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Anesthetic gases as an occupational hazard — A review

by Christer Edling, MD¹

EDLING C. Anesthetic gases as an occupational hazard — A review. *Scand j work environ health* 6 (1980) 85-93. This review is a survey of the literature on the different health effects of long-term exposure to anesthetic gases.

Key terms: anesthetic gases, occupational exposure.

Inhalation anesthesia was first used in 1842, when an American physician administered diethyl ether (common ether) to a patient. Since then many different compounds have been used as inhalation anesthetic agents, and many of these have later been utilized as industrial solvents, eg, trichloroethylene and chloroform. The first report to indicate that people working in operating rooms could become ill as a consequence of exposure to anesthetic gases, especially chloroform, came at the end of the 19th century. Nevertheless, the physical properties of anesthetic agents have attracted the most interest. Especially questions concerning volatility, flammability and dangers of explosion have come to the fore. Thus systems for the elimination of anesthetic gases from operating rooms were described at the beginning of the 20th century, and the anesthetic compounds have become less explosive and flammable through the introduction of halogenated anesthetic agents in the mid 1950s. During the last decade, however, interest has more and more been focused on the health hazards for operating room personnel.

Initially, acute subjective effects on operating room personnel were pointed out, eg, headache and tiredness. However, there is also information on organ damage. As early as 1922 a case report appeared of an anesthetist with nephritis, and in 1949 a German case report concerned personnel who had been exposed to ether for 4 to 14 a and showed electrocardiographic evidence of myocardial damage.

This review elucidates the studied side effects of long-term exposure.

Teratogenicity and mutagenicity

Bacterial tests

The studies on the mutagenicity of anesthetic agents in bacterial systems are few and contradictory. Halothane, methoxyflurane, enflurane, trichloroethylene, and isoflurane have been tested, but no evidence of mutagenicity was found (3, 4, 67). On the other hand, fluroxene was mutagenic in the same test system (4), and another study has reported trichloroethylene as a mutagen (34). The urine of anesthesiologists exposed to halothane induced mutations in the conventional Ames assay (48), and halothane has been described as an "insufficiently positive mutagen" (36).

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Animal tests

The results of many animal studies have been published concerning the teratogenic effect of nitrous oxide and halogenated anesthetic agents. A review of these reports is given in the criteria document on waste anesthetic gases and vapors (51) that has been published by the US National Institute for Occupational Safety and Health (NIOSH). In most of the studies very high exposure levels were used, and it is therefore difficult to compare the results of the animal experiments with what could be expected from the far lower exposure levels in operating rooms. In a recently published study (66), however, pregnant rats exposed day and night for 19 d to a mixture of 0.5 % nitrous oxide in air, ie, about the same level of pollution as in operating rooms, showed a much greater percentage of damage to the fetus, ie, fetal resorption and skeletal anomalies, in comparison with nonexposed rats. In another study (54) an animal model was used to investigate the fetal toxicity of halothane, nitrous oxide, and methoxyflurane. High subanesthetic concentrations of all the inhalation anesthetics could cause fetal growth retardation, but this phenomenon was unaccompanied by significant fetal loss. It was concluded that the study did not implicate any specific inhalation anesthetic agent in fetal toxicity, and that the effects of additional factors, such as stress, must be considered.

Epidemiology

The first epidemiologic study of spontaneous abortion and malformations was published in 1967 when Vaisman (64) reported a Russian study on 303 (193 men and 110 women) anesthesiologists. The author noted that among 31 earlier pregnant anesthesiologists, aged 24–38 a, one pregnancy in three had ended in spontaneous abortion, two women gave birth prematurely, and in one case the child had congenital malformations. The anesthetic gas in use during the period of exposure was mostly ether, but even nitrous oxide and halothane had been used.

This report was later followed by a Danish study (1) in which 578 nurses of anes-

thetic departments and 174 female and male anesthetists were questioned by means of questionnaires. A total of 212 pregnancies before and 392 during exposure to anesthetic gases was reported. The abortion frequency was significantly higher for the exposed women (20 %) in comparison with the nonexposed ones (10 %). In this study the authors even reported a higher frequency of spontaneous abortions among nonexposed women whose husbands worked as anesthesiologists. Similar results were reported in an American study from 1975 (17), in which wives of exposed dentists had a higher frequency of spontaneous abortion in comparison with nonexposed referents. In two English questionnaire surveys (42, 43), in which 1,431 male and 849 female anesthesiologists answered, the results indicated a higher rate of spontaneous abortion among exposed women, whereas the husbands' exposure did not seem to influence the outcome of pregnancy. Findings of a higher frequency of spontaneous abortion among exposed women have been reported in several studies from many countries, eg, Sweden (31), Finland (56), West Germany (29), and Czechoslovakia (51). In a recently published English study on anesthetists' health problems, including 10 % of all anesthesiologists in England and Wales, the author reported a higher frequency of spontaneous abortion among female anesthesiologists than among nonexposed women (63).

In some of the studies, eg, those by Cohen et al (16), Knill-Jones et al (43) and Göthe et al (31), a higher risk of malformations among children born by women exposed to anesthetic gases during pregnancy was also shown. In the study by Göthe and his co-workers, a difference was even found between smokers and nonsmokers in that nonsmokers more often bore malformed children, whereas pregnancies among smoking women more often ended in spontaneous abortion, the possibilities of malformations occurring thereby being diminished. In his study of English anesthesiologists (63), Tomlin reported an increased frequency of malformations, especially in the central nervous and musculoskeletal systems. Paroah et al (53) surveyed the obstetric

history of 5,700 women physicians in England and Wales; conceptions that occurred when the mother was in an anesthetic appointment resulted in smaller babies, higher stillbirth rates, and more congenital malformations of the cardiovascular system than those of other women physicians. There was, however, no significant difference in the spontaneous abortion rate between the two groups. A Swedish study (5) reported the pregnancy outcome, ie, perinatal mortality and congenital malformations, for women working in medical occupations before giving birth. The outcome of pregnancies was checked with the aid of existing central registers and compared with the outcome of pregnancies for the whole country. There was no difference in the observed and expected number of perinatal mortality and congenital malformations among women working in anesthesia and operation departments.

Carcinogenicity

During the last several years the possibility of a carcinogenic effect of anesthetic gases has attracted some attention. The anxiety about this effect is not totally unjustified, since there are many structural similarities between some known human carcinogens (ie, dibromoethane, dichloroethane, bischloromethyl ether, and chloromethyl methyl ether) and several of the inhalation anesthetic agents now in use. Besides, anesthetic compounds can be transformed into reactive metabolites which can combine with tissue macromolecules (15) and thereby turn into chemical carcinogens (7).

Animal tests

Studies on rats and mice have demonstrated that at least some of the volatile anesthetic agents are capable of inducing cancer. In an early experiment, Eschenbrenner (27) induced hepatoma by giving mice very high doses of chloroform perorally. In 1976 the National Cancer Institute (NCI) (49) reported animal tests in which rats had been given chloroform perorally in doses of one-fifth to one-tenth

of those of Eschenbrenner. A significant increase in kidney tumors, as well as hepatocellular carcinomas, was observed. The NCI has even made animal studies regarding the carcinogenicity of trichloroethylene. By gastric intubation trichloroethylene was administered to rats; the result was an increase in hepatocellular carcinomas (50). However, in all these three studies, the methods of exposure were quite unusual when compared with occupational exposure in an operating room. Therefore, no conclusion can be drawn on the basis of these studies, except that the investigations indicate that the tested substances have some carcinogenic potential.

As for halogenated anesthetic gases, an animal experiment was made by Corbett (18) in which pulmonary and hepatic neoplasms were induced in the offspring of mice by repeated exposure of the mother during pregnancy and of the offspring after delivery to subanesthetic concentrations of isoflurane (0.1–0.5 % isoflurane). In another study (26), mice were exposed, both in utero during the last half of pregnancy and after delivery, to low doses of either enflurane, isoflurane, halothane, methoxyflurane, or nitrous oxide. The result did not confirm the suggestion that isoflurane is a hepatocarcinogen, nor did the data suggest that inhaled anesthetics currently in use pose a significant threat of carcinogenicity.

Coate et al (14) studied the effects of prolonged exposure to low-concentration combinations of halothane and nitrous oxide on tumor incidence. Rats were exposed to filtered air, 1 ppm of halothane and 50 ppm of nitrous oxide or 10 ppm of halothane and 500 ppm of nitrous oxide. Histologic evaluation of the reticuloendothelial system and of other major organs did not reveal any enhancement of the spontaneous tumor rate or any unusual neoplasms.

Epidemiology

In a retrospective cohort study (9) the mortality among anesthesiologists, in 1947–1966, was studied. An increased frequency of malignant diseases in the

lymphoid and reticuloendothelial system was reported among the 441 deceased persons (9). A later follow-up of the mortality during 1967—1971 did not, however, reveal any increase in deaths from tumors (10). In another large American study, in which morbidity was followed in a questionnaire survey of 73,496 persons, it was found that women, but not men, exposed to anesthetic gases had a higher frequency of cancer, especially leukemia and lymphoma (16). In other American studies (19, 20) the incidence of malignant diseases among 525 anesthetic nurses was followed. Excluding skin cancer, a higher incidence of unusual tumors, such as malignant lymphoma, leiomyosarcoma, hepatocellular carcinoma, and cancer of the pancreas, was found. Furthermore, the occurrence of cancer among children born by anesthetic nurses was studied, and for them also a higher cancer incidence was found. The same findings, cancer among children, were also observed by Tomlin (63). These data could indicate that anesthetic gases can act as a transplacental chemical carcinogen, as has been reported for some other substances in man, ie, diethylbestrol (37), barbiturates (32), chlorinated pesticides (39), and smoking (52). A few English studies (24, 43, 53) have not disclosed any increase in cancer among anesthesiologists, but in a newly published investigation from the same country a higher cancer risk among this group is claimed (63). It must also be mentioned that both a Swedish (2) and Finnish (62) cohort study on industrial exposure to trichloroethylene showed no increased cancer incidence.

Other organ effects

Liver

In many animal experiments liver damage has been reported after exposure to high doses of halothane and methoxyflurane (51), and also after long-term exposure to subanesthetic concentrations of halothane, isoflurane, and diethyl ether (61). On the other hand, there are very few reports

available on the effects on operating room personnel. There are, however, case reports of liver damage among patients anesthetized with halothane and a report on a temporary increase of liver transaminases among operating personnel working with halothane (30). There are also case reports on icterus and liver cirrhosis among anesthetists exposed to halothane (6, 41). In some of the larger epidemiologic studies made in America (16, 17) and Czechoslovakia (51), an increased frequency of liver disease among anesthesiologists was observed. In England Spence & Knill-Jones (60) reported significantly more liver disease among anesthesiologists than among other hospital personnel.

Kidneys

In animal experiments kidney damage has been reported after exposure to low levels (100—500 ppm) of halothane (13). An effect on man has been reported on several occasions, where side effects have been noticed in patients anesthetized with methoxyflurane (21, 22). In 1968 there was a retrospective cohort study made among anesthetic personnel; it reported an increase in chronic kidney disease (9). In the earlier mentioned studies by Cohen et al (16) and Uhlirva & Pokorny (51), there was a higher frequency of kidney disease among exposed persons, especially women. In a Swedish report (23) a moderate and temporary effect on kidney function was shown among patients, as well as personnel, exposed to methoxyflurane.

Bone marrow

Animal studies, as well as clinical experience, on the effect of prolonged exposure to high concentrations of nitrous oxide have shown that leukopenia may be induced (33, 45). This effect has been used in the treatment of chronic and acute myeloid leukemia (25). However, because of the rapid recovery of marrow, it has been ineffective as a choice of treatment for leukemia (68). As to the effect on exposed personnel, there are no reports concerning bone marrow depression.

Central nervous system

Many of the industrial solvents now in use have earlier been used as anesthetic agents. Solvents, as well as anesthetic agents, are fat-soluble, which is also one of the conditions for the narcotic effects. Besides, anesthetic gases can form toxic metabolites (15) in the same manner as many solvents; these metabolites react on the cellular level and can induce cell damage there (58). The chronic damage caused by solvents has been studied to a great extent during the last 10 a, and many studies have shown effects on the central nervous system as a consequence of long-term exposure to solvents (38). Today there are no studies on the chronic central nervous effects on anesthetic personnel exposed for many years to anesthetic gases. However, animal and human experiments indicate that exposure to anesthetic gases does affect the central nervous system (CNS).

Animal experiments (11, 12, 55) have shown CNS damage in rats after exposure to halothane in concentrations of 8–12 ppm for 8 h a day 5 d a week.

In a laboratory study (8) 100 healthy male students were examined. They were subdivided into five groups with 20 persons in each. The groups were exposed to different combinations of anesthetic agents, ie, from 25 ppm of nitrous oxide and 0.5 ppm of halothane up to 500 ppm of nitrous oxide and 10 ppm of halothane. These concentrations were supposed to be in agreement with the levels very often existing in operating rooms during operations. The results showed that as little as 50 ppm of nitrous oxide led to an impairment of performance of about 5 %. When 1 ppm of halothane was added, the impairment of performance was about 10 %, when measured by different psychological functional tests.

In another study, where the behavioral toxicity of anesthetic gases on operating room personnel was studied (59), halothane levels of 1–3.9 ppm and nitrous oxide concentrations of about 0–176 ppm were registered. The exposed group was compared with a reference group, but there was no evidence of any acute reversible disturbance, measured by psycho-

metric tests, but the possibility of subtle but irreversible deficits could not be ruled out.

In Sweden, Gamberale et al (28) published a study in which they measured reaction time and perceptive speed among nurses who were exposed to anesthetic gases in their daily work. The results were compared with those of 20 nurses with intensive care duties but without exposure to anesthetic gases. No measurable impairment in the reaction time of the anesthetic personnel was observed in comparison to that of intensive care personnel. In one of the tests of reaction time, however, the result showed that the range of the individual reaction times among the anesthetic nurses was greater than that of the reference group.

In a study (35) from Gothenburg, Sweden, 32 anesthetic nurses were compared with a nonexposed matched reference group. The study comprised a psychological test battery, a questionnaire measuring feelings, a questionnaire measuring symptoms, and, finally, a purely medical phase. For only two of the 18 psychological test variables were the anesthetic nurses significantly inferior to the reference group. Moreover, there was only one subjective symptom that showed a significant difference between the groups, namely, pricking and numbness in any part of the body. However, in the psychological test and in regard to symptoms, there was a clear-cut tendency towards poorer test results and more symptoms among the anesthetic nurses than among the referents. The authors also tried to divide the exposed groups according to high- and low-level exposure, years in exposed work being used as the measure. When the level of exposure was related to the test results, they found a tendency towards poorer performance in the high exposure group when it was compared with the low exposure one.

In Finland Korttila et al (44) looked into the driving skills of operating room nurses after occupational exposure to halothane (0–43.7 ppm) and nitrous oxide (100–1,200 ppm). The driving skills of 19 nurses were measured and compared to those of 11 younger nurses working in the wards of the same hospital but with no exposure

to anesthetic agents. The authors stated that no impairment of driving skills could be expected after daily exposure to halothane and nitrous oxide among long-term employees working in operating rooms.

Peripheral nervous system

In accordance with the earlier mentioned similarities between industrial solvents and anesthetic gases now in use, it is not surprising to find that nitrous oxide can possibly cause neuropathy. Layzer et al (47) reported a disabling peripheral neuropathy in three health workers who habitually abused nitrous oxide. Nerve conduction studies suggested an axonal rather than demyelinating neuropathy. The neurologic disorder improved slowly when the patients abstained from further nitrous oxide abuse (47).

In another study Layzer (46) reported a neurologic disorder in 15 patients after prolonged exposure to nitrous oxide. Thirteen of the patients had abused nitrous oxide to some extent for periods ranging from three months to several years, but two patients were exposed to nitrous oxide only professionally, as dentists, during work in poorly ventilated offices. Neurologic examinations showed sensorimotor polyneuropathy and a picture similar to that of subacute combined degeneration of the spinal cord. The author claimed that it is possible that nitrous oxide interferes with the action of vitamin B₁₂ in the nervous system.

There is also a report (57) of toxic polyneuropathy, in a 23-year-old woman, after excessive intentional inhalation of nitrous oxide. The chronology of the patient's abuse correlated clearly with two episodes of recurrent polyneuropathy, primarily involving the peripheral nerves, although some signs suggested a possible effect on the cerebellum or its connections. Biopsy of the sural nerve showed axonal degeneration. The patient had inhaled nitrous oxide, dispensed from cartridges, through a canister normally used for whipped cream. Gas chromatographic analysis revealed exposure to, besides nitrous oxide, 26 other compounds. Three of these, trichloroethylene, toluene and phenol, are known neurotoxins.

Information about exposure

In the existing epidemiologic studies measures of exposure have rarely been given, but other references (30, 31, 40, 44, 51) indicate that the levels of anesthetic gases in operating rooms are highly variable. Usually the levels of halothane are about 1–70 ppm and those of nitrous oxide 400–3,000 ppm in older operating rooms with poor general ventilation. However, even in new facilities, there can be high levels, the tendency towards leakage being especially influenced by the anesthetic technique used, ie, face mask or intubation. This great variation in exposure has made it very difficult to settle on a safe exposure level for anesthetic gases. Based on epidemiologic studies, animal experiments, exposure measurements, and experimental studies, especially that of Bruce & Bach (8), NIOSH has concluded that a safe level of exposure to the halogenated agents cannot be defined, but it recommends that exposure be controlled to levels around 2 ppm and that the permissible level of exposure to nitrous oxide alone should be 25 ppm during the period of administration (51). It must, however, be stressed that today there are no settled threshold limit values (TLVs) for waste anesthetic gases in the United States. In Sweden a TLV for halothane of 5 ppm has been in effect since 1979, and one for nitrous oxide is under preparation. In Denmark the Labor Inspection Service has suggested a TLV of 1 ppm for halothane and 25 ppm for nitrous oxide. In Finland and Norway the subject is under consideration, but no information is available.

Summary

During the last 10 a, several studies have shown different health hazards for operating room personnel. Even if there are methodological weaknesses in many of the epidemiologic studies, such as low response rates or a lack of or poor definition of reference groups or no information on the anesthetic agents used or the environmental concentrations of the gases present, many studies indicate a higher risk for spontaneous abortion among women ex-

posed to anesthetic gases. Even very critical reviews (60, 65) conclude that available data provide reasonably convincing evidence of a moderate increase in the risk of spontaneous abortion among exposed females. Less agreement is found in the information on the increased risk for spontaneous abortion among women whose husbands have been exposed to anesthetic gases or on the increased risk of exposed women having malformed children. The same discrepancy applies to the reports on liver and kidney disease and the risk of cancer. However, the reports on a higher risk of cancer are worth attention in that the urine of anesthesiologists has been found to be mutagenic and there are structural similarities between some known human carcinogens and several inhalation anesthetic agents. Another growing concern is the possible CNS effects of long-term exposure to waste anesthetic gases. As yet no such studies have been performed. Consequently, there is a need for epidemiologic studies on the frequency of cancer, with special emphasis on leukemia and lymphoma, and behavioral deficits.

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References

1. Askrog V, Harvald B. Teratogen effekt af inhalationsanestetika. *Nord med* 83 (1970) 498—500.
2. Axelson O, Andersson K, Hogstedt C, Holmberg B, Molina G, De Verdier A. A cohort study on trichloroethylene exposure and cancer mortality. *J occup med* 20 (1978) 194—196.
3. Baden JM, Brinckenhoff M, Wharton RS, Hitt BA, Simmon VF, Mazze R. Mutagenicity of volatile anesthetics: Halothane. *Anesthesiology* 45 (1976) 311—318.
4. Baden JM, Kelley M, Wharton RF, Hitt B, Simmon VF, Mazze R. Mutagenicity of halogenated ether anesthetics. *Anesthesiology* 46 (1977) 346—350.
5. Baltzar B, Ericson A, Källen B. Delivery outcome in women employed in medical occupations in Sweden. *J occup med* 21 (1979) 543—548.
6. Belfrage S, Ahlgren J, Axelson S. Halothane hepatitis in an anesthetist. *Lancet* 2 (1966) 1466—1467.
7. Boyland E. Biochemistry of occupational cancer. *J soc occup med* 27 (1977) 97—101.
8. Bruce DL, Bach MJ. Trace effects of anesthetic gases on behavioral performance of operating room personnel. US Department of Health, Education and Welfare, Public Health Service, Center for Disease Control, National Institute for Occupational Safety and Health, Cincinnati, OH 1976. (HEW publication no (NIOSH) 76—169).
9. Bruce DL, Eide KA, Linde HW, Eckenhoff JE. Causes of death among anesthesiologists — A 20-year survey. *Anesthesiology* 29 (1968) 565—569.
10. Bruce DL, Eide KA, Smith MJ, Seltzer F, Dykes MHM. A prospective survey of anesthesiologists' mortality 1967—1971. *Anesthesiology* 41 (1974) 71—74.
11. Chang L, Dudley AW Jr, Katz J, Martin AH. Nervous system development following in utero exposure to trace amounts of halothane. *Teratology* 9 (1974) A-15.
12. Chang LW, Dudley AW Jr, Lee YK, Katz J. Ultrastructural changes in the nervous system after chronic exposure to halothane. *Exp neurol* 45 (1974) 209—219.
13. Chang LW, Dudley AW Jr, Lee YK, Katz J. Ultrastructural changes in the kidney following chronic exposure to low levels of halothane. *Am j pathol* 78 (1975) 225—232.
14. Coate WB, Ulland BM, Lewis TR. Chronic exposure to low concentrations of halothane, nitrous oxide: Lack of carcinogenic effect in the rat. *Anesthesiology* 50 (1979) 306—309.
15. Cohen EN. Toxicity of inhalation anesthetic agents. *Br j anaesth* 50 (1978) 665—675.
16. Cohen EN, Brown BW, Bruce DL, Cascorbi HF, Corbett TH, Jones TW, Whitcher CH. Occupation disease among operating room personnel: A national study. *Anesthesiology* 41 (1974) 321—340.
17. Cohen EN, Brown BW, Bruce DL, Cascorbi HF, Corbett TH, Jones TW, Whitcher CH. A survey of anesthetic health hazards among dentists. *J am dent assoc* 90 (1975) 1291—1296.
18. Corbett TH. Cancer and congenital anomalies associated with anesthetics. *Ann ny acad sci* 271 (1976) 58—66.
19. Corbett TH, Cornell RG, Endres JL, Lieding K. Birth defects among children of nurse-anesthetists. *Anesthesiology* 41 (1974) 341—344.
20. Corbett TH, Cornell RG, Lieding K, Endres JL. Incidence of cancer among Michigan nurse-anesthetists. *Anesthesiology* 38 (1973) 260—263.
21. Cousins MJ, Greenstein LR, Hitt BA, Mazze RI. Metabolism and renal effects of enflurane in man. *Anesthesiology* 44 (1974) 44—53.
22. Cousins MJ, Mazze RI. Methoxyflurane nephrotoxicity: A study of dose-response in man. *J am med assoc* 225 (1973) 1611—1616.

23. Dahlgren B-E. Fluoride concentration in urine of delivery ward personnel following exposures to low concentrations of methoxyflurane. *J occup med* 21 (1979) 624—626.
24. Doll R, Peto R. Mortality among doctors in different occupations. *Br med j* 1 (1977) 1433—1436.
25. Eastwood DW, Green CD, Lambdin MA, Gardner R. Effect of nitrous oxide on the white cell count in leukemia. *N engl j med* 268 (1963) 297—299.
26. Eger EI II, White AE, Brown CL, Biava CG, Corbett TH, Stevens WC. A test of the carcinogenicity of enflurane, isoflurane, halothane, methoxyflurane and nitrous oxide in mice. *Anesth analg* 57 (1978) 678—694.
27. Eschenbrenner AB. Induction of hepatomas in mice by repeated oral administration of chloroform with observations on sex differences. *J natl cancer inst* 5 (1945) 251—255.
28. Gamberale F, Svensson G, Andersson B. Narkosgasers effekt på psykomotoriska funktioner hos narkosköterskor. Arbetskyddsverket, Stockholm 1973. (Arbete och hälsa nr 5).
29. Garstka K, Wagner KL, Hamacher M. Pregnancy complications in anesthesiologists. Presented at the 159th Meeting Lower Rhine, Westphalia, Gynecology and Obstetric Association, Bonn, West Germany, June 23, 1974.
30. Götell P, Ståhl R. Halothanexposition hos narkosköterskor. *Läkartidningen* 69 (1972) 6179—6183.
31. Göthe C-J, Dahlgren B-E, Hultén B, Olander L, Övrum P, Westerholm P. Narkosgaser som yrkesrisk. *Läkartidningen* 73 (1976) 2553—2563.
32. Gold E, Gordis L, Tonascia I, Szklo M. Increased risk of brain tumors in children exposed to barbiturates. *J natl cancer inst* 60 (1978) 1031—1034.
33. Green CD, Eastwood DW. Effects of nitrous oxide inhalation on hemopoiesis in rats. *Anesthesiology* 24 (1963) 341—345.
34. Greim H, Bonse G, Radwan Z. Mutagenicity in vitro and potential carcinogenicity of chlorinated ethylenes as a function of metabolic oxyrane formation. *Biochem pharmacol* 24 (1975) 2013—2017.
35. Hedström C-E, Olsson B. Undersökning av narkosköterskor jämte matchad kontrollgrupp — en psykologisk och medicinsk studie. Göteborgs Stads Förvaltningshälsövård, Göteborg 1979. (FHV-rapport nr 55).
36. Hemminki K, Sorsa M, Vainio H. Genetic risks caused by occupational chemicals. *Scand j work environ health* 5 (1979) 307—327.
37. Herbst AL, Ulfelder H, Poskanzer DC. Adenocarcinoma of the vagina: Association of maternal stilbestrol therapy with appearance in young women. *New engl j med* 284 (1971) 878—881.
38. Hogstedt C, Hane M, Axelson O. Arbetsmedicinska aspekter på organiska lösningsmedel — en översikt. Nord företags hälsövård 1 (1978) 44—63.
39. Infante PF, Epstein SS, Newton WA. Blood dyscrasia and childhood tumors in exposure to chlorodane and heptachlor. *Scand j work environ health* 4 (1978) 137—150.
40. Jynge H, Gjelstad M, Lie A, Thorud S. Narkosgasser i operasjonsrom. *Tidskr nor laegeforen* 99 (1979) 1508—1512.
41. Klatsking G, Kimberg DW. Recurrent hepatitis attributable to halothane sensitization in an anesthetist. *New engl j med* 280 (1969) 515—522.
42. Knill-Jones RP, Newman BJ, Spence AA. Anaesthetic practice and pregnancy: Controlled survey of male anaesthetists in the United Kingdom. *Lancet* 2 (1975) 807—809.
43. Knill-Jones RP, Rodrigues LV, Moir DD, Spence AA. Anaesthetic practice and pregnancy: Controlled survey of women anaesthetists in the United Kingdom. *Lancet* 1 (1972) 1326—1328.
44. Korttila K, Pfäffli P, Linnoila M, Blomgren E, Hänninen H, Häkkinen S. Operating room nurses' psychomotor and driving skills after occupational exposure to halothane and nitrous oxide. *Acta anaesthesiol scand* 22 (1978) 33—39.
45. Lassen HCA, Henriksen E, Neukirch R, Kristensen HS. Treatment of tetanus: Severe bone marrow depression after prolonged nitrous oxide anaesthesia. *Lancet* 1 (1956) 527—530.
46. Layzer RB. Myeloneuropathy after prolonged exposure to nitrous oxide. *Lancet* 2 (1978) 1227—1230.
47. Layzer RB, Fishman RA, Schafer JA. Neuropathy following abuse of nitrous oxide. *Neurology* 28 (1978) 504—506.
48. McCoy EC, Hankel R, Robbins K, Rosenkrantz HS, Ginfrida IY, Bizzari DV. Presence of mutagenic substances in the urines of anesthesiologists. *Mutat res* 53 (1978) 71.
49. National Cancer Institute. Report on carcinogenesis bioassay of chloroform. Carcinogenesis Program, Division of Cancer Cause and Prevention. Bethesda, MD 1976.
50. National Cancer Institute. Carcinogenesis bioassay of trichloroethylene. CAS no. 79-01-06. Washington, DC 1976. (Natl cancer inst tech rep series no 2, Feb 1976). US Department of Health, Education and Welfare, Washington, DC 1976. (DHEW publ no (NIH) 76-802).
51. National Institute for Occupational Safety and Health. Occupational exposure to waste anesthetic gases and vapors. US Department Health, Education and Welfare, Washington, DC 1977.
52. Neutel CJ, Buck C. Effect of smoking during pregnancy on the risk of cancer in children. *J natl cancer inst* 47 (1971) 59—63.
53. Pharaoh POD, Alberman E, Doyle P, Chamberlain G. Outcome of pregnancy among women in anaesthetic practice. *Lancet* 1 (1977) 34—36.
54. Pope WD, Halsey NJ, Landsdown AB, Simmonds A, Bateman PE. Fetotoxicity in

- rats following chronic exposure to halothane, nitrous oxide or methoxyflurane. *Anesthesiology* 48 (1978) 11—16.
55. Quimby KL, Aschenase LJ, Bowman RE, Katz I, Chang LW. Enduring learning deficits and cerebral synaptic malformation from exposure to 10 parts of halothane per million. *Science* 185 (1974) 625—627.
 56. Rosenberg P, Kirves A. Miscarriages among operating theater staff. *Acta anaesthesiol scand* 53 (1973) 37—42.
 57. Sahenk Z, Mendell JR, Couri D, Nachman I. Polyneuropathy from inhalation of N₂O cartridges through a whipped-cream dispenser. *Neurology* 28 (1978) 485—487.
 58. Savolainen H. Some aspects of the mechanism by which industrial solvents produce neurotoxic effects. *Chem Biol Interact* 18 (1977) 1—10.
 59. Snyder BD, Thomas RS, Gyorky Z. Behavioral toxicity of anesthetic gases. *Ann Neurol* 3 (1978) 67—71.
 60. Spence AA, Knill-Jones RP. Is there a health hazard in anaesthetic practice? *Br J Anaesth* 50 (1978) 713—719.
 61. Stevens WC, Eger EI II, White A, Halsey MJ, Munger W, Gibbons RD, Dolan W, Shargol R. Comparative toxicities of halothane, isoflurane and diethyl ether at sub-anesthetic concentrations in laboratory animals. *Anesthesiology* 42 (1975) 408—419.
 62. Tola S, Vilhunen R, Järvinen E, Korkala M-L. Mortalitätsundersökning av triklorätylen-exponerade arbetare. In: 28:e Nordiska Yrkeshygieniska Mötet i Sverige. Arbetskyddsstyrelsen Arbetsmedicinska avdelningen, Solna 1979, p 2: 11.
 63. Tomlin PJ. Health problems of anaesthetists and their families in the West Midlands. *Br med j* 1 (1979) 779—784.
 64. Vaisman AI. Working conditions in surgery and their effect on the health of anesthesiologists. *Eksp khir anesteziol* 12 (1967) 44—49.
 65. Vessey MP. Epidemiological studies of the occupational hazards of anaesthesia — A review. *Anaesthesia* 33 (1978) 430—438.
 66. Vieira E. Effect of the chronic administration of nitrous oxide 0.5 % to gravid rats. *Br j anaesth* 51 (1979) 283—287.
 67. Waskell LA. A study of the mutagenicity of anesthetics and their metabolites. *Mutat res* 57 (1978) 141—153.
 68. ———. Editorial: Nitrous oxide and the bone marrow. *Lancet* 2 (1978) 613—614.

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