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Occupational Exposure to Entonox (Nitrous Oxide)

1. **Environmental and occupational risks with use of nitrous oxide (Entonox) for labour analgesia: a qualitative analysis of midwives' attitudes in the United Kingdom**

   Item Type: Journal Article

   Authors: Craig R.;O'Carroll J.;Bampoe S.;Odor P.M. and Kamming D.

   Publication Date: 2025

   Journal: International Journal of Obstetric Anesthesia 62, pp. 104359

   Abstract: Background: Nitrous oxide carries significant environmental impact and has been linked to harm related to occupational exposure. In the United Kingdom, midwives are primarily responsible for administering nitrous oxide in the form of Entonox. The aim of this study was to understand midwives' perceptions related to the effects of nitrous oxide and barriers to change in the pursuit of net zero emissions. Method(s): This qualitative study was conducted at a single teaching hospital. An interview guide was developed for the conduct of this study with thematic analysis conducted using an inductive approach to determine common themes. A total of 10 participants consented and participated in semi-structured interviews. Result(s): Three themes were identified; mixed awareness of environmental and occupational risk; midwifery culture as a barrier to change; and the identification of drivers

for innovation and change. Conclusion(s): Efforts to mitigate the environmental and occupational effects of nitrous oxide may require focused early educational policies and engagement with midwives to co-design demand- and supply-side mitigations to reduce harmful emissions from Entonox delivery.Copyright © 2025 Elsevier Ltd

Access or request full text: https://libkey.io/10.1016/j.ijoa.2025.104359

2. **An increased risk of spontaneous abortion, congenital anomalies, and stillbirth among women occupationally exposed to anaesthetic gases: a meta-analysis of observational studies**

Item Type: Journal Article

Authors: Kumar P.;Lehucher-Michel M.-P.;Loundou A.;Bregeon F.;Martin F. and Bouhadfane M.

Publication Date: 2025

Journal: International Archives of Occupational and Environmental Health 98(9-10), pp. 913–928

Abstract: PURPOSE: The aim of this meta-analysis was to evaluate the risk of spontaneous abortions, congenital anomalies, and stillbirths among women professionally exposed to anaesthetic gases. METHOD(S): This study was registered in the International Prospective Register of Systematic Reviews (PROSPERO), and we followed the PRISMA 2020 checklist to develop the study protocol. A systematic search was conducted in PubMed using specific keywords to identify observational studies involving women professionally exposed to anaesthetic gases. Data were extracted and analysed using a random-effects model. RESULT(S): A total of 32 studies were included, involving 155,437 healthcare professionals exposed to anaesthetic gases. The analysis revealed an increased risk of spontaneous abortions (OR = 1.47; 95% CI 1.19-1.81]), congenital anomalies (OR = 1.37; 95% CI 1.09-1.73]), and stillbirths (OR = 1.43; 95% CI: 1.09-1.86]) among these women. The risks varied across different professions and countries, with moderate heterogeneity observed in the analyses. CONCLUSION(S): This study confirms an elevated risk of spontaneous abortions, congenital anomalies, and stillbirths in women professionally exposed to anaesthetic gases. These findings highlight the need for preventive measures to minimize exposure and underscore the importance of further research to clarify the risks and develop effective strategies. REGISTRATION: International prospective register of systematic reviews; registration number: CRD42023450226.Copyright © 2025. The Author(s), under exclusive licence to Springer-Verlag GmbH Germany, part of Springer Nature.

Access or request full text: https://libkey.io/10.1007/s00420-025-02182-3

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3. **High anesthetic exposure leads to oxidative damage and gene expression changes in physicians during medical residency: a cohort study**

Item Type: Journal Article

Authors: Aun A.G.;Damasceno D.C.;Sinzato Y.K.;Nogueira F.R.;Souza K.M.;Lawi Y.S.A.;Guedes J.L.;Silva M.A.P.;de Carvalho L.R.;Braz L.G. and Braz M.G.

Publication Date: 2023

Journal: Environmental Science and Pollution Research International 30(29), pp. 73202–73212

Abstract: Evaluation of the possible toxic effects of occupational exposure to anesthetics is of great importance, and the literature is limited in assessing the possible association between occupational exposure to anesthetics and oxidative stress and genetic damage. To contribute to the gap of knowledge in relation to cause-effect, this cohort study was the first to monitor exposure assessment and to evaluate oxidative stress, DNA damage, and gene expression (OGG1, NRF2, HO-1, and TP53) in young adult physicians occupationally exposed to the most modern halogenated anesthetics (currently the commonly used inhalational anesthetics worldwide) in addition to nitrous oxide gas during the medical residency period. Therefore, the physicians were evaluated before the beginning of the medical residency (before the exposure to anesthetics-baseline), during (1 1/2 year) and at the end (2 1/2 years) of the medical residency. Anesthetic air monitoring was performed in operating rooms without adequate ventilation/scavenging systems, and biological samples were analyzed for lipid peroxidation, protein carbonyl content, primary and oxidative DNA damage, antioxidant enzymes and plasma antioxidant capacity, and expression of some key genes. The results showed induction of lipid peroxidation, DNA damage, glutathione peroxidase activity, and NRF2 and OGG1 expression up to the end of medical residency. Plasma antioxidant capacity progressively increased throughout medical residency; oxidative DNA damage levels started to increase during medical residency and were higher at the end of residency than at baseline. Protein carbonyls increased during but not at the end of medical residency compared to baseline. The antioxidant enzyme superoxide dismutase activity remained lower than baseline during and at the end of medical residency, and HO-1 (related to antioxidant defense) expression was downregulated at the end of medical residency. Additionally, anesthetic concentrations were above international recommendations. In conclusion, high concentrations of anesthetic in the workplace induce oxidative stress, gene expression modulation, and genotoxicity in physicians during their specialization period.

Access or request full text: https://libkey.io/10.1007/s11356-023-27577-y

4. **Immunotoxicity induced by occupational inhalation exposure to waste anesthetic gases: a historical cohort study**

Item Type: Journal Article

Authors: Neghab M.;Amiri F.;Zare M. and Zareei F.

Publication Date: 2023

Journal: Annals of Medicine and Surgery 85(6), pp. 2313–2318

Abstract: Background: This study was undertaken to ascertain whether long-term occupational exposure to inhalational anesthetic, was associated with any significant alteration in the parameters of immune function. Material(s) and Method(s): This was a historical cohort study in which 30 male participants with at least one year of work experience in the operating room at the time of the study and 30 unexposed referent subjects were investigated. Exposure levels were quantified by measuring the urinary concentrations of nitrous oxide (N2O), isoflurane, and sevoflurane gases by headspace gas chromatography-mass spectrometry. Serum concentrations of interleukin-4 (IL-4), Th2-type cytokines, and interferon-gamma (IFN-gamma) were measured by the ELISA method. Additionally, an automated hematology analyzer was used for the white blood cell count and white blood cell differential test. The data were analyzed using SPSS software for Windows version 21. Result(s): Mean urinary concentrations of N2O, isoflurane, and sevoflurane were found to be 211.57 +/- 75.15, 4.06 +/- 0.96, and 19.51 +/- 12.96 ppb, respectively. In simplistic statistical data analysis, significant differences were noted between exposed and control groups as far as the mean serum cytokines levels (IFN-gamma, IL-4) were concerned. Furthermore, after adjusting for important confounders, statistical analysis showed that the IFN-gamma, IL-4, and the ratio of IFN-gamma/IL-4 were significantly higher in the exposed group than in the referent subjects. Conclusion(s): These findings provide corroborative evidence to further substantiate the contention that exposure to anesthetics agents (N2O, isoflurane, and sevoflurane) is associated with subtle, subclinical, prepathological changes in the parameters of immune function. The long-term ramification of these changes requires further investigation.Copyright © 2023 The Author(s). Published by Wolters Kluwer Health, Inc.

5. **Evaluation of genetic instability, oxidative stress, and metabolism-related gene polymorphisms in workers exposed to waste anesthetic gases**

Item Type: Journal Article

Authors: Silva M.A.P.;Figueiredo D.B.S.;Lara J.R.;Paschoalinotte E.E.;Braz L.G. and Braz M.G.

Publication Date: 2023

Journal: Environmental Science and Pollution Research International 30(4), pp. 9609–9623

Abstract: Professionals who work in operating rooms (ORs) may be exposed daily to waste anesthetic gases (WAGs) due to the use of inhalational anesthetics. Considering the controversial findings related to genetic damage and redox status in addition to a lack of knowledge about the effect of polymorphisms in genes related to phase I and II detoxification upon occupational exposure to WAGs, this cross-sectional study is the first to jointly evaluate biomarkers of genetic instability, oxidative stress, and susceptibility genes in professionals occupationally exposed to high trace amounts of halogenated (>= 7 ppm) and nitrous oxide (165 ppm) anesthetics in ORs and in individuals not exposed to WAGs (control group). Elevated rates of buccal micronucleus (MN) and nuclear bud (NBUD) were observed in the exposure group and in professionals exposed aged more than 30 years. Exposed males showed a higher antioxidant capacity, as determined by the ferric reducing antioxidant power (FRAP), than exposed females; exposed females had higher frequencies of MN and NBUD than nonexposed females. Genetic instability (MN) was observed in professionals with greater weekly WAG exposure, and those exposed for longer durations (years) exhibited oxidative stress (increased lipid peroxidation and decreased FRAP). Polymorphisms in metabolic genes (cytochrome P450 2E1 (CYP2E1) and glutathione S-transferases (GSTs)) did not exert an effect, except for the effects of the GSTP1 (rs1695) AG/GG polymorphism on FRAP (both groups) and GSTP1 AG/GG and GSTT1 null polymorphisms, which were associated with greater FRAP values in exposed males. Minimizing WAG exposure is necessary to reduce impacts on healthcare workers.

6. **Hepatotoxic and neuroendocrine effects in physicians occupationally exposed to most modern halogenated anesthetics and nitrous oxide**

Item Type: Journal Article

Authors: Aun A.G.;Souza K.M.;Guedes J.L.;Figueiredo D.B.S.;Lara J.R.;Silva M.A.P.;Braz L.G. and Braz M.G.

Publication Date: 2021

Journal: Environmental Toxicology and Pharmacology 81, pp. 103515

Abstract: The lack of data on hepatic and hormonal markers for occupational exposure to most modern halogenated anesthetics has stimulated our research, which assessed liver enzymes, high-sensitivity C-reactive protein (hs-CRP) and neuroendocrine response. The study investigated 106 physicians who were categorized in an exposed group (primarily exposed to isoflurane and sevoflurane and less to desflurane and nitrous oxide) as well as as a control group. Anesthetic air monitoring was performed, and biological samples were analyzed for the most important liver enzymes, hs-CRP, adrenocorticotrophic hormone, cortisol and prolactin. No biomarkers were significantly different between the groups. Exposed males showed significant increases in cortisol and prolactin compared to unexposed males. However, values were within the reference ranges, and 22 % of exposed males versus 5 % of unexposed males exhibited higher prolactin values above the reference range. This study suggests that occupational exposure to the most commonly used inhalational anesthetics is not associated with hepatotoxicity or neurohormonal changes.Copyright © 2020 Elsevier B.V.

7. **High concentrations of waste anesthetic gases induce genetic damage and inflammation in physicians exposed for three years: A cross-sectional study**

Item Type: Journal Article

Authors: Braz, Mariana G.;Carvalho, Lorena I. M.;Chen, Chung-Yen O.;Blumberg, Jeffrey B.;Souza, Katina M.;Arruda, Nayara M.;Filho, Daniel A. A.;Resende, Ludimila O.;Faria, Renata T. B. G.;Canario, Clara d'A;de Carvalho, Lidia,R.;Correa, Camila R.;Braz, Jose Reinaldo C. and Braz, Leandro G.

Publication Date: 2020

Journal: Indoor Air 30(3), pp. 512–520

Abstract: This cross-sectional study analyzed the impact of occupational waste anesthetic gases on genetic material, oxidative stress, and inflammation status in young physicians exposed to inhalational anesthetics at the end of their medical residency. Concentrations of waste anesthetic gases were measured in the operating rooms to assess anesthetic pollution. The exposed group comprised individuals occupationally exposed to inhalational anesthetics, while the control group comprised individuals without anesthetic exposure. We quantified DNA damage; genetic instability (micronucleus-MN); protein, lipid, and DNA oxidation; antioxidant activities; and proinflammatory cytokine levels. Trace concentrations of anesthetics (isoflurane: 5.3 +/- 2.5 ppm, sevoflurane: 9.7 +/- 5.9 ppm, and nitrous oxide: 180 +/- 150 ppm) were above international recommended thresholds. Basal DNA damage and IL-17A were significantly higher in the exposed group 27 +/- 20 a.u. and 20.7(19.1;31.8) pg/mL, respectively] compared to the control group 17 +/- 11 a.u. and 19.0(18.9;19.5) pg/mL, respectively], and MN frequency was slightly increased in the exposed physicians (2.3-fold). No significant difference was observed regarding oxidative stress biomarkers. The findings highlight the genetic and inflammatory risks in young physicians exposed to inhalational agents in operating rooms lacking adequate scavenging systems. This potential health hazard can accompany these subjects throughout their professional lives and reinforces the need to reduce ambient air pollution and consequently, occupational exposure.

8. **A review of the effects of the anesthetic gas nitrous oxide on the immune system; a starting point for future experiences**

Item Type: Journal Article

Authors: Mohsenzadegan M.;Kourosh arami M.;Oshaghi M. and Sedigh Maroufi S.

Publication Date: 2020

Journal: Immunopharmacology and Immunotoxicology 42(3), pp. 179–186

Abstract: Nitrous oxide is a common gas used as an anesthetic agent and analgesic medication in operating rooms. The gas inhibits vitamin B12 dependent-methionine synthase, which converts L-homocysteine and 5-methyltetrahydrofolate to L-methionine and tetrahydrofolate, respectively, via a methylation process. The immune system has been frequently reported to be suppressed in anesthetized subjects during the postoperative period. Although previous reviews have focused on the pathophysiologic role of nitrous oxide, none of them has considered the harmful effects of nitrous oxide on the Defense system of the host. In this article, the authors review current studies on the effects of nitrous oxide on the immune system of both patients undergoing surgery and occupational exposure, as well as preclinical studies. Moreover, this paper opens a new horizon for future studies in the context of underlying mechanisms of nitrous oxide actions on the immune system.Copyright © 2020, © 2020 Informa UK Limited, trading as Taylor & Francis Group.

Access or request full text: https://libkey.io/10.1080/08923973.2020.1735412

9. **Toxic responses of the liver and kidneys following occupational exposure to anesthetic gases**

Item Type: Journal Article

Authors: Neghab M.;Amiri F.;Soleimani E.;Yousefinejad S. and Hassanzadeh J.

Publication Date: 2020

Journal: EXCLI Journal 19, pp. 418–429

Abstract: This study was undertaken to determine whether exposure of operating room personnel to inhalation anesthetics, including nitrous oxide, isoflurane, and sevoflurane was associated with any hepatotoxic or nephrotoxic changes. Fifty-two operating room personnel and 52 non-exposed subjects were studied. A questionnaire pertaining to demographic characteristics and medical history of participants was completed. Fasting blood samples were tak-en from all subjects to measure the functional parameters of kidneys and liver. Biological monitoring was also performed to detect the urinary concentration of IAs. Urinary concentrations of nitrous oxide, isoflurane, and sevoflurane were found to be 175.8 +/- 77.52, 4.95 +/- 3.43, and 15.0 3+/- 16.06 ppm, respectively. The mean levels of alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase, gamma-glutamyltransferase, Al-pha-glutathione-S-transferase, as well as the serum levels of kidney injury molecule-1, creatinine and calcium were significantly higher in the exposed group. Statistically significant associations were observed between exposure to inhalation anesthetics and the mean levels of aspartate aminotransferase, alanine aminotransferase, and gamma-glutamyltransferase, serum creatinine, kidney injury molecule-1, and calcium.

Under the exposure sce-nario described in the present study, occupational exposure to inhalation anesthetics was associated with subtle, subclinical, pre-pathologic changes in the parameters of liver and kidneys. Additionally, Alpha-glutathione-S-transferase and kidney injury molecule-1 were found to be sensitive markers for early detection of subclinical changes in the parameters of kidney and liver function in subjects who are exposed to inhalation anesthetics.

Access or request full text: https://libkey.io/10.17179/excli2019-1911

10. **Global burden related to nitrous oxide exposure in medical and recreational settings: A systematic review and individual patient data meta-analysis**

Item Type: Journal Article

Authors: Oussalah A.;Julien M.;Levy J.;Hajjar O.;Franczak C.;Stephan C.;Laugel E.;Wandzel M.;Filhine-Tresarrieu P.;Green R. and Guean J.-L.

Publication Date: 2019

Journal: Journal of Clinical Medicine 8(4), pp. 551

Abstract: The risk of adverse effects of nitrous oxide (N2O) exposure is insuffciently recognized despite its widespread use. These effects are mainly reported through case reports. We conducted an individual patient data meta-analysis to assess the prevalence of clinical, laboratory, and magnetic resonance findings in association with N2O exposure in medical and recreational settings. We calculated the pooled estimates for the studied outcomes and assessed the potential bias related to population stratification using principal component analysis. Eighty-five publications met the inclusion criteria and reported on 100 patients with a median age of 27 years and 57% of recreational users. The most frequent outcomes were subacute combined degeneration (28%), myelopathy (26%), and generalized demyelinating polyneuropathy (23%). A T2 signal hyperintensity in the spinal cord was reported in 68% (57.2-78.8%) of patients. The most frequent clinical manifestations included paresthesia (80%; 72.0-88.0%), unsteady gait (58%; 48.2-67.8%), and weakness (43%; 33.1-52.9%). At least one hematological abnormality was retrieved in 71.7% (59.9-83.4%) of patients. Most patients had vitamin B12 deficiency: Vitamin B12 15 ffmol/L (90.3%; 79.3-100%), and methylmalonic acid >0.4 ffmol/L (93.8%; 80.4-100%). Consistently, 85% of patients exhibited a possibly or probably deficient vitamin B12 status according to the cB12 scoring system. N2O can produce severe outcomes, with neurological or hematological disorders in almost all published cases. More than half of them are reported in the setting of recreational use. TheN2O-related burden is dominated by vitamin B12 deficiency. This highlights the need to evaluate whether correcting B12 deficiency would prevent N2O-related toxicity, particularly in countries with a high prevalence of B12 deficiency.

Access or request full text: https://libkey.io/10.3390/jcm8040551

11. **Early, subclinical hematological changes associated with occupational exposure to high levels of nitrous oxide**

Item Type: Journal Article

Authors: Amiri F.;Neghab M.;Shouroki F.K.;Yousefinejad S. and Hassanzadeh J.

Publication Date: 2018

Journal: Toxics 6(4), pp. 70

Abstract: This study was undertaken to determine whether exposure of operating room personnel to inhalation anesthetics, nitrous oxide, isoflurane, and sevoflurane was associated with any hematological changes. This historical cohort study was performed in 2018 at a large public hospital in Shiraz, where 52 operating room personnel and 52 administrative staff were investigated. The blood sample was taken from all individuals for Complete Blood Count. Furthermore, demographic information was collected through questionnaires. Mean atmospheric concentrations of nitrous oxide, isoflurane, and sevoflurane, to which subjects were exposed, were 850.92, 2.40, and 0.18 ppm, respectively. The hematological parameters were within the normal range in both groups. However, the mean values of hemoglobin, hematocrit, mean corpuscular hemoglobin, mean corpuscular hemoglobin concentration, and red blood cell count in the exposed group were significantly lower than the control group. No significant differences were noted between the two groups as far as other hematological factors were concerned. These findings provide circumstantial evidence to further substantiate the notion that occupational exposure to inhalation anesthetics, under the exposure scenario explained in this study, is associated with subtle, subclinical, prepathologic hematological changes. Long-term consequence and ramifications of these effects require further investigation. The range of exposure levels to anesthetic gases in operating rooms.

Access or request full text: https://libkey.io/10.3390/toxics6040070

12. **Monitoring early cell damage in physicians who are occupationally exposed to inhalational anesthetics**

Item Type: Journal Article

Authors: Aun A.G.;Golim M.A.;Nogueira F.R.;Souza K.M.;Arruda N.M.;Braz J.R.C.;Braz L.G. and Braz M.G.

Publication Date: 2018

Journal: Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis 812, pp. 5–9

Abstract: Worldwide, millions of professionals who work in operating rooms are occupationally exposed to inhalational anesthetics. Thus, the potential health effects of the continuous exposure to inhalational anesthetics on individuals in the operating room remain a subject of debate. Human biomonitoring is a potentially useful tool for assessing the health of exposed professionals. No report has yet evaluated the possible cytotoxic and genotoxic effects of the most commonly used inhalational anesthetics on young professionals who are occupationally exposed. Considering the importance of this issue, we monitored physicians who were exposed to inhalational anesthetics during their first year of a medical residency program to evaluate the possible early damage events. Twenty-six young physicians who had been occupationally exposed to the anesthetics isoflurane, sevoflurane, desflurane, and nitrous oxide and who worked in operating rooms using modern anesthesia workstations during their medical residency program, participated in this study. Blood samples were evaluated before the start of the program (before the exposure), and after 1/2 year and 1 year of exposure. We monitored the subjects by assessing the cytotoxicity (early apoptosis and loss of the mitochondrial membrane potential) using flow cytometry and genotoxicity using the comet assay. No significant changes were observed in the biomarkers of cytotoxicity or genotoxicity ($p > 0.05$). Thus, biomonitoring showed that short-term exposure to inhalational anesthetics did not induce early cell damage during the first year of medical residency. Based on the results, brief occupational exposure to anesthetics does not induce either cytotoxicity or genotoxicity in mononuclear cells under the conditions of this study. Thus, young physicians should undergo additional biomonitoring at the beginning of their careers to determine possible toxic effects on their cells and genetic material, and further investigations are warranted to determine whether a longer exposure to inhalational anesthetics results in mitochondrial depolarization, apoptosis and DNA breaks.Copyright © 2018 Elsevier B.V.

13. **Detrimental effects detected in exfoliated buccal cells from anesthesiology medical residents occupationally exposed to inhalation anesthetics: An observational study**

Item Type: Journal Article

Authors: Braz, Mariana G.;Souza, Katina M.;Lucio, Lorena M. C.;Di Renzo, Giulia,C.C.;Feliciano, Luciana M.;Marcondes, Joao Paulo C.;Chen, C-Y O.;Braz, Jose Reinaldo C. and Braz, Leandro G.

Publication Date: 2018

Journal: Mutation Research.Genetic Toxicology and Environmental Mutagenesis 832-833, pp. 61–64

Abstract: Operating room professionals are scarcely aware of their individual occupational exposure to waste anesthetic gases (WAGs). Medical residents spend several hours per day in operating rooms and consequently experience occupational exposure to WAGs. Considering that no studies have yet evaluated the potential toxicity in medical residents exposed to WAGs using the buccal micronucleus cytome (BMCyt) assay, this pioneering study aimed to compare the BMCyt assay markers, including DNA damage, cell proliferation, and cell death in the exfoliated buccal cells of surgery and anesthesiology residents occupationally exposed to WAGs. The study enrolled a total of 60 physicians, including internal medicine residents (unexposed group), and residents from surgery and anesthesiology programs who were occupationally exposed to sevoflurane, isoflurane and nitrous oxide. WAGs were measured, and the mean values were higher than the international recommendation. The anesthesiology residents (high exposure) showed statistically significant lower frequencies of basal cells, and statistically significant higher frequencies of micronuclei, karyorrhexis, pyknosis, and differentiated cells than did the unexposed group; karyolysis frequencies were significantly higher in anesthesiology residents than were those in the unexposed group or in surgical residents (low exposure). The findings suggest a genetic risk for young professionals exposed to WAGs at the beginning of their careers. Thus, exposure to high WAGs concentrations leads to impairment of the buccal cell proliferative potential, genomic instability and cell death, especially in anesthesiology residents, demonstrating an early impact on their health.

14. **Occupational exposure to anesthetics leads to genomic instability, cytotoxicity and proliferative changes**

Item Type: Journal Article

Authors: Souza K.M.;Braz L.G.;Nogueira F.R.;Souza M.B.;Bincoleto L.F.;Aun A.G.;Corrente J.E.;Carvalho L.R.;Braz J.R.C. and Braz M.G.

Publication Date: 2016

Journal: Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis 791-792, pp. 42–48

Abstract: Data on the genotoxic and mutagenic effects of occupational exposure to the most frequently used volatile anesthetics are limited and controversial. The current study is the first to evaluate genomic instability, cell death and proliferative index in exfoliated buccal cells (EBC) from anesthesiologists. We also evaluated DNA damage and determined the concentrations of the anesthetic gases most commonly used in operating rooms. This study was conducted on physicians who were allocated into two groups: the exposed group, which consisted of anesthesiologists who had been exposed to waste anesthetic gases (isoflurane, sevoflurane, desflurane and nitrous oxide - N2O) for at least two years; and the control group, which consisted of non-exposed physicians matched for age, sex and lifestyle with the exposed group. Venous blood and EBC samples were collected from all participants. Basal DNA damage was evaluated in lymphocytes by the comet assay, whereas the buccal micronucleus (MN) cytome (BMCyt) assay was applied to evaluate genotoxic and cytotoxic effects. The concentrations of N2O and anesthetics were measured via a portable infrared spectrophotometer. The average concentration of waste gases was greater than 5 parts per million (ppm) for all of the halogenated anesthetics and was more than 170 ppm for N2O, expressed as a time-weighted average. There was no significant difference between the groups in relation to lymphocyte DNA damage. The exposed group had higher frequencies of MN, karyorrhexis and pyknosis, and a lower frequency of basal cells compared with the control group. In conclusion, exposure to modern waste anesthetic gases did not induce systemic DNA damage, but it did result in genomic instability, cytotoxicity and proliferative changes, which were detected in the EBC of anesthesiologists. Thus, these professionals can be considered at risk for developing genetic alterations resulting from occupational exposure to these gases, suggesting the need to minimize this exposure.

15. **Laughing Gas in a Pediatric Emergency Department-Fun for All Participants: Vitamin B12 Status Among Medical Staff Working With Nitrous Oxide**

Item Type: Journal Article

Authors: Staubli, Georg;Baumgartner, Matthias;Sass, Jorn Oliver and Hersberger, Martin

Publication Date: 2016

Journal: Pediatric Emergency Care 32(12), pp. 827–829

Abstract: The efficiency of nitrous oxide in an equimolar mixture with oxygen or in concentrations up to 70% is approved for short painful procedures. Evaluation of the vitamin B12 levels in anesthetic staff applying nitrous oxide showed reduced vitamin B12 plasma levels. This study examines the vitamin B12 status of medical staff working with nitrous oxide in a pediatric emergency department (ED). Medical staff of the ED at the University Children's Hospital Zurich participated. The vitamin B12 status was evaluated by measuring homocysteine, methylmalonic acid, vitamin B12, blood count, and the MTHFR C677T genotype. As a control group, medical personnel working in the "nitrous oxide-free" pediatric intensive care unit were recruited., RESULTS: The parameters for the vitamin B12 status of all participants were in the reference range, and there were no significant differences for the 2 groups. By trend, the ED staff showed higher vitamin B12 levels. The ED staff members were slightly older (P = 0.07) and had higher hemoglobin levels (P < 0.04) compared with the pediatric intensive care unit staff., CONCLUSIONS: The use of nitrous oxide (50%-70%) with a demand valve is safe for the vitamin B12 status of medical personnel in the ED.

16. **Does occupational exposure to anesthetic gases lead to increase of pro-inflammatory cytokines?**

Item Type: Journal Article

Authors: Chaoul, Mauricio Martins;Braz, Jose Reinaldo C.;Lucio, Lorena Mendes C.;Golim, Marjorie A.;Braz, Leandro Gobbo and Braz, Mariana Gobbo

Publication Date: 2015

Journal: Inflammation Research : Official Journal of the European Histamine Research Society ...[Et Al.] 64(12), pp. 939–42

Abstract: INTRODUCTION: There is great concern about the possible harmful effects of exposure to volatile anesthetics. The current study aimed at evaluating, for the first time, the effects of occupational exposure to anesthetic gases on physicians who work in operating rooms, by determining several inflammatory cytokines., MATERIALS AND METHODS: Plasma inflammatory cytokines (IL-1beta, -6, -8, -10, -12, TNF-alpha) were investigated in 30 individuals who were allocated into two groups of 15: the exposed group, consisting of operating room medical personnel exposed to a mixture of anesthetic gases for 3 years, and a control group composed of medical personnel not exposed to anesthetic gases. The concentrations of volatile anesthetics were measured in the operating room by means of an infrared portable analyzer, RESULTS AND CONCLUSIONS: Our findings suggest an increase of the pro-inflammatory IL-8 ($p<0.05$) in medical personnel exposed to high concentrations of anesthetic gases, even for a relatively short period.

Access or request full text: https://libkey.io/10.1007/s00011-015-0881-2

17. **Is nitrous oxide a genotoxic carcinogen?**

Item Type: Journal Article

Authors: O'Donovan M.R. and Hammond T.G.

Publication Date: 2015

Journal: Mutagenesis 30(4), pp. 459–462

Abstract: Nitrous oxide (N2O) has been widely used as a dental and surgical anaesthetic for over 150 years. However, results from a recent study suggested that increased DNA damage was seen in lymphocytes from surgical patients and this led to its continued clinical use to be questioned. The data can be challenged on technical grounds and must be considered with other studies in order to assess any possible risk. There are other studies indicating that N2O has weak genotoxicity in man, but these are confused by exposure of the populations to other anaesthetic gases including isoflurane and sevoflurane, both of which have also been reported to increase DNA damage. It should be noted that the suggested genotoxic mechanisms are all indirect, including folate deficiency, oxidative stress and homocysteine toxicity. Further, results from in vitro studies indicate that N2O has no direct DNA reactivity as negative results were obtained in a bacterial mutation (Ames) test and an assay for mutation at the hprt locus in Chinese hamster lung cells. Although not performed to definitive study designs, no evidence of carcinogenicity was seen in two long-term tests in mice and another in rats. Although there is some evidence that N2O is weakly genotoxic in humans, this appears to be similar to that reported for isoflurane and

sevoflurane and all the postulated mechanisms have clear thresholds with no evidence of direct DNA reactivity. Because any potential genotoxic mechanism would have a threshold, it seems reasonable to conclude that neither occasional high exposure to patients as an anaesthetic nor low-level exposure to staff within published recommended exposure limits presents any significant carcinogenic risk.

Access or request full text: https://libkey.io/10.1093/mutage/gev024

18. **The adverse effects of nitrous oxide**

Item Type: Journal Article

Authors: Ferner R.E.;Mackenzie A.A. and Aronson J.K.

Publication Date: 2014

Journal: Adverse Drug Reaction Bulletin (285), pp. 1099–1102

Abstract: Nitrous oxide (N2O) has been used as an anaesthetic agent since 1844. It has two well recognized adverse effects: it oxidizes Co(I) to Co(II) and so inactivates vitamin B12, and its high partial pressure in blood allows it to expand into cavities in the body such as the pleural space. Impairment of the action of vitamin B12 can cause both megaloblastic anaemia and, especially in recreational users of N2O, the syndrome of subacute combined degeneration of the spinal cord. The overall cardiovascular effects in noncardiac surgery seem to be minor. N2O is probably a human teratogen.

Access or request full text: https://libkey.io/10.1097/FAD.0000000000000003

19. **DNA damage and antioxidant status in medical residents occupationally exposed to waste anesthetic gases**

Item Type: Journal Article

Authors: Paes E.R.C.;Braz M.G.;da Lima J.T.;da Silva M.R.G.;de Sousa L.B.;Lima E.S.;de Vasconcellos M.C. and Braz J.R.C.

Publication Date: 2014

Journal: Acta Cirurgica Brasileira 29(4), pp. 280–286

Abstract: PURPOSE: To investigate the effects of occupational exposure to waste anesthetic gases on genetic material and antioxidant status in professionals during their medical residency. METHOD(S): The study group consisted of 15 medical residents from Anesthesiology and Surgery areas, of both genders, mainly exposed to isoflurane and to a lesser degree to sevoflurane and nitrous oxide; the control group consisted of 15 young adults not exposed to anesthetics. Blood samples were drawn from professionals during medical residency (eight, 16 and 22 months of exposure to waste anesthetic gases). DNA

damage was evaluated by comet assay, and antioxidant defense was assessed by total thiols and the enzymes glutathione peroxidase (GPX), superoxide dismutase (SOD) and catalase (CAT). RESULT(S): When comparing the two groups, DNA damage was significantly increased at all time points evaluated in the exposed group; plasma thiols increased at 22 months of exposure and GPX was higher at 16 and 22 months of exposure. CONCLUSION(S): Young professionals exposed to waste anesthetic gases in operating rooms without adequate scavenging system have increased DNA damage and changes in redox status during medical residency. There is a need to minimize exposure to inhalation anesthetics and to provide better work conditions.

Access or request full text: https://libkey.io/10.1590/S0102-86502014000400010

20. **Homocysteine levels and bad obstetric outcome among female operating room personnel occupationally exposed to nitrous oxide**

Item Type: Journal Article

Authors: Uzun S.;Saricaoglu F.;Ayhan B.;Topatan B.;Akinci S.B. and Aypar U.

Publication Date: 2014

Journal: Bratislavske Lekarske Listy 115(6), pp. 372–376

Abstract: It is known that nitrous oxide (N2O) inactivates vitamin B12 and causes hyperhomocysteinemia. The personnel working at the operating theatres are repeatedly exposed to N2O in the ambient air. This prompted us to investigate the biochemical indices of vitamin B12 metabolic status among female personnel working under various levels of N2O exposure. In this study, the homocysteine and folic acid levels were assessed and bad obstetric outcome was questioned. Sixty operating theatre female personnel were examined. Vitamin B12 and folic acid, total homocysteine level, anticardiolipin IgM, IgG, antiphospholipid IgM, IgG levels were measured in serum. A questionnaire inquiring about obstetric history was given. The serum concentration of folic acid was 10 +/- 3.3 nmol liter-1. The vitamin B12 level was 332 +/- 134 pmol liter-1, the serum concentration of homocysteine was 9.1 +/- 2.4 nmol liter-1 and all were within normal ranges. There was no difference regarding homocysteine, folic acid, vitamin B12 levels and the obstetric history between the subjects who had abortus history and the subjects who had not abortus history. Exposure to N2O in healthcare workers was not associated with alterations of homocysteine, folic acid status and bad obstetric outcome (Tab. 4, Ref. 18).

URL: https://libkey.io/libraries/2828/openurl?genre=article&sid=OVID:embase&id=pmid:25023429&id=doi:&issn=0006-9248&isbn=&volume=115&issue=6&spage=372&pages=372-376&date=2014&title=Bratislavske+lekarske+listy&atitle=Homocysteine+levels+and+bad+obstetric+outcome+among+female+operating+room+personnel+occupationally+exposed+to+nitrous+oxide&aulast=Uzun&pid=%3Cauthor%3EUzun+S.%3BSaricaoglu+F.%3BAyhan+B.%3BTopatan+B.%3BAkinci+S.B.%3BAypar+U.%3C%2Fauthor%3E%3CAN%3E373815584%3C%2FAN%3E%3CDT%3EArticle%3C%2FDT%3E

21. **Exposure to anesthetic gases and Parkinson's disease: A case report**

Item Type: Journal Article

Authors: Mastrangelo G.;Comiati V.;dell'Aquila M. and Zamprogno E.

Publication Date: 2013

Journal: BMC Neurology 13, pp. 194

Abstract: Background: The administration of anesthetics determines depression of the central nervous system and general anesthesia by inhalation may cause an environmental pollution of the operating rooms. It may therefore conceive a possible occupational etiology of Parkinson's Disease (PD).Case presentation: In a Caucasian male aged 59 years, PD was diagnosed by brain scans with a presynaptic radioactive tracer of the dopaminergic system. Family history was negative for Parkinson's disease or essential tremor. He was a smoker, a moderate consumer of coffee and alcohol, and never exposed to pesticides/metals. For 30 years (since the age of 29 until today), he worked as an anesthesiologist in private clinics in the Veneto (Northern Italy), exposed to anesthetic gases. The time elapsed from first exposure to onset of disease is 22 years, fulfilling the requirement of the induction/latency period. A literature search demonstrated unacceptable levels of anesthetic gases in public hospitals of the Veneto region from 1990 to 1999. This exposure was presumably high also in private hospitals of the region until at least 2007, when an overexposure to sevoflurane was repeatedly measured in this patient. The association between occupational exposure to anesthetic gases and risk of Parkinson's disease was supported by a case-control study (reporting a two-fold increase in the risk of PD associated with a clinical history of general anesthesia) and a cohort study comparing mortality from PD between US anesthesiologists and internists (showing a statistically significant excess (p=0.01) in anesthesiologists compared to internists). Numerous recent mechanistic studies (in vitro essays and in vivo short-term studies) strengthened the association between exposure to anesthetic gases (nitrous oxide, halothane, isoflurane, levoflurane) and PD. Conclusion(s): In view of the limited evidence of human studies and the sufficient evidence of experimental studies, the high exposure to anesthetic gases could have induced PD in the subject under study. © 2013 Mastrangelo et al.; licensee BioMed Central Ltd.

Access or request full text: https://libkey.io/10.1186/1471-2377-13-194

22. **Exposure to nitrous oxide during pregnancy is no laughing matter**

Item Type: Journal Article

Authors: Schafer, Jodi

Publication Date: 2013

Journal: The Journal of the Michigan Dental Association 95(4), pp. 22–70

URL: https://libkey.io/libraries/2828/openurl?genre=article&sid=OVID:medline&id=pmid:23741955&id=doi:&issn=0026-2102&isbn=&volume=95&issue=4&spage=22&pages=22%2C+70&date=2013&title=Journal

+of+Michigan+Dental+Association&atitle=Exposure+to+nitrous+oxide+during+pregnancy+is+no+laughing+matter.&aulast=Schafer&pid=%3Cauthor%3ESchafer+J%3C%2Fauthor%3E%3CAN%3E23741955%3C%2FAN%3E%3CDT%3EJournal+Article%3C%2FDT%3E

23. **Oxidative DNA damage and oxidative stress in subjects occupationally exposed to nitrous oxide (N(2)O)**

Item Type: Journal Article

Authors: Wronska-Nofer, Teresa;Nofer, Jerzy-Roch;Jajte, Jolanta;Dziubaltowska, Elzbieta;Szymczak, Wieslaw;Krajewski, Wojciech;Wasowicz, Wojciech and Rydzynski, Konrad

Publication Date: 2012

Journal: Mutation Research 731(1-2), pp. 58–63

Abstract: OBJECTIVES: Occupational exposure to nitrous oxide (N(2)O) and/or halogenated hydrocarbons has been suggested to induce damage of genetic material, but the underlying mechanisms remain obscure. This study investigated the role of oxidative processes in the genotoxicity associated with exposure to waste anaesthetic gases., METHODS: The study was performed in 36 female nurses and in 36 unexposed female health care workers matched for age and employment duration. Genotoxic effects were examined by Comet test modification employing formamidopyrimidine glycosylase (FPG) that allows assessment of oxidative DNA damage. Reactive oxygen species (ROS) in leukocytes were investigated by fluorescence spectroscopy with 2',7'-dichlorofluorescin diacetate. Oxidative stress markers including 8-iso-prostaglandin F(2alpha) (8-iso-PGF(2alpha)), thiobarbituric acid-reacive substances (TBARS), alpha-tocopherol, and glutathione peroxidise (GPX) activity were measured immuno- or colorimetrically. N(2)O, sevoflurane and isoflurane were monitored by gas chromatography and mass spectrometry., RESULTS: The study documents for the first time the positive correlation between the oxidative DNA damage and the N(2)O levels in the ambient air. By contrast, no association was observed between genotoxic effects and sevoflurane or isoflurane. In addition, ROS generation and plasma and urine concentrations of TBARS and 8-iso-PGF(2alpha), respectively, were elevated, while GPX activity was reduced in nurses exposed to waste anaesthetic gases. Path analysis pointed to a causal relationship between N(2)O exposure, oxidative stress and DNA damage., CONCLUSION: Occupational exposure to N(2)O is associated with increased oxidative DNA damage and the level of exposure plays a critical role in this regard. Increased oxidative stress may represent a mechanistic link between chronic N(2)O exposure and genotoxicity.

Access or request full text: https://libkey.io/10.1016/j.mrfmmm.2011.10.010

24. **Safety and Risks of Nitrous Oxide Labor Analgesia: A Review**

Item Type: Journal Article

Authors: Rooks J.P.

Publication Date: 2011

Journal: Journal of Midwifery and Women's Health 56(6), pp. 557–565

Abstract: Introduction: This review of the safety and risks of nitrous oxide (N2O) labor analgesia presents results of a search for evidence of its effects on labor, the mother, the fetus, the neonate, breastfeeding, and maternal-infant bonding. Concerns about apoptotic damage to the brains of immature mammals exposed to high doses of N2O during late gestation, possible cardiovascular risks from hyperhomocysteinemia caused by N2O, a hypothesis that children exposed to N2O during birth are more likely to become addicted to amphetamine drugs as adults, and possible occupational risks for those who provide care to women using N2O/O2 labor analgesia are discussed in detail. Method(s): Research relevant to the 4 special concerns and to the effects of N2O analgesia on labor and the mother-child dyad were examined in depth. Three recent reviews of the biologic, toxicologic, anesthetic, analgesic, and anxiolytic effects of N2O; 3 reviews of the safety of 50% N2O/oxygen (O2) in providing analgesia in a variety of health care settings; and a 2002 systematic review of N2O/O2 labor analgesia were used. Result(s): Nitrous oxide analgesia is safe for mothers, neonates, and those who care for women during childbirth if the N2O is delivered as a 50% blend with O2, is self-administered, and good occupational hygiene is practiced. Because of the strong correlation between dose and harm from exposure to N2O, concerns based on effects of long exposure to high anesthetic-level doses of N2O have only tenuous, hypothetical pertinence to the safety of N2O/O2 labor analgesia. Discussion(s): Nitrous oxide labor analgesia is safe for the mother, fetus, and neonate and can be made safe for caregivers. It is simple to administer, does not interfere with the release and function of endogenous oxytocin, and has no adverse effects on the normal physiology and progress of labor. © 2011 by the American College of Nurse-Midwives.

25. **Genotoxic effects of anesthetic agents: An update**

Item Type: Journal Article

Authors: Schifilliti D.;Mondello S.;D'Arrigo M.G.;Chill G. and Fodale V.

Publication Date: 2011

Journal: Expert Opinion on Drug Safety 10(6), pp. 891–899

Abstract: Introduction: Exposure to anesthetics in the health environment may entail a health risk for patients and operating room personnel. Knowing the effects of anesthetic agents on genetic material could be a valuable basic support for anesthesia care providers to improve treatment performance, increase patient safety and reduce the risks for patients and staff in the operating room. Areas covered: Relevant literature was identified using MEDLINE, CINAHL and Cochrane Library databases. Over 200 abstracts for articles published from 1980 to 2010 were examined. Original articles were reviewed and relevant citations from these articles were also considered. Expert opinion: Despite some conflicting results, the current available data indicate that exposure to anesthetics, especially nitrous oxide and halogenated agents, is associated with general and genotoxic risks, whereas intravenous agents, such as propofol and its metabolites are not associated with genotoxic effects. Moreover, given that different anesthetic drugs are used in combination it is, thus, very difficult to understand whether the observed effects or absence of effects are due to an individual agent action or linked to a synergy action of different anesthetics involved. Further clinical and experimental evidence is warranted. © 2011 Informa UK, Ltd.

26. **Exposure to anesthetic gases and congenital anomalies in offspring of female registered nurses**

Item Type: Journal Article

Authors: Teschke K.;Abanto Z.;Arbour L.;Beking K.;Chow Y.;Gallagher R.P.;Jong B.;Le N.D.;Ratner P.A.;Spinelli J.J. and Dimich-Ward H.

Publication Date: 2011

Journal: American Journal of Industrial Medicine 54(2), pp. 118–127

Abstract: Background: Studies of offspring of mothers exposed to anesthetic gases have shown associations with congenital anomalies reported by the mothers, but rarely in studies with objectively ascertained outcomes. We conducted a retrospective cohort study to examine associations between registry-ascertained congenital anomalies in offspring and anesthetic gas exposure of mothers employed as nurses. Method(s): A cohort of registered nurses in British Columbia, Canada, was linked to records of births and congenital anomalies from 1990 to 2000. Exposures were assessed via a survey of anesthetic gas use in all hospitals in the province and records of nurses' jobs, departments, and hospitals. Result(s): Departments most frequently reporting anesthetic gas use were operating rooms, post-anesthetic recovery rooms, and maternity units. In the cohort of 15,317 live-borne children of 9,433 mothers, 1,079 had congenital anomalies. Anomalies were associated with ever and probable maternal exposure to halogenated gases (ORs: 1.49, 95% CI: 1.04-2.13; and 2.61, 95% CI: 1.31-5.18, respectively) and to nitrous oxide (ORs: 1.42, 95% CI: 1.05-1.94; and 1.82, 95% CI: 1.11-2.99). Anomalies most frequently associated with exposure were those of the heart (OR, halogenated gases: 2.31, 95% CI: 1.07-4.97) and integument (OR, halogenated gases: 3.56, 95% CI: 1.53-8.32; OR, nitrous oxide: 3.02, 95% CI: 1.37-6.64). Gases most frequently associated with anomalies were halothane (predominantly used early in the study period), isoflurane, and sevoflurane (predominantly used later in the period). Conclusion(s): In this study, where both exposures and outcomes were assessed objectively, certain congenital anomalies were associated with estimated anesthetic gas exposure. © 2010 Wiley-Liss, Inc.

27. **DNA damage induced by nitrous oxide: Study in medical personnel of operating rooms**

Item Type: Journal Article

Authors: Wronska-Nofer T.;Palus J.;Krajewski W.;Jajte J.;Kucharska M.;Stetkiewicz J.;Wasowicz W. and Rydzynski K.

Publication Date: 2009

Journal: Mutation Research - Fundamental and Molecular Mechanisms of Mutagenesis 666(1-2), pp. 39–43

Abstract: Occupational exposure to anaesthetics such as nitrous oxide (N2O) and halogenated hydrocarbons has been suggested to increase risk of genetic damage. However, the dose-dependency of genotoxic effects has not been unequivocally established and their relation to occupational exposure limit (OEL) remain obscure. In this study, the genotoxicity associated with occupational exposure to anaesthetics has been investigated in a group of 55 female nurses and 29 male anaesthesiologists active for at least 5 years in a working environment containing variable concentrations of N2O and halogenated hydrocarbons. 83 unexposed health care workers (52 female nurses and 31 male doctors) matched for age, gender, smoking habit and employment duration were included in the control group. Genotoxicity has been assessed using comet test. Concentrations of nitrous oxide, sevoflurane and isoflurane monitored by gas chromatography and mass spectrometry made possible to relate the extent of DNA damage to the level of exposure. Our results for the first time document a positive correlation between the DNA damage and the N2O levels in the ambient air. By contrast, no correlation has been observed between genotoxic effects and concentrations of sevoflurane and isoflurane. The extent of genetic injury was especially aggravated among nurses and anaesthesiologists exposed to N2O in concentrations exceeding OEL (180 mg/m3). We conclude that occupational exposure to N2O is associated with increased DNA damage and that the level of exposure plays a critical role in this regard.

Access or request full text: https://libkey.io/10.1016/j.mrfmmm.2009.03.012

28. **Persistent cognitive functioning deficits in operating rooms: two cases**

Item Type: Journal Article

Authors: Dreyfus, Elsa;Tramoni, Eve and Lehucher-Michel, Marie

Publication Date: 2008

Journal: International Archives of Occupational and Environmental Health 82(1), pp. 125–30

Abstract: BACKGROUND: To date, chronic toxic encephalopathy (CTE) has never been described in operating room personnel., CASE REPORT: We report two cases of anaesthetists who developed this pathology. They have both used anaesthetic gases for many years in paediatric surgery. Air conditioning was deficient during three years in operating rooms and atmospheric anaesthetics concentration was high (N(2)O mean concentration: 311 ppm, peak levels 1,600 ppm; halogenated: 16 ppm, peak levels: 1,600 ppm)., CLINICAL SYMPTOMS: Mood troubles and non-specific neuropsychic deficits gradually evolved until they had to stop working. Neuropsychological assessment showed important deficits in attention, executive functioning, short-term memory and visuo-spatial organization. Blood tests, VEPs, MRI, neuroSPECT and cardiovascular exams were normal. Troubles had slowly improved after cessation of exposure and sequels still remain., CONCLUSION: These CTE cases seem to be the consequence of a long-term exposure to important levels of anaesthetic gases, and particularly nitrous oxide. It points out the importance of preventive measures in operating rooms, where occupational hazards are varied.

Access or request full text: https://libkey.io/10.1007/s00420-008-0302-8

29. **Genotoxic effects of anesthetic agents**

Item Type: Journal Article

Authors: Fodale, V.;Mondello, S.;Aloisi, C.;Schifilliti, D. and Santamaria, Lb

Publication Date: 2008

Journal: Expert Opinion on Drug Safety 7(4), pp. 447–58

Abstract: BACKGROUND: Preliminary research results indicate that exposure to anesthetics affects health., OBJECTIVE: To provide, with evidence-based knowledge, the answer to the question: What are the genotoxic effects threatening people exposed to anesthetics?, METHOD: A systematic review of scientific literature. A systematic search of The Cochrane Library, MedLine, and CINAHL resulted in a screening of 212 abstracts of which 54 articles were assessed for quality. The 54 articles assessed covered areas on general health effects (neurobehavioral effects, immunology) and, in particular, genotoxic effects., RESULTS/CONCLUSION: In the scientific literature reviewed, there is evidence of exposure to anesthetics, especially nitrous oxide and halogenated gases, being associated with general health and genotoxic risks, but conflicting results have been obtained. The result of this review further stresses the need for scientific knowledge in this area and enhances the studies, above all, on people exposed for long periods.

30. **Impaired vitamin B12 metabolic status in healthcare workers occupationally exposed to nitrous oxide**

Item Type: Journal Article

Authors: Krajewski W.;Kucharska M.;Pilacik B.;Fobker M.;Stetkiewicz J.;Nofer J.-R. and Wronska-Nofer T.

Publication Date: 2007

Journal: British Journal of Anaesthesia 99(6), pp. 812–818

Abstract: Background. Previous studies demonstrated inactivation of vitamin B12 by nitrous oxide (N2O). The intraoperative exposure to N2O was shown to induce megaloblastic anaemia and myelopathy in subjects with subclinical vitamin B12 deficiency. In contrast, no data concerning the influence of occupational exposure to N2O on vitamin B12 metabolic status are available to date. In the present study, the vitamin B12 status in operating theatre personnel was assessed in relation to the extent of exposure. Methods. Ninety-five operating theatre nurses with the history of exposure to N2O and 90 unexposed counterparts were examined. Vitamin B12 and folic acid were measured by immunoassay. Total homocysteine (tHcy), an indicator of impaired vitamin B12 metabolism, was determined by high performance liquid chromatography. N2O concentration was monitored by adsorption gas chromatography and mass spectrometry. Results. No significant differences were found between both groups with respect to haematological parameters and folic acid. However, subjects exposed to N2O presented with lower vitamin B12 372.8 (12.1) vs 436.8 (13.2) pmol litre-1, P<0.001] and higher tHcy 11.2 (0.5) vs 8.9 (0.5) mumol litre-1, P=0.006]. The changes in vitamin B12 status were aggravated in subjects exposed to N 2O in concentrations substantially exceeding occupational exposure limit (180 mg m-3) vitamin B12: 341.9 (17.7) vs 436.8 (13.2) pmol litre-1, P=0.006; tHcy: 12.9 (0.7) vs 8.9 (0.5) mumol litre -1, P=0.047]. Conclusions. Exposure to N2O in healthcare workers is associated with alterations of vitamin B12 metabolic status, the extent of which depends on the level of exposure. © The Board of Management and Trustees of the British Journal of Anaesthesia 2007. All rights reserved.

Access or request full text: https://libkey.io/10.1093/bja/aem280

31. **Exposure to nitrous oxide may be associated with high homocysteine plasma levels and a risk for clinical depression**

Item Type: Journal Article

Authors: Levine, Joseph and Chengappa, K. N.

Publication Date: 2007

Journal: Journal of Clinical Psychopharmacology 27(2), pp. 238–9

Access or request full text: https://libkey.io/10.1097/01.jcp.0000264982.02239.48

32. **Reproductive outcomes among dental personnel: a review of selected exposures**

Item Type: Journal Article

Authors: Olfert, Sandra M.

Publication Date: 2006

Journal: Journal (Canadian Dental Association) 72(9), pp. 821–5

Abstract: Since the late 1960s, investigators have assessed the risks associated with exposure to a variety of potentially harmful agents used in dental practice. This paper provides a brief overview of the epidemiologic literature examining the associations between occupational exposures to elemental mercury and anesthetic gases and reproductive outcomes, such as spontaneous abortion, congenital abnormalities and reduced fertility. Most of the epidemiologic evidence points to a significant relationship between exposure to nitrous oxide and both spontaneous abortion and reduced fertility. There is also evidence for an association between exposure to ethylene oxide and spontaneous abortion, but on the basis of the limited research available, this relationship does not appear to be statistically significant. At this time, evidence of a relationship between exposure to elemental mercury and spontaneous abortion, congenital abnormalities and reduced fertility is limited. Good mercury hygiene by dental personnel and the use of scavenging equipment on nitrous oxide systems and exhaust systems on ethylene oxide sterilizers may reduce the risk of adverse reproductive outcomes.

URL: https://libkey.io/libraries/2828/openurl?genre=article&sid=OVID:medline&id=pmid:17109802&id=doi:&issn=0709-8936&isbn=&volume=72&issue=9&spage=821&pages=821-5&date=2006&title=Journal+%28Canadian+Dental+Association%29&atitle=Reproductive+outcomes+among+dental+personnel%3A+a+review+of+selected+exposures.&aulast=Olfert&pid=%3Cauthor%3EOlfert+SM%3C%2Fauthor%3E%3CAN%3E17109802%3C%2FAN%3E%3CDT%3EJournal+Article%3C%2FDT%3E

33. **Increased incidence of micronuclei assessed with the micronucleus assay and the fluorescence in situ hybridization (FISH) technique in peripheral blood lymphocytes of nurses exposed to nitrous oxide**

Item Type: Journal Article

Authors: Lewinska, D.;Stepnik, M.;Krajewski, W.;Arkusz, J.;Stanczyk, M. and Wronska-Nofer, T.

Publication Date: 2005

Journal: Mutation Research 581(1-2), pp. 1–9

Abstract: It has been postulated that exposure to nitrous oxide and halogenated anaesthetics is associated with various adverse health effects such as neurological and reproductive abnormalities or impairment of hepatic functions. In spite of the quite well known genotoxic effects of exposure to nitrous oxide in vivo, the mechanisms of these effects are still not clear. The aim of this study was to assess the frequency of micronuclei and to identify the type of chromosomal damage (clastogenic or aneugenic) in peripheral blood lymphocytes of operating-room nurses exposed to nitrous oxide. The study group comprised 46 women working at departments where the concentration of nitrous oxide

ranged from 14 to 2308 mg/m3. The control population was composed of 28 women employed in the same hospitals but in non-surgical departments. The clastogenic/aneugenic effect of nitrous oxide was evaluated in lymphocytes using the standard micronucleus (MN) assay in combination with the fluorescence in situ hybridization (FISH) technique with pancentromeric probes. The results show a significant increase of the MN frequency in lymphocytes of exposed nurses compared with the control group (4.36+/-2.23 versus 9.02+/-4.67). The multiple regression analysis revealed a statistically significant relationship (p=0.0009) between MN frequency and exposure status, indicating that the level of exposure was the main factor affecting chromosomal damage. As assessed by FISH analysis, the overall frequencies of centromere-positive MN in the control and exposed groups were 43 and 49%, respectively. The increase observed in the exposed group may suggest a slight, statistically insignificant pro-aneugenic effect of exposure to nitrous oxide.

Access or request full text: https://libkey.io/10.1016/j.mrgentox.2004.10.018

34. **Effects of chronic exposure to anaesthetic gases on some immune parameters**

Item Type: Journal Article

Authors: Bargellini A.;Rovesti S.;Barbieri A.;Vivoli R.;Roncaglia R.;Righi E. and Borella P.

Publication Date: 2001

Journal: Science of the Total Environment 270(1-3), pp. 149–156

Abstract: A cross-sectional survey was carried out to evaluate the relation between occupational exposure to low levels of anaesthetic gases (nitrous oxide and isoflurane) and immune parameters. Fifty-one anaesthetists were recruited among different Services of Anaesthesiology and Reanimation. The control group consisted of non-exposed physicians, similar for gender, age, and job grade. Total number of lymphocytes, lymphocyte subpopulations and the natural killer (NK) cytotoxic activity were measured. Information on personal and professional characteristics and on short- and long-term exposure was collected. Percentages of T cells (CD3) decreased significantly in anaesthetists compared to controls, whereas numbers of NK cells (CD16+CD3-) increased. After correction for confounders, short-term (last 2 weeks) exposure was associated with a decrease in percentages of total T and T helper (CD4) cells. Furthermore, T helper percentages were significantly reduced with increasing individual exposure score evaluated on the basis of working days and levels of anaesthetic gases in operating rooms. A significant X-ray-associated increase of numbers and percentages of NK cells was lastly observed. Despite limited present exposure to anaesthetic gases, a specific derangement in lymphocyte subpopulations, with T lymphocytes more affected than B, has been observed.

Access or request full text: https://libkey.io/10.1016/S0048-9697

35. **Sister chromatid exchanges and micronuclei in lymphocytes of operating room personnel occupationally exposed to enfluorane and nitrous oxide**

Item Type: Journal Article

Authors: Pasquini, R.;Scassellati-Sforzolini, G.;Fatigoni, C.;Marcarelli, M.;Monarca, S.;Donato, F.;Cencetti, S. and Cerami, F. M.

Publication Date: 2001

Journal: Journal of Environmental Pathology, Toxicology and Oncology : Official Organ of the International Society for Environmental Toxicology and Cancer 20(2), pp. 119–26

Abstract: The objective of this article is to assess whether occupational exposure to anesthetics increases genotoxic risk. We investigated two cytogenetic biomarkers, sister chromatid exchanges (SCE) and micronuclei (MN), in the peripheral blood lymphocytes of 46 anesthesiologists (24 men), working in operating rooms and mostly exposed to enfluorane and nitrous oxide, and 66 controls (35 men), not exposed to chemicals and living in the same area. Contrary to what was expected, a lower frequency of SCE was found in male anesthesiologists than in controls. Smoking status was found to be positively associated with SCE frequency in each group, while no relation to age was evident. On the contrary, MN frequency was significantly higher in female, but not male, anesthesiologists than in controls. Age and smoking status did not modify the association. No relationship between MN frequency and duration of employment was found in anesthesiologists. Smoking status and mean number of cigarettes smoked per day in smokers were not associated with MN frequency in either anesthesiologists or in controls. MN analysis seems to be a sensitive index of possible genotoxic effects of occupational exposure to anesthesiologists, and women appear to be more susceptible to these effects than men.

URL: https://libkey.io/libraries/2828/openurl?genre=article&sid=OVID:medline&id=pmid:11394710&id=doi:&issn=0731-8898&isbn=&volume=20&issue=2&spage=119&pages=119-26&date=2001&title=Journal+of+Environmental+Pathology%2C+Toxicology+%26+Oncology&atitle=Sister+chromatid+exchanges+and+micronuclei+in+lymphocytes+of+operating+room+personnel+occupationally+exposed+to+enfluorane+and+nitrous+oxide.&aulast=Pasquini&pid=%3Cauthor%3EPasquini+R%3BScassellati-Sforzolini+G%3BFatigoni+C%3BMarcarelli+M%3BMonarca+S%3BDonato+F%3BCencetti+S%3BCerami+FM%3C%2Fauthor%3E%3CAN%3E11394710%3C%2FAN%3E%3CDT%3EJournal+Article%3C%2FDT%3E

36. **Environmental health risk of chronic exposure to nitrous oxide in dental practice**

Item Type: Journal Article

Authors: Szymanska J.

Publication Date: 2001

Journal: Annals of Agricultural and Environmental Medicine 8(2), pp. 119–122

Abstract: Nitrous oxide may be used to alleviate dental anxiety and to diminish or eliminate dental pain. The benefit of nitrous oxide sedation is a cooperative and satisfied patient. By reducing the patient's perception of pain it allows them to relax and cooperate during dental procedures. However, the dental surgery personnel, chronically exposed to N2O, are at serious risk. The chronic effects of occupational exposure to nitrous oxide have long been the subject of debate. Safety standards have been established in the United States and Europe since many years. The potential detrimental action on the reproductive, neurological, haematological, hepatic and renal systems, plus the possibility of increased cancer risk have been the subject of active research, although absolute occupational effects are still uncertain. To provide a safer work-place for those at risk of exposure to waste anesthetic gases, preventive measures are recommended.

URL: https://libkey.io/libraries/2828/openurl?genre=article&sid=OVID:embase&id=pmid:11748867&id=doi:&issn=1232-1966&isbn=&volume=8&issue=2&spage=119&pages=119-122&date=2001&title=Annals+of+Agricultural+and+Environmental+Medicine&atitle=Environmental+health+risk+of+chronic+exposure+to+nitrous+oxide+in+dental+practice&aulast=Szymanska&pid=%3Cauthor%3ESzymanska+J.%3C%2Fauthor%3E%3CAN%3E34016730%3C%2FAN%3E%3CDT%3EReview%3C%2FDT%3E

37. **The association of shift work and nitrous oxide exposure in pregnancy with birth weight and gestational age**

Item Type: Journal Article

Authors: Bodin L.;Axelsson G. and Ahlborg Jr. G.

Publication Date: 1999

Journal: Epidemiology 10(4), pp. 429–436

Abstract: We examined the relation between shift work and occupational nitrous oxide exposure in the second trimester of pregnancy and birth weight and gestational age at delivery among the members of the Swedish Midwives Association. Eighty-four per cent of members who were registered in 1989 responded to a postal questionnaire concerning occupational exposures, including work schedule and the use of nitrous oxide, in relation to each of their pregnancies. We obtained information on births from the Swedish Medical Birth Register. We used models with allowance for dependence between births for the same woman and found that night work was associated with preterm birth (<37 weeks) odds ratio (OR) = 5.6; 95% confidence limits (CL) = 1.9, 16.4] and to a lesser extent with low birth weight OR = 1.9 (95% CL = 0.6, 5.8)]. Three-shift work schedule (day, evening, and night rotation) showed a possible association with preterm birth OR = 2.3 (95% CL = 0.7, 7.3)]. Exposure to nitrous oxide use was associated with reduced birth weight (-77 gm; 95% CL = -129, -24) and an increase in the odds of infants being small for gestational age (<=10th percentile of weight for gestational week) (OR = 1.8; 95% CL = 1.1, 2.8).

Access or request full text: https://libkey.io/10.1097/00001648-199907000-00015

38. **Genetic damage in operating room personnel exposed to isoflurane and nitrous oxide**

Item Type: Journal Article

Authors: Hoerauf K.;Lierz M.;Wiesner G.;Schroegendorfer K.;Lierz P.;Spacek A.;Brunnberg L. and Nusse M.

Publication Date: 1999

Journal: Occupational and Environmental Medicine 56(7), pp. 433–437

Abstract: Objectives - To evaluate genetic damage as the frequency of sister chromatid exchanges and micronuclei in lymphocytes of peripheral blood of operating room personnel exposed to waste anaesthetic gases. Methods - Occupational exposure was measured with a direct reading instrument. Venous blood samples were drawn from 10 non-smokers working in the operating room and 10 non-smoking controls (matched by age, sex, and smoking habits). Lymphocytes were cultured separately over 72 hours for each assay with standard protocols. At the end of the culture time, the cells were harvested, stained, and coded for blind scoring. The exchanges of DNA material were evaluated by counting the number of sister chromatid exchanges in 30 metaphases per probe or by counting the frequency of micronuclei in 2000 binucleated cells. Also, the mitotic and proliferative indices were measured. Results - The operating room personnel at the hospital were exposed to an 8 hour time weighted average of 12.8 ppm nitrous oxide and 5.3 ppm isoflurane. The mean (SD) frequency of sister chromatid exchanges was significantly higher (10.2 (1.9) v 7.4 (2.4)) in exposed workers than controls ($p = 0.036$) the proportion of micronuclei (micronuclei/500 binucleated cells) was also higher (8.7 (2.9) v 6.8 (2.5)), but was not significant ($p = 0.10$). Conclusion - Exposure even to trace concentrations of waste anaesthetic gases may cause dose-dependent genetic damage. Concerning the micronuclei test, no clastogenic potential could be detected after average chronic exposure to waste anaesthetic gas. However, an increased frequency of sister chromatid exchanges in human lymphocytes could be detected. Although the measured differences were low, they were comparable with smoking 11-20 cigarettes a day. Due to these findings, the increased proportion of micronuclei and rates of sister chromatid exchanges may be relevant long term and need further investigation.

39. **Short-term neurobehavioural effects in anaesthetists with low exposure to nitrous oxide**

Item Type: Journal Article

Authors: Isolani L.;Fiorentini C.;Violante F.S. and Raffi G.B.

Publication Date: 1999

Journal: Arhiv Za Higijenu Rada i Toksikologiju 50(4), pp. 381–388

Abstract: The aim of this study was to assess whether a sample of 37 anaesthetists occupationally exposed only to N2O showed any deterioration in vigilance and/or mood. The anaesthetists were examined with three neurobehavioural tests (Simple Reaction Time and Colour Word Vigilance to measure the vigilance and Mood Rating Scale to evaluate the level of stress and arousal) and underwent N2O biological monitoring (to correlate the test results with the N2O exposure) on the first and on the last day of the work week, before and after work in the operating room. No significant relationship was found between the biological monitoring and the test results. The only significant statistical difference was found between the beginning and the end of each workday in the arousal level, regardless of the result of the biological monitoring.

URL: https://libkey.io/libraries/2828/openurl?genre=article&sid=OVID:embase&id=pmid:10851742&id=doi:&issn=0004-1254&isbn=&volume=50&issue=4&spage=381&pages=381-388&date=1999&title=Arhiv+za+Higijenu+Rada+i+Toksikologiju&atitle=Short-term+neurobehavioural+effects+in+anaesthetists+with+low+exposure+to+nitrous+oxide&aulast=Isolani&pid=%3Cauthor%3EIsolani+L.%3BFiorentini+C.%3BViolante+F.S.%3BRaffi+G.B.%3C%2Fauthor%3E%3CAN%3E30262153%3C%2FAN%3E%3CDT%3EArticle%3C%2FDT%3E

40. **Nitrous oxide safety: how safe is it for staff? What can be done to make it safer?**

Item Type: Journal Article

Authors: Quarnstrom F.

Publication Date: 1999

Journal: Dentistry Today 18(12), pp. 70–77

URL: https://libkey.io/libraries/2828/openurl?genre=article&sid=OVID:embase&id=pmid:10803155&id=doi:&issn=8750-2186&isbn=&volume=18&issue=12&spage=70&pages=70-72%2C+74-77&date=1999&title=Dentistry+today&atitle=Nitrous+oxide+safety%3A+how+safe+is+it+for+staff%3F+What+can+be+done+to+make+it+safer%3F&aulast=Quarnstrom&pid=%3Cauthor%3EQuarnstrom+F.%3C%2Fauthor%3E%3CAN%3E31319026%3C%2FAN%3E%3CDT%3EReview%3C%2FDT%3E

41. **Hazards of nitrous oxide exposure in healthcare personnel**

Item Type: Journal Article

Authors: Smith, D. A.

Publication Date: 1998

Journal: AANA Journal 66(4), pp. 390–3

Abstract: Nitrous oxide, a commonly used agent in the dental and anesthesia practice, carries serious risks to healthcare providers. Complications from its exposure can range from hematological abnormalities and neurological deficits to increased risk of spontaneous abortions in women. A concentrated effort by all anesthesia personnel is necessary to prevent the adverse effects associated with the use of this agent.

URL: https://libkey.io/libraries/2828/openurl?genre=article&sid=OVID:medline&id=pmid:9830866&id=doi:&issn=0094-6354&isbn=&volume=66&issue=4&spage=390&pages=390-3&date=1998&title=AANA+Journal&atitle=Hazards+of+nitrous+oxide+exposure+in+healthcare+personnel.&aulast=Smith&pid=%3Cauthor%3ESmith+DA%3C%2Fauthor%3E%3CAN%3E9830866%3C%2FAN%3E%3CDT%3EJournal+Article%3C%2FDT%3E

42. **Neurobehavioral functions in operating theatre personnel: A multicenter study**

Item Type: Journal Article

Authors: Lucchini R.;Belotti L.;Cassitto M.G.;Faillace A.;Margonari M.;Micheloni G.;Scapellato M.L.;Somenzi V.;Spada T.;Toffoletto F. and Gilioli R.

Publication Date: 1997

Journal: Medicina Del Lavoro 88(5), pp. 396–405

Abstract: The study was conducted to evaluate neuropsychological symptoms, subjective stress and response speed functions in subjects occupationally exposed to low levels of anesthetic gases. A group of 112 operating theatre personnel exposed to anesthetic gases (nitrous oxide and isoflurane), and 135 non exposed hospital workers from 10 hospitals in Northern Italy were examined before and after the shift on the first and the last day of the working week. Three different tasks were administered: a complex reaction time test (the Stroop Color Word); a questionnaire for neuropsychological symptoms (EURO-QUEST); the block design subtest (WAIS). Biological and atmospheric indicators of exposure were measured. In the exposed group, the geometric mean of urinary nitrous oxide at the end of the shift was 7.1 mug/1 (95th percentile 12.4, range 1.5-43) on the first and 7.8 mug/l (95th percentile 21.5, range 1.0-73.3) on the last day of the working week. On the same days, end of shift urinary isoflurane was 0.7 mug/l (95th percentile 2.6, range 0-4.7) on the first day and 0.8 mug/l (95th percentile 2.0, range 0-5.6) on the last. The exposed and control subjects were comparable for both basic intellectual abilities and subjective stress levels. No statistical differences were observed between exposed and control subjects for neuropsychological tests and symptoms. No dose-effect relationships were observed between the exposure indicators and the test results. In conclusion, no early behavioral effect on the central nervous system was detectable at the exposure levels measured. The biological exposure limits of 13 mug/l for nitrous oxide and 1.8 mug/l for isoflurane corresponding respectively to the atmospheric concentrations of 25 ppm and 0.5 ppm seem

to be adequately protective for the integrity of workers' neurobehavioral functions, as measured with the tests used.

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43. **Shift work, nitrous oxide exposure and subfertility among Swedish midwives**

Item Type: Journal Article

Authors: Ahlborg Jr. G.;Axelsson G. and Bodin L.

Publication Date: 1996

Journal: International Journal of Epidemiology 25(4), pp. 783–790

Abstract: Background. Shift work and nitrous oxide exposure have both been suspected of having adverse influence on the reproductive performance of health workers. Time to pregnancy has been suggested as a sensitive measure of fecundity in occupationally exposed groups. We investigated the effects of shift work and nitrous oxide exposure on the fertility of Swedish midwives. Methods. A questionnaire was mailed to all members of the Swedish Midwives Association who were born 1940 or thereafter, 3985 in all. Eighty-four per cent responded. Detailed information on the number of menstrual cycles required to achieve pregnancy and the working conditions during that period were obtained concerning the most recent, planned pregnancy occurring after 1983. The per cycle probability of becoming pregnant was calculated for each exposure category, and the relation to the unexposed was expressed as fecundability ratios. Results. Midwives who worked two-shift, three-shift rotas, or only nights had reduced fertility compared to those working in the day time. The fecundability ratios were 0.78 (95% confidence interval CI]: 0.65-0.94), 0.77 (95% CI: 0.60-0.98), and 0.82 (95% CI: 0.64-1.03), respectively, after adjustment for covariates. No effect of nitrous oxide exposure was noted except in the small group reporting that they assisted at more than 30 deliveries per month when nitrous oxide was used (fecundability ratio = 0.64; 95% CI: 0.44-0.95). Conclusion. Shift work and frequent, high occupational exposure to nitrous oxide may have a negative influence on the ability of women to become pregnant.

Access or request full text: https://libkey.io/10.1093/ije/25.4.783

44. **Shift work, nitrous oxide exposure, and spontaneous abortion among Swedish midwives**

Item Type: Journal Article

Authors: Axelsson, G.;Ahlborg, G. J. and Bodin, L.

Publication Date: 1996

Journal: Occupational and Environmental Medicine 53(6), pp. 374–8

Abstract: OBJECTIVES: To study the relation between irregular work hours, nitrous oxide (N2O) exposure, and the risk of spontaneous abortion., METHODS: All 3985 female members of the Swedish Midwives Association in 1989, born in 1940 or later, received a questionnaire on exposure before and during all of their pregnancies. Questions on work conditions covered occupation, extent of employment, workplace, work schedules, use of anaesthetics, and work load. The association between exposure variables and spontaneous abortion was analysed by logistic regression models., RESULTS: Night work and three shift schedules among midwives showed increased odds ratios (ORs) (95% confidence intervals (95% CI)) 1.63 (0.95-2.81) and 1.49 (0.86-2.59), respectively. The ORs of late spontaneous abortions (after the 12th week of pregnancy) was increased for night work 3.33 (1.13-9.87). Use of N2O (> 50% of the deliveries) was not associated with increased risk of spontaneous abortion OR 0.95 (0.62-1.47). Frequent or permanent shortage of staff was related to an increased risk of spontaneous abortions before the 13th week of pregnancy., CONCLUSIONS: The results support the hypothesis that night work and high work load increase the risk of spontaneous abortion.

45. **Nitrous oxide in blood and urine of operating theatre personnel and the general population**

Item Type: Journal Article

Authors: Brugnone F.;Perbellini L.;Cerpelloni M.;Soave C.;Cecco A. and Giuliari C.

Publication Date: 1996

Journal: International Archives of Occupational and Environmental Health 68(1), pp. 22–26

Abstract: Nitrous oxide (N2O) was assayed in 676 urine samples and 101 blood samples provided after exposure by operating theatre personnel from nine hospitals. The blood and urine assays were repeated in 25 subjects 18 h after the end of exposure. For 80 subjects, environmental N2O was also measured during intraoperative exposure. Mean urinary N2O in the 676 subjects at the end of exposure was 40 mug/l (range 1-3805 mug/l); in 10 of the 676 subjects, urinary N2O was in the range 279-3805 mug/l (mean 1202 mug/l). The 98th percentile was 120 mug/l. Mean blood N2O at the end of exposure, measured in 101 subjects, was 21 mug/l (median 16 mug/l, range 1-75 mug/l). Blood and urine N2O (1.5 mug/l and 4.9 mug/l, respectively) in 25 subjects, 18 h after exposure, was significantly higher than in occupationally non-exposed subjects (blood 0.91 mug/l, urine 1 mug/l). Environmental exposure was significantly related to blood and urinary N2O (r = 0.59 and r = 0.64, respectively). Blood and urinary N2O were significantly related to each other (r = 0.71), and were equivalent to about 25% of the environmental exposure level. The mean urinary N2O of 1202 mug/l in 10/676 subjects was not related to environmental exposure in the operating theatre. The highest urinary N2O levels measured in these 10/676 subjects could be explained by an asymptomatic urinary infection.

Access or request full text: https://libkey.io/10.1007/BF01831629

46. **Increased micronucleus formation in nurses with occupational nitrous oxide exposure in operating theaters**

Item Type: Journal Article

Authors: Chang, W. P.;Lee, S.;Tu, J. and Hseu, S.

Publication Date: 1996

Journal: Environmental and Molecular Mutagenesis 27(2), pp. 93–7

Access or request full text: https://libkey.io/10.1002/(SICI)1098-2280(1996)27:2

47. **Neurotoxicity in operating room personnel working with gaseous and nongaseous anesthesia**

Item Type: Journal Article

Authors: Lucchini R.;Placidi D.;Toffoletto F. and Alessio L.

Publication Date: 1996

Journal: International Archives of Occupational and Environmental Health 68(3), pp. 188–192

Abstract: Occupational exposure to high concentrations of anesthetic gases (more than 500 ppm of nitrous oxide and more than 15 ppm of halothane and enflurane) can cause neurobehavioral effects in operating room personnel. Factors such as stress and work organization play an additional role in reducing performance capacities. It is still unclear whether these conditions may become the predominant factor in behavioral impairment when exposure to anesthetic gases is reduced; in addition, we wished to ascertain the extent of neurobehavioral and neuroendocrine effects at relatively low levels of exposure to such gases. Therefore the same group of 30 operating room personnel was examined with neurobehavioral tests during gaseous and nongaseous anesthesia. In this way, the neuropsychological performance was examined under the same stress conditions, but with different exposure levels to anesthetic gases. Serum cortisol was measured as an additional 'biological stress indicator.' Prolactin secretion was examined to study possible interference of anesthetic gases with the dopaminergic system. The results were compared with those in a control group of 20 hospital workers from other departments, with similar characteristics in respect of age, sex, and education. During work with gaseous anesthesia, average airborne concentrations (geometric mean) of nitrous oxide were 50.9 ppm (SD 20.8) on the first day of the working week and 54.2 ppm (SD 22.1) on the last day of the working week, whereas average urinary nitrous oxide (geometric mean) were 21.54 mug/l on the first day of the working week and 25.67 mug/l on the last day of the working week. The operating room workers showed slower reaction times at the end of the week with gaseous anesthesia, compared with workers using nongaseous anesthesia and the control group. At the same time they also showed increased secretion of prolactin, whereas cortisol remained unchanged. Therefore, it can be concluded that lower levels of exposure to anesthetic gases (and not only high exposure levels) cause an impairment of neurobehavioral performance, with the action of stress being less relevant. The mechanism of anesthetics' neurotoxic action seems to be related to interference with the dopaminergic system.

48. **The hazards of chronic exposure to nitrous oxide: an update**

Item Type: Journal Article

Authors: Donaldson D. and Meechan J.G.

Publication Date: 1995

Journal: British Dental Journal 178(3), pp. 95–100

Abstract: This paper reviews the potential occupational hazards associated with chronic exposure to nitrous oxide. The evidence that chronic exposure to the gas produces problems related to reproduction in dental personnel is convincing. Recent evidence suggests that scavenging systems decrease the adverse effects which nitrous oxide has on fertility of dental surgery assistants. However, even in the presence of scavenging systems trace levels of the gas can exceed recommended minimum levels.

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49. **Nitrous oxide and spontaneous abortion in female dental assistants**

Item Type: Journal Article

Authors: Rowland, A. S.;Baird, D. D.;Shore, D. L.;Weinberg, C. R.;Savitz, D. A. and Wilcox, A. J.

Publication Date: 1995

Journal: American Journal of Epidemiology 141(6), pp. 531–8

Abstract: The relation between anesthetic gas exposure and spontaneous abortion remains unresolved. We examined the effect of nitrous oxide on spontaneous abortion among female dental assistants. Questionnaires were sent to 7,000 dental assistants aged 18-39 years who were registered in California in 1987; 4,856 (69%) responded. Analysis was based on 1,465 respondents whose most recent pregnancy was conceived while working full time. Women were asked how many hours a week they worked with nitrous oxide during this pregnancy and whether the excess gas was scavenged (vented). Relative risk of spontaneous abortion (through week 20) was calculated using a person-week model. This allowed women with current pregnancies (13%) or induced abortions (10%) to be included for appropriate time periods of risk. A total of 101 pregnancies (7%) ended as spontaneous abortions. An elevation in risk of spontaneous abortion was seen among women who worked with nitrous oxide for 3 or more hours per week in offices not using scavenging equipment (relative risk = 2.6, 95% confidence interval 1.3-5.0, adjusted for age, smoking, and number of amalgams prepared per week), but not among those using nitrous oxide in offices with scavenging equipment. This relation changed little when analyses were restricted to confirmed pregnancies or examined for several types of potential bias. Scavenging equipment appears to be important in protecting the reproductive health of women working with nitrous oxide.

50. **Reproductive hazards: an overview of exposures to health care workers**

Item Type: Journal Article

Authors: Shortridge-McCauley, L.

Publication Date: 1995

Journal: AAOHN Journal : Official Journal of the American Association of Occupational Health Nurses 43(12), pp. 614–21

Abstract: 1. Anesthetic gases, particularly nitrous oxide, have been investigated for potential reproductive, mutagenic, and carcinogenic effects. Waste gases have been found in high concentrations, even with work settings with scavenger systems in place. 2. Antineoplastic drugs, commonly used to treat persons with cancer, are virtually all considered to be embryo-fetal toxic. OSHA has issued comprehensive guidelines covering staff training, handling practices, and use of protective equipment. 3. The toxic effect of non-ionizing radiation has been a frequent topic of public and scientific debate. At this time no evidence exists of a reproductive hazard to health care workers. 4. Biologic agents such as rubella, hepatitis, cytomegalovirus, varicella, and human immunodeficiency virus frequently have the potential for adverse effects on the fetus. Administration of a vaccine or care of patients with active infection may be contraindicated in pregnancy.

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51. **Age-dependent haematological disturbances in anaesthetic personnel chronically exposed to high occupational concentrations of halothane and nitrous oxide**

Item Type: Journal Article

Authors: Peric, M.;Petrovecki, M. and Marusic, M.

Publication Date: 1994

Journal: Anaesthesia 49(12), pp. 1022–7

Abstract: Anaesthetic staff chronically exposed to high occupational concentrations of halothane and nitrous oxide were tested for numerous haematological and cellular function parameters at the peak of the working season and after 3 weeks vacation. The analysis of data was performed to compare differences in subjects younger and older than the age of 40 years, respectively when compared with normal controls. The analysis revealed a higher recovery of erythrocyte count in the blood of older staff, and stronger disturbance of leucocyte formation in younger staff. In contrast, monocytes appeared to be more stable in the younger staff as were the T and B lymphocyte counts. After stimulation with PHA, Con A and PWM mitogens, lymphocytes from the older age group incorporated a significantly higher amount of tritiated thymidine, but stimulation indices did not differ. Natural killer cell numbers appeared equally affected; natural killer cell activity was unaffected, but there was an increase in activity in the younger staff after the vacation. Serum immunoglobulin concentrations tended to be more affected in older individuals at the peak of the working season.

Access or request full text: https://libkey.io/10.1111/j.1365-2044.1994.tb04347.x

52. **Occupational exposure to nitrous oxide - Not a laughing matter**

Item Type: Journal Article

Authors: Baird P.A.

Publication Date: 1992

Journal: New England Journal of Medicine 327(14), pp. 1026–1027

Access or request full text: https://libkey.io/10.1056/NEJM199210013271411

53. **The effects of volatile anaesthetic agents on human immune system function via occupational exposure**

Item Type: Journal Article

Authors: Karakaya A.;Tuncel N.;Yucesoy B.;Akin M.;Cuhruk H.;Sardas O.S. and Beksac M.

Publication Date: 1992

Journal: Immunopharmacology and Immunotoxicology 14(1-2), pp. 251–259

Abstract: The immunological status of individuals occupationally exposed to low levels of halothane and nitrous oxide has been examined and compared with that of non-exposed controls. No differences in the serum concentrations of IgG, IgM, IgA, peripheral blood lymphocytes and lymphocyte subpopulations between the groups were observed.

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54. **Reduced fertility among women employed as dental assistants exposed to high levels of nitrous oxide**

Item Type: Journal Article

Authors: Rowland A.S.;Baird D.D.;Weinberg C.R.;Shore D.L.;Shy C.M. and Wilcox A.J.

Publication Date: 1992

Journal: New England Journal of Medicine 327(14), pp. 993–997

Abstract: Background. Fertility is reduced in female rats exposed to levels of nitrous oxide similar to those found in some dental offices. Epidemiologic studies have suggested an association between exposure to mixed anesthetic gases and impaired fertility. We investigated the effects of occupational exposure to nitrous oxide on the fertility of female dental assistants. Methods. Screening questionnaires were mailed to 7000 female dental assistants, ages 18 to 39, registered by the California Department of Consumer Affairs. Sixty-nine percent responded. Four hundred fifty-nine women were determined to be eligible, having become pregnant during the previous four years for reasons unrelated to the failure of birth control, and 91 percent of these women completed telephone interviews. Detailed information was collected on exposure to nitrous oxide and fertility (measured by the number of menstrual cycles without contraception that the women required to become pregnant). Results. After controlling for covariates, we found that women exposed to high levels of nitrous oxide were significantly less fertile than women who were unexposed or exposed to lower levels of nitrous oxide. The effect was evident only in the 19 women with five or more hours of exposure per week. These women were only 41 percent (95 percent confidence interval, 23 to 74 percent; P<0.003) as likely as unexposed women to conceive during each menstrual cycle. Conclusions. Occupational exposure to high levels of nitrous oxide may adversely affect a woman's ability to become pregnant.

Access or request full text: https://libkey.io/10.1056/NEJM199210013271405

55. **Fetal injury and abortion associated with occupational exposure to inhaled anesthetics**

Item Type: Journal Article

Authors: Eger 2nd. E.I.

Publication Date: 1991

Journal: AANA Journal 59(4), pp. 309–312

Abstract: While the actual risk associated with occupational exposure to inhaled anesthetics has not precisely been defined, a growing body of data has accumulated so that we may begin to make certain valid inferences. Published studies of the teratogenic, mutagenic and carcinogenic effects of exposure to nitrous oxide and isoflurane suggest that a causal role of these inhaled agents appears to be very low or nonexistent.

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+E.I.%3C%2Fauthor%3E%3CAN%3E21870806%3C%2FAN%3E%3CDT%3EReview%3C%2FDT%3E

56. **Immunological disturbances in anaesthetic personnel chronically exposed to high occupational concentrations of nitrous oxide and halothane**

Item Type: Journal Article

Authors: Peric M.;Vranes Z. and Marusic M.

Publication Date: 1991

Journal: Anaesthesia 46(7), pp. 531–537

Abstract: Immunological changes in anaesthetic personnel exposed to occupational concentrations of holothane and nitrous oxide 10-60 times greater than the advised maximum were studied during routine work and after 3-4 weeks holiday. Red cell count, haemoglobin concentration and haematocrit decreased during exposure although not significantly, in comparison with a control group, but all had increased significantly after the holidays. Other changes were altered neutrophils and lymphocyte counts. Basophils disappeared from the blood during the exposure. Monocytes were not affected during the exposure, but increased after its cessation. Percentages of CD2 and CD4 lymphocytes increased significantly, but numbers of cells in T lymphocyte subpopulations (total, helper and cytotoxic/supressor lymphocytes) were not significantly altered. B lymphocytes were most strongly affected: they decreased during working periods and did not recover after holidays. Natural killer (NK) cells, on the other hand, decreased significantly during exposure, but fully recovered during holidays. After stimulation with mitogens, phytohaemaglutin, concanavalin A, and pokeweed, lymphocytes from exposed personnel incorporated significantly more 3H-thymidine than those from control subjects, but stimulation indices did not differ. The natural killer-cell activity, serum Ig concentrations and phagocytosis by granulocytes were not altered.

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57. **Health hazards and nitrous oxide: a time for reappraisal**

Item Type: Journal Article

Authors: Yagiela J.A.

Publication Date: 1991

Journal: Anesthesia Progress 38(1), pp. 1–11

Abstract: Recent adoption by the American Conference of Governmental Industrial Hygienists of a Threshold Limit Value of 50 ppm for an 8-hour average exposure to nitrous oxide (N2O) increases the likelihood for its regulation by state and federal occupational health agencies. This review outlines current information on the health risks of N2O inhalation to provide a basis from which safe and reasonably attainable exposure limits can be proposed. Although N2O was for many years believed to have no toxicity other than that associated with its anesthetic action, bone marrow depression in patients administered N2O for extended periods of time and neurological abnormalities in health care workers who inhaled N2O recreationally have disproved this notion. Retrospective surveys of dental and medical personnel have also linked occupational exposure to N2O with a number of health problems and reproductive derangements. Nitrous oxide reacts with the reduced form of vitamin B12, thereby inhibiting the action of methionine synthase, an enzyme that indirectly supports methylation reactions and nucleic acid synthesis. Many, if not all, of the nonanesthetic-related adverse effects of N2O may be ascribed to this action. Animal and human studies indicate that the toxic effects of N2O are concentration- and time-dependent. It is suggested that a time-weighted average of 100 ppm for an 8-hour workday and/or a time-weighted average of 400 ppm per anesthetic administration would provide adequate protection of dental personnel and be achievable with existing pollution control methods.

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58. **Nitrous oxide anaesthesia: risks to health personnel**

Item Type: Journal Article

Authors: Schumann D.

Publication Date: 1990

Journal: International Nursing Review 37(1), pp. 214–217

Abstract: Although nitrous oxide is the most commonly administered inhalation anaesthetic, it is not an innocuous agent. Adverse haematologic, neurologic, immune and reproductive effects have been identified in health personnel, among them operating room nurses, anaesthetists and anaesthesiologists. These groups are especially vulnerable to toxicity, owing to trace amounts that may accumulate over a lifetime from occupational exposure. Worldwide, nitrous oxide is commonly used for obstetric analgesia, placing midwives and obstetric nurses among those susceptible to toxicity from excessive and lengthy contact. Despite standards to control hazardous exposure, health personnel cannot become complacent with its use. Below, an examination of current evidence about exposure risks to health personnel and a review of the status of research explaining the genesis of organ-related dysfunction.

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59. **Potential problems associated with occupational exposure to nitrous oxide**

Item Type: Journal Article

Authors: Kestenberg S.H. and Young E.R.

Publication Date: 1988

Journal: Journal (Canadian Dental Association) 54(4), pp. 277–286

URL: https://libkey.io/libraries/2828/openurl?genre=article&sid=OVID:embase&id=pmid:3288306&id=doi:&issn=0709-8936&isbn=&volume=54&issue=4&spage=277&pages=277-286&date=1988&title=Journal+%28Canadian+Dental+Association%29&atitle=Potential+problems+associated+with+occupational+exposure+to+nitrous+oxide&aulast=Kestenberg&pid=%3Cauthor%3EKestenberg+S.H.%3BYoung+E.R.%3C%2Fauthor%3E%3CAN%3E18755742%3C%2FAN%3E%3CDT%3EReview%3C%2FDT%3E

60. **Toxicity of bone marrow in dentists exposed to nitrous oxide**

Item Type: Journal Article

Authors: Sweeney B.;Bingham R.M. and Amos R.J.

Publication Date: 1985

Journal: British Medical Journal 291(6495), pp. 567–569

Abstract: The morphology of the bone marrow of 21 dentists who habitually used nitrous oxide in their surgeries was investigated. Exposure to nitrous oxide was measured with an atmospheric sampling device, and each dentist was invited to fill in a questionnaire giving details of medical history, diet, and intake of alcohol. During the trial of full neurological and haematological investigation was carried out and a bone marrow aspirate was examined both morphologically and by the deoxyuridine suppression test. Mean exposures to nitrous oxide ranged from 159 to 4600 parts per million. In all subjects serum vitamin B12 and folate concentrations were within normal limits. Abnormal results of deoxyuridine suppression tests were obtained in three of the 20 dentists tested; two of these three had abnormal white cells in their peripheral blood films. This study provides direct evidence that occupational exposure to nitrous oxide may cause depression of vitamin B12 activity resulting in measurable changes in bone marrow secondary to impaired synthesis of deoxyribonucleic acid.

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61. **Hepatic microsomal enzyme function in technicians and anesthesiologists exposed to halothane and nitrous oxide**

Item Type: Journal Article

Authors: Dossing M. and Weihe P.

Publication Date: 1982

Journal: International Archives of Occupational and Environmental Health 51(1), pp. 91–98

Abstract: It is controversial whether daily occupational exposure to halothane stimulates (induces) the hepatic microsomal enzyme function in man. We investigated two groups of persons with different degrees of exposure to halothane: Six technicians who for years had been employed with repair and control of anesthesiologic equipment resulting in exposure to about 7 ppm of halothane and 50 ppm of nitrous oxide, and seven anesthesiologists exposed during months to about 2 ppm of halothane and 75 ppm of nitrous oxide. The clearance of antipyrine was determined from saliva concentrations before and 4 wk after discontinuation of exposure. Matched control persons were investigated simultaneously. No significant differences were found between the half-life, apparent volume of distribution, or clearance of antipyrine either within the groups or between the groups. If the antipyrine data from both exposure groups were compared to those of the control groups, the data exclude (95% confidence limit) and antipyrine metabolism increased by more than 3% during exposure to waste anesthetics. This indicates that occupational exposure to halothane in concentrations above the proposed maximal time weighted average concentration of 2 ppm does not change the microsomal activity.

Access or request full text: https://libkey.io/10.1007/BF00378414

62. **The effects of trace concentrations of nitrous oxide on performance and related health problems in medical and dental personnel**

Item Type: Journal Article

Authors: Gratton T.B.

Publication Date: 1982

Journal: Journal of Environmental Health 45(1), pp. 24–28

Abstract: Nitrous oxide has been used as an anesthetic for 100 years by the health care profession. Until recently, it has been considered safe from the standpoint of the patient. There have been less physical impairments and anesthesia complications with this agent than others. However, evidence has been accumulating that long term exposure to trace amounts of nitrous oxide could have a detrimental effect on personnel administering the anesthetic or working in close proximity to it. Chronic exposure to nitrous oxide has been implicated in causing liver and kidney damage, spontaneous abortions and birth defects along with impairment of shorterm memory, coordination and hearing among those exposed. The author briefly reviews some of the evidence that led to the NIOSH criteria document on the occupational exposure to waste anesthetic gases and vapors.

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63. **Serum methionine and hepatic enzyme activity in anaesthetists exposed to nitrous oxide**

Item Type: Journal Article

Authors: Nunn J.F.;Sharer N. and Royston D.

Publication Date: 1982

Journal: British Journal of Anaesthesia 54(6), pp. 593–597

Abstract: Normal serum concentrations of methionine, leucine, isoleucine and valine have been found in 10 anaesthetists using nitrous oxide under their regular working conditions without scavenging of patients' exhaled gas. Mean inhaled concentrations of nitrous oxide ranged from 150 to 400 p.p.m. The results indicate either that there was no significant inhibition of methionine synthase (attributable to oxidation of vitamin B12 by nitrous oxide) or that methionine concentrations were maintained by dietary intake or by the alternative betaine pathway of methylation of homocysteine. In either case, anaesthetists working under these conditions should not be at risk from reduced methionine concentrations. We also report normal serum activities of aspartate transaminase and gamma glutamyl transpeptidase.

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64. **Exposure to nitrous oxide and neurologic disease among dental professionals**

Item Type: Journal Article

Authors: Brodsky J.B.;Cohen E.N.;Brown Jr. B.W.;Wu M.L. and Whitcher C.E.

Publication Date: 1981

Journal: Anesthesia and Analgesia 60(5), pp. 297–301

Abstract: Questionnaires, mailed to approximately 30,000 dentists and an equal number of dental assistants requesting information regarding professional exposure to anesthetics and health problems, showed an increased incidence of neurologic complaints in dental professionals who worked with nitrous oxide. The most striking differences were noted in individuals reporting symptoms of numbness, tingling, and/or muscle weakness. For dentists heavily exposed to nitrous oxide, the rate of these complaints was 4-fold greater than for nonanesthetic-exposed dentists. For dental assistants heavily exposed to nitrous oxide, a 3-fold increase in these same complaints was noted. In view of recent evidence that nitrous oxide abuse may lead to polyneuropathy, the results suggest that occupational exposure to nitrous oxide by both dentists and dental assistants may be associated with similar neuropathy.

Access or request full text: https://libkey.io/10.1213/00000539-198105000-00003

65. **Operating room nurses' psychomotor and driving skills after occupational exposure to halothane and nitrous oxide**

Item Type: Journal Article

Authors: Korttila K.;Pfaffli P. and Linnoila M.

Publication Date: 1978

Journal: Acta Anaesthesiologica Scandinavica 22(1), pp. 33–39

Abstract: Concentrations of halothane and nitrous oxide were assayed by gas chromatography throughout a working day in three operating theaters and in the end tidal air of 19 nurses 15 and 60 min after leaving the theaters. Perceptual, psychomotor and driving skills were measured in these nurses and in 11 younger nurses working in the wards of the same hospital. A complicated psychomotor test battery and a driving simulator were used. End tidal air concentrations of halothane and nitrous oxide were positively correlated with the exposure level of these gases in the operating theaters. Some of the operating room nurses had greater amounts of halothane in their end tidal air (average 15 to 10 ppm) than student volunteers 4.5 hr after 3.5 min of general anesthesia with a combination of halothane nitrous oxide oxygen (10 ppm halothane). These volunteers had worse psychomotor and driving performances when measured than controls who had not been anesthetized. No correlations were found between the concentrations of halothane or nitrous oxide in end tidal air and psychomotor or driving performance. Despite their higher age and exposure to the operating room environment, the driving skills of the operating room nurses were similar to those of the ward nurses. The results suggest that tolerance to anesthetic gases develops among operating room personnel. No impairment of driving skills can be expected after daily exposure to halothane and nitrous oxide among long term

employees in operating theaters.

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Search Strategy

Ovid MEDLINE(R) ALL <1946 to January 16, 2026>

1	exp Nitrous Oxide/	16774
2	(Entonox or nitrous oxide).tw,kw.	19817
3	1 or 2	25951
4	exp Occupational Exposure/	72800
5	(expos* adj3 occupation*).tw,kw.	38610
6	4 or 5	91764
7	3 and 6	436
8	limit 7 to english language	354
9	from 8 keep 15,18,32-33,43-44,46,52,55-56,60,63-64,79,91,96,105,109,115,124,151,155-156,182,184,217-218,226,234-235,249,278,282,284,33835	
10	exp Environmental Exposure/	393329
11	environmental exposur*.tw,kw.	21587
12	10 or 11	406114
13	exp Health Personnel/	673511
14	3 and 12 and 13	154
15	limit 14 to english language	134

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1	exp nitrous oxide plus oxygen/	2017
2	(Entonox or nitrous oxide).tw,kw.	22822
3	1 or 2	23743
4	exp occupational exposure/	96944
5	(expos* adj3 occupation*).tw,kw.	49810
6	4 or 5	113445
7	3 and 6	431
8	limit 7 to english language	367
9	limit 8 to "remove clinical trial (clinicaltrials.gov) records"	363
10	from 9 keep 11,23-24,27,40,42,46,49,57,62-63,75,81,84-85,88,92,101,105-106,109,114,134,178-179,193-194,202-203,206,215,217,231,234,244,280-281,284,290-291,294,299,312,316-317,328,335,337,355	49
11	exp environmental exposure/	139992
12	exp health care personnel/	2348147
13	3 and 11 and 1227	
14	limit 13 to english language	26