Moderate	We are moderately confident in the effect estimate: The be close to the estimate of effect, but there is a substantially different
Low	Our confidence in the effect estimate is limited: Th substantially different from the estimate of the effect
Very low	We have very little confidence in the effect estimate: T to be substantially different from the estimate of effect

Norwegian Institute of Public Health review pro

We follow the process of Norwegian Institute of Public Health where experts and two internal research directors are invited to review and project plan. The plan will then be approved by the management group ledermøtet) before publication at NyeMetoder.no. The final report will b two external experts together with the same two internal research directo be approved by the HTA-unit before submission to the comm (https://nyemetoder.no/metoder), will be done latest 10 days afte commissioner.

Activities and schedule

Following activities are planned in the project, and presented in a Gantt d

- Find and include external reviewers
- Discuss project plan with internal and external reviewers
- Approval of project plan
- Search for literature
- Select studies according to inclusion/exclusion criteria
- Evaluate methodological quality (RoB)
- Extract data on efficacy and safety and conduct statistical analy
- GRADE evaluation for each outcome
- Write and review the draft report
- Approve and submit the report

Date for commision

27. February 2017

Start date (for FHI.no)

10. June 2017

End date

27. February 2018

Publication / dissemination

The end product will be a report from Division of Health Services, Norw Public Health, under Nye Metoder (https://nyemetoder.no/metoder), scientific article.

Indexing for web page

Adolescent, Anaesthesia, Analgesia, Child, Conscious Sedation, Infan Procedures, Nitrous Oxide, Anti-Anxiety Agents, Hypnotics and Sedatives

Internal pediatrics related projects/publicatio

There are no related ongoing projects or related publications publ Institute of Public Health.

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folkehelseinstituttet

Project plan:

Effectiveness and safety of nitrous oxide alone, or in comb with other drugs, as sedation regimen in children - ADDENDUM

Project number	2015_049
Addendum prepared (dd.mm.åååå):	02.02.2018

Background for change in project plan

In the original plan, the population was identified as children undergoing short and pa hospital procedures. However, the commission wanted to assess safety data, although specified safety for who. According to the "Forslag", however, safety for health personn issue. We therefore extend the project plan to include safety for health personnel in ad the patients.

Added search

According to this experience, we decided to perform a new search where safety of healt workers were more specific addressed. Following PICO were established:

Population	Health workers
Intervention	Occupational exposure of nitrous oxide
Control	None-exposed health worker
Outcome	Toxic effects of N2O, short and long term (i.e. fertility-related toxic effect, DNA dan interference, neurological effects)
Study design	Preferably controlled trials.

Handling search result

To ensure to cover all potential safety issues for N2O, we will include studies also wher not the sole component of exposure. However, data will be handled differently depend the nature of the exposure, see table below.

Sub-group	Explanation	Data-extraction
General anaesthetics	The study does not differentiate between exposure gases and N2O is not mentioned.	These papers will be pooled and summarized based on: - Population - Population size - Intervention (when type specified) - Study type - Outcome A short narrative will be made for studies with more than for a specific outcome. Other data-handling or summarie performed. Only English language is included.
Combination	The study mention N2O specifically but it is in combination with other anaesthetic gases.	
N2O	The population is exposed to N2O only as stated in the study.	Results from these studies will be grouped and analysed outcomes. We will also assess risk of bias and evaluate t confidence we have to the evidence. No language restric

NIPH

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