criteria for a recommended standard....

OCCUPATIONAL EXPOSURE TO WASTE ANESTHETIC GASES AND VAPORS

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PREFACE

The Occupational Safety and Health Act of 1970 emphasizes the need for standards to protect the health and safety of workers exposed to an ever-increasing number of potential hazards at their workplace. The National Institute for Occupational Safety and Health has projected a formal system of research, with priorities determined on the basis of specified indices, to provide relevant data from which valid criteria for effective standards can be derived. Recommended standards for occupational exposure, which are the result of this work, are based on the health effects of exposure. The Secretary of Labor will weigh these recommendations along with other considerations such as feasibility and means of implementation in developing regulatory standards.

It is intended to present successive reports as research and epidemiologic studies are completed and as sampling and analytical methods are developed. Criteria and standards will be reviewed periodically to ensure continuing protection of the worker.

The population being addressed by this waste anesthetic gases criteria document differs from those addressed by previous documents. The majority of workers involved with and exposed to waste anesthetic gases are members of the health care delivery profession. Certain provisions usually included as part of a recommended standard, such as personal protective equipment and clothing, do not appear in this document. This is due to the critical nature of the work involved and to the different circumstances of potential exposure compared to what may be considered the usual type of industrial exposure. The recommendations presented herein should in no way

preclude proper patient care and safety, particularly if patient needs arise that require deviation from the recommended standard.

I am pleased to acknowledge the contributions to this report on waste anesthetic gases and vapors by members of NIOSH staff and the valuable, constructive comments by the Review Consultants on Waste Anesthetic Gases and Vapors, by the ad hoc committees of the American Society of Anesthesiologists, the American Association of Nurse Anesthetists, the American Dental Association, the American Hospital Association, the American Society of Oral Surgeons, the American Veterinary Medical Association, the Association of Operating Room Nurses, and the Association of Operating Room Technicians, and by Robert B. O'Connor, M.D., NIOSH consultant in occupational medicine. The NIOSH recommendations for standards are not necessarily a consensus of all the consultants and professional societies that reviewed this criteria document on waste anesthetic gases. Lists of the NIOSH Review Committee members and of the Review Consultants appear on the following pages.

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CRITERIA DOCUMENT: RECOMMENDATIONS FOR AN OCCUPATIONAL EXPOSURE STANDARD FOR WASTE ANESTHETIC GASES AND VAPORS

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I. RECOMMENDATIONS FOR A STANDARD ON WASTE ANESTHETIC GASES AND VAPORS

The National Institute for Occupational Safety and Health (NIOSH) recommends that occupational exposure to waste gases from anesthetic procedures be controlled by adherence to the following sections. The standard applies to all workers, including students and volunteers, regardless of status, who are exposed to inhalation anesthetic agents that escape into locations associated with the administration of, or recovery from, anesthesia. It is designed to protect the health and safety of workers during their working lifetime in locations where exposures to waste anesthetic gases and vapors occur. Compliance with all sections of the standard should minimize potential adverse effects of waste anesthetic gases on the health and safety of workers and their unborn children.

The recommended permissible levels of exposure contained in the following sections, however, cannot be defined as safe levels since information on adverse health effects is not completely definitive and many unknown factors still exist. Therefore, the environmental limits presented should be regarded as the upper boundry of exposure, and every effort should be made to maintain exposures as low as is technically feasible.

The standard is measurable by techniques that are valid and available to industry and government agencies. Sufficient technology exists to permit compliance with the recommended standard in situations where a mixture of agents is used for anesthesia. A special area of concern is the use of nitrous oxide as the sole anesthetic agent, such as in dental procedures, and the health-based recommended exposure level may not be completely achievable at this time. The standard will be subject to review and revised as necessary.

Section 1 - Definitions

(a) Waste inhalation anesthetic gases and vapors are those which are released into work areas (operating room, recovery room, delivery room, or other areas where workers may be subject to job-related exposure) associated with, and adjacent to, the administration of a gas for anesthetic purposes, and include both gaseous and volatile liquid agents. Waste gases and vapors are herein referred to as waste anesthetic gases.

(b) Occupational exposure to waste anesthetic gases includes exposure to any inhalation anesthetic agents that escape into locations associated with, and adjacent to, anesthetic procedures. Such locations shall include, but shall not be limited to, operating rooms, delivery rooms, labor rooms, recovery rooms, and dental operatories.

(c) Scavenging is defined as the collection of waste anesthetic gases from anesthetic breathing systems and subsequent removal of the gases from the workplace.

Section 2 - Environmental (Workplace Air)

(a) Concentration

Work practices and engineering controls shall be implemented so that occupational exposures to waste anesthetic gases are controlled in accordance with the following sections. Such practices and control procedures shall be kept current and updated as necessary to control occupational exposures to waste anesthetic gases to the lowest feasible levels.

(1) Occupational exposure to halogenated anesthetic agents shall be controlled so that no worker is exposed at concentrations greater

than 2 ppm of any halogenated anesthetic agent, based on the weight of the agent collected from a 45-liter air sample by charcoal adsorption over a sampling period not to exceed 1 hour. Agents that shall be controlled, with their respective weights corresponding to 2 ppm, are as follows: chloroform, 9.76 mg/cu m; trichloroethylene, 10.75 mg/cu m; halothane, 16.15 mg/cu m; methoxyflurane, 13.5 mg/cu m; enflurane, 15.1 mg/cu m; fluroxene, 10.31 mg/cu m. When such agents are used in combination with nitrous oxide, levels of the halogenated agent well below 2 ppm are achievable. In most situations, control of nitrous oxide to a time-weighted average (TWA) concentration of 25 ppm during the anesthetic administration period will result in levels of approximately 0.5 ppm of the halogenated agent.

(2) Occupational exposure to nitrous oxide, when used as the sole anesthetic agent, shall be controlled so that no worker is exposed at TWA concentrations greater than 25 ppm during anesthetic administration. Available data indicate that with current control technology, exposure levels of 50 ppm and less for nitrous oxide are attainable in dental offices.

(b) Sampling and Analysis

Procedures for sampling and analysis of air in exposure areas shall be as provided in Appendices II-IV, or by any methods equivalent in sensitivity, accuracy, and precision.

Section 3 - Control Procedures and Work Practices

(a) Control Procedures

As soon as practicable after promulgation of a standard for occupational exposure to waste anesthetic gases, anesthetic delivery systems shall be equipped for scavenging as described below, or by other methods equivalent in effectiveness.

(1) Collection of Waste Anesthetic Gases

Anesthetic gas machines, nonrebreathing systems, and T-tube devices shall be fitted with an effective scavenging device that collects all waste anesthetic gases. Nose masks shall be of the double-suction design, or an equally effective alternative.

(2) Disposal of Waste Anesthetic Gases

Waste anesthetic gases, collected from anesthetic delivery systems, shall be conveyed to disposal sites in such a manner that occupational reexposure does not occur. Disposal methods shall be in compliance with existing local or federal environmental pollution control regulations.

(3) Pressure Balance

A pressure balance between the waste gas-collecting device on anesthetic delivery systems and disposal systems shall be assured so that the gas-collection system does not interfere with proper operation of the anesthetic delivery system.

(b) Work Practices

Work practices shall be utilized to obtain and maintain minimum waste anesthetic gas concentrations and shall include, but shall not be limited to, the following sections.

(1) Prior to the beginning of administration of an anesthetic agent, waste gas disposal systems shall be connected and proper operation determined.

(2) If a face mask is to be used for administration of anesthetics, it shall provide as effective a seal as possible against leakage into the ambient air.

(3) Vaporizers shall be filled in a ventilated area and in a manner to minimize spillage of the liquid agent. When feasible, vaporizers should be filled when the location where the anesthetic will be administered is not in use. The vaporizers shall be turned off when not in use.

(4) Low pressure leak tests, specified in Appendix I, shall be conducted daily for the complete anesthetic machine. All leaks shall be corrected to the extent specified in Appendix I before use of the anesthetic delivery system.

(5) Starting anesthetic gas flow before induction of anesthesia shall be prohibited.

(6) When the breathing circuit is disconnected from the patient after administration of the anesthetic agent has started, anesthetic flowmeters shall be turned off or the Y-piece sealed.

(7) The breathing bag shall be emptied into the scavenging system before it is disconnected from the anesthetic delivery system.

(c) Ventilation

(1) Recovery rooms, labor and delivery rooms, anesthetic gas storage areas, and other related areas in which scavenging techniques are not used shall be provided with air exchange rates in compliance with those specified by the US Department of Health, Education, and Welfare in Minimum Requirements of Construction and Equipment for Hospital and Medical Facilities (HEW Publication No. 74-4000, Rockville, Maryland, 1974).

(2) Recirculating air-conditioning systems may be used if the environmental limits prescribed in Section 2 are not exceeded and the systems comply with ventilation requirements in Section 3(c)(1).

(3) Ventilation systems shall be subject to regular preventive maintenance and cleaning to ensure maximum effectiveness, which shall be verified at least quarterly by airflow measurements.

(d) Anesthetic Equipment Maintenance

(1) Leak tests, as described in Appendix I, shall be made on both high- and low-pressure components so that waste anesthetic gas levels are maintained at a minimum.

(2) Within 180 days after promulgation of a standard for occupational exposure to waste anesthetic gases and at least quarterly thereafter, equipment for administering anesthetic agents shall be tested in accordance with Appendix I to ensure that the low-pressure leak rate is less than 100 ml/minute at 30 cm water pressure, or an equivalent pressure drop, and during the quarter less than 1 liter/minute at 30 cm water pressure. Tests for high-pressure leaks shall be conducted by an appropriate technique presented in Appendix I or equivalent. All new equipment for the administration of anesthetic agents shall meet these requirements. Mechanical ventilators employed for the administration of anesthetic agents shall be tested quarterly for proper functioning.

(3) Low-pressure leak tests, as described in Appendix I, shall be performed daily for the complete anesthetic machine. Low-pressure leaks shall be less than 100 ml/minute at 30 cm water pressure, or an equivalent pressure drop. If the leak rate is in excess of the recommendations, the leaks shall be located and repaired before use of the equipment.

(4) After each cleaning, face masks, tubing, breathing bags, and endotracheal tubes shall be inspected for cracks and other leak

sources. Damaged equipment shall not be used.

(5) Whenever room concentrations exceed the environmental limits prescribed in Section 2, leak sources shall be located and repaired prior to the next use of the anesthetic equipment.

Section 4 - Medical

Medical surveillance, as outlined below, shall be made available to all employees subject to occupational exposure to waste anesthetic gases.

(a) Comprehensive preplacement medical and occupational histories shall be obtained and maintained in the employees' medical records, with special attention given to the outcome of pregnancies of the employee or spouse, and to the hepatic, renal, and hematopoietic systems which may be affected by agents used as anesthetic gases. This information should be updated at least yearly and at any other time considered appropriate by the responsible physician.

(b) Preplacement and annual physical examinations of employees exposed to anesthetic gases are recommended and, when performed, the results shall be maintained in the employees' permanent medical records.

(c) Employees shall be advised of the potential undesirable effects of exposure to waste anesthetic gases, such as spontaneous abortions, congenital abnormalities in their children, and effects on the liver and kidneys.

(d) Any abnormal outcome of the pregnancies of employees or of the spouses of employees exposed to anesthetic gases shall be documented as part of the employees' medical records, and the records shall be maintained for the period of employment plus 20 years. This medical information shall

be available to the designated medical representatives of the Secretary of Health, Education, and Welfare, of the Secretary of Labor, of the employee or former employee, and of the employer.

Section 5 - Labeling and Posting

(a) Labeling

Containers of gaseous and volatile anesthetic agents shall carry labels as listed in Table I-1.

(b) Posting

Locations adjacent to areas where occupational exposure to anesthetic gases is likely shall be posted with an appropriate sign as listed in Table I-1.

The posting required in this section shall be printed both in English and in the language most predominant among non-English-reading workers, unless they are otherwise trained and informed of the hazardous areas.

Section 6 - Fire, Explosion, and Sanitation Practices

Applicable guidelines and regulations concerning fire, explosion, and sanitation shall be met when instituting scavenging and engineering controls.

TABLE I-1

LABELING/POSTING REQUIREMENTS

Flammable Agents	Nonflammable Agents
(NAME OF AGENT) CAUTION:HARMFUL IF INHALED CONTINUOUSLY Keep away from heat, sparks, and open flames. Use with adequate ventilation and/or scavenging equipment.	(NAME OF AGENT) CAUTION:HARMFUL IF INHALED CONTINUOUSLY Use with adequate ventilation and/or scavenging equipment.

Section 7 - Informing Employees of Hazards from Anesthetic Gases

On assignment, and at least annually thereafter, each worker shall be informed of the possible health effects of exposure to waste anesthetic gases. This information shall emphasize the potential risks to workers of reproductive age and to their unborn children. Each worker shall be instructed as to the availability of such information, which shall be kept on file and accessible to the worker at each place of employment where potential exposure to waste anesthetic gases exists.

Section 8 - Monitoring Requirements

The monitoring program shall be supervised by a knowledgeable individual familiar with sampling and monitoring techniques or by a professional industrial hygienist. The agent to be monitored and the

method chosen will depend on the frequency of the agent's use, availability of sampling and analysis instrumentation, and on whether the facility chooses to initiate its own monitoring program or take advantage of a commercial service.

(a) Sampling shall be conducted in areas that are representative of the concentrations at which workers are exposed during routine procedures incorporating any inhalation anesthetic. The sampling sites shall be chosen by surveying each location to which the standard applies to determine typical waste anesthetic gas distribution patterns, or shall be representative of the breathing zone of the exposed workers.

(b) For purposes of air monitoring, the inhalation anesthetic agent most frequently used by the institution must be chosen for sampling and analysis. Depending on the circumstances of use, mixed agents versus nonmixed agents, the environmental limits prescribed in Section 2 shall be used as a guideline for determining the effectiveness of the engineering control procedures and work practices required in the standard.

(c) Within 180 days of the promulgation of an occupational waste anesthetic gases standard, all locations with the potential of worker exposure to waste anesthetic gases shall be sampled. Sampling shall be conducted during periods of anesthetic administration and sampling time shall not exceed 1 hour.

Repetitive sampling shall be conducted on a quarterly basis in locations in which mixed inhalation anesthetic agents are used and whenever ventilation, anesthetic equipment, or scavenging techniques are modified.

Section 9 - Recordkeeping Requirements

(a) Records of all collected air samples shall be maintained including date of sample, sampling methods, sample location, analytical method, and measured concentrations. If waste anesthetic gas levels are found above the environmental limit prescribed in Section 2, corrective actions shall be taken and recorded. Results of environmental measurements shall be made available to exposed employees upon request.

(b) Air sampling results and results of leak tests shall be maintained for at least 20 years.

(c) Medical records shall be kept for the duration of employment plus 20 years following an employee's termination of employment or termination of work of a self-employed person.

II. INTRODUCTION

This report presents the criteria and the recommended standard based thereon which were prepared to meet the need for preventing occupational diseases arising from chronic exposure to waste anesthetic gases during the use of gaseous and volatile anesthetic agents in anesthetizing procedures. The criteria document fulfills the responsibility of the Secretary of Health, Education, and Welfare, under Section 20(a)(3) of the Occupational Safety and Health Act of 1970 to "...develop criteria dealing with toxic materials and harmful physical agents and substances which will describe exposure levels... at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

The National Institute for Occupational Safety and Health (NIOSH), after a review of data and consultation with others, formalized a system for the development of criteria upon which standards can be established to protect the health of workers from exposure to hazardous chemical and physical agents. It should be pointed out that any recommended criteria for a standard should enable management and labor to develop better engineering controls resulting in more healthful work practices and should not be used as a final goal.

These criteria and recommended standard for chronic exposure to waste anesthetic gases are part of a continuing series of criteria developed by NIOSH. The proposed standard applies only to the occupational use of anesthetic agents as applicable under the Occupational Safety and Health Act of 1970. The standard was not designed for the population-at-large,

and any extrapolation beyond occupational exposures is not warranted. The standard is intended to protect against development of systemic effects related to chronic exposure to waste anesthetic gases associated with inhalation anesthesia, and it is considered to be attainable with existing technology.

Current scientific evidence obtained from human and animal studies suggests that chronic exposure to anesthetic gases increases the risk of both spontaneous abortion and congenital abnormalities in offspring among female workers and wives of male workers. Risks of hepatic and renal diseases are also increased among exposed personnel. In addition, psychologic functions may be impaired. A few studies have suggested an increased risk of cancer. Effects on the central nervous system (CNS) due to acute exposures to anesthetic gases have been associated with headaches, nausea, fatigue, irritability, etc. However, the exposure levels attainable with the control procedures and work practices presented in the recommended standard in this document should prevent the effects caused by such acute exposures and significantly reduce the risks associated with long-term exposure.

Although most of the human studies conducted and reported herein deal with hospital operating room personnel, it is the opinion of NIOSH that the health effects of chronic exposure to waste anesthetic gases in other anesthetizing locations could be similar. Therefore, these criteria and the standard were developed for application to all locations where inhalation anesthetics are administered.

More information is needed from the dental and veterinary medical areas to determine the feasible levels to which exposures can be reduced

and the possible presence of adverse health effects related to exposure. A health survey among exposed dentists and their employees should provide some of the information needed to answer these questions.

It is highly recommended that this document be supplemented with the NIOSH technical information publication Development and Evaluation of Methods for the Elimination of Waste Anesthetic Gases and Vapors in Hospitals (GPO Order No. 1733-00061, Superintendent of Documents, US Government Printing Office, Washington, DC 20402).

III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Inhalation anesthesia was first used in 1842 [1,2]. Since then, a number of different chemical compounds have been used as inhalation anesthetic agents. Table III-1 lists the most widely used agents and the year each was introduced as an anesthetic. The more important physical and chemical properties of these anesthetic agents are presented in Table XIII-1 [3-11].

TABLE III-1

INHALATION ANESTHETIC AGENTS

Generic Name	Commercial Name	Year of Introduction
Diethyl ether	Ether	1842
Nitrous oxide	Nitrous oxide	1844
Chloroform	Chloroform	1847
Cyclopropane	Cyclopropane	1933
Trichloroethylene	Trilene	1934
Fluroxene	Fluoromar	1954
Halothane	Fluothane	1956
Methoxyflurane	Penthrane	1960
Enflurane	Ethrane	1974
Isoflurane	Forane	Investigational

Derived from references 1 and 2

Many of the earlier inhalation anesthetics, such as diethyl ether and cyclopropane, are flammable and explosive and have been largely replaced by nonexplosive, nonflammable agents, such as halothane and methoxyflurane. Halothane and nitrous oxide are currently the two most widely used inhalation anesthetic agents in the United States. Diethyl ether is still used to some extent.

It has been estimated that approximately 20 million patients are anesthetized each year with inhalation anesthetics in the 25,000 hospital operating rooms throughout the United States [1,2] and about 4.5 million patients are anesthetized by dentists [12]. In addition, dentists deliver a much larger number of analgesic sedations than anesthesias. Approximately 50,000 hospital operating room personnel are exposed daily to waste anesthetic gases in the US. This figure does not include surgeons, who usually do not operate every day. Table III-2 [12,13] lists by professional group the number of potentially exposed operating room and dental personnel in the United States in 1975.

In addition to hospital operating room and dental personnel, veterinarians and their technical assistants have the potential for exposure to waste anesthetic gases; their estimated number is also presented in Table III-2. Similarities in the practice of anesthesia in human and veterinary hospitals and clinics result in many of the same problems of exposure for both groups. Exposures among veterinarians may range from sporadic to almost continuous on a daily basis.

TABLE III-2

NUMBER OF OPERATING, DENTAL, AND VETERINARY
PERSONNEL POTENTIALLY EXPOSED TO ANESTHETIC GASES

Professional Group	Membership
Anesthesiologists (ASA)	13,700
Nurse-anesthetists (AANA)	17,546
Operating room nurses (AORN)	21,600
Operating room technicians (AORT)	12,000
Dentists and assistants (ASOS,ADA,ADAA)	100,000
Veterinarians and employees (AVMA)	50,000

Derived from reference 12 and 13

Historical Reports

Diethyl ether was first used as an inhalation anesthetic in Jefferson, Georgia, in 1841 [2,2]. Crawford Long, a general practitioner, anesthetized a patient with diethyl ether and removed a tumor from his neck. The procedure went unrecognized until several years later. William Morton used diethyl ether as an anesthetic at the Massachusetts General Hospital in 1846 to produce surgical anesthesia and is generally recognized as the one who introduced the technique.

Nitrous oxide was used by Horace Wells to alleviate the pain of dental extractions. He attempted to introduce nitrous oxide as an

inhalation anesthetic in 1844 at the Massachusetts General Hospital but failed. Despite this failure, nitrous oxide is now the inhalation anesthetic most widely used in medical and dental practice.

Chloroform was introduced as an inhalation anesthetic in 1847 by James Simpson, an English surgeon and obstetrician, who reported his discovery that same year [14,15]. He advocated the use of chloroform because it was more pleasant to inhale than diethyl ether and required only a small amount to produce narcosis. He recommended chloroform especially for the obstetrical patient. The deleterious effects of exposure to decomposing chloroform on operating room personnel was observed during the late 1880's [16].

Halothane, presently the most commonly used halogenated anesthetic agent, was introduced in 1956 [17]. It seemed to be the most promising of a number of fluorinated agents because of its volatility, non-explosiveness when mixed with oxygen, and apparent lack of any serious physiologic side effects.

Recognition by anesthesiologists of possible deleterious effects from repeated exposure to anesthetic gases during their administration to patients was the subject of a 1922 editorial [18]. It paid tribute to a noted Chicago anesthesiologist, Edward Costain, who had administered anesthetics to more than 30,000 people during 30 years of practice. Gilbert Fitzpatrick, an associate of Dr. Costain, was quoted as saying, "While we have not been able to prove it definitely, still we have much evidence to show that the administration of anesthetics, over a long period of years, produces a condition of nephritis that results fatally."

Hirsch and Kappus [19] reported, in 1929, the first quantitative study of concentrations of anesthetic gases in the air of operating rooms. They cited references in the German literature of reports from operating room personnel of headaches, fatigue, and, in older surgeons, heart complaints. Chloroform and ether were the anesthetic agents associated with these adverse effects.

The case studies on three persons from a surgical team (surgeon, surgical nurse, and anesthesiologist) who were exposed to ether vapor over a period of 4-14 years were reported in 1949 by Werthmann [20]. The exposed personnel showed signs and symptoms of general fatigue, rapid exhaustion, frequent headache, lymphocytosis, eosinophilia, and in the case of the eldest of the three, of electrocardiographic evidence of myocardial damage.

Effects on Humans

Much of the data on side effects of acute exposure have been obtained by studying patients who experienced some type of complication following clinical anesthesia. Since it is not known if acute effects will be experienced after chronic exposure, the side effects of acute exposure are reviewed here.

(a) Acute Effects on the Liver and Kidneys

A retrospective survey of the incidence of massive hepatic necrosis and death in patients after general anesthesia in 34 hospitals from 1959 to 1962 was reported by the National Academy of Sciences [21] in 1966. The main conclusion was that fatal postoperative massive hepatic necrosis was rare. It could usually be explained on the basis of circulatory shock,

sepsis, or preexisting hepatic disease. The possible rare occurrence of halothane-induced hepatic necrosis after single or multiple administrations could not be ruled out.

Other studies [21-32] of the hepatotoxicity of halothane inhalation anesthesia have been reported and are noted here but not summarized. The extent to which this might occur in workers chronically exposed to subanesthetic concentrations is unknown.

A series of reports of possible renal toxicity following methoxyflurane general anesthesia have appeared since 1966 [34-39]. The primary signs of such toxicity were increased blood urea nitrogen (BUN), increased urinary inorganic and nonvolatile organic fluoride levels, and polyuria. Five fatal cases were reported following methoxyflurane anesthesia [34,35] with the most significant post-mortem finding being oxalate crystals within the distal, cortical, and medullary kidney tubules. The authors speculated that fluoride and oxalate are both nephrotoxic and possible metabolites of methoxyflurane.

(b) Psychologic Effects

Several studies have been conducted with human volunteers to measure the effects on psychologic performance from exposure to low concentrations of trichloroethylene [40-45]. Kylin et al [40] exposed 12 subjects to trichloroethylene at 1,000 ppm for 2 hours. They concluded that exposure had an effect on the CNS based on the development of optokinetic nystagmus, but the effect was less marked than in similar tests with alcohol.

Vernon and Ferguson [41] reported the results of experimental 2-hour exposures of eight young male volunteers, aged 21-30, to trichloroethylene at concentrations of 0, 100, 300, and 1,000 ppm. On the basis of various

psychophysiologic tests, statistically significant decrements in performance were reported only at 1,000 ppm. One subject exposed at 300 ppm complained of lightheadedness and dizziness.

Stopps and McLaughlin [42] reported the results of psychophysiologic testing of one human subject exposed to trichloroethylene for 2.5-hour periods at concentrations of 100, 200, 300, and 500 ppm. Their studies indicated no significant effects on psychomotor performance at the 100-ppm level. There was a slight decline in performance at 200 ppm, which became progressively more pronounced at the 300- and 500-ppm concentrations.

Stewart et al [43,45] reported the results of a series of experimental exposures of human subjects to trichloroethylene. Time-weighted average (TWA) exposures of 265 ppm and 211 ppm were used for periods of 83 and 190 minutes, respectively. Results of psychophysiologic testing were reported normal in all subjects. In a second study [45], Stewart et al conducted a series of experimental 7-hour exposures of five human subjects to a nonfluctuating 200-ppm level of trichloroethylene on 5 consecutive days. After 30 minutes, two of the subjects complained of throat dryness and one of them of mild eye irritation. The investigators noted that the results of the performance tests were normal. One consistent response was the complaint of "feeling fatigued" on the 4th and 5th days of the exposure.

In 1971, Salvini et al [44] reported the exposure of six male volunteers to trichloroethylene at 110 ppm for two 4-hour periods separated by 1.5-hour intervals. The study showed a significant decrease in performance ability for the perception test with tachistoscopic presentation, the Wechsler Memory Scale, a complex reaction time test, and

a manual dexterity test using a crossed scheme analysis. The authors concluded that such concentrations interfered with the psychologic efficiency of the volunteers.

Stewart et al [46], under NIOSH contract, attempted to duplicate the study of Salvini et al [44] but were unable to corroborate their findings. No significant decrements in performance of the four behavioral tests were found following exposure to trichloroethylene at 110 ppm for 4 hours.

Perceptual, cognitive, and motor skills were studied by Bruce et al [47] using 40 male medical and dental students, 20-30 years old. The subjects were exposed on two occasions to 4 hours of inhalation of either air (control) or 500 ppm nitrous oxide in air with or without 15 ppm halothane. Compared with responses after breathing air, responses after exposure to nitrous oxide and halothane showed statistically significant decreases in the performance of tasks in which attention was divided between auditory and visual signals, a visual tachistoscopic test, and memory tests involving digit span and recall of word pairs. Subjects exposed to nitrous oxide alone scored significantly lower on the digit-span test only. Subsequently, Bruce and Bach [48] exposed 30 human subjects for 4 hours to nitrous oxide at 500 ppm with or without 15 ppm enflurane in air. Within 5 minutes, the subjects were given a 35-minute battery of psychologic tests. Performance of a divided-attention audiovisual task and a digit-span memory test was significantly decreased compared with control data obtained following exposure to air. A pattern-recognition task, four tests from the Wechsler Memory Scale, and five others from the Wechsler Adult Intelligence Scale were unaffected. The 30 subjects exposed at 500 ppm nitrous oxide in air scored significantly lower on the digit-span test

only. The authors concluded from both studies that trace anesthetic concentrations in amounts found in unscavenged operating rooms may interfere with optimum performance on psychologic tests measuring perceptual, cognitive, and motor skills and that if the tests had been performed while the subjects were being exposed, the performance decrements probably would have been even greater.

Further studies by Bruce and Bach [49] showed measurable decrements in performance of volunteers exposed during testing at concentrations as low as 50 ppm of nitrous oxide and 50 ppm nitrous oxide with 1 ppm halothane. A total of 100 male subjects, all between the ages of 20 and 30, were exposed to the anesthetics and each volunteer was tested twice. Visual perception, immediate memory, and a combination of perception, cognition, and motor responses required in a task of divided attention to simultaneous visual and auditory stimuli were tested. Testing began 2 hours after each subject had begun breathing the appropriate gas mixture. Exposure to the anesthetics continued throughout the entire testing period. Exposure at 50 ppm nitrous oxide with 1 ppm halothane caused performance decrements in four of the seven tests administered. Similar effects were not seen in subjects exposed to nitrous oxide at 25 ppm with 0.5 ppm halothane. Exposure at 500 ppm nitrous oxide alone caused performance decrements in six of the seven tests administered. Exposure at 50 ppm nitrous oxide resulted in performance decrements in audiovisual tasks only. A 3-minute and 7-minute audiovisual task was administered approximately 2.75 and 4 hours, respectively, after the subjects had begun breathing the gas mixture.

(c) Metabolism Studies

Kelley and Brown [50] reviewed the literature on biotransformation of trichloroethylene in man. Trichloroethylene is biotransformed into chloral hydrate, trichloroacetic acid, and trichloroethanol. Oxidation of trichloroethylene to chloral hydrate is accomplished by the liver microsomal enzymes, requiring the presence of NADPH and oxygen. Trichloroacetic acid is excreted into the urine unchanged and trichloroethanol is first conjugated with glucuronic acid and then excreted in urine.

The literature on biotransformation of diethyl ether and chloroform was reviewed by Van Poznak [51]. Both agents are biotransformed by liver microsomal enzymes. Although the metabolic pathways for degradation of diethyl ether and chloroform have not been extensively studied, Van Poznak postulated that diethyl ether may form acetaldehyde, which is subsequently reduced to ethanol or oxidized to carbon dioxide. Chloroform is known to be metabolized to carbon dioxide; however, other possible metabolites have not been determined.

Mazze and Cousins [52,53] reviewed the literature on the metabolism of methoxyflurane, enflurane, and isoflurane and on the toxicity of their metabolites. Although several pathways have been suggested for each of these agents, none has been widely accepted. High concentrations of serum and urinary inorganic fluoride and increased levels of urinary oxalic acid have been demonstrated in patients receiving methoxyflurane. Serum and urinary fluoride were increased following enflurane and isoflurane anesthesia. Carbon dioxide, dichloroacetic acid, and difluromethoxyacetic acid have also been suggested as metabolites of methoxyflurane. Mazze and

Cousins suggested that the inorganic fluoride metabolites are possibly the chief etiologic agents for methoxyflurane nephrotoxicity.

Studies of fluroxene metabolism were reviewed by Cascorbi [54]. The observed metabolites are trifluoroethanol, trifluoroacetic acid, and carbon dioxide, although the exact pathway for this metabolism is unknown. Studies using volunteers have shown that 12-15% of the administered dose is metabolized within 24 hours.

Rehder and Sessler [55], Sawyer and Eger [56], Cascorbi [57], and Van Dyke [58] have reviewed the literature concerning biotransformation of halothane. Although not well elucidated, the most widely accepted mechanism is the formation of trifluoroacetic acid with resulting urinary excretion of trifluoroacetic acid and bromide. Man is one of the species most capable of carrying out this reaction, since the rate of conversion to trifluoroacetic acid and bromide is much higher than in other species studied. These metabolities may be found in patients up to 15 days after administration of halothane. Chloride ions have also been considered a metabolite of halothane.

In 1970, Holaday et al [59] reported on the metabolism and excretion of 14-C-labeled methoxyflurane in 12 human subjects, 5 of whom were exposed to methoxyflurane through anesthetic procedures. Biodegradation of the methoxyflurane began immediately after exposure and continued for 9-12 days after which storage areas of the drug approached depletion. In addition to the exhalation of unaltered methoxyflurane, identified products of biotransformation included carbon dioxide, fluoride, dichloroacetic acid and 2,2-methoxyfluoroacetic acid.

Johnstone et al [60] noted serum bromide concentrations after halothane anesthesia in which seven healthy male volunteers received 6.6% hours (SE $\pm$ 0.5) (% concentration X hours of administration) halothane-oxygen anesthesia without surgery. Venus blood samples were obtained immediately before and after anesthesia and 1, 2, 3, 6, and 9 days after anesthesia. In addition, urine samples were taken before and immediately after anesthesia and also 1 and 2 days after anesthesia. Serum bromide and plasma and urinary fluoride analyses were performed. Serum bromide concentrations increased from 0.6 mEq/liter (SE $\pm$ 0.1) before anesthesia to 2.9 mEq/liter (SE $\pm$ 0.2) on the 2nd day after anesthesia. On the 9th day, serum bromide was still elevated to 2.5 mEq/liter (SE $\pm$ 0.1). Plasma and urinary fluoride concentrations did not increase significantly. The authors [60] stated that the concentrations of bromide observed were 50% of toxic concentrations and probably represented sedative levels which may account for some cases of postoperative psychosis and depression.

Although a dose-response relationship for halogenated anesthetic agent toxicity has not been defined, it has been suggested that increased levels of toxicity may result from repeated anesthetic administrations in humans [22-33] or from chronic low-level exposures in animals [61]. Individual variances in response might include hypersensitivity, an immune-type response, an abnormally high rate of metabolism, or an inability to excrete toxic metabolites. It appears that microsomal enzyme induction and metabolism of the anesthetic agents play a major role in their potential toxicity.

It has been shown that exposure at low levels to the halogenated anesthetic agents results in an increased metabolism rate of the agent in

man [62-66]. The possible accumulation of toxic metabolites is presumably greater in a person chronically exposed to such agents than in someone receiving a massive dose of the agents.

Cascorbi et al [62,63] observed that urinary excretion of halothane metabolites was greater when a dose of low-level radioactive tracer was injected into unanesthetized subjects than when injected into the same subjects but under anesthesia. Also, four of five anesthetists excreted more radioactivity during the first 2 hours after tracer injections than four pharmacists who had not been exposed professionally to anesthetic gases or vapors. The elevated metabolism suggested a microsomal enzyme induction caused by chronic exposure to halothane vapor.

Cohen et al [64] studied the urinary metabolites of halothane in man by utilizing 14-C-labeled halothane. The study included five individuals given tracer doses (25 microcuries) and three subjects (heart donors) given large doses (1 millicurie). Identification of three halothane metabolites, trifluroacetic acid, N-trifluoroacetyl-2-aminoethanol, and N-acetyl-S-(2-bromo-2-chloro-1,1-difluroethyl)-L-cysteine was determined by nuclear magnetic resonance and mass spectrometry. The authors concluded that the formation of these metabolites suggest the presence of reactive intermediates which could be the source of potential hepatotoxicity. In reviewing this work, Van Dyke [65] cautioned about the use of urinary metabolites as a means of determining toxic biotransformation. However, he did not rule out the significance of the findings and indicated that the work did contribute to the needed information on the biochemistry of halothane.

Cascorbi et al [66] reported on investigations of halothane metabolism in humans after an intravenous injection of 14-C-labeled halothane. Although the authors found a wide variation in the metabolism rate from person to person, the studies showed that occupational exposure to halothane vapor could cause an increased rate of halothane biotransformation in man. Controls, including identical and fraternal twins, were used for comparison with those injected. Urine excretion and breath samples were utilized to monitor metabolism.

In 1974, Evers and Racz [67] reported preliminary results of studies of blood enzymes and serum proteins in anesthesia residents. A total of 15 new residents with either minimal anesthesia exposure or none at all were followed for periods ranging from 12 to 48 months. The investigators observed increases in serum glutamic-oxaloacetic transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), lactic drogdrogenase (LDH), and alkaline phosphatase, which peaked between the 9th and the 15th month of training and then leveled off or returned to near normal values. Abnormal transaminase levels were not frequently found nor were there significant changes in the hematologic data. Blood albumin levels showed frequent decreases and changes in globulins (alpha 1, alpha 2, beta, and gamma), considered by the authors to be consistent with a chronic disease process, and appearing 3-6 months after the beginning of training.

Johnstone and coworkers [68] reported measurements of serum bromide concentrations in anesthetists and operating room personnel. Serum bromide concentrations were measured in 12 operating room workers (primarily anesthetists) from two hospitals where halothane was administered; operating room halothane concentrations ranged from 30 to 104 ppm. A

comparison was made with 10 healthy laboratory technicians. Serum bromide concentrations in the halothane-exposed group ranged from 0.24 to 0.97 millimole/liter and averaged 0.53 millimole/liter, whereas values for the laboratory workers ranged from 0.11 to 1.25 millimoles/liter and averaged 0.38 millimole/liter. The authors reported that the differences were not significant at the 5% level.

Epidemiologic Studies

A number of epidemiologic studies have been conducted in an attempt to identify any prominent health effects associated with chronic exposure to waste anesthetic gases. Nearly all the studies were questionnaire surveys conducted among nurses, anesthetists, and operating room technicians. Several of the surveys suffer from low response rates, lack of or poor definition of control groups, and potential biases on the part of respondents. In all of the surveys, no information was presented on the anesthetic agents used or on the environmental concentrations of the gases present. The main health effects seen with consistency from one study to another were an increased incidence of spontaneous abortions and an increased incidence of congenital malformations among the children of exposed females and wives of exposed males.

In 1966, Vaisman [69] surveyed by questionnaire 303 Russian anesthesiologists (193 men and 110 women). Ninety-eight percent reported using diethyl ether; 59%, nitrous oxide; 28%, halothane; and 21%, other agents. Scavenging of waste anesthetic gases was not practiced and concentration levels were not presented. A high incidence of headache, fatigue, irritability, nausea, and itching was reported. The authors also

noted that 18 of 31 pregnancies among anesthesiologists who were between the ages of 24 and 38 ended in spontaneous abortions. In addition, there were two premature births and one child was born with a congenital malformation. It was also reported that two of the women discontinued working in the operating room because of threatened abortion. The anesthesiologists with abnormal pregnancies had exposures of 25 hours/week or more while those with normal pregnancies did not exceed 15 hours/week.

In 1968, Bruce et al [70] reported on a retrospective cohort mortality analysis of the causes of death in anesthesiologists over the 20-year period of 1947 to 1966. The study was based on an analysis of 441 deaths among members of the American Society of Anesthesiologists (ASA). The survey revealed a trend toward higher than normal incidences of death from suicide, reticuloendothelial and lymphoid malignancies, and a low incidence of lung cancer and coronary artery disease. The 441 deaths were grouped by age at death, year of death, and cause of death according to the International Classification of Diseases, Injuries and Causes of Death, 7th Revision, into two 10-year periods, 1947-1956 and 1957-1966. Ratios of observed-to-expected deaths for white males were determined for each group using data obtained from the US Bureau of Vital Statistics, and white male policyholders with the Metropolitan Life Insurance Company as the comparison group. The comparison groups were adjusted to ASA population distributions.

A prospective study of anesthesiologist mortality for the period 1967-1971 was published by Bruce et al [71] in 1974. Their earlier finding of an apparently high death rate from malignancies of the lymphoid and reticuloendothelial tissues, which included lymphosarcoma, Hodgkin's

disease, multiple myeloma, and lymphoma, was not confirmed in the prospective study. The ASA suicide rate was found to be 3 times that of a comparable control group, which made it consistent with the finding reported in the 20-year retrospective study, which was 2.7 times as high as the control group.

Askrog and Harvald [72] reported the results of a 1970 questionnaire survey of 578 nurses in anesthesia departments and of 174 female and male anesthetists. The survey was intended to determine if long-term, low-dosage inhalation of anesthetics had a teratogenic effect. Five hundred and seventy questionnaires were usable and included information on 212 pregnancies started before and 392 started during employment in the anesthesia department. The abortion frequency was significantly higher during employment (20%) than before (10%), not only for exposed female personnel but also for the wives of anesthesiologists. Though not statistically significant, the number of male children born in all groups was decreased. The authors [72] did not find a significant difference between the frequency of congenital malformation in children conceived before or during employment.

In 1971, Cohen et al [73] presented the results of a double survey conducted among California nurses and female physicians. The first study consisted of personally interviewing 67 female operating room nurses and 92 female general duty nurses (control). The nurses were unaware of the purpose of the study in order to avoid any possible bias. The second study was a questionnaire survey in which responses were obtained from 50 female anesthesiologists and 82 female physicians in specialties other than anesthesia who were used as controls. The results from the nurses,

surveyed from 1966 to 1970, showed that 29.7% of pregnancies in operating room nurses ended in spontaneous miscarriage compared with 8.8% in the control group, which is statistically significant (P = 0.045). For the period 1965-1970, the anesthetists showed a 37.8% spontaneous miscarriage rate compared with 10.3% in the control group, which is statistically significant (P = 0.0035). Miscarriages occurred earlier in both operating room nurses and anesthetists compared with their control groups (8th versus 10th week). The anesthetic gas concentrations and the types of gases to which the study group was exposed were not reported. The operating room nurses averaged 78% full-time employment in the operating room.

A questionnaire survey of 1,241 female anesthetists and 1,678 female physicians not associated with anesthesia was reported in 1972 by Knill-Jones et al [74]. The responses of 563 married female anesthetists and 828 nonanesthetist married female physicians were usable in analysis of the survey returns. The frequency of spontaneous abortion was significantly higher (18.2%) for anesthetists working during the first and second trimester than for the control group (14.7%, P<0.025), but not significantly different from that of the anesthetists who were not working while pregnant (13.7%). Also, anesthetists working during pregnancy had a significantly higher frequency of congenital abnormalities in live births (6.5%) than did those not at work (2.5%), but not a significantly higher frequency than the control group (4.9%). Involuntary infertility among anesthetists (12%) was twice as frequent as in the control group. There was no significant difference between the anesthetists and the control group in sex ratio, stillbirths, neonatal deaths, or total number of children with congenital abnormalities. Types of anesthetic gases or

concentrations at which the anesthetists had been exposed were not reported.

In 1973, Corbett et al [75] reported the results of their questionnaire survey of 621 female nurse-anesthetists in Michigan, with 525 usable responses. The survey was conducted to determine whether there was a higher than expected incidence of malignancies in the group. A total of 33 malignancies were diagnosed in 31 nurse-anesthetists during a period of 1-31 years after beginning anesthesia training. Of the tumors reported, several were of unusual types, including malignant thymoma, hepatocellular carcinoma, and leiomyosarcoma of subcutaneous tissue. The incidence of malignancy in the Michigan nurse-anesthetists was compared to age-adjusted statistics from the Connecticut Tumor Registry. It was found that, excluding skin cancers, the study group had a three-fold excess in malignancies, which was statistically significant, at the 3.1% level. Types of anesthetic gases and concentrations at which the study group were exposed were not presented.

Corbett and coworkers [76] conducted a further analysis of their 1973 survey. The purpose of the study was to evaluate the incidence of birth defects among the offspring of the Michigan female nurse-anesthetists. It was found that in children whose mothers worked during pregnancy, 16.4% had birth defects, compared with an incidence of 5.7% among children whose mothers did not work during pregnancy (significant at $P<0.005$). Excluding anomalies of the skin, the total number of birth defects among offspring of the working exposed mothers was 8.8%, while the total among the nonexposed group was 3.8% (significant at $P<0.025$). Three neoplasms were reported in two children whose mothers worked during pregnancy. One child had a

neuroblastoma at birth and developed a thyroid malignancy at puberty. Another child developed a parotid tumor at the age of 22. A single case of leukemia at age 3 was reported in one of the children from the group of mothers who did not practice anesthesia during pregnancy.

American Society of Anesthesiologist (ASA) Ad Hoc Committee on the Effects of Trace Anesthetics reported the results of a national study of occupational diseases among hospital operating room personnel and dentists, including oral surgeons [12,13]. The study was conducted by mailing questionnaires to: (1) 49,585 operating room personnel in four professional societies (anesthesiologists, nurse-anesthetists, operating room nurses, and operating room technicians); (2) 4,797 general dental practitioners and 2,642 oral surgeons; and (3) 23,911 individuals in two other professional societies (pediatricians and general nurses). Data on types of anesthetic agents and concentration levels at which the study groups were exposed were not presented for either survey [12,13]. It was reported that approximately 20% of the exposed respondents from the hospital setting worked in operating rooms with waste anesthetic gas scavenging devices of unknown efficiency. The response rates were: 67% for male anesthesiologists, 75.7% for female anesthesiologists, 65.4% for male nurse-anesthetists, 59.3% for female nurse-anesthetists, 53.5% for male operating room nurses and technicians, 55.4% for female operating room nurses and technicians, 38.9% for the general dentists, and 64.5% for the oral surgeons. The general nurse and pediatrician control groups had response rates of 44.3% for male nurses, 41.8% for female nurses, 41.2% for male pediatricians, and 72.1% for female pediatricians.

The results indicated that female anesthesiologists, nurse-anesthetists and operating room nurses and technicians in the operating room-exposed group (exposure during first trimester of pregnancy and the preceding year) were subject to a statistically significant risk of spontaneous abortion, 1.3-2 times that of unexposed personnel. It was also found that there was evidence of an increased risk of congenital abnormalities among the live-born babies of exposed female respondents in the survey. An intragroup analysis of the children of the exposed nurse-anesthetists compared with the unexposed members of this group indicated an increase in congenital abnormalities of more than 60% ($P<0.01$) in the former group. The exposed female anesthesiologists showed a two-fold increase in congenital abnormalities in their children compared with the unexposed female physician anesthesiologists and female pediatricians ($P=0.13$ and 0.07, respectively). There was also an increase of 25% in the incidence of congenital abnormalities for children of the wives of exposed physician anesthesiologists ($P=0.04$).

The authors [12] reported that the collected data suggested an increased occurrence of cancer in the exposed female respondents compared with those in unexposed control groups. The increases ranged from approximately 1.3 to somewhat less than two-fold, with $P = 0.05$, 0.01, and 0.07 for the anesthesiologists, the nurse-anesthetists, and the operating room nurses and technicians, respectively. Analyses by type and location of tumor indicated that, with the exception of leukemia and lymphoma, there was no significant difference as to the location or type of malignancy. The increased incidence of cancer was not found in exposed male respondents. Hepatic disease was reported more frequently in the exposed

female respondent groups than in the unexposed controls (even after excluding serum hepatitis). The range of increase was approximately 1.3- to 2.2-fold, with P values of 0.04, <0.01, and 0.08 for the three group comparisons. A statistically significant increase in hepatic disease was reported by the exposed male anesthesiologists compared with the male pediatricians (P<0.01). The exposed female groups reported higher rates of renal disease (pyelonephritis and cystitis excluded) ranging from 1.2- to 1.4-fold in magnitude (P = 0.28, 0.01 and 0.05 for the female physicians, nurse anesthetists, and operating room nurses, respectively). No increased risk of renal disease for male physician anesthetists was observed.

Among general practitioner dentists and oral surgeons, it was reported that 20.2% and 74.8%, respectively, of the respondents had anesthetic exposures (type and levels not given) exceeding 3 hours/week. Results were analyzed according to the anesthetic exposure of the dental respondent. Respondents who reported that they worked in dental surgery with anesthetics a minimum of 3 hours/week during the calendar year preceding their spouse's pregnancy were separated from those who reported no exposure to anesthetics. Individuals with intermediate exposure (less than 3 hours/week) were not included in the analysis. In the analysis for cancer, liver, and kidney disease among the dental respondents, exposure to anesthetics was defined as at least 1 year of exposure, but not necessarily including the immediate year before onset of the disease. Respondents from both dental groups were combined into single exposed and unexposed groups since the effects of exposure to anesthetic gases proved to be similar.

For the dental portion of the study [13], the investigators found that the incidence of spontaneous abortion was increased about 78% (P<0.01)

in the wives of exposed dentists compared with the spouses of unexposed dentists. Congenital abnormality rates appeared to be slightly higher in the children of wives of exposed dentists than in the children of persons in the unexposed control group. Although the differences were not statistically significant, the children of women in the exposed group showed a 15% increase in fetal abnormalities over those found for the children of the unexposed dentists' wives. The of cancer incidence (35%) in the male respondents appeared higher in the exposed group than in the control group. The sample sizes were small and the authors concluded that the difference was not statistically significant.

The incidence of liver disease, calculated after excluding cases of serum hepatitis to eliminate possible differences in exposure to blood and blood products, increased 156% in the exposed group compared with that of the unexposed control group [13]. This difference was highly significant ($P<0.01$). There were no noteworthy differences in incidence of kidney disease between the two groups.

A questionnaire survey of members of the German Anesthesia and Reanimation Association was reported by Garstka et al [77] in 1974 to clarify whether there was an increased incidence of certain complications during pregnancy among anesthesiologists. Of the 877 questionnaires mailed, 257 replies were usable. The authors formed the following groups in evaluating the replies: Group A, pregnancies in exposed female anesthesiologists; Group B, pregnancies in women married to exposed anesthesiologists; Group C, pregnancies in exposed married anesthesiologist couples plus groups A and B; Group D, pregnancies before exposure of individuals in group C. They found a significant difference

($P < 0.05$) in abortion frequency between pregnancies in group A (17.9%) and those in group D (10.6%). They also compared the abortion frequency of the exposed female anesthesiologists (17.9%), which they noted to be relatively high, compared with national German and United States statistics (not age-adjusted) of 13.5 and 15%, respectively, but drew no conclusions. The authors stated that their study agreed with the ASA Ad Hoc Committee study [12] in that there was no increased frequency of abortion in wives of exposed anesthesiologists.

The authors [77] also reported premature births in 19.7% of the pregnancies of exposed female anesthesiologists and concluded that such a rate was high. In regard to pregnancy complications (not defined by the authors), they reported a statistically significant difference ($P<0.05$) between complications among exposed female anesthesiologists (8.0%) compared to group D (1.5%). They agreed with the ASA Ad Hoc Committee findings [12] which reported a higher malformation incidence in the children of female anesthesiologists but did not find an increase in malformations in the children of the wives of exposed anesthesiologists (group B). Garstka et al [77] noted that the anesthesiologists who had given birth to malformed babies had been exposed to halothane for an average of 20 months before the start of their pregnancies and for 6-7 months during the pregnancies in question. Data on concentration levels were not presented.

In 1972, Uhlirova and Pokorny [78] conducted a questionnaire survey of 857 workers (200 male and 657 female physicians, nurses, and technicians) in the anesthesiology and resuscitation (operating and recovery rooms) divisions in Czechoslovakia to determine occupationally

related health problems. The survey was of a preliminary nature and aimed at obtaining fundamental information. The authors [78] stated that control groups were not used but would be created for future studies. Workers were divided into those with less than 1 year of service, less than 5 years of service, and more than 5 years of service. As work experience in the field increased, the number of workers reporting problems increased. Increased incidences of headache, excessive fatigue, and allergic diseases were reported to be directly proportional to work experience in anesthesiology. An increasing trend of spontaneous abortions was reported in those with more than 5 years of service (8.1%) compared with those with less than 5 years of service (4.8%). The authors also reported an increase in parenchymal damage in the liver, in kidney dysfunction, and in hematologic disorders in the respondents commensurate with the length of service. Anesthetic agents or exposure levels were not identified.

Wyatt and Wilson [79] published the results of a limited survey to determine the sex ratio of children of anesthetists. All anesthetists of registrar grade or above in the Sheffield Hospital Region were asked to complete a postal questionnaire giving their age and sex, the date they started regular anesthetic practice, and the sex and dates of birth of their offspring. A total of 117 questionnaires (75%) were answered and of these, 21 respondents were childless and 9 were women in regular anesthesia practice. The remainder (87) were men in regular anesthesia practice whose wives had 157 live-born children. Of these children, 56.8% were females compared with 48.6% females for the Sheffield Region or England and Wales. The authors concluded that the difference was significant ($P<0.05$).

A questionnaire survey of 7,949 physicians was conducted in the United Kingdom by Knill-Jones et al [80] to determine whether there was a relationship between operating room exposures and abnormalities in the obstetric history of the respondents. The 5,507 usable replies were given by anesthetists (26%), surgeons (9%), radiologists (1%), other hospital staff (17%), nonhospital physicians (39%), and others (8%). The investigators reported there was no apparent influence of paternal exposure on the frequency of spontaneous abortion (exposed 11.1%, not exposed 10.9%). However, maternal exposure was associated with an abortion frequency of 15.5% compared with 10.9% where neither parent was exposed. The apparent effect of maternal exposure was highly significant ($P<0.01$). Exposure had no obvious effect on the average length of gestation prior to abortions: no exposure, 11.2 weeks; father exposed, 10.9 weeks; mother exposed, 11.2 weeks. Female exposure in the first pregnancy was associated with a 16.1% frequency of abortion compared with 7.7% when there was no exposure ($P<0.001$). The corresponding values for the second pregnancy were 11.2 and 9.2%, respectively, a difference which was not statistically significant.

Congenital abnormalities were described as major (life threatening, resulting in either major surgery or serious disability) and minor. Male exposure and nonexposure were associated with similar frequencies of major abnormalities (1.08% vs 1.05%). Female exposure was associated with a frequency of 1.59% for major abnormalities, although this represented only seven children. There was an increase in minor abnormalities in children of exposed males, 3.09%, compared with those of nonexposed male parents, 2.35% ($P<0.02$). Female exposure to anesthetic gases was associated with a

frequency of 3.19% in minor abnormalities in children but this represented only 14 children. The frequency of reporting of all abnormalities (including some which could not be classified as major or minor) in exposed females was 5.5% compared with 3.6% in nonexposed pregnancies ($P<0.05$). However, the abnormality rate of 4.5% associated with male exposure was significantly higher than in the nonexposed group rate of 3.6% ($P<0.05$). When either parent had been exposed during the pregnancy, there were 63 stillbirths out of a total of 6,414 births (0.98%) compared with 59 out of a total of 7,296 (0.80%) for nonexposed parents. The difference was not statistically significant.

Parental exposure had no apparent effect on the frequency of perinatal death of children (1.85% for both exposed and nonexposed groups), or on the frequency of cancer or leukemia in children (exposed, 0.20%; non-exposed, 0.26%). Among males, there were 117 (9.7%) anesthetists, 132 (10.6%) other hospital physicians, and 234 (10.8%) physicians not working in hospitals who reported involuntary infertility. There was no significant difference between the exposed and nonexposed groups of males concerning involuntary infertility.

The authors [80] also matched the pregnancies for maternal smoking habits, birth order, and maternal age at the time of birth. Of all pregnancies in which male exposure had occurred, 4,074 (69.2%) were matched successfully with pregnancies where there was no male or female exposure. For these matched groups, there was no significant difference in the frequency of spontaneous abortion between the exposed group (10.6%) and the nonexposed group (9.8%). A 4.5% frequency of all types of congenital abnormalities in the exposed group was significantly greater than the 3.2%

reported by the nonexposed group ($P<0.01$), and this was explained largely by an increase in the reporting of minor congenital abnormalities by the exposed group. Exposure had no effect on the stillbirth rate. All the pregnancies in exposed females were matched by maternal smoking habits, birth order, maternal age at the time of birth, and paternal age at the time of response (both ages within 2 years). There was a striking difference in the frequency of spontaneous abortion in the exposed group (14.9%) compared with the nonexposed group (5.5%) ($P<0.001$). The exposed group had a significantly greater frequency of all types of congenital abnormalities, attributable to increased reporting of both major and minor abnormalities. However, in this analysis, the total number of anomalies was small.

To increase the size of the control group, the authors [80] also matched each exposed pregnancy with two control groups; 73.8% of the pregnancies were matched successfully. These analyses also showed that a clear increase in the frequency of spontaneous abortion was associated with female exposure. However, there was no significant difference in the frequency of congenital abnormalities.

The authors [80] concluded: (1) matched and unmatched data showed that there was an increased frequency of congenital abnormalities in liveborn children of exposed men, but this was attributable to an increase in the frequency of minor abnormalities as the authors defined them; (2) the present data confirmed their earlier findings [74] that female exposure was associated with an increased frequency of spontaneous abortion; and (3) the results of their earlier survey [74] suggested a possible increase in the frequency of congenital abnormalities associated with maternal

exposure, but the present data did not support this, except for a possible increase in the reporting of minor congenital abnormalities. Types of anesthetic agents and exposure levels were not presented by the authors.

Animal Toxicity

(a) Acute Effects

The acute effects of exposure to chloroform and trichloroethylene were presented in the NIOSH documents Criteria for a Recommended Standard...Occupational Exposure to Chloroform [81] and Criteria for a Recommended Standard...Occupational Exposure to Trichloroethylene [82]. A number of studies have shown that chloroform causes fatty infiltration and necrosis of the liver [83-89] and fatty degeneration and necrosis of the convoluted tubules in the kidney [83,90]. Inhalation studies using trichloroethylene showed it to be less hepatotoxic than chloroform, causing mild fatty degeneration of the liver [84,91,92].

Green [93] exposed 30 Sprague-Dawley and 18 Long-Evans rats to a 70% nitrous oxide (700,000 ppm)/20% oxygen/10% nitrogen mixture or to air (control) for 8 days. White blood cell and differential counts were determined, along with analyses for RNA and DNA of bone marrow and thymus. The exposed Long-Evans rats showed a 25% decrease in white blood cell count with a predominance of lymphocytes in the differential count compared to controls. No change was seen in white blood cell or differential counts of the Sprague-Dawley rats. There was a moderate alteration in the RNA/DNA ratio in the Long-Evans rats, while only a small effect was seen in the Sprague-Dawley rats.

Hughes and Lang [94] observed hepatic necrosis in guinea pigs following repeated administration of halothane. Seventy female Dunkin-Hartley guinea pigs were randomly divided into seven groups of 10 animals each. Two groups were used as controls with one group breathing room air and the second group breathing 100% oxygen. The five experimental groups (50 animals) were anesthetized one to five times for 1 hour each using 1% (10,000 ppm) halothane with oxygen. Five guinea pigs from each group were killed immediately after the last period of anesthesia; the remaining five were killed a week later. Blood samples were measured for SGPT and SGOT, total LDH, and isoenzyme fractions.

Total leukocyte counts, differential counts, SGPT, SGOT, and total LDH showed no significant differences between any of the groups [94]. Eosinophilia or lymphocytosis were not found. Seven of the anesthetized animals showed focal hepatic lesions visible by light microscopy while no similar lesions were observed in any control animals. Both the number of animals with lesions and the severity of the lesions increased with the number of times the animals were anesthetized. Animals with one to three anesthesia administrations showed early hepatic necrosis. These lesions, which radiated from the central vein along the hepatic cord, showed swollen hepatic cells with basophilic cytoplasm and shrunken nuclei which were irregularly shaped and without nucleoli. Animals anesthetized four to five times showed more lesions, characterized by degenerating hepatocytes, mononuclear cells, and cellular debris. These lesions were located around the central vein and extended into the lobule. Larger areas of necrosis were usually seen in the midzonal regions. Electron microscopic studies not reported.

Kosek et al [95] exposed 75 male Fischer 344 rats to methoxyflurane at 0.25% (2,500 ppm) for 1.5 hours, at 0.5% (5,000 ppm) for 3 hours, and at 0.75% (7,500 ppm) for 6 hours without the usual premedicant drugs, induction agents, or nitrous oxide. The renal damage produced by methoxyflurane was proportional to the dose of anesthetic received. One to 7 days after anesthesia, rats receiving the highest dose (0.75%) had advanced changes in the convoluted tubules. Calcium oxalate crystals were frequently found in the kidney tubules, sometimes accompanied by tubular disruptions and peritubular edema. Electron microscopic examination of kidneys of all rats receiving the high dose showed severe mitochondrial swelling and destruction in most of the proximal convoluted tubules. Four to seven days after anesthesia, the rats exposed to an intermediate dose showed normal mitochondria but an apparent increase in the number and size of dense bodies. Kidney sections of rats treated with the low dose (0.25%) of methoxyflurane appeared normal at 7 days when examined with light and electron microscopy.

(b) Chronic Effects

Chenoweth et al [96] reported on the comparative chronic inhalation toxicities of methoxyflurane, halothane, and diethyl ether on rats, guinea pigs, and rabbits. The exposure concentrations were at one-tenth the average anesthetic concentrations for dogs and humans. Animal groups were exposed 7 hours/day, 5 days/week for 7 weeks to methoxyflurane at 200 ppm, to halothane at 500 ppm, to diethyl ether at 2,000 ppm or to filtered air as a control. Each animal group consisted of 20 Wistar rats, 12 guinea pigs, and 4 rabbits (species not given), all divided equally as to sex. Food and water were withdrawn from the animals during the 7-hour exposure

period. Determinations of SGPT and SGOT levels were carried out on representative groups of rats, guinea pigs, and rabbits at the termination of exposure. Gross and histopathologic examinations and organ-to-body weight ratios were determined on all animals after they were killed at the end of the experiment. P values less than 0.01 were considered by the authors to be statistically significant.

Terminal body weight data showed a significant decrease in the female rats exposed to halothane and in male guinea pigs exposed to methoxyflurane [96]. The most noteworthy change in organ-to-body weight ratios was the significant increase of liver ratios in male and female rats exposed to halothane and in female guinea pigs exposed to halothane and methoxyflurane. No significant changes were seen in SGOT and SGPT levels. Rabbits which developed pathologic changes showed elevated SGOT and SGPT levels after exposure to methoxyflurane. Several male rats exposed to methoxyflurane had a minimal amount of focal hepatic fatty infiltration. Most guinea pigs exposed to halothane and methoxyflurane had a minimal to moderate amount of central lobular fatty infiltration in the liver and several had significant fatty infiltration. Several rabbits exposed to halothane and methoxyflurane had minimal central lobular fatty infiltration in the liver, and one rabbit exposed to methoxyflurane had a minimal amount of central lobular necrosis. Diethyl ether did not cause any noteworthy hepatotoxic responses. The authors suggested that their finding of fatty infiltration in the liver following chronic exposure to subanesthetic concentrations of halothane and methoxyflurane bears on the question of chronic toxicity to operating room workers.

In 1975, Stevens et al [61] exposed groups of 16 Sprague-Dawley rats, 16 Hartley guinea pigs, and 48 ICR mice to halothane at 15, 50, 150, and 300 ppm; to isoflurane at 150, 500, and 1,500 ppm; or to diethyl ether at 1,000 and 10,000 ppm. The animals were young and in an active phase of growth. Exposures were continuous over a 5-week period, except in the 10,000-ppm ether experiment, in which the guinea pigs and mice were killed after 20 days. In the 150-ppm halothane study, 31% of the mice and 38% of the guinea pigs died before 35 days. Control groups were treated identically except for receiving the anesthetic agent.

Halothane produced a dose-related detrimental effect on weight gain in all species. The ratio of liver-to-total body weight in the halothane and ether exposures was smallest with the lowest concentrations. No significant change in liver weight was found by the investigators [61] with isoflurane. Animals exposed to isoflurane and ether showed little or no increase in lesions compared to their controls. Livers from halothane-exposed animals developed degenerative lesions which increased in frequency with an increasing dose. Degenerative lesions in the liver included granular and vacuolar degeneration, zonal centrilobular lipidosis, focal lipidosis, and focal necrosis. A probit analysis by the authors [61] suggested that a 50% incidence of lesions would occur at 140 ppm halothane in mice and at 100 ppm in rats. Table III-3 presents the number of hepatic lesions found in exposed groups compared to their controls.

TABLE III-3

DEGENERATIVE HEPATIC LESIONS FOUND AFTER CONTINUOUS SUBANESTHETIC EXPOSURE TO HALOTHANE, ISOFLURANE, AND DIETHYL ETHER*

Anesthetic Agent	Concentration, ppm	Mice Con	Mice Ex	Rats Con	Rats Ex	Guinea Pigs Con	Guinea Pigs Ex
Halothane	300	3/77	35/38	7/32	16/16	6/25	14/15
	150		12/35		12/16		16/16
	50		9/27		5/16		16/16
	15		8/37		2/16		4/16
Isoflurane	1,500	10/65	8/31	2/24	4/16	6/21	6/16
	500		2/32		0/16		3/16
	150		3/30		0/16		3/15
Diethyl ether	10,000	0/64	4/20	0/16	0/16	1/16	2/16
	1,000		0/32		0/16		2/14

*Animals with lesions/animals available for microscopic examination;
Con = Control, Ex = Exposed

Adapted from Stevens et al [61]

Chang et al [97] exposed 10 young Sprague-Dawley rats, male and female, to low levels of halothane over 4-8 weeks. Five animals were exposed to halothane at 10 ppm, 8 hours/day, 5 days/week for 8 weeks, and five animals were exposed at 500 ppm, 8 hours/day, 5 days/week for 4 weeks. A control group of six animals was exposed to room air. The animals were killed at the end of the exposure periods and cerebral cortex tissues were examined by electron microscopy. In the group exposed at 10 ppm for 8 weeks, the authors found collapse of the neuronal rough endoplasmic reticulum and reported that ribosomes were associated only with the noncollapsed portions of the membranes. Dilatations of the Golgi complex and focal cytoplasmic vacuolation were seen in some cortical neurons.

Severe dilatation and vacuolar degeneration of the Golgi complex was found in the group exposed to halothane at 500 ppm for 4 weeks [97]. Occasional membranous degeneration of the neuronal mitochondria, coagulative necrosis of the cortical neurons, and intracellular edema of the glial cells were also reported. The investigators considered halothane to be neurotoxic under the conditions of low concentrations and chronic exposure.

Chang et al [98,99] reported ultrastructural changes found in the rat kidney and liver following chronic exposure to low levels of halothane. Twenty-four Sprague-Dawley rats, of both sexes, were divided into three groups of eight animals each. Group I was exposed to halothane at 10 ppm for 8 hours/day, 5 days/week for 8 weeks. Group II was exposed at 500 ppm for 8 hours/day, 5 days/week for 4 weeks and Group III was the control. The animals were killed at the end of the exposures and kidney and liver tissues were examined by both light and electron microscopy.

Kidney tissues, under light microscopy, [98] showed cellular injury in the proximal convoluted tubules (PCT) of animals exposed at 10 ppm and more severe damage in animals exposed at 500 ppm. The control group showed no cellular damage. Ultrastructural changes in the kidneys were more prominent and more frequently observed in the animals exposed to halothane at 500 ppm. Many epithelial cells in the PCT contained an accumulation of membranous bodies presumably linked to rapid mitochondrial degeneration. The report [98] also described an increase in lysosomes in many PCT cells, frequently fused to form dense bodies. Clusters of smooth endoplasmic reticulum, areas of focal cytoplasmic degradation, and swelling of mitochondria were occasionally found in the PCT cells.

Chang et al [99] also examined liver tissues by electron microscopy from the rats exposed to halothane at 10 and 500 ppm. The animals exposed at 10 ppm showed an increase in the matrical density in mitochondria of some hepatocytes. Animals exposed at 500 ppm showed all the changes seen in those exposed at 10 ppm as well as severe dilation of the biliary canaliculi and focal cytoplasmic degradation. No remarkable pathologic or ultrastructural changes were reported in the livers of the control animals.

(c) Metabolism Studies

Many studies substantiated and described the metabolism of volatile anesthetics by liver microsomal enzymes [50-58,63,100]. If toxic metabolites of the anesthetic agents are a prerequisite to liver damage, then studies dealing with metabolism of the agents at low concentrations (occupational) are of prime interest.

Van Dyke [101] saw an enhancement in the methoxyflurane ether-cleaving and halothane and methoxyflurane dechlorination systems when male Wistar rats were pretreated with phenobarbital, a known microsomal enzyme-inducing agent. In vivo studies were conducted by exposing the pretreated rats to methoxyflurance at 300 ppm, 7 hours/day for 10 days, and in vitro studies were conducted using a mixture of rat liver microsomes in cell supernate. A significant finding reported by the author [101] was that rats exposed only to subanesthetic doses of methoxyflurane with no phenobarbital pretreatment showed an enhanced rate of metabolism of the agent. This study was the first to indicate the possibility of low level exposure to anesthetic agents as being responsible for microsomal enzyme induction and a resultant increase in metabolism of the anesthetic.

Liebman and McAllister [102] reported an increased rate of in vitro metabolism of trichloroethylene to chloral hydrate by rat liver microsomal enzyme preparations when male Holtzman rats were pretreated with trichloroethylene at 4,000 ppm for 0.5 hour/day for 4 days. A more significant increase in metabolism was seen when the rats were pretreated with trichloroethylene at 40,000 ppm, 6 hours/day for 4 days.

Linde and Berman [103] noted the ability of subanesthetic concentrations of inhalation anesthetics to stimulate drug metabolizing liver microsomal enzymes in male Sprague-Dawley rats. The extent of drug metabolism was judged by differences in hexabarbital sleeping time between exposed and control rats. Significant reductions in hexobarbital sleeping time occurred after a single 7-hour exposure to subanesthetic concentrations of diethyl ether (16,000 ppm), isopropyl ether (8,000 ppm), fluroxene (15,000 ppm), enflurane (6,000 ppm), and isoflurane (2,900 ppm). Two 7-hour/day exposures to halothane (4,000 ppm) were necessary to produce a significant reduction in sleeping time. Neither nitrous oxide nor cyclopropane caused any decrease in hexobarbital sleeping time.

In 1972, Ross and Cardell [104] reported on the ability of repeated halothane administrations to increase the capacity of hepatic microsomal enzymes to dechlorinate methoxyflurane. Male Sprague Dawley rats were exposed to halothane at 2,500 ppm in air 7 hours/day for 7 days. The animals were then killed and their livers removed for the metabolism study. Microsomes from the halothane-treated rats demonstrated approximately 2.6 times the capacity to dechlorinate methoxyflurane than microsomes from control animals.

(d) Reproductive Effects

The effects of anesthetic concentrations of inhalation anesthetics on reproduction have been reported by many authors [105-127].

Chang et al described the effects of in-utero exposure of rat fetuses to halothane [111-113]. Eight female Sprague-Dawley rats were exposed, after conception, to halothane at 10 ppm for 8 hours/day, 5 days/week throughout pregnancy. The pups were born in a halothane-free atmosphere. An equal number of pregnant female controls were used. Four randomly chosen pups from each litter were killed within 24 hours after birth, and tissue samples from the liver, kidney, and brain were examined. The investigators examined the liver tissues by electron microscopy [111]. No ultrastructural or histologic changes were seen in the control animals. However, cellular damage was seen in the livers of pups exposed to halothane. Myelin figures, large areas of focal cytoplasmic degradation, and accumulation of lipids within the hepatocytes were found. Areas of focal necrosis were reported in more than 50% of the tissue samples. The authors [111] suggested that halothane, at the levels normally associated with occupational exposure, may be hazardous to fetal development based on demonstrated hepatotoxic effects on the fetal liver.

Chang et al [112] also examined tissue samples from the renal cortex. No significant pathologic lesions were reported in the control animal kidneys when examined with light or electron microscopy. Most of the renal lesions in the halothane exposed rats were confined to the proximal convoluted tubules (PCT). The distal convoluted tubules and glomeruli were reported to appear normal. The pathologic changes reported included a flattening or absence of basal infoldings in many PCT cells, accumulation

of large lipid droplets in many PCT cells, formation of clusters of smooth endoplasmic reticulum, an increase in lysosomes, and severe swelling of some mitochondria. The authors [112] suggested that the formation of clusters of smooth endoplasmic reticulum may represent the detoxification response of the neonatal kidney.

According to Chang et al [113], no gross anomalies were observed when neonatal brain tissues were examined following fetal exposure to halothane. However, ultrastructural study of the brain tissues revealed focal weakening and disruption of the nuclear envelope of cortical neurons, neuronal vacuolation, myelin figure formation, and occasional neuronal necrosis. The postsynaptic membrane density failed to form in many synapses. The authors [113] stated that such abnormal synaptic complexes, persisting through adulthood, could contribute to behavioral changes and poorer learning abilities.

In a 1974 report, Quimby et al [119] addressed the question of whether chronic exposure to halothane at 10 ppm would produce lasting behavioral deficits and CNS damage. The investigators exposed Sprague-Dawley rats to halothane at a concentration ranging from 8 to 12 ppm for 8 hours/day, 5 days/week. Four experimental groups were treated as follows: the first group was exposed throughout early development, from conception to 60 days of age; the second group was exposed from 60 days of age through the end of the behavioral testing period (75-105 days); the third group was exposed throughout both age periods; and the fourth group was a control. All groups were tested for behavior and learning ability at 130 and 150 days of age. The results indicated that early exposure to halothane in trace amounts apparently caused permanent learning deficits (groups one and

three). Exposure to halothane only after 60 days of age produced no behavioral deficits in learning tasks (group two). With electron microscopy, cerebral cortex tissue samples from rats exposed from conception showed evidence of neuronal degeneration as well as permanent failure of formation of the synaptic web and postsynaptic membrane density in 30% of the postsynaptic membranes. Only slight neuronal damage was evident in rats exposed to halothane as adults. The authors [119] raised the question of whether or not pregnant women should avoid chronic halothane exposure even at trace levels of 10 ppm, as a precaution against possible lasting damage to the brain of the fetus.

In 1974, Schwetz et al [120] demonstrated the effects of repeated exposures to chloroform on the rat embryo and fetal development. Pregnant Sprague-Dawley rats were exposed to chloroform at 30, 100, or 300 ppm for 7 hours/day on days 6-15 of gestation. Pregnant rats exposed at 100 ppm showed a significant increased incidence of fetal abnormalities compared to controls. There were significantly increased incidences of acaudia (taillessness), imperforate anus, subcutaneous edema, missing ribs, and delayed skull ossification. Rats exposed at 30 ppm showed significant increased incidences of delayed skull ossification and wavy ribs, but no other effects compared to controls.

Fink et al [108,109] investigated the potential teratogenicity of nitrous oxide in female Sprague-Dawley rats, presumed to be in estrus by the presence of a copulatory plug and vaginal spermatozoa. The rats were exposed on day 8 of pregnancy to nitrous oxide at 50% (500,000 ppm), 21-25% oxygen, and 25-29% nitrogen for 2, 4, or 6 days, or for a single day to 70% nitrous oxide/30% oxygen within days 5-11. After exposure, the animals

were returned to a standard cage until day 20, when they were killed, the fetuses examined, and the number of implantations plus resorptions (similar to spontaneous abortion in man) determined. The most common anomalies from exposure to 50% nitrous oxide were death and resorption of embryos and abnormalities of the vertebrae and ribs. The male/female sex ratio among the surviving fetuses was significantly smaller ($P=0.023$) than those in the controls. Exposures for a single 24-hour period within day 5 through 11 indicated that a peak incidence of malformation occurred after exposure on day 9. The skeletal abnormalities were similar to, but less marked than, those seen in animals exposed for more than 1 day.

In 1968, Basford and Fink [110] reported the exposure of female Sprague-Dawley rats in estrus to halothane at 8,000 ppm in 25% oxygen for 12-hour periods at different stages of pregnancy. Nine experimental and nine control groups were used. Experimental groups were exposed on day 6, 7, 8, 9 or 10 (9 AM-9 PM) or on day 6.5, 7.5, 8.5 or 9.5 (9 PM-9 AM). On day 20, the rats were killed and the number of fetuses and resorptions noted. Incidences of skeletal malformations in fetuses near term were significantly higher ($P<0.001$) following exposure on day 8 or 9.5 of pregnancy when compared to control groups. The authors concluded that halothane appeared to be teratogenic in rats with the degree of change varying directly with concentration and duration of exposure during a critical period.

Short periods of anesthesia with halothane were found by Smith et al [121] to be teratogenic in pregnant C-57 mice. Pregnant mice (154) were anesthetized with 1 or 1.5% halothane for 3 hours on day 12, 13, 14, or 15 of gestation or, alternatively, on 3 consecutive days in the same period.

Examination of 752 live fetuses, 675 of which were cleared for skeletal examination, showed a definite increase of cleft palate, limb hematomas, and ossification defects in the limbs of exposed animals. No cleft palate and fewer than 1% of other defects were seen in 541 control fetuses, 410 of which were cleared for skeletal examination.

Bussard et al [116] studied fetal changes in hamsters anesthetized with nitrous oxide and halothane. Pregnant hamsters (54) were divided randomly into three exposure and three control groups. Each of the experimental groups was exposed to 60% nitrous oxide with 0.6% (6,000 ppm) halothane for 3 hours on the 9th, 10th, or 11th day of gestation with controls placed in identical chambers but receiving no anesthetic. Chamber oxygen was carefully maintained at 40% for both the exposed and the control groups. Compared with controls, the number of resorptions was increased ($P<0.05$) only in those anesthetized on day 11. Statistically significant decreases were seen in fetal weight for the hamsters exposed on days 10 and 11 ($P<0.001$) and in crown-rump length for day 10 ($P<0.001$) and day 11 ($P<0.02$) compared to control groups. The ratios of female fetuses-to-total surviving fetuses were similar in exposed and in control groups.

In 1975, Doenicke et al [117] published their study in which 505 pregnant female Sprague-Dawley rats were anesthetized for 6-12 hours with various mixtures of halothane, nitrous oxide, and oxygen between days 6-10 of pregnancy. A group of exposed rats was used as controls. The abortion rates are summarized in Table III-4.

TABLE III-4

ABORTION RATES IN RATS EXPOSED TO
NITROUS OXIDE AND HALOTHANE

Anesthetic Agent	Concentration Vol %	Length of Exposure, Hours	Abortion Rate %
Halothane/nitrous oxide	0.8/25	12	44
"	0.8/25	6	30
"	1.25/25	6	39
Halothane/oxygen	0.8/100	12	50
Nitrous oxide/oxygen	75/25	12	18
"	50/50	12	7.7
"	25/75	12	10
None	-	-	15
Oxygen	100	12	21

Adapted from reference 117

The authors [117] concluded that halothane demonstrated an abortive effect directly proportional to the concentration inhaled and that nitrous oxide did not have such an effect. Although this study did not clearly establish a relationship between nitrous oxide exposure concentrations and abortion rate, neither did it rule out such a relationship.

Doenicke and Wittmann [118] reported a study in which 252 pregnant Sprague-Dawley rats were exposed to various mixtures of halothane, nitrous oxide, and oxygen to identify any teratogenic effects of the anesthetic agents. Approximately 9,000 embryos were examined for vertebral and rib anomalies. The authors concluded that they could not find an association between vertebral malformations in the embryos and the concentration of halothane to which the mothers were exposed. They did state that there was a teratogenic effect proportional to the concentration of halothane regarding costal development.

In 1973, Corbett et al [122] published the results of a study in which they exposed pregnant rats (Simmonson Laboratories) to nitrous oxide in concentrations of 0 (control), 100, 1,000 and 15,000 ppm for either 8 or 24 hours/day on various days during pregnancy. The authors found that the rats exposed at 15,000 ppm and 1,000 ppm for 24 hours/day had higher fetal death rates and lower pregnancies/rat ratios than did the controls. Also, two groups exposed at 1,000 ppm for 8 hours/day had a fetal death rate significantly higher than that of the controls. The 8-hour daily exposures did not significantly alter the pregnancies/rat ratio.

Bruce [123] exposed male and female mice of three different strains to air or to air containing 16 ppm halothane for 7 hours/day, 5 days/week for 6 weeks. Male and female animals were then paired and exposed daily to the same conditions. No significant difference was found between the exposed animals and the controls on examination for splenic weights and any histologic changes of liver, spleen and testes in the males, and the number of pregnancies, implantations/pregnancy, and resporption/pregnancy in females.

In 1976, Kripke et al [124] reported the effects of chronic exposure to nitrous oxide at subanesthetic concentrations on spermatogenesis in male rats. The study was conducted to determine what, if any, toxic effect nitrous oxide might have on dividing cells, possibly giving some indication of the teratogenic potential of the agent. The investigators exposed 135 male LEW/f Mai rats to an atmosphere of 20% (200,000 ppm) nitrous oxide, 20% oxygen, and 60% nitrogen for either 8 hours or 24 hours/day for up to 35 days. After 14 days, evidence of damage to the seminiferous tubules was found in all animals. The toxic effect appeared to be confined to the

spermatogenic cells with a reduction in the number of mature spermatozoa and the appearance of multinucleated forms. Recovery of normal spermatogenesis occurred after a return to room air for more than 3 days. Other cells within the testes were not damaged.

Kennedy et al [125] investigated the effect of halothane at anesthetic concentrations on reproduction in rats exposed before mating, on fetal development in rats and rabbits exposed during various stages of gestation, and on fetal survival in rats whose dams were exposed during late stages of pregnancy. The fertility and general reproduction studies used three control and six experimental groups of Charles River albino rats, CD strain, with at least 10 male and 20 female rats in each group. The experimental groups were exposed to halothane for 1 hour/day prior to pairing for 1-5, 6-10, or 11-15 days at mean concentrations of 1.48% (14,800 ppm), 1.34% (13,400 ppm), and 1.40% (14,000 ppm), respectively. The authors reported neither an indication of any effect on mating and fertility nor any differences in population and survival data for offspring between control and exposed groups. No gross abnormalities were observed on examination of offspring at birth and at weaning.

Teratologic studies were conducted by the same investigators [125] in rats and rabbits. Pregnant Charles River rats, CD strain, and impregnated New Zealand albino rabbits were used. In the study, 24 rats were exposed for 1 hour/day on gestation days 1-5, 12 rats on days 6-10, or 12 rats on days 11-15 to mean halothane concentrations of 1.35% (13,500 ppm), 1.43% (14,300 ppm), and 1.43% (14,300 ppm), respectively. Separate groups of 15 rabbits were exposed on gestation days 6-9, 10-14, or 15-18 to mean halothane concentrations of 2.16% (21,600 ppm), 2.16% (21,600 ppm), and

2.30% (23,000 ppm), respectively. No significant differences were reported between rat control and test groups when killed at an interim or terminal period with respect to the number of corpora lutea, implantation and resorption sites, and viable fetuses. Fetuses from rats exposed on days 11-15 showed increases in the percentages of incompletely ossified or nonossified sternum sections. In rabbits, the reactions were essentially the same as in rats. No apparent exposure-related effect was reported regarding reproductive data. Skeletal findings included incompletely ossified or nonossified sternum sections, supernumerary ribs, and thickened ribs. The authors considered these skeletal effects to be incidental and not specific drug-related structural defects.

Pregnant Sprague-Dawley rats were exposed by Lansdown et al [126] to subanesthetic concentrations of halothane to determine any effect on fetal development. Groups of eight pregnant rats were exposed to halothane at 50, 100, 200, 800, 1,600, and 3,200 ppm for 8 hours/day on days 8-12 of gestation. In a second series of experiments, groups of 8 pregnant rats were exposed to halothane at 1,600 or 3,200 ppm for 8 hours/day on days 1-21 of pregnancy. Control groups were used for each exposure concentration. All rats were killed and examined on day 22. Animals exposed at 3,200 ppm from day 1 became drowsy and failed to feed normally resulting in data from this group being excluded from the reported results. Exposure to halothane at 50-3,200 ppm on days 8-12 of gestation caused no statistically significant reduction in the mean litter size or in the fetal and placental weights. However, rats exposed at 1,600 ppm throughout pregnancy had statistically significant reductions in fetal weight and crown-rump length ($P<.001$), even though there was no reduction in placental weight. The

authors observed that maternal food intake was reduced and may have been a factor in these results. No appreciable differences between control and experimental groups were reported in the number of centers of ossification in the skull or postcranial skeleton. Several skeletal anomalies were identified in both groups but their frequency was independent of exposure.

Halothane was tested for possible mutagenicity by Baden et al [127] in an in-vitro microbial assay system using two histidine-dependent mutants of Salmonella typhimurium, TA98 and TA100. Halothane, in concentrations ranging from 0.1% to 30% (1,000 ppm to 300,000 ppm), was incubated with the bacteria in the presence or absence of a metabolic activation system prepared from either rat liver treated with Aroclor 1254 or from human liver. Trifluoroacetic acid, a major metabolite of halothane, and urine from patients anesthetized with halothane were also tested. Halothane, trifluoroacetic acid, and patients' urine were reported to have no mutagenic effect on the bacterial systems.

Several studies utilized chick embryos to determine the effects of exposure to anesthetic gases on fetal development [105-107,114,115]. Anesthetic agents used in the chick embryo exposure studies included methoxyflurane, halothane, fluroxene, diethyl ether, nitrous oxide, and cyclopropane. The exposure concentrations were very high compared to those in other animal studies and, in some cases, exceeded the levels normally used in clinical anesthesia. The value of these studies may be limited to an indication of gross effects or of increasing trends of abnormal fetal development resulting from such excessive exposures. Major effects seen in the chick embryos included a death rate among exposed chicks higher than in controls, a significant increase in fetal anomalies, a reduction of the

neural tube mitotic index, and a decreased growth rate.

(e) Carcinogenicity

The carcinogenicity of specific inhalation anesthetic agents, ie, chloroform and trichloroethylene, has been identified. Eschenbrenner [128] in 1945 reported the effects of repeated oral doses of chloroform on induction of hepatomas in mice. Hepatomas were produced in 7 of 10 female mice fed 30 doses of 600 or 1,200 mg/kg at 4-day intervals over a 4-month period. Male mice receiving similar doses died within the first week of the experiment.

The National Cancer Institute (NCI) released results of the chloroform carcinogenicity bioassay program in March 1976 (Report on Carcinogenesis Bioassay of Chloroform, National Cancer Institute, March 1, 1976). Osborne-Mendel rats were fed chloroform in corn oil (at 90 and 180 mg/kg body weight for males and at 100 and 200 mg/kg for females) for 111 weeks. A significant increase in epithelial tumors of the kidneys in treated male rats was observed. Of the 13 tumors of renal tubular cell epithelium seen in 12 of the 50 high-dose male rats, 10 were carcinomas and 3 adenomas; 2 of the carcinomas were found to have metastasized. Two carcinomas and two adenomas of renal tubular epithelium were observed in the 50 low-dose male rats. The tubular cell adenocarcinomas were widely metastasized. An increase in thyroid tumors in chloroform-treated female rats was also seen which NCI did not consider significant.

In the same bioassay, mice (B6C3F1) were fed chloroform for 92-93 weeks at doses of 138 and 277 mg/kg for males and at 238 and 477 mg/kg for females. A highly significant increase in hepatocellular carcinomas was observed in both sexes of treated mice when compared with control animals.

The incidence of hepatocellular carcinoma was 98% for males and 95% for females at the high dose, and 36% for males and 80% for females at the low dose compared with 6% in both matched and colony control males, none in matched control females, and 1% in colony control females. Nodular hyperplasia of the liver was observed in many of the male mice fed low doses that had not developed hepatocellular carcinoma. A bulletin on chloroform was released by NIOSH in March 1976 to alert the occupational health community of these findings (J Finklea, written communication, March 15, 1976).

In 1975, Lloyd et al described information released by the NCI [129] about the carcinogenicity of trichloroethylene in rats. Male and female rats (Osborne-Mendel) and mice (B6C3F1) exposed by gastric intubation were used in the study. Both sexes of rats were given doses at either 1,000 mg/kg or 500 mg/kg, 5 times/week for 18 months, with an observation period of 6 months following exposure. Male mice were given 2,400 or 1,200 mg/kg and female mice 1,800 mg/kg or 900 mg/kg doses 5 times/week for 18 months, followed by an observation period of 3 months. Hepatocellular carcinomas were not seen in the rats; 30 of the 98 (30.6%) mice given the low dose, and 41 of the 95 (43.2%) mice given the higher dose had hepatocellular carcinomas. Only 1 (2.5%) of the 40 control mice developed a carcinoma. Various tumors also were found in other organs in the exposed mice. Although the investigators did indicate that their study results were preliminary, they expressed a definite concern about occupational and environmental exposures to trichloroethylene. Therefore, NIOSH alerted the occupational health community about the carcinogenic potential of trichloroethylene [129]. The suspected carcinogenicity of chloroform and

trichloroethylene and their limited availability for clinical use should encourage the curtailment and elimination of their use as anesthetic agents. The interpretation of these results remains to be defined because the agents were administered by a route different from normal anesthetic delivery and in concentrations approximately 25 times the anesthetizing dose.

Corbett [130] reported a study in which "timed-pregnant" Swiss/ICR mice were exposed to either 0.5% isoflurane on days 12, 14, 16, and 18 of pregnancy (Group I) or to 0.1% isoflurane on days 12, 14, and 16 of pregnancy (Group II). The offspring of these two groups were then exposed to 0.1% isoflurane every other day beginning at 5 days of age for 25 exposures. Each exposure period lasted 2 hours. A control group and their offspring were exposed to room air only. The investigators found more pulmonary adenomas in the exposed groups than in the control groups, but the difference was not statistically significant. At the end of 15 months, 27% (10/37) of the males in Group I had hepatic neoplasms with three of the animals having multiple tumors. Seventeen percent (5/30) of the Group II males had hepatic neoplasms, while none were observed in the 23 male control animals. These differences were statistically significant. Hepatic neoplasms were not observed in the females of any group. The author concluded that, even though there were certain experimental design deficiencies and the results did not prove isoflurane to be a carcinogen, the data are ample to consider isoflurane as highly suspicious of being carcinogenic. On pathologic examination of the liver tissue of affected animals, Farber (written communication, September 1975) indicated that the animals showed a neoplastic process in the liver which may have been either

benign or malignant and recommended that the use and marketing of isoflurane be stopped until further tests could be conducted.

Correlation of Exposure and Effect

Early reports in the medical literature attributed adverse health effects seen among anesthetists and operating room personnel to exposure to vapors of anesthetic agents [16,18-20], and anesthetists and surgeons began implementing venting and control procedures as early as 1922 [19]. Health effects reported in 1929 among surgeons, anesthetists, and operating room nurses included headache, fatigue, and heart complaints [19]. The common anesthetics in use at that time were nitrous oxide, diethyl ether, and chloroform. A 1949 report [20] attempted to ascribe signs and symptoms of three members of a German surgical team, including fatigue, headache, lymphocytosis, eosinophilia, and electrocardiographic evidence of myocardial damage to their exposure to anesthetic vapors over periods of 4-14 years. The most relevant information on current occupational exposure is in the epidemiologic [12,13,69,72-80] and mortality studies [70,71] reported between 1967 and 1975. The epidemiologic studies, conducted among operating room and dental personnel, suffer from a lack of quantitative data on exposure levels and identification of anesthetic agents used.

In most cases, workers were exposed to a mixture of agents and possibly several different agents throughout the day. Environmental measurements [131-150] placed usual operating-room exposures at 1-10 ppm for halothane and other volatile agents, and 400-3,000 ppm for nitrous oxide. Usual dental exposures were approximately 3,000 ppm nitrous oxide, 15 ppm halothane, and 25 ppm trichloroethylene. Epidemiologic findings,

supplemented by known acute exposure effects on human and supportive animal studies, permit some correlation between anesthetic gas exposure and observed health effects. The five most commonly used anesthetic agents in the 1975 survey conducted by NIOSH were nitrous oxide, halothane, enflurane, methoxyflurane, and diethyl ether (Table XIII-10). Nitrous oxide, diethyl ether, and chloroform were the primary anesthetics used until the introduction of the fluorinated hydrocarbon anesthetics in the mid 1950's.

An increased incidence of spontaneous abortion in exposed female workers and of congenital abnormalities among their children, and the same increases among the wives and children of exposed men are the major adverse health effects identified in the epidemiologic studies. Effects on the liver, kidneys, and CNS have also been described following exposure to anesthetic gases. Increased risk of cancer is also suggested in three epidemiologic studies and one mortality study.

(a) Spontaneous Abortion

Vaisman [69] reported that 18 of 31 pregnancies in a group of Russian female anesthetists, exposed 25 hours/week or more, ended in spontaneous abortion. Nitrous oxide, diethyl ether, and halothane were the main anesthetics in use at the time of the survey. This particular survey involved a small population and had no control group, but it was the first study to identify a high incidence of spontaneous abortion among exposed women. A survey of Danish nurses and female anesthetists [72] revealed a 10% spontaneous abortion rate in pregnancies started before exposure in anesthesia practice, and a 20% spontaneous abortion rate in pregnancies started after exposure. These data allowed the first attempt at

correlating an increased incidence of spontaneous abortion with exposure to anesthetic gases. A new factor surfaced in the Danish study when it was learned that the wives of exposed anesthetists also had a higher than normal incidence of spontaneous abortion. This finding was also seen in later studies [12,13]. Table III-5 summarizes the spontaneous abortion rate data gathered from various groups occupationally exposed to anesthetic gases. Groups chosen for study were anesthetists, operating room nurses, oral surgeons, and dentists, representing the personnel most heavily exposed in a chronic manner to waste anesthetic gases.

TABLE III-5

SUMMARY OF SPONTANEOUS ABORTION RATES
FROM EPIDEMIOLOGIC STUDIES* IN PERSONNEL
EXPOSED TO ANESTHETIC GASES

Exposed Group (E)	Spontaneous Abortion Rate,% E	C	Control Group (C)	Ref.
Operating room nurses	29.7	8.8	General duty nurses	73
Female anesthetists	37.8	10.3	Female physicians	73
"	18.2	14.7	"	74
"	17.1	8.9	"	12
Nurse-anesthetists	17.0	15.1	General duty nurses	12
Operating room nurses	19.5	15.1	"	12
Wives of exposed dentists	16.0	9.0	Wives of unexposed dentists	13
Female anesthetists	17.9	10.6	Before exposure	77
Maternal exposure	15.5	10.9	Neither parent exposed	80

*Studies listed are limited to those utilizing a control group.

Several investigators have described increased rates of fetal resorptions in animals following exposure to anesthetic gases [108,109,116,117,122]. The majority of these studies used anesthetic

quantities of nitrous oxide , alone or with halothane. Significant increases in resorptions were reported [108,109,116,117] but the exposure levels greatly exceeded those normally associated with occupational exposure. In a study by Corbett et al [122], pregnant rats were exposed to nitrous oxide at levels of 15,000, 1,000, and 100 ppm, within the range of occupational exposure. The most significant increases in fetal death rate followed 8-hour exposures at 1,000 or 100 ppm on days 10-13 or 14-19 of pregnancy. Fetal death rates of 14.5-18.4% were seen among the exposed animals compared to 11.1% among controls.

(b) Congenital Abnormality

The survey by Knill-Jones et al [74] was the first to attempt a correlation between occupational exposure to anesthetic gases and congenital abnormalities in the children of exposed personnel. The incidence of such abnormalities, 6.5%, was significantly greater among children of female anesthetists who had worked during the first six months of pregnancy than in the children of those who had not worked during this period, 2.5% ($P<0.02$). Care must be taken in interpreting these results as the control group had a congenital abnormality incidence of 4.9%. The greatest value in the study [74] is that a health effect was seen in the most heavily exposed persons, the anesthetists, while exposed, but was reduced in the same group when not exposed. The same trend was seen by Corbett et al [76] when they surveyed a group of nurse-anesthetists. Out of the total number of births in the survey, the mothers worked at some time during 62.4% of the pregnancies, and did not work during 37.6% of the pregnancies. The rate of congenital abnormalities among children of mothers who worked during pregnancy was 16.4%, while the rate of such

abnormalities among children of mothers who did not work during pregnancy was 5.7%. The difference was statistically significant ($P<0.005$). The incidence of birth defects in the general population, 8.4%, was used as a control value. Epidemiologic studies that followed [12,13,80] also identified a higher than normal incidence of congenital abnormalities among the children of personnel exposed to anesthetic gases. A summary of these data is presented in Table III-6. The studies indicate a trend toward higher rates of congenital abnormality among the children of exposed personnel but, once again, no direct causal relationship between the effect seen and extent of exposure to anesthetic agents can be drawn.

TABLE III-6

SUMMARY OF CONGENITAL ABNORMALITY RATES FROM EPIDEMIOLOGIC STUDIES* IN PERSONNEL EXPOSED TO ANESTHETIC GASES

Exposed Group (E)	Congenital Abnormality Rate,% E	C	Control Group (C)	Ref.
Female anesthesiologists	5.9	3.0	Female pediatricians	12
Nurse-anesthetists	9.6	7.6	General duty nurses	12
"	9.6	5.9	Unexposed nurse-anesthetists	12
Wives of exposed dentists	4.7	4.1	Wives of unexposed dentists	13
Maternal Exposure	5.5	3.6	Neither parent exposed	80
Paternal Exposure	4.5	3.6	"	80

*Studies listed are limited to those utilizing a control group.

The teratogenic potential of specific anesthetic agents has been demonstrated in several animal exposure studies [105-116,118,120,121]. Exposing pregnant rats and mice to halothane and nitrous oxide at levels

well above those encountered in an occupational environment resulted in significant developmental anomalies in the offspring [108-110,118,120,121]. While these studies establish the teratogenic potential of halothane and nitrous oxide at high levels, they do not permit a correlation between occupational exposure and congenital malformation. Reports by Chang et al [111-113], attempted to duplicate occupational exposure conditions by exposing pregnant female Sprague-Dawley rats to halothane at 10 ppm for 8 hours/day , 5 days week throughout pregnancy. Liver, kidney, and brain tissues from the offspring were examined for anomalous development. Focal cytoplasmic degradation and areas of necrosis were reported in 50% of the liver tissues [111]. Damage to the proximal convoluted tubules was observed when kidney tissues were examined [112]. Ultrastructural examination of the neonatal brain tissues [113] revealed several anomalies, including occasional neuronal necrosis and failure of the postsynaptic membrane density to form. The anomalies seen after exposure to halothane at 10 ppm were not as immediately visible as the rib and vertebral malformations occurring after exposures at higher levels, yet they do establish a teratogenic effect following exposure at levels encountered in an occupational situation.

(c) Liver and Kidney Effects

Hepatic dysfunction and massive hepatic necrosis have been documented in patients following clinical anesthesia [21-32]. These cases involved exposure conditions completely different from those of occupational exposure. Occupational exposure has been suggested as the cause of two cases of hepatic dysfunction [151,152] in anesthetists, but substantial proof was not provided.

Effects on the liver and kidneys have been reported in three epidemiologic studies following occupational exposure to anesthetic gases [12, 13, 78]. Exposure in two of the studies [12,13] was defined as at least 1 year's duration but not necessarily the year immediately before onset of the signs and symptoms. Hepatic disease, excluding serum hepatitis, was reported more frequently in exposed female operating room personnel than in unexposed controls. Table III-7 summarizes the hepatic disease rate in various exposed groups in the US [12,13]. A survey of anesthetists and operating room nurses [78] in Czechoslovakia revealed a trend toward an increased rate of hepatic disease with increased length of service and, presumably, increased exposure. The only control utilized by the Czechoslovakian survey was the group of exposed personnel with less than 1 year of service.

TABLE III-7

SUMMARY OF HEPATIC DISEASE RATES FROM EPIDEMIOLOGIC STUDIES* IN PERSONNEL EXPOSED TO ANESTHETIC GASES

Exposed Group (E)	Hepatic Disease Rate,%		Control Group (C)	Ref.
	E	C		
Female anesthesiologists	4.9	2.9	Female pediatricians	12
Female nurse-anesthetists	3.8	1.7	General duty nurses	12
Operating room nurses	2.1	1.7	"	12
Male anesthesiologists	4.1	2.6	Male pediatricians	12
Male nurse-anesthetists	4.7	5.1	Male nurses	12
Male operating room nurses	4.2	5.1	"	13
Exposed male dentists	5.9	2.3	Unexposed male dentists	13

*Studies listed are limited to those utilizing a control group.

Possible toxic damage to the kidneys following methoxyflurane anesthesia has been described [34-39] but, once again, the exposure conditions were different from occupational exposure. The same three surveys discused above [12,13,78] examined the incidence of kidney disease among exposed personnel. Among the US personnel surveyed [12,13], only the exposed female groups reported rates of renal disease higher than those among controls. The nurse -anesthetists showed the most statistically significant rate increase. Kidney damage reported in the Czechoslovakian study [78] showed only a small increase consistent with increased length of service.

Adverse effects on the liver and kidneys have occurred in animals following exposure to anesthetic agents at levels near or equal to those needed to produce anesthesia [83-90,93,94]. The value of these studies is that they demonstrate effects on the liver and kidneys after high-level exposures and raise the question of the same effects following exposure to levels associated with an occupational environment. Animal studies attempting to investigate the effects of chronic low-level exposure to various volatile halogenated anesthetics have shown minimal to moderate toxicity to the liver and kidneys [61,96,98,99]. Exposure studies, using the range of occupational exposure for volatile agents of 1-10 ppm, reported only slight damage in liver and kidneys on ultrastructual exami nation. More readily apparent were the organ lesions seen at higher levels, 500 ppm and above; such levels were not found in an occupational environment. Situations such as the anesthesia induction period may produce levels of halogenated anesthetics high enough to be a factor in the reported increased incidence of liver and kidney diseases in exposed personnel.

(d) Central Nervous System Effects

Anesthetic agents act on the CNS by producing narcosis. Two epidemiologic studies have suggested CNS effects in exposed personnel [69,78] who reported an increased incidence of headache, fatigue, irritability, and disturbance of sleep. Damage to cerebral cortical neurons was seen following the exposure of young adult rats to halothane at 10 ppm for 8 hours/day, 5 days/week for 8 weeks [97]. Permanent learning deficits and neuronal damage was seen in rats exposed to halothane at 8-12 ppm, 8 hours/day, 5 days/week from conception to 60 days of age [119]. Exposure of pregnant rats to halothane at 10 ppm, 40 hours/week throughout pregnancy produced ultrastructural anomalies in cerebral cortical neurons in the offspring [113]. Neuronal damage and learning deficits diminished when exposure to halothane was begun at a progressively increasing age of the exposed animals [119], suggesting that the developing fetus may be most susceptible to permanent CNS damage as a result of exposure to anesthetic gases.

(e) Carcinogenicity

A retrospective mortality study among members of the American Society of Anesthesiologists [70] and an epidemiologic survey of a group of nurse-anesthetists [75] have raised the question of a possible increased incidence of cancer among persons occupationally exposed to anesthetic gases. A prospective mortality study did not substantiate the increased malignancy rate among the ASA members [71]. The range of age at diagnosis (27-62), the year in which anesthesia practice began (1926-1968), and the year of diagnosis (1935-1971) have raised a question as to the significance of the nurse-anesthetist study [75]. However, a more recent epidemiologic

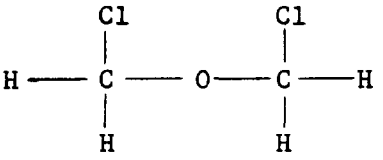
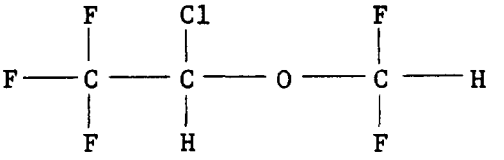
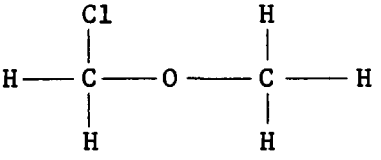
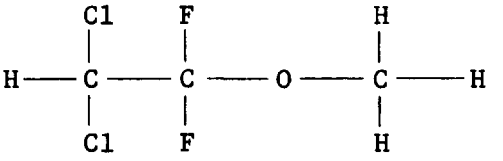
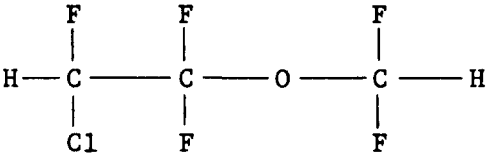
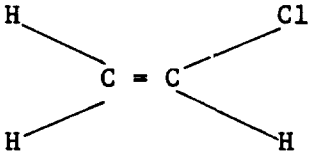
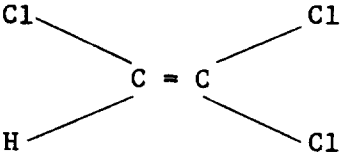
study involving a large population of exposed (7,136) and unexposed (6,560) female hospital personnel [12] has indicated that there is a significant increased occurrence of cancer in exposed females compared with unexposed controls. The increases ranged from approximately 1.3- to 1.9-fold, with probabilities of 0.05, < 0.01, and 0.07 for the female anesthesiologists, nurse-anesthetists, and operating room nurses, respectively. The increased occurrence of cancer was not observed in exposed males.

The carcinogenic potential of chloroform, trichloroethylene, and isoflurane has been demonstrated at levels well above those considered to be occupational exposures [128-130, Carcinogenesis Bioassy of Chloroform, NCI, March 1976]. This does not mean that a correlation could not be drawn between exposure at occupational levels to these agents, or any other anesthetic agents, and an increased incidence of cancer in exposed persons.

Structural similarities exist between some known human carcinogens and several inhalation anesthetic agents. Chloromethyl methyl ether and bis(chloromethyl) ether were predicted by Van Duuren [153] to be carcinogenic and later identified as being responsible for an outbreak of lung cancer among industrial workers exposed to bis(chloromethyl) ether [154,155]. Some halo-ether anesthetics have structures similar to these chlorinated ethers. Trichloroethylene is structurally similar to vinyl chloride, a known carcinogen [156,157]. Table III-8 demonstrates the structural similarities between the known human carcinogens and several inhalation anesthetics. No conclusions can be drawn, nor are they intended to be, from the presentation of these elementary structural similarities.

TABLE III-8

STRUCTURAL COMPARISON OF SEVERAL KNOWN HUMAN CARCINOGENS
WITH CERTAIN INHALATION ANESTHETIC AGENTS

Human Carcinogens	Inhalation Anesthetics
	
Bis(chloromethyl)ether	Isoflurane
	
Chloromethyl methyl ether	Methoxyflurane
	
	Enflurane
	
Vinyl chloride	Trichloroethylene

Adapted from reference 130

Summary Tables of Exposure and Effect

The effects of exposures on humans to inhalation anesthetics that e presented in Chapter III are summarized in Table XIII-14. The effects of short- and long-term exposures on animals to inhalation anesthetics are summarized in Table XIII-15.

IV. ENVIRONMENTAL DATA AND BIOLOGIC EVALUATION OF EXPOSURE

Inhalation Anesthesia Techniques and Sources of Waste Anesthetic Gases

The principal source of waste anesthetic gases in the unscavenged operating room is the intentional outflow or discharge from the anesthetic breathing circuit. The magnitude of this source depends on a number of variables, the major ones being the breathing circuit used to administer the gases and the flow rates and concentrations of the gases used. After effective scavenging techniques have been applied, other sources of leaks from the anesthesia equipment and anesthetist work practices are considered to be primary sources of waste anesthetic gases.

Inhalation anesthetic breathing circuits can be divided into those that absorb carbon dioxide exhaled by the patient and those that do not [1,158]. These two major classes are further subdivided based on the physical characteristics of the breathing circuits, such as rebreathing and access of the pulmonary system to the atmosphere. The breathing system classes are outlined in Table XIII-6.

In systems without carbon dioxide absorption, the open drop and insufflation techniques are the most difficult to control from a waste gases standpoint. In the open drop method, a volatile anesthetic agent is dropped onto the surface of a gauze-covered metal mask where the agent is volatilized, diluted, and drawn into the lungs of the patient on inhalation. With the insufflation technique, an anesthetic mixture is introduced into the patient's naso- or oropharynx and delivery is completed upon inhalation. High gas flow rates are often required because of

dilution of the anesthtic agent by room air.

The Mapleson-type systems are represented by a number of breathing circuits, the most common being the Magill and Ayre's T-piece. The Magill system provides the patient with fresh gases and the expired gases pass out of an expiratory valve. If the patient's respiration is spontaneous and an adequate amount of fresh gas is supplied, the Magill system could be regarded as a nonrebreathing system.

The T-tube apparatus has its greatest application in pediatric anesthesia, since circuit resistance and dead space are minimal. Gases from an anesthetic gas machine flow into a T, where they are inhaled through one branch and exhaled through the other. Rebreathing is reduced by a high flow of gases. The system has been modified (Summer's modification) to include a reservoir bag for assisted inspiration and partial rebreathing. Although this technique discharges all exhaled gases to the atmosphere at flows of 3-10 liters/minute, efficient scavenging methods have been developed. Nonrebreathing or nonreturn systems deliver only fresh gas to the patient during inspiration and are equipped with a nonreturn valve. Self-administration of an anesthetic agent is a common practice in hospital labor rooms and makes use of a nonrebreathing system.

The group of breathing circuits that have carbon dioxide absorption include the to-and-fro system and the circle system, both of which deliver exhaled gases from the patient to a soda-lime absorber for carbon dioxide absorption and back to the patient. In the circle system, the gases are passed through tubing before being returned to the patient. Both the circle and to-and-fro systems are used in a closed or semiclosed manner, depending on whether the expiration valve is closed or open. The

absorption system's disadvantage is that, at low flow rates of fresh gases, it is difficult to determine the concentrations of anesthetic and oxygen being delivered to the patient. However, the majority of inhalation anesthesia is administered by a semiclosed, circle carbon dioxide absorption system.

All of the breathing systems described above require the use of numerous components such as valves, connections, and tubing which are potential sources of gas leakage if not properly maintained and tightly connected. Ill-fitting face masks and improperly inflated endotracheal tube cuffs are significant leak sources. Mechanical ventilators, which are frequently used during prolonged surgical procedures to assist respiration, are also major leak sources which must be controlled. Finally, the waste anesthetic gas scavenging system itself, if improperly designed, installed, or maintained, may be a source of gas leakage [159].

Environmental Concentrations and Sampling and Analysis Methods

Analytical methods used to determine concentrations of anesthetic gases and vapors have included the manometric method of Van Slyke and Neill [160,161], the combustion method of Hirsch and Kappus [19], several gas chromatographic methods [162-166], and several infrared spectrophotometric methods [167-169]. Gas chromatographic and infrared analyses are the two major analytical methods used in the reporting of environmental concentrations presented below.

(a) Without Anesthetic Gas Scavenging

Anesthetic gas concentrations in rooms not equipped with gas scavenging may be influenced by a number of factors including the types and

concentrations of anesthetic gases used, type of anesthetic breathing system, method of anesthetic administration (face mask versus endotracheal tube), room air movement, and operating room configuration.

The first quantitative data on the concentration of inhalation anesthetic agents in operating room air were published by Hirsch and Kappus [19] in 1929. The investigators used a combustion method which they had developed to measure the levels of ether in several operating rooms during surgical procedures. Measured air samples were burned over incandescent copper oxide and the quantity of carbonic acid produced was determined titrimetrically. Ether levels ranged from 10 to 100 ppm prior to any attempt to remove the waste ether vapor.

Detailed measurements of occupational exposure of operating room personnel to anesthetic gases were reported by Linde and Bruce [131] in 1969. In their study, 104 air samples from 21 operating rooms were collected by drawing air into glass syringes with subsequent analysis using gas chromatography (minimum detectable limit: 20 ppm nitrous oxide, 0.5 ppm halothane). Nitrous oxide and halothane were administered during the surgical cases sampled, with the anesthesic machine discharge valve usually in the open position. These investigators found peak concentrations of 27 ppm halothane and 428 ppm nitrous oxide. The overall average concentrations of all measurements in all operating rooms sampled were 130 ppm nitrous oxide and 10 ppm halothane. Anesthetic gas concentrations were found to be fairly uniform throughout the rooms sampled.

In 1970, Askrog and Peterson [132] reported average concentrations of 85 ppm halothane and 7,000 ppm nitrous oxide in the breathing zone of anesthesiologists when a nonrebreathing system was used. Also in 1970,

Hallen et al [133] reported measurements of halothane in the operating room in which nonrebreathing techniques with a face mask were used during all measurements. Total anesthetic gas flows ranged from 5 to 6 liters/minute with 0.25-1.5 vol% halothane. Breathing zone samples were collected in polyvinylidene chloride sample bags and analyzed by gas chromatography using a flame ionization detector (minimum detectable limits were not given). These researchers found halothane concentrations of 0-28 ppm at distances greater than 25 cm from the gas discharge point (probably representative of anesthetist exposures) with a mean of 8.0 ppm. Values as high as 290 ppm of halothane were found near the gas discharge point. These investigators found a relatively uniform distribution of halothane throughout the operating room.

In 1971, Corbett and Ball [134] reported levels of methoxyflurane ranging from 2 to 10 ppm in the breathing zone of anesthetists and 1-2 ppm in the breathing zone of surgeons. Studies of halothane exposures showed similar concentrations as those found for methoxyflurane for both anesthetists and surgeons. The investigators also measured nitrous oxide exposures and found values ranging from 330 to 9,700 ppm in the breathing zone of the anesthetists and 310 to 550 ppm near the surgeons.

Corbett et al [135] also measured exposures of operating room personnel to trichloroethylene. With a nonrebreathing system administering trichloroethylene at 0.25-1.0% with a flow of 9 liters/minute in an operating room equipped with a nonrecirculating air-conditioning system, the concentrations in the vicinity of the surgeons ranged from 0.3 to 1.5 ppm. All samples were collected in glass syringes and analyzed by gas chromatography using a flame ionization detector (minimum detectable concentrations: 10 ppb).

Whitcher et al [136] noted halothane levels present in the operating room during the use of both nonrebreathing (10 liters/minute) and semiclosed circle (4-5 liters/minute) anesthesia systems using 1% halothane. Atmospheric samples were collected through polyethylene tubing at nine different locations reflecting concentrations in the vicinity of the anesthesia machine (ie, anesthetist's exposure) and at four distant positions representative of other operating room personnel exposures. Samples were analyzed using a quadripole mass spectrometer. Concentrations of halothane in the vicinity of the gas machine averaged 8.69 ppm (SE $\pm$ 0.91 ppm) using a nonrebreathing system and 4.93 ppm (SE $\pm$ 0.96 ppm) using a semiclosed circle system. Nonrecirculating air-conditioning systems were used in all operating rooms sampled.

Nikki et al [137] presented the results of measurements of halothane and nitrous oxide in six operating rooms and in three recovery rooms where trace anesthetic gases were exhaled by patients. Samples were collected during consecutive 30-minute periods by slowly filling a plastic sample bag and subsequently analyzed by gas chromatography. A flame ionization detector was used for halothane and an electron capture detector for nitrous oxide. Sample locations were chosen to reflect the anesthetist and recovery room personnel exposures. Anesthetic gas flow rates ranged from 4 to 10 liters/minute with 70 vol% nitrous oxide and 0.5 to 1.5 vol% halothane. Sample results in the operating room showed a mean concentration of 13.85 ppm for halothane (SD 10.43 ppm) and 929 ppm for nitrous oxide (SD 659 ppm). Uniform gas distribution within the operating room was observed. In the recovery rooms, halothane concentrations averaged 2.77 ppm (SD 1.42 ppm) and nitrous oxide averaged 146 ppm (SD 115

ppm). It must be noted that concentrations measured in the recovery rooms may have been elevated because of their proximity to the operating rooms. In addition, recovery rooms had little air movement (0.2-1.2 air changes/hour). The operating room tested also had very low air exchange rates, with none greater than 3 changes/hour.

Pfaffli et al [138] also reported results of measurements of halothane and nitrous oxide in unscavenged operating rooms and in recovery rooms using the same sampling and analysis techniques described above by Nikki et al [137]. Halothane concentrations in the operating rooms ranged from 2.1 to 57 ppm with a mean of 10.9 ppm, while nitrous oxide ranged from 60 to 4,900 ppm with a mean of 1,080 ppm. Recovery room concentrations of halothane were found to range from 0.9 to 8.2 ppm with a mean of 3.0 ppm and nitrous oxide ranged from 20 to 1,600 ppm with a mean of 305 ppm. All operating rooms and recovery areas had minimal air exchange rates.

Bruce and Linde [139] published the results of an extensive study of halothane in recovery room air. Patients in two recovery rooms after halothane anesthesia of at least 1 hour were studied by collecting samples 24 inches from their heads every 15 minutes for 1 hour. Samples were collected in gastight glass syringes and analyzed by gas chromatography with a flame ionization detector (minimum detectable concentration: 0.1 ppm). Five minutes after completion of surgery, concentrations averaged 0.36 ppm in one recovery room and 0.61 ppm in the other room. After 1 hour, no halothane was detected in one recovery room; however, concentrations in the other room averaged 0.32 ppm. No recovery room ventilation data are given in this report.

Gotell and Sundell [140] took halothane concentration measurements in the breathing zones of six nurse-anesthetists in five different operating rooms. Personnel samples were taken using activated charcoal tubes followed by halothane analysis by gas chromatography. TWA halothane exposures ranged from 14 to 59 ppm. The authors noted that halothane concentrations in expired air samples of these six subjects taken 15 minutes, 6 hours, and 16 hours after the end of anesthesia were directly proportional to the extent of exposure.

Usubiaga et al [141] reported results of halothane concentration measurements in operating rooms and in nearby rooms. Samples were collected near the face of the anesthetist using 10-ml airtight glass syringes with subsequent analysis by gas chromatography using an electron capture detector (lower limit of detection: 0.1 ppm). In one operating room, a total of 28 surgical cases were sampled in which anesthetic gas flow rates ranging from 1 to 6 liters/minute were used. A recirculating air-conditioning system was employed in the rooms sampled. Halothane concentrations varied from 1.3 to 9 ppm when anesthetic gas flows were 1-2 liters/minute with 1.0% halothane being delivered; however, concentrations of 20-30 ppm were observed when the halothane delivery concentration was 1.0% and anesthetic gas flows were increased from 5 to 6 liters/minute. Concentrations of approximately 60 ppm were observed when 3% halothane was administered at a total gas flow of 5 liters/minute. Halothane concentrations in nearby laboratories and offices ranged from 0.4 to 6.2 ppm.

According to Strunin et al [142], halothane exposures occur during dental surgery. They determined the breathing zone halothane

concentrations for both anesthetists and surgeons by collecting samples in clean, grease-free 20-ml syringes and analyzing by gas chromatography using a flame ionization detector (minimum detectable limits not given). Anesthetic gases were delivered by a nasal mask. Concentration measurements were made with the air-conditioning system off, with the air-conditioning system on (5 air changes/hour), with the air-conditioning system on and a small fan 3 meters from the nose mask expiratory valve blowing in the direction of the patient's face, and with the air-conditioning system on and waste gases vented to the floor from the expiratory valve. With the air-conditioning system off, mean halothane exposures for the anesthetist and dental surgeon were 23.1 and 68.3 ppm, respectively. Exposures were not significantly reduced when the air-conditioning system was on, 56.8 ppm for anesthetist and 73.8 for dental surgeon, nor when the local fan was employed, 46.3 ppm for anesthetist and 45.6 ppm for dental surgeon. When room ventilation was on and waste gases vented to the floor, mean concentrations of 25.2 and 18.5 ppm were determined for the anesthetist and surgeon, respectively. The authors concluded that while venting gases to the floor did reduce the oral surgeon's exposure, both the anesthetist and the oral surgeon were still exposed to a significant level of halothane.

Capon [143] measured concentrations of trichloroethylene in dental operations using trichloroethylene detector tubes (lower limit of detection: 10 ppm). All cases sampled used a gas flow of 8 liters/minute at a concentration of 1.5% trichloroethylene with no waste gas scavenging. Concentrations of approximately 25 ppm were found in the anesthetist's breathing zone when the patient's head was covered with a towel, and 50 ppm

when the patient's head was not covered. An average concentration of 25 ppm was obtained during a simulated operating session using no general room ventilation.

Lane [144] checked halothane concentrations and distribution in an operating room with and without waste gas scavenging. Air samples were collected at the floor, breathing zone, and ceiling by filling 20-ml syringes and analyzed by gas chromatography using a flame ionization detector. Concentrations at the breathing zone level were 1 to 14 ppm without scavenging. Halothane concentrations at the ceiling ranged from 10 to 20 ppm and at floor level ranged from 5 to 10 ppm. Diverting waste gases to the floor did not significantly change overall concentrations. An injector scavenging system significantly reduced concentrations to approximately 1.0 ppm.

Lecky [145] conducted an analysis of air sample data from a number of operating rooms and dental operatories not using gas scavenging. These data were obtained from a consultant laboratory offering a central testing service for analysis of anesthetic trace gases. Samples were collected 30 minutes after the beginning of surgery by filling a leakproof aluminum container. Samples were sent to a central location and analyzed by gas chromatography (lower detectable limit not given). In the operating room, nitrous oxide concentrations ranged from 0 to 1,281 ppm (mean 177 ppm), enflurane from 0 to 234 ppm (mean 9.8 ppm), and halothane from 0 to 199 ppm (mean 11.7 ppm). In dental operatories, nitrous oxide ranged from 94 to 3,000 ppm (mean 793 ppm) and halothane from 1.5 to 36 ppm (mean 15.5 ppm). The author concluded that the higher concentrations in the dental operatories probably reflected both the exclusive use of nonrebreathing

circuits in dental procedures and high anesthetic gas flow rates.

In 1974, Millard and Corbett [146] published their findings of exposure of dental personnel to nitrous oxide. During six different operative procedures using a nasal mask, breathing zone samples taken every 15 minutes with 600-ml gastight syringes were analyzed using gas chromatography with a helium ionization detector (no minimum detectable concentrations were given). The authors found that breathing zone nitrous oxide concentrations rose during the procedures. After 60 minutes of nitrous oxide administration, exposures for dentists averaged 6,767 ppm (SE $\pm$ 2,466 ppm) with exposures for the dental assistants averaging 5,867 ppm (SE $\pm$ 1,685 ppm).

Nicholson [147] reported measurements of halothane concentrations in four operating rooms, two recovery rooms, and adjoining halls and offices in two separate hospitals. Air samples were collected by filling 100-ml glass sampling bulbs using a syringe, and analyzed by gas chromatography using an electron capture detector (lower detectable limit: 0.001 ppm). Sixteen measurements were made in each area sampled. The operating room concentrations for the individual samples ranged from 0 to 1.59 ppm, with the highest average concentration being 0.38 ppm and the lowest average 0.03 ppm. Recovery room individual sample concentrations ranged from 0 to 0.62 ppm, with the highest average concentration at 0.09 ppm. Concentrations as high as 0.86 ppm were noted in the hallway of one hospital in addition to concentrations as high as 0.16 ppm in offices at that same hospital. This study lacks any specification regarding the types of anesthetic circuits employed, concentration and flow rates of anesthetic gases delivered, presence or absence of waste gas scavenging systems, and type of room air-conditioning used.

In another study, Nicholson et al [148] measured residual halothane concentrations in the same four operating rooms, two recovery rooms, adjoining halls and offices at two hospitals previously studied [147]. Room air samples were collected at 7 AM and 12 noon in each area for 12 days. Anesthesia was not being administered during any of the sampling. Air samples were collected by filling 100-ml glass sampling bulbs using a 50-ml syringe and then analyzed by gas chromatography using an electron capture detector. Duplicate analyses were performed on each sample and repeated if a variation greater than 5% was observed. Halothane concentrations increased in each area sampled between 7 AM and 12 noon. In the operating room, mean concentrations ranged from 0.003 ppm at 7 AM to 0.645 ppm at noon; in the recovery room, mean concentrations ranged from 0.007 ppm at 7 AM to 0.134 ppm at noon; and mean concentrations in adjoining halls and offices ranged from 0.003 ppm at 7 AM to 0.386 ppm at noon. Waste anesthetic gas control measures being utilized in the operating rooms sampled were not specified.

Mehta et al [149] reported the effect on halothane levels of commonly used anesthetic circuits, gas flows, clinical concentrations of halothane, and gas scavenging systems in the operating rooms and the expired air of operating room personnel. Three operating rooms were studied with two rooms having room air exchange rates of 10/hour and the third having no mechanical ventilation. Three anesthetic circuits were used. These were a semiclosed circuit with 7 liters/minute anesthetic gas flow (1.5-2% halothane), a respirator (mechanical ventilator) circuit with 7 liters/minute anesthetic gas flow (0.5% halothane), and a closed-circuit system with an anesthetic gas flow of 3 liters/minute (1.5-2% halothane).

Each patient was intubated with a cuffed endotracheal tube inflated to minimize anesthetic leakage. Air samples were taken during the middle of each operating session by filling 20-ml gastight syringes. Samples were taken approximately 5 feet above floor level at various distances from the patient's head and also at floor level. End tidal breath samples were also taken from anesthetists while they were administering anesthesia. All samples were analyzed by gas chromatography using a flame ionization detector.

The highest concentration of halothane (13.6 ppm) found by Mehta et al [149] was within a 2-foot radius of the patient's head and in the breathing zone of the anesthetist when a semiclosed circuit was used in a room without mechanical ventilation. These values were reduced by approximately 75% when room air exchange rates of 10/hour were used. With a closed anesthesia system, an overall average concentration of 3.3 ppm was observed with no room ventilation and 1.3 ppm with a room air exchange rate of 10/hour. With the mechanical respirator circuit, an overall average concentration of 2.7 ppm was observed without room ventilation and 0.2 ppm with room ventilation. These data also demonstrated uniform distribution of halothane throughout the operating room. Halothane in end expired air of the anesthetist followed closely the ambient halothane concentrations.

In two NIOSH Health Hazard Evaluation investigations, Levy [150,170] reported environmental surveys of operating rooms and recovery rooms in two hospitals that were not using waste gas scavenging. Samples were taken in the breathing zones of operating room personnel to evaluate exposures to halothane, nitrous oxide, and cyclopropane. Breathing zone halothane samples were collected using charcoal tubes with subsequent analysis by gas

chromatography. Samples of nitrous oxide were collected by filling 30-liter sample bags and analyzed by infrared spectroscopy.

In the first hospital [150], nitrous oxide concentrations in the operating room ranged from 5 to 6,000 ppm with a median of 525 ppm. Halothane concentrations ranged from 0 to 21.3 ppm with an average of approximately 3.5 ppm. All recovery room halothane concentrations were below 0.1 ppm. In the second hospital, [170] nitrous oxide concentrations in cystoscopy rooms were 20 to 6,000 ppm with a median of 155 ppm, whereas general operating rooms concentrations ranged from 150 to 3,000 ppm with a median of 43.0 ppm. Halothane concentrations in the cystoscopy rooms ranged from 0.04 to 29.3 ppm with a median of 1.0 ppm and in the general operating rooms ranged from 0.3 to 7.0 ppm.

In 1975, Barton and Nunn [171] reported halothane levels in operating room air when totally closed anesthetic circuits were used to administer halothane at concentrations of 0.5-1.0%. Samples were collected in the 400-sq ft operating room, supplied with air-conditioning (20 air changes/hour), by filling 20-ml syringes for halothane analysis using gas chromatography (lower detectable limit: 0.01 ppm). Samples were collected prior to the start of anesthesia, when no halothane had been used during the previous 2 hours, and toward the end of the surgical procedure. A control concentration of 0.02 ppm was observed prior to the administration of halothane. At the end of the surgical procedure, halothane concentrations had risen only slightly, with the highest concentration observed being only 0.03 ppm.

Exposure levels and acceptable control procedures for dental procedures requiring inhalation anesthesia have been the subjects of

research sponsored by NIOSH [172]. In a pediatric dental office without scavenging, Whitcher et al [172] noted that exposures of dentists averaged 1,100 ppm nitrous oxide (SD $\pm$ 330 ppm). In the oral surgeon's office, mean concentrations averaged 1,000 ppm (SD $\pm$ 630 ppm). These levels were determined by using a direct reading infrared absorption meter. The samples were time-weighted and collected during nitrous oxide administration.

A limited study, sponsored by NIOSH, was conducted by Whitcher and Hart at the Veterinary Medical Teaching Hospital, University of California at Davis, to determine the occupational exposure of veterinary personnel to inhalation anesthetics [written communication, December 1976]. Standard hospital anesthesia machines were used and breathing systems ranged from the Jackson-Reese modified T-tube for small animals to a standard circle absorber for medium-and large-size animals. The average breathing zone concentration of nitrous oxide, in the absence of control measures, was 310 ppm for two anesthetists during two different small animal surgical procedures. During surgery in a gelding, halothane concentrations in the anesthetist's breathing zone averaged 7.1 ppm. Measurements were obtained using an infrared gas analyzer.

The above studies, summarized in Table XIII-2, have shown significant exposure to all presently used inhalation anesthetic agents when waste anesthetic gas scavenging is not employed. While exposures were reduced when the operating theater was provided with high dilution rates by mechanical room ventilation, exposures still remained high.

(b) With Anesthetic Gas Scavenging

Several investigators have devised methods of scavenging waste anesthetic gases from anesthesia circuits and have made measurements of their control efficiency. The earliest report of scavenging efficiency was by Hirsch and Kappus [19] in 1929. The investigators used a crude scavenging system, consisting primarily of a vacuum cleaner and a large funnel. The decrease in ether levels in several operating rooms ranged from 34 to 72%. More recent measurements of waste gas exposures following adaptation for scavenging were reported by Whitcher et al [136]. When a scavenging popoff valve was attached to a wall suction system, halothane concentrations in the vicinity of the anesthesia machine (ie, anesthetist's exposures) averaged 0.79 ppm (SE $\pm$ 0.15 ppm). Using a scavenging nonrebreathing valve, concentrations averaged 0.73 ppm (SE $\pm$ 0.10 ppm). Sampling methods used by these authors have been described in subsection (a) of this chapter.

Nikki et al [137] reported the results of halothane and nitrous oxide measurements following adaptation of nonrebreathing and Ayre's T-piece systems for scavenging. Halothane concentrations averaged 0.85 ppm with a range of 0.01-1.9 ppm. Nitrous oxide concentrations ranged from 25 to 380 ppm with an average of 135 ppm. Pfaffli et al [138], using the same operating rooms studied by Nikki et al [137], reported similar concentrations following adaptation for scavenging.

Bruce [173] observed the efficiency of waste anesthetic gas scavenging using a scavenging popoff valve connected to the exhaust grille of a nonrecirculating air-conditioning system. Forty-five to 75 minutes after anesthesia induction, air samples, taken in the vicinity of the

anesthesiologist by filling airtight syringes, were analyzed for nitrous oxide by gas chromatography (minimum detectable level: 20 ppm). Nitrous oxide was not detectable (<20 ppm) in 19 of the 25 air samples collected. Bruce reported an estimated average concentration of 24 ppm nitrous oxide.

In 1971, Corbett and Ball [134] reported the results of 10 determinations of methoxyflurane concentrations made during use of a gas trap over the anesthesia machine discharge valve. This trap consisted of a balloon fitted over the valve, with vapors shunted to the operating room's central suction system. With this device, room concentrations ranged from 0.015 to 0.095 ppm.

Usubiaga et al [141] determined scavenging control efficiency in their study of halothane exposures in the operating room. A rubber balloon was attached to the discharge valve (popoff valve) of the gas machine with waste gases from the balloon vented to wall suction (flow rates not given). With this rather simple system, exposures were generally reduced to below 1-2 ppm even when high gas flow rates (5 liters/minute) to administer 3% halothane were used.

Levels found in operating rooms using scavenging were reported by Lecky [145], though the scavenging methods were not specified. Nitrous oxide levels were 0-135 ppm with a mean of 35.5 ppm, enflurane ranged from 0 to 5.6 ppm with a mean of 0.90 ppm, and halothane ranged from 0 to 1.8 ppm with a mean of 0.24 ppm.

In a study of halothane concentrations in the operating room, Mehta et al [149] noted the efficiency of various waste gas scavenging techniques. The expired gases from a circle system and semiclosed system were vented through a scavenging gas relief valve and either released at

the floor level or discharged outside the hospital through a metal pipe buried in the floor. The study demonstrated that releasing halothane at the floor level did not significantly reduce ambient concentrations. However, when waste gas scavenging was used in addition to a room air exchange rate of 10 changes/hour, overall halothane concentrations were reduced to below 0.2 ppm, irrespective of the type of anesthesia circuit, gas flows, and halothane concentration.

Kemi et al [174] used an empty operating room at Tokyo University to study the effects on halothane concentrations of nonrecirculating air-conditioning as the sole means of waste gas scavenging. The air-conditioning system was capable of 15 room air changes/hour. When the air-conditioner was on, halothane levels ranged from 0.19 to 0.93 ppm at the ceiling to 3.8 to 16.6 ppm 50 cm from the popoff valve. With the air-conditioning off, halothane levels ranged from 0.01 to 1.51 ppm at the ceiling to 3.68 to 50.20 ppm 50 cm from the popoff valve. When the air-conditioner was in use, no halothane was detected 3 hours after the vaporizer had been shut off. Without the air-conditioner, halothane was detected in the operating room 24 hours after the vaporizer had been shut off. This study demonstrated the value of good room ventilation in controlling the levels of waste anesthetic gases.

While the above studies generally demonstrated the feasibility of controlling waste anesthetic gases in the operating room to the levels prescribed in the recommended standard, none of them were performed with a complete waste anesthetic gas management program, including careful equipment maintenance, leak testing, and proper anesthetist work practices. Such a study was conducted by Whitcher et al [159]. Waste gas scavenging

techniques and anesthetist work practices, as later presented in this chapter, were used with a semiclosed system with 5 liters/minute anesthetic gas flow. Measurements were made during steady state conditions (anesthesia in progress at least 30 minutes, patient not disconnected within preceding 15 minutes, and vaporizer not filled during immediate 15 minutes before sampling). Under these conditions, average anesthetic gas concentrations (at the air-conditioning exhaust grille) were kept below 1 ppm nitrous oxide and 0.025 ppm halothane.

In addition to determining minimum achievable levels, Whitcher et al [159] used a number of sampling techniques to determine both average room concentrations and personnel exposures under normal operating conditions employing scavenging. Average room concentrations (at the air-conditioning exhaust grille) of nitrous oxide were determined by collecting samples in gastight syringes throughout the workday with subsequent analysis by infrared spectroscopy. The mean concentration of nitrous oxide determined from 461 samples was 16 ppm (SE $\pm$ 1.8 ppm). These concentrations were found to be similar regardless of anesthetic technique (ie, face mask, endotracheal tube with or without ventilator) as illustrated in Table XIII-4. To more accurately determine average exposures, long-term samples were collected at the exhaust grille by filling gastight sample bags with a low flow air pump for several hours. Analysis for nitrous oxide was performed by infrared spectroscopy and halothane by gas chromatography with a flame ionization detector. Mean concentrations were 19 ppm (SE $\pm$ 3.0 ppm) for nitrous oxide and 0.24 ppm (SE $\pm$ 0.05 ppm) for halothane. Samples obtained in the proximity of operating personnel showed almost identical results, indicating uniform distribution of waste anesthetic gases in the operating

room. Such a distribution is applicable when leaks are at a minimum. These data are summarized in Table XIII-5.

Control techniques for anesthetic procedures employing nasal masks, used primarily in the dental area, have been developed by Whitcher et al [172]. Using the control procedures recommended in this chapter (double mask, oral suction hook, and concentration equalizing fan), nitrous oxide exposures, determined by infrared spectroscopy, have been shown to average 14 ppm (SE $\pm$ 1.5 ppm) in the dentist's breathing zone. Average room concentrations were 13 ppm (SE $\pm$ 1.4 ppm).

Whitcher and Hart demonstrated the feasibility and effectiveness of control procedures in a veterinary hospital as part of a limited study sponsored by NIOSH [written communication, December 1976]. The control measures included the use of anesthesia machines which had been serviced to minimize leakage, and waste gas scavenging, which consisted of collecting the excess gases at the anesthetic breathing system and their disposal at the exhaust grilles of the nonrecirculating air-conditioning system. Average breathing zone concentrations for anesthetists were reduced to 7.8 ppm for nitrous oxide and 0.35 ppm for halothane.

A summary of the above studies on control by use of scavenging techniques is presented in Table XIII-3. These data demonstrate the feasibility of controlling concentrations to those prescribed in the recommended standard.

Summary of Presently Used Anesthetics and

Inhalation Anesthetic Techniques

A Hospital Inhalation Anesthesia Practices Survey [175] was conducted by NIOSH to determine: (1) which anesthetic agents are presently being used and to what extent, (2) types of anesthesia administration techniques being used, and (3) methods presently in use to reduce waste anesthetic gas exposures to operating room personnel. Hospitals surveyed were chosen from the 1972 List of Health Care Institutions published by the American Hospital Association. Institutions were grouped according to five categories and are shown in Table XIII-7. To keep the number of hospitals surveyed manageable and to optimize the amount of information within the limits of available resources, only those institutions with 100 beds or more were surveyed. All hospitals in three of the categories with fewer than 500 institutions were surveyed. Randomly selected hospitals were surveyed from the two categories which included more than 500 institutions. Questionnaire response statistics are shown in Table XIII-8. There was a response rate of approximately 80%, which is considered excellent because of the complex nature of the questionnaire and the fact that response was strictly voluntary.

The survey results for the types of anesthetics used in hospitals in 1974 are given in Tables XIII-9 and 10. The most commonly used inhalation anesthetics were nitrous oxide, halothane, enflurane, cyclopropane, methoxyflurane, and diethyl ether. Approximately 5% of the hospitals surveyed used trichloroethylene in addition to limited use of chloroform and isoflurane (experimental).

The percentage of utilization of the five most common breathing circuits is presented in Table XIII-11. Table XIII-12 shows that the face mask and endotracheal inhalation are the most common methods of inhalation anesthesia administration (approximately 90%). The insufflation technique, which is difficult to control from a waste anesthetic gas exposure standpoint, was used in less than 2% of administrations.

The extent to which waste gas scavenging techniques were used in 1974 is summarized in Table XIII-13. Approximately 70% of the hospitals surveyed indicated that some form of waste anesthetic gas scavenging was being used. The efficiency of these scavenging techniques could not be ascertained from this survey.

Biologic Evaluation of Exposure

Corbett and Ball [134,176,177] reported breath decay curves for several anesthetics in anesthesiologists after routine occupational exposure and in patients following clinical anesthesia. Methoxyflurane was detectable in the end-expired air of patients for 10-18 days after anesthesia and for as long as 30 hours after exposure in anesthesiologists. Air samples collected in the area of the anesthesiologist contained 1.3-9.8 ppm methoxyflurane [134]. Halothane was detectable in end-expired air of patients 11-20 days after anesthesia. Halothane was detected in end-expired air of one anesthesiologist for 26 hours after a 70-minute exposure and for 64 hours following a 390-minute exposure. Halothane levels in the operating room air ranged from 1 to 10 ppm [176].

Levels of nitrous oxide present in the breathing zone of the anesthesiologist, while administering 60% nitrous oxide at 5 liters/minute,

were reported by Corbett et al [177] to be 330-5,050 ppm. Nitrous oxide was detectable in end-expired air from 3 to 7 hours following routine occupational exposures ranging from 13 to 305 minutes. The limit of detection was 0.2 ppm. Halothane was detectable from 7 to 64 hours following occupational exposure of 20-390 minutes. Operating room levels of halothane ranged from 1 to 10 ppm.

Halothane concentrations in end-expired air of anesthetists were reported in 1969 by Linde and Bruce [131]. Following operating room exposures of 1-3 hours, the end-expired air of 24 anesthetists contained 0-12.2 ppm halothane (average 1.8 ppm). The overall average room concentration of halothane was 10 ppm.

Hallen et al [133] measured halothane concentrations in expired air and venous blood of operating room personnel. Expired-air samples were collected by having the subject fill a 5-liter plastic bag with a number of expirations and subsequent rebreathing six to eight times. Halothane concentrations were determined by gas chromatography. Venous blood samples were taken from exposed personnel at the end of a day's exposure with subsequent halothane analysis by gas chromatography. Halothane concentrations in the operating room at approximately the anesthetist's breathing zone ranged from 15 to 290 ppm with a mean of 67 ppm and a median of 29 ppm. Expired air concentrations ranged from a trace to 31 ppm with a mean of 5.2 ppm. Venous blood halothane concentrations ranged from 0.021 to 0.63 ppm with a mean of 0.16 ppm.

In 1971, Whitcher et al [136] reported end-tidal concentrations of halothane in breath samples of operating room personnel. Concentrations of halothane in end-tidal samples of 9 anesthetists (36 samples) and 27

operating room nurses (81 samples) were measured by mass spectrometry at intervals throughout the day. A control sample was obtained for each individual early in the morning before work in the operating room. During the workday, end-tidal halothane concentrations for nurses rose from 0.01 ppm to an average of 0.21 ppm while end-tidal halothane concentrations for anesthetists rose from 0.08 ppm to an average of 0.46 ppm. End-tidal concentrations greater than 1.0 ppm were found in six samples from the anesthetists and in samples from one nurse. Without scavenging, halothane concentrations in the operating rooms ranged from a mean of 8.69 ppm with nonrebreathing systems to 4.93 ppm with semiclosed circle systems.

Nikki et al [178] reported end-tidal and blood concentrations of halothane and nitrous oxide in surgical personnel before and after application of waste gas scavenging. End-tidal breath samples were collected in plastic bags before and after work with subsequent analysis by gas chromatography. Venous blood samples were also measured for halothane content by gas chromatography. In operating rooms without scavenging, mean expired air halothane concentrations rose from 0.13 at the beginning of the day to 1.28 ppm at the end of the workday. However, when gas scavenging was employed, mean concentrations rose from 0.05 to 0.12 ppm. Recovery room personnel also showed slight elevations of halothane concentrations in end-tidal air at the end of the workday. Nitrous oxide was only detected in a few of the samples from personnel working in unscavenged operating rooms (mean: 20.0 ppm).

In the same study [178], halothane concentrations in venous blood rose from a mean of 2.4 to 8.4 ppm in personnel working in operating rooms without scavenging. Personnel working in rooms with scavenging or in

recovery rooms also demonstrated significant increases in venous blood halothane concentrations. The authors reported halothane concentrations in the air of operating rooms averaged 10.9 ppm without scavenging and 0.8 ppm with scavenging. Recovery room concentrations averaged 3.0 ppm [178]. Some expired air concentrations of personnel exposed to halothane are summarized in Table IV-1.

TABLE IV-1

HALOTHANE CONCENTRATIONS
IN EXPIRED AIR OF OPERATING ROOM PERSONNEL

Range of Anesthetic Exposure, ppm	Halothane in Expired Air, ppm
15 - 290	Trace - 31
4.9 - 8.7	0.21 - 1.0
0.8 - 10.9	0.12 - 1.3
0.6 - 12.9	0.8 - 12.2

Adapted from references 131,133,136,178

V. DEVELOPMENT OF STANDARD

Basis for Previous Standards

The United States does not have occupational exposure standards for gaseous and volatile chemicals when used as anesthetics. Specific occupational standards for chloroform, trichloroethylene, and diethyl ether, as promulgated by the Occupational Safety and Health Administration, Department of Labor (29 CFR 1910.1000) are:

Chloroform - 50 ppm, 8-hour TWA concentration;

Trichloroethylene - 100 ppm, 8-hour TWA concentration, with a ceiling limit of 200 ppm and a 300 ppm maximum peak above the acceptable ceiling for 5 minutes in any 2 hours;

Diethyl ether - 400 ppm, 8-hour TWA concentration.

The chloroform and diethyl ether standards were adapted from the recommendations of the American Conference of Governmental Industrial Hygienists (ACGIH). The chloroform recommendation [179] was based on CNS and liver effects while the diethyl ether value [180] was based on nasal irritation and possible narcosis. The trichloroethylene standard, which was based on CNS depression caused by the chemical, was adapted from the American National Standards Institute Z-37 standard. Subsequently, NIOSH recommended that the permissible level of exposure for chloroform be 10 ppm as a TWA with a ceiling of 50 ppm based on a 10-minute sample [81]. NIOSH also recommended that the trichloroethylene standard of 100 ppm as a TWA be retained but that the ceiling be reduced to 150 ppm based on a 10-minute sample [82]. Based on information from the National Cancer Institute (NCI) [Chloroform Bioassy Results, National Cancer Institute, March 1, 1976],

NIOSH revised its recommendation for exposure to chloroform and recommended that it be considered a carcinogen and that the allowable exposure levels be reduced to 2 ppm in a 45-liter air sample. NIOSH is currently reevaluating its recommendations for a trichloroethylene standard based on animal studies conducted by the NCI and discussed by Lloyd et al [129].

Sweden's Labor Protection Board issued the Narcosis Specifications guide in November 1974 [181] for the protection of personnel against health risks through exposure to gaseous anesthetics in patient casework. The guide noted that it was not possible to expect that health risks for personnel could be reduced by replacing anesthetics now in use with others, and that the only effective preventive measure was to conduct operations in such a way that operating room personnel would not be exposed to anesthetic gases. Operating rooms were required to have 17 air exchanges/hour; preparatory and anesthesia rooms, 10 exchanges/hour; and recovery rooms, 6 exchanges/hour. Point aspiration was required so that gases flowing out of valves on the anesthetic equipment would be carried away from the work area. The standard also required a program of educating workers about the potential risks that may be associated with working with anesthetic gases. There were no environmental limits promulgated in the Swedish standard [181] for any of the anesthetic agents.

The Hospital Engineering Cooperative Groups of Denmark made recommendations in 1974 to prevent pollution by anesthetic gases in operating rooms, recovery rooms, and similarly equipped rooms [182]. The document was developed on the principle of practical experience available and information in the medical literature on possible health effects and procedures for exposure control [69,72,73,75,132,136,139,176,178,183,184].

The authors stated that the lowest concentration of anesthetic gases which offers any risk upon long term exposure is unknown, making it necessary to attempt to remove all excess gases and vapors. The highest average concentrations recommended as allowable in the breathing zone of anesthesia personnel by the Denmark group are presented in Table V-1. Recommendations were also made for high- and low-pressure leak tests. An air monitoring program, taking six samples over 1 hour with glass pipettes, was recommended.

TABLE V-1

HIGHEST PERMISSIBLE AVERAGE CONCENTRATION IN BREATHING ZONE OF ANESTHESIA PERSONNEL RECOMMENDED BY THE HOSPITAL ENGINEERING COOPERATIVE GROUPS OF DENMARK

Anesthetic Agent	Highest Permissible Average Concentration, ppm
Chloroform	1
Halothane	1
Methoxyflurane	1
Vinyl ether	2
Diethyl ether	3
Fluroxene	3
Trichloroethylene	3
Cyclopropane	5
Nitrous oxide	10

Derived from reference [182]

The Council of the Associztion of Anesthetists of Great Britain and Ireland [185] set up a Working Party in 1974 which issued a special notice to members recommending that steps be taken to lower anesthetic agent concentrations in exposure areas to the lowest practicable levels and not

to wait for the development of adequate monitoring programs or an agreed standard on maximum permissible environmental limits. Passive and active scavenging procedures were presented with some suggested work practices.

Basis for the Recommended Standard

A number of epidemiologic studies have been conducted among operating room and dental personnel exposed to anesthetic gases [12,13,69,72-80]. Spontaneous abortions in increasing numbers were the most frequently encountered adverse health effect in anesthetists and nurses exposed to anesthetic gases. Most of the epidemiologic studies used control groups of female physicians and nurses who were not exposed to anesthetic agents in their work environment [12,13,73,74,76,80]. Environmental levels of anesthetic agents were not presented in the epidemiologic studies but the large number of environmental determinations made have established the usual occupational exposure levels at 1-10 ppm for halothane and other volatile agents, and 400-3,000 ppm for nitrous oxide [131-150,170].

An increased number of resorptions (similar to abortions in humans) was seen in pregnant animals exposed to halothane and nitrous oxide at concentrations of 10-8,000 ppm halothane and 1,000-700,000 ppm nitrous oxide [108-110,116,117,122]. One study reported no significantly increased number of resorptions per pregnancy when pregnant mice were exposed to halothane at 16 ppm, 7 hours/day, 5 days/week for 6 weeks [123].

An increased incidence of congenital abnormalities among children of exposed personnel was also identified in the epidemiologic studies [12,13,74,76,77,80]. Organ and skeletal anomalies were seen in the offspring of pregnant animals exposed to halothane, chloroform, and nitrous

oxide. The halothane exposures ranged from 10 ppm for 8 hours/day, 5 days/week for 8 weeks, to single anesthetic doses of the agent. Chloroform exposures ranged from 30 to 300 ppm 7 hours/day on days 6-15 of pregnancy in rats. Nitrous oxide exposures in rats ranged from 1,000 ppm for 1 day during pregnancy to 700,000 ppm. Reproductive effects were seen following acute exposures to all three agents. The animal studies did not identify a level at which the anesthetic agents had no teratogenic effects.

In three studies, the wives of exposed personnel exhibited a higher incidence of spontaneous abortion and of congenital abnormalities in their children than did the wives and offspring of unexposed men [12,13,72]. One animal study [124] demonstrated a detrimental effect by nitrous oxide on spermatogenesis in male rats. Extended exposures to nitrous oxide at 200,000 ppm had a detrimental, but reversible, effect on spermatozoa production.

In addition to the adverse effects on reproduction, which are the primary concern in developing a recommended standard, three epidemiologic studies report evidence of increased incidence of liver and kidney diseases among personnel exposed to anesthetic gases [12,13,78], especially among female workers. Many animal studies have been conducted with anesthetics to investigate their liver and kidney toxicities. Organ damage has been found following acute exposures [83,85-90,93-95], and liver and kidney damage has been reported in some animal studies following chronic, low level exposure but the levels at which the damage was seen were usually above those considered usual for occupational exposure [61,96,98,99]. Animal studies of chronic exposure would indicate that the lowest levels at which liver and kidney damage is seen were 200 ppm for methoxyflurane [96],

50-150 ppm for halothane [61], 1,500 ppm for isoflurane [61], and 10,000 ppm for diethyl ether [61]. It must be pointed out that these were short-term (4-8 weeks) experiments attempting to induce and identify basic liver and kidney lesions and not any carcinogenic potential of the anesthetic agents. Also, decrements in performance, cognition, audiovisual ability, and dexterity have been shown in human volunteers at exposure levels as low as 50 ppm nitrous oxide, with or without 1 ppm halothane. Significant effects were not seen when the subjects were exposed to nitrous oxide at 25 ppm with 0.5 ppm halothane [47-49]. These results bear on the question of possible CNS effects following chronic exposure to anesthetic gases. Three animal studies [97,113,119] have demonstrated damage to the CNS of unborn and young rats following exposure to halothane at 8-12 ppm, 8 hours/day, 5 days/week throughout the pregnancy of the mother or during early life of offspring (to age 60 days).

NIOSH recognizes both adverse reproductive effects in exposed female personnel and congenital abnormalities in the offspring of exposed personnel as the primary health concerns in the development of the recommended standard for exposure to mixed anesthetic gases or to halogenated agents when used alone. Based on the available health information, a safe level of exposure to the halogenated agents cannot be defined. Since a safe level of occupational exposure to halogenated anesthetic agents cannot be established by either animal or human investigations, NIOSH recommends that exposure be controlled to levels no greater than the lowest level detectable using the sampling and analysis techniques recommended by NIOSH in this document. The weights of anesthetic agents given in Chapter I, Section 2(a)(1), are the smallest

weights of each compound which can be analytically detected with reliability and reproducibility using charcoal adsorption sample collection and gas chromatographic analysis. These weights, when collected from a 45-liter air sample, result in a concentration of 2 ppm for each compound. This is the method recommended by NIOSH for field use. Controlling exposure to these levels should also help to prevent the occurrence of adverse effects on the liver and kidneys in humans as well as prevent decreases in psychologic performance and any other CNS effects.

Most of the human studies mentioned were based primarily on hospital operating room personnel. Since the available information associates the health effects in these areas with exposure to anesthetic gases, and taking into consideration the seriousness of such effects, NIOSH recommends that a similar degree of concern be given to other areas where inhalation anesthetics such as halothane, methoxyflurane, and enflurane, are used. The recommended standard, therefore, is applicable to all occupational exposures to anesthetic gases. The recommended standard should protect against adverse health effects associated with exposure to a number of anesthetic agents. Most routine occupational exposures involve mixtures of agents and usually more than two agents/day. The heaviest exposures are to nitrous oxide, halothane, methoxyflurane, enflurane, cyclopropane, and diethyl ether (Tables XIII-9 and 10).

An estimated 100,000 dentists and their assistants are potentially exposed to anesthetics used in dental and oral surgical procedures. An epidemiologic survey was conducted among all 2,600 male members of the American Society of Oral Surgeons (ASOS) and in 4,800 members of the ADA [13]. No estimation was made of the number of dentists using nitrous oxide

alone versus mixed agents. The statistically significant findings were a 78% increase in spontaneous abortions among exposed dentists' wives and a 156% increase in the incidence of liver disease in exposed dentists. Dentists and oral surgeons exposed for less than 3 hours/week to the anesthetics were used as the control group. A 15% increase in congenital abnormalities among dentists' children and a 35% increase in the incidence of cancer were also found in the exposed group, but the increases were not statistically significant. Information on any possible adverse health effects among dental assistants or hygienists is not available. Such effects in exposed female operating room personnel [12] emphasize the need for more information from the dental profession.

Different concerns about adverse health effects are present in the information on nitrous oxide. Often, a situation arises where nitrous oxide is the sole anesthetic agent being administered and its effects alone must be considered.

Bruce and Bach [49] were able to demonstrate statistically significant decrements in audiovisual task performance in human volunteers exposed to nitrous oxide at 50 ppm. At 500 ppm, the subjects showed statistically significant performance decrements in all but one of the behavioral tests. Such decrements were seen in four of the seven tests when the volunteers were exposed to a mixture of 50 ppm nitrous oxide and 1 ppm halothane. A correlation to clinical performance was not established in this study.

Animal exposure studies with nitrous oxide have been directed primarily at reproductive effects [93,106,108,109,115,117,118,122,124]. Most of these investigations used very high concentrations of nitrous

oxide, except for a study by Corbett et al [122], where concentrations of nitrous oxide near the usual dental exposure values were used. A higher fetal death rate among exposed pregnant rats was seen but the effect was not proportional to the concentrations of the exposures. A second study by Doenicke et al [117] reported similar results using higher concentrations of nitrous oxide.

Based on the information on adverse health effects among hospital operating room personnel [12,69,72-80] and their association with exposure to anesthetic gases, similar exposures to nitrous oxide and halothane when used in dental and oral surgical procedures must be viewed with equal concern. The information available to support conclusions on reproductive effects resulting from exposure to nitrous oxide as a sole agent is not felt to be definitive. Nevertheless, a degree of concern should be associated with such exposures. The adverse effects of prime concern involve decrements in performance, cognition, audiovisual ability, and in dexterity during exposures to nitrous oxide. Such effects have been observed at exposure levels to nitrous oxide at 500 ppm. At levels as low as 50 ppm, audiovisual decrements were observed in exposed volunteers. This demonstrates the potential for this substance to impair functional capacities of exposed workers. Similar decrements were not observed at 25 ppm nitrous oxide with 0.5 ppm halothane. Based on this information NIOSH recommends that where exposures are limited to nitrous oxide alone, the permissible level of exposure should be a TWA concentration of 25 ppm during the period of administration.

Basis for Control Procedures and Work Practices

The control procedures and work practices required in the recommended standard, or their equivalent, have been demonstrated to reduce anesthetic gas concentrations to the recommended levels and are commercially available and reasonably attainable [159,172].

Scavenging in combination with good room ventilation is recommended over trapping volatile anesthetic agents on an adsorbing medium such as activated charcoal. Charcoal adsorption canisters may be used to control limited quantities of halogenated agents but they have little effect in controlling the levels of nitrous oxide and other gaseous agents released into the work environment [186-188]. Simple scavenging techniques and adequate ventilation reportedly resulted in fewer health complaints from operating room personnel [20,69]. It is believed that the control procedures and work practices recommended can effectively reduce occupational exposure levels to the concentrations presented in the recommended standard.

The procedures and practices will reduce occupational exposures, as evidenced in Table XIII-3. These controls will also provide the necessary reductions in anesthetic gas concentrations for agents that have nonanesthetic occupational exposure limits, including chloroform, trichloroethylene, and diethyl ether. Based on operating room engineering control studies, the attainable TWA concentrations during administration of mixed anesthetics are 0.5 ppm for halothane and other volatile agents, and 25 ppm for nitrous oxide. Therefore, instituting engineering control procedures and work practices to control exposure to all anesthetic agents to the lowest feasible level should also keep exposure to halogenated agents well below the 2-ppm recommended limit.

During inhalation anesthesia and analgesia in dentistry, the anesthetic agents leak into the room air from the exhalation valve, around the nasal mask, and through the patient's mouth. Dentists deliver anesthetics at higher flow rates than those used under usual operating room conditions. Because of the open breathing systems, high flow rates of anesthetics, and the proximity to the patient's head, the dentist, anesthetist, and dental assistant may be exposed to high concentrations of anesthetic agents. Nitrous oxide receives the greatest amount of use by dentists and is sometimes given in combination with halothane by oral surgeons. Environmental levels of nitrous oxide, halothane, and trichloroethylene in dental operatories have been reported in the literature [142,143,145,146] and this information is summarized in Table V-2.

TABLE V-2

SUMMARY OF DENTAL PERSONNEL EXPOSURES TO ANESTHETIC AGENTS

Anesthetic	Exposure		Ref.
Halothane	5.5-68 ppm	Oral surgeons' breathing zone	142
Trichloroethylene	25-50 ppm	Anesthetists' breathing zone	143
Nitrous oxide	94-3,000 ppm	Dentists' breathing zone	145
Halothane	1.5-36 ppm	"	145
Nitrous oxide	5,900 ppm (mean)	Dental assistants' breathing zone	145
"	6,800 ppm (mean)	Dentists' breathing zone	146

Devices and procedures for controlling exposures of dental personnel to anesthetics have been developed by Whitcher et al [172]. These procedures have been shown to be feasible, available, and effective in

attaining TWA concentrations approaching 50 ppm during administrations of nitrous oxide when it is used as the sole anesthetic. Tables III-5, 6,and 7 summarize the major adverse health effects identified in epidemiologic surveys of hospital and dental personnel.

Similarities in practice and in anesthetic agents used result in many of the same problems of exposure in veterinary personnel as among hospital operating room personnel. Nitrous oxide, halothane, and methoxyflurane are the anesthetics most frequently used in veterinary anesthesia and the equipment used to administer anesthetics is basically the same as that used in human hospital operating rooms. Problems of good fit with nose and face masks and frequent use of the T-tube for smaller animals could result in significant exposure to veterinary personnel. NIOSH, therefore, recommends that work practices and control procedures be instituted in veterinary facilities to control occupational exposure to waste anesthetic gases to the same levels recommended for mixed anesthetic agent use.

Basis for Environmental Monitoring

Personal monitoring using long- or short-term monitoring is not required in this standard because of the critical nature of the work performed by personnel in the occupational environments covered by the standard. Sampling the breathing zone or the immediate work area of those most heavily exposed (anesthetist, oral surgeon) should provide an adequate index of exposure. Waste anesthetic gas distributions in inhalation anesthetizing areas have also been shown to be relatively uniform, except for normally expected hot spots. With good distribution studies, locations for general area monitoring can be determined. The nonrequirement for

personal monitoring does not preclude that such monitoring be used to sample for effectiveness of implemented work practices and control procedures, utilizing appropriate sampling and analytical techniques.

The recommended standard does not require the monitoring of all anesthetic agents used. Only the agent(s) most frequently used needs to be monitored, since the recommended work practices and control procedures should reduce all agents proportionately.

Charcoal adsorption sampling and gas chromatographic analysis is recommended for monitoring exposure to halogenated anesthetics. This method is economical and readily available to an individual in charge of an air monitoring program and is the method most often used to monitor halogenated hydrocarbons. However, it does not have the sensitivity of other methods. The halogenated anesthetics are usually administered with nitrous oxide. In this situation the recommended standard requires monitoring nitrous oxide. Sample collection and analysis techniques are presented in Appendices II-IV. Direct infrared analysis of nitrous oxide is the most desirable method. Gas bag or syringe sampling followed by infrared or gas chromatographic analysis is acceptable. Halothane may be measured by using gas bag or syringe sampling if the analysis is performed within a short time of sample collection. Proper work practices and scavenging procedures should reduce the levels of halogenated anesthetics, when administered with nitrous oxide, to below the sensitivity limit of the charcoal tube method. Because of this, it is recommended that nitrous oxide be monitored.

Basis for Medical Monitoring

Medical monitoring of exposed personnel is recommended but is not a required part of the recommended standard. Maintenance of medical histories, with emphasis on the outcome of pregnancies in exposed women and in wives of exposed males, is required. The most significant adverse health effects seen among exposed personnel are the reproductive effects among exposed women and among wives of exposed personnel. Medical counseling and care should be available to women of child-bearing age who feel their exposure to anesthetic gases may result in an adverse reproductive effect. Until some direct causal relationship between exposure to anesthetic gases and reported adverse health effects in exposed personnel is either proved or disproved, it is recommended that the medical histories of exposed personnel, especially women, be maintained during their period of employment plus 20 years.

VI. ENGINEERING CONTROLS AND WORK PRACTICES

Using well-designed, low-leak anesthesia equipment and scavenging systems, the work practices employed by the anesthetist may be the principal contributors to anesthetic gas levels in the operating room. Other relevant factors include poorly connected scavenging hoses, improperly fitted face masks and endotracheal tubes, spillage of volatile anesthetic agents during filling of vaporizers, and leaving vaporizers turned on when not in use. Whitcher et al [159] estimated that anesthetist work practices may contribute from 94 to 99% of the waste anesthetic gases in the scavenged operating room.

A complete waste anesthetic gas management program includes (1) application of a well designed waste anesthetic gas scavenging system, (2) anesthetists' work practices minimizing gas leakage, and (3) application of a routine equipment maintenance program so gas leaks are minimized. Equipment maintenance requirements are given in Chapter I, Section 3.

(a) Scavenging Systems

A scavenging system consists of three major components: (1) a collecting device (scavenging adapter) to collect waste anesthetic gases; (2) a disposal route (ventilation) to carry waste gases from the operating room; and (3) a method or device for limiting both positive and negative pressure variations in the breathing circuit which may be caused by the scavenging systems. The first waste control system was described by Hirsch and Kappus [19] in 1929. Epstein and Berlin [189], in 1944, used charcoal adsorption to collect waste ether vapor. Bullough and Lond [190] described

a simple gas scavenging system in 1954.

A variety of waste anesthetic gas collection systems [159,183,184,191-210] and several methods of waste anesthetic gas disposal [173,188,211] have recently been developed and described in the literature. However, with few exceptions, the efficiency of these devices has not been documented. Studies of scavenging techniques have shown them to be effective. However, other methods not mentioned may also be used, if they are as effective as scavenging techniques and present no safety hazard to the patient, such as the application of excess negative or positive pressure to the anesthesia breathing system.

(1) Methods of Collecting Waste Anesthetic Gases from the Breathing Systems

(A) Circle Absorber

All popoff valves for circle absorber breathing circuits must be equipped for waste gas scavenging. These valves must be leak-proof, as determined by the low-pressure leak test described in Appendix I. One such typical device is shown in Figure XIII-1.

(B) Nonrebreathing Systems

In a nonrebreathing system, fresh anesthetic gases enter at the breathing bag and all excess gases leave through the scavenging systems. Nonrebreathing valves equipped for scavenging are commercially available. One typical nonrebreathing valve equipped for scavenging is shown in Figure XIII-2.

(C) T-Tube Systems

A commonly used T-tube system is the Summer's modification to allow for assisted breathing. An acceptable scavenging

adapter for this system has been designed and successfully applied by Whitcher et al [159]. This device is shown in Figure XIII-3. A clamp permits adjustment of gas outflow to maintain proper bag filling with a plastic tube inserted to prevent accidental occlusion of the tail of the bag. The system shown in Figure XIII-3 or an equivalent system should be used for all T-tube breathing system applications.

(D) Ventilators

All new ventilators are equipped for waste anesthetic gas scavenging and old ventilators can be adapted [206]. One convenient method for connecting ventilators for scavenging is shown in Figure XIII-4. With this method, both the ventilator and gas machine are interconnected to the scavenging exhaust, thus eliminating the need to reattach the disposal tubing when alternating between ventilator and manual breathing. Some ventilators (Ohio 300 series, Monoghan, Ventimeter and Bird) may require a one-way check valve to be located at point "C" in Figure XIII-4 to prevent gas leakage through it from the anesthesia machine when the circuit is attached to the disposal system but disconnected from the patient.

(2) Disposal of Waste Anesthetic Gases

Waste anesthetic gases, once collected at the anesthetic breathing machine, should be vented to the atmosphere at a point away from personnel areas and in such a manner that contamination of hospital intake air or of areas where personnel are working does not occur. All applicable air pollution rules and regulations should be met. Three systems have been successfully used for this purpose. These include (1) the nonrecirculating air-conditioning system, (2) the central room suction system, and (3) a separate duct system devoted solely to disposal of waste anesthetic gases.

(A) Air-Conditioning Exhaust Grille Method

If the operating room air-conditioning is of the nonrecirculating (one pass) design, disposal of waste anesthetic gases via this route can be inexpensive and effective. As shown in Figure XIII-5, the scavenging tube terminates at the air-conditioning exhaust grille where the sweeping effect of the air flowing into the grille carries away all waste gases. Negative pressure in the waste gas disposal system is minimal [159] when this method is used and no excess pressure relief device (pressure balancing) is needed. Pressure compensation is easily accomplished with the usual popoff valve resistance adjustment.

In some rooms, the air-conditioning exhaust vent may be distant from the anesthesia machine, requiring a long disposal tube. This objectionable feature can be eliminated by arranging the tube to follow the same path as the anesthetic gas supply hoses. A wall or ceiling service panel may be connected to a permanently concealed waste anesthetic gas line joined to the air-conditioning exhaust duct in the crawl space, as shown in Figure XIII-6. If such a connection is made, pressures should be balanced so that the patient's breathing is not compromised. This may be accomplished by careful selection of the point of connection to the air-conditioning system (negative pressure in the duct increases with proximity to the fan) or using pressure relief techniques described in later sections of this chapter.

(B) Room Suction Method

Providing sufficient flow capacity is available, the room central suction system may be used as a waste gas disposal route. If such a method is used, a vacuum break (pressure balancing system) should be

located between the central vacuum suction outlet and the anesthesia breathing circuit so that negative pressure at the breathing circuit is less than 5 mmHg [159].

Ideally, three separate suction outlets, entering the same suction line, should be provided with one line devoted to waste gases. However, a single line may be branched as shown in Figure XIII-7. A suction flow meter, control valve, and reservoir bag should be provided with all suction/scavenging systems. The pressure relief apparatus shown in Figure XIII-7 is described in the following sections of this chapter. A scavenging flow of at least 20 liters/minute should be maintained [159]. Explosive agents must not be disposed of by this method [212] except when a water-sealed central vacuum pump is used [159]. The exhaust of the suction pump should be located outside the exposure area at a point remote from air intakes.

(C) Specialized Duct Systems

A duct system solely for disposal of waste anesthetic gases can be used for one or more rooms. One such system which has been successfully used is shown in Figure XIII-8.

If the special duct system is used, a scavenging flow of at least 30 liters/minute should be provided to each machine scavenged. If negative pressures exceed 5 mmHg [159] at the connection to the anesthesia circuit, negative pressure relief shall be provided as described in the following sections of this chapter. Explosive anesthetic gases should not be vented in this system unless they are diluted to less than their lower explosive limit. Alternately, a nonsparking exhaust fan can be used. The scavenging system should exhaust at a point remote from hospital air intakes or

employee work areas. All ducts should be constructed of materials resistant to anesthetic gases.

(3) Pressure Balancing or Interfacing

Marked pressure differences between the anesthetic breathing system and the waste anesthetic gas disposal system must not be allowed to interfere with operation of the breathing system, such as collapse of the breathing bag. Pressure balancing is also necessary to ensure patient safety.

If the disposal system presents a negative pressure of 5 mmHg or less, balancing can be achieved by the usual adjustment of the scavenging popoff valve. Nonrebreathing systems, which are particularly sensitive to slight negative pressure balancing, require special attention. The bag outlets and the inhalation valve are connected so that waste anesthetic gases from the nonrebreathing valve are introduced into the exhalation valve and passed through the popoff valve to the disposal system. Proper bag inflation is maintained by adjustment of the circle popoff valve.

Negative pressures greater than 5 mmHg should be reduced using interfacing equipment for additional pressure equalization. Pressure balancing equipment is commercially available. An example of an interfacing unit, developed by Whitcher et al [159], that can be used for all scavenging disposal systems is shown in use (liquid-sealed interface device) in Figure XIII-9. Figure XIII-10 shows a scale drawing of this device. A reservoir bag of at least 2-liter capacity should be used with this system, as shown in Figure XIII-9. A scavenging flow of at least 30 liters/minute should be used with this device.

(b) Nose Mask Applications

Nitrous oxide is the most commonly used gas when nose masks are utilized in dental surgery, although sometimes volatile anesthetic agents, such as halothane, are used. These gases are delivered with a nose mask through an open breathing system with intermittent or continuous gas flow.

Whitcher et al [172] developed appropriate control procedures for nose mask applications. This system includes the use of a nose mask designed to scavenge any gas leakage, regardless of mask fit, and a small concentration-equalizing fan located so any anesthetic gases leaking into the dentist's breathing zone will be diluted and blown away from dental personnel.

The essential features of the scavenging nose mask are shown in Figure XIII-11. Such a device, or its equivalent, should be used for all anesthesia requiring a nose mask. A vacuum (scavenging) flow of at least 45 liters/minute should be maintained at the mask with the popoff valve adjusted to maintain proper breathing bag inflation.

(c) Anesthetist Work Practices

Whitcher et al [159] estimated that work practices of the anesthetist may contribute from 94 to 99% of all waste anesthetic gases in an operating room equipped with properly designed scavenging components. Improper practices, such as poor choice of the face mask, insufficiently inflated endotracheal tubes, and spillage of volatile anesthetic agents when filling vaporizers, are the chief contributors. Anesthetist work practices, as required in the recommended standard portion of this document, must be followed to reduce this contribution.

(d) Equipment Maintenance

Equipment maintenance is a key factor in the prevention of anesthetic gas leaks and in the prompt correction of leaks that do occur. The maintenance procedures presented are based on the fingings of the studies on equipment leakage discussed by Whitcher et al [159]. Leak test procedures are presented in Appendix I.

(1) Anesthesia machines should receive preventive maintenance at 3-month (minimum) intervals by the manufacturer's service representatives or by other qualified personnel. Following this maintenance, high-pressure leakage should be less than that which will raise room concentration to 2 ppm nitrous oxide. The low-pressure leak rate should be less than 100 ml/minute at 30 cm water, or an equivalent pressure drop in the breathing circuit.

(2) The low pressure systems of the anesthesia machines (from the flowmeters to the breathing tubes) should be leak-tested daily and whenever the soda-lime is changed. This can be readily done by hospital-based personnel.

(3) Ventilators should receive preventive maintenance at 4-month (minimum) intervals by service representatives or other qualified personnel.

(4) Breathing hoses attached to the anesthesia machines should be leak-tested as part of the low-pressure test. Breathing hoses associated with the T-tube, nonrebreathing system, and ventilators should be tested at 4-month intervals. All leaking hoses should be replaced.

(5) Breathing bags attached to the anesthesia machines should be leak-tested as a separate procedure at the time of the low-pressure test.

Other breathing bags associated with the T-tube, nonrebreathing system, and ventilators should be tested at 3-month intervals.

(6) Waste gas disposal tubing should be leak tested at 3-month intervals. Leaking tubing should be replaced.

(7) New equipment should be leak-tested by the manufacturer before being placed in service. Requirements of the recommended standard should be met.

VII. RESEARCH NEEDS

The recommended standard is based primarily on epidemiologic data and the level of anesthetic gases at which the first adverse effects of any type are seen. Adverse effects to the liver, kidneys, and central nervous system have been reported but are ill-defined. While not considered essential, this type of information should be obtained during the course of other studies.

Inferences and conjectures have been made about the mutagenic potential of anesthetic agents, yet no definitive studies have been reported on the matter. Animal testing of anesthetic agents for mutagenic potential is needed at both acute and chronic exposure concentrations.

Epidemiologic data suggest that there is a higher than normal incidence of congenital abnormalities in children born to exposed women or to wives of exposed personnel. In animals, the teratogenic potential of anesthetic agents has been reported under a variety of conditions but few studies attempted to simulate average occupational conditions. Because the limited data available on congenital abnormalities and spontaneous abortions among children born to wives of exposed dentists, further studies are needed to substantiate the presence or absence of this adverse health effect. This is particularly important because nitrous oxide is the principal inhalation anesthetic used in dentistry. Further animal studies are needed which more closely simulate occupational exposure to any of the anesthetic agents.

Two epidemiologic studies [12,75] have been cited which raise the issue of whether or not anesthetic agents have contributed to an increased

incidence of cancer in exposed female workers. There is an urgent need for a thorough animal study of the carcinogenic potential of the principal anesthetic agents in use at present. These studies should include chronic exposure to low-level concentrations.

A prospective health survey should be conducted to determine the effects of the improved working environment on the possible adverse effects on reproduction among exposed female workers and wives of male workers. This study should be conducted only after adequate data have been collected on the extent to which waste gas control programs have been implemented.

In April 1976, the Food and Drug Administration (FDA), on the recommendation of the Respiratory and Anesthetic Drugs Advisory Committee, proposed rules amending regulations on new drugs (21 CFR310) under the federal Food, Drug, and Cosmetic Act. This will require animal testing of halogenated inhalation anesthetics and nitrous oxide to determine the carcinogenic potential and reproductive effects, including teratogenicity potential, of such drug products (Federal Register 41:14888-14890, April 8, 1976). The FDA plans to hold meetings with federal research institutes, anesthesiologists, and anesthetic drug producers to establish a common protocol for animal testing so that interpretable data on the comparative potential risk of each drug may be developed.

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IX. APPENDIX I

LEAK TEST PROCEDURES FOR ANESTHETIC EQUIPMENT

Low-Pressure Components: Flowmeters to Y-Piece

This test measures the leak rate of low-pressure components in a carbon dioxide absorption system, beginning at the flowmeters and extending forward to the Y-piece. The test is easily performed with the breathing system connected in the usual manner for clinical anesthesia. The breathing bag and tubing are included and require no special testing. The total contribution of the gas machine tc nitrous oxide levels in the room air can be estimated by performing this test in combination with the high-pressure component test.

The low-pressure leak rate should be less than 100 ml/minute; if it is greater than 1 liter/minute the machine should not be used.

(a) Assemble the anesthesia machine as in the ususal manner for clinical anesthesia with breathing tubes, Y-piece, breathing bag, and high-pressure hoses or cylinders connected.

(b) Occlude the Y-piece securely with the thumb or palm of hand.

(c) Pressurize the breathing system to 30 cm water, observed on the absorber pressure gauge. This may be accomplished by using the oxygen flush valve.

(d) Add a sufficient flow of oxygen through the low-range flowmeter to maintain a constant pressure of 30 cm water in the breathing system. The oxygen flow required to maintain the pressure is a measure of the leak rate. This test may be abbreviated by using an oxygen flowrate of 100 ml/minute. If pressure in the system increases, the breathing system is below the maximum allowed leak rate.

(e) Determine the presence of check valves downstream from the flowmeters by consulting the manufacturer or a serviceman. These valves must be tested differently. With oxygen flowing as indicated in (d), briefly turn off in turn each flowmeter which is equipped with a check valve until there is a rise in pressure on the absorber gauge. An increase in pressure indicates absence of leakage in the circuit tested.

High-Pressure Components: Hose Connections at Wall to Flowmeters

High-pressure components include wall connectors, supply hoses, connectors at rear of gas machine, and plumbing within the machine up to the flowmeter control valves. Potential leak sites are numerous and leak testing with conventional methods (soap solution) is cumbersome. A convenient method for rapidly testing all rooms in the suite employs the infrared nitrous oxide analyzer. The principle of the test is that at a given fresh air exchange rate, provided by the air-conditioning system and assuming perfect mixing of gases, a given leak rate of nitrous oxide into the room air equilibrates at a predictable concentration. A relatively leak-free high-pressure system will contribute less than 1 ppm nitrous oxide to the room concentration. Room concentrations in excess of 5 ppm nitrous oxide indicate excessive leakage, which should be corrected. High-pressure leak tests should be conducted quarterly.

(a) Do not use the machine for at least 1 hour prior to the test. High pressure hoses must be attached.

(b) Use a nitrous oxide analyzer in each room to determine and record the nitrous oxide concentration.

Scavenging Tubing

Scavenging tubing leading from relief (popoff) valve to interface, if used, to disposal system is leak tested quarterly.

(a) Pressurize the tubing to 10 mmHg.

(b) No pressure drop, except for the initial fall due to stretching of materials, should be noticeable during a 15-second observation period.

Ventilators and Miscellaneous Equipment

No reasonably simple rapid method has been developed to screen ventilators for leakage. Careful assembly following cleaning and quarterly preventive maintenance by qualified servicemen will minimize leakage. When unexpectedly high nitrous oxide concentrations are detected during surgery, the ventilator should be suspected. In cases involving excess leakage, connect the ventilator to the anesthesia machine in conjunction with a test lung, and search for leakage using a gas analyzer, soap solution, etc.

Other equipment such as special bags not associated with the circle system, tubing, and miscellaneous accessories should be inspected at least quarterly.

Accessory Flowmeter: Pressure-Gauge Method

If the anesthetic machine is not equipped with a low-range flowmeter or pressure gauge, they can be applied at the anesthetic gas outlet by attaching a "T" connector in the gas delivery tubing. The low-pressure leak test procedures are then completed, with the precaution that the

tubing be occluded between the absorber and the "T."

Immersion Method for Localizing Leakage in Absorber

Employ immersion testing to identify leakage not found by less cumbersome methods. Prepare the machine according to the first three steps in the low pressure test. Precaution must be taken concerning pressurization and the possibility of subsequent damage to the pressure gauge. Caution: the gauge must be kept dry, and screening should be installed if necessary to prevent soda lime from entering the breathing-hose connectors.

Tests to Determine Leakage in Miscellaneous Equipment

Equipment such as breathing bags, hoses, and devices with metal-to-metal connections suspected of leakage are tested by standard procedures (standard soap solution. leak detectors, and pressurization-immersion).

Leakage from ventilators exists when trace gas concentrations increase when ventilators are in use. After cleaning, inspect the components and assemble with care, checking that all gaskets are in place and properly fitted.

X. APPENDIX II

SAMPLING PROCEDURES FOR COLLECTION OF ANESTHETIC GASES

An evaluation of several available sampling and analysis methods was made by Whitcher et al [159] under NIOSH contracts HSM 99-73-73 and CDC 210-25-0007. All the methods tested were shown to be feasible. Table XII-6 presents some of the sampling and analytical equipment available for air monitoring programs.

General Requirements

(a) Air samples representative of the breathing zones of the most heavily exposed workers (anesthetist, oral surgeon) must be collected to characterize the exposure from each job or specific operation in each work area.

(b) Samples collected must be representative of exposure of individual workers.

(c) Suggested records:

(1) The date and time of sample collection.

(2) Sampling duration.

(3) Total sample volume.

(4) Location of sampling.

(5) Temperature, pressure, and relative humidity at time of sampling.

(6) Other pertinent information.

Sampling

(a) Samples should be collected as near as practicable to the breathing zone of workers without interfering with freedom of movement.

(b) Samples should be collected to permit determination of TWA workday exposures for every job involving exposure to anesthetic gases in sufficient numbers to express the variability of the exposures in the work situation.

Charcoal Tube Sampling

Charcoal tube sampling is possible for many of the volatile agents (halothane, trichloroethylene, methoxyflurane, etc). A general procedure is presented.

(a) Apparatus

(1) Pump, battery-operated, complete with clip for attachment to the worker. Airflow through the pump shall be within 5% of the desired rate.

(2) Charcoal tubes: Glass tube with both ends flame-sealed, 7-cm long, 6-mm O.D. and 4-mm I.D., containing two sections of 20/40 mesh activated coconut shell charcoal separated by a 2-mm portion of urethane foam. The first is the adsorbing section and contains 100 mg of charcoal from coconut shells. The second, or reserve section, contains 50 mg. A 3-mm portion of urethane foam is placed between the outlet of the tube and the reserve section. A plug of glass wool is placed in front of the adsorbing section. The pressure drop across the tube when in use must be less than 1 inch of mercury at a flowrate of 1 liter/minute.

(b) Calibration of Sampling Instruments

(1) Air sampling instruments should be calibrated with a representative charcoal tube in line, over a normal range of flowrates (25-1,000 ml/minute). Calibration curves must be established for each sampling pump and should be used in adjusting the pump prior to and during each field use. New calibration curves should be established for each sampling pump after making any repairs or modifications to the sampling system.

(2) The flowrate through the sampling system should be spot checked and the proper adjustments made before and during each study to ensure obtaining accurate airflow data.

(c) Collection and Handling of Samples

(1) Immediately before sampling, break both ends of the tube to provide openings at least one-half the I.D. of the tube (2 mm).

(2) The smaller section of charcoal is used as a reserve and should be positioned nearest the sampling pump.

(3) The charcoal tube should be placed in a vertical position during sampling.

(4) Tubing may be used to connect the back of the tube to the pump, but air being sampled should not be passed through any hose or tubing before entering the charcoal tube.

(5) The sample can be taken at flowrates of 25-1,000 ml/minute, depending on the pump. Total sample volumes of 1-12 liters are recommended, eg, a sample could be collected at 200 ml/minute for 15 minutes to give a total sample of 3 liters, or at 25 ml/minute for 8 hours to give a total sample volume of 12 liters. However, it is also recommended that each sample be collected in 4 hours or less.

(6) Samples should be collected over 15-minute periods at times when the highest exposure is expected. The TWA determination can be made from collecting a series of 15-minute samples.

(7) The charcoal tubes should be capped with inert plastic caps immediately after sampling. Under no circumstances should rubber caps be used.

(8) One charcoal tube, serving as an analytical blank, should be handled in the same manner as the sample tube (break, seal, and transport) except that no air is sampled through this tube.

Bag Sampling

Using sample bags or evacuated containers is a second method for collecting air samples to be analyzed for anesthetic gas content. Infrared or gas chromatographic methods of analysis may be used for samples collected in this manner.

(a) Apparatus

(1) A peristaltic sampling pump, diaphragm pump, or vacuum pump with filtered outlet to remove oil should be used.

(2) Sampling bags of Tedlar, Mylar, or Saran, or evacuated containers may be used.

(b) Collection of Samples

The sampling containers should be flushed or evacuated before use. Obtain samples by filling the sampling containers with air either by using a sampling pump to fill a bag or by opening the valve on an evacuated container and allowing it to reach atmospheric pressure. After the sample has been taken, all parts should be sealed to minimize leakage in or out of

the containers. Care must be taken not to alter or damage the existing sample while transporting it to the laboratory.

Syringe Sampling

A clean, gastight, grease-free syringe should be filled in a representative exposure area. The syringe must be capped and the sample analyzed by a satisfactory method. Disadvantages of this sampling technique include failure to give a representative exposure level from a single sample and vulnerability to hot spots usually occurring during normal anesthetic procedures. Multiple samples over a period of time will be necessary to obtain a representative exposure level.

XI. APPENDIX III

ANALYTICAL PROCEDURE FOR DETERMINATION OF HALOTHANE BY GAS CHROMATOGRAPHY

The analytical procedure presented in this appendix is adaptable to a number of anesthetic agents including trichloroethylene, fluroxene, methoxyflurane, enflurane, and nitrous oxide. Only modification of the chromatographic operating conditions should be necessary. Halothane, because of its predominant use, is used here as an example compound.

Principle of the Method

(a) A known volume of air is drawn through a charcoal tube to trap the halothane vapor.

(b) The halothane is desorbed from the charcoal with carbon disulfide.

(c) An aliquot of the desorbed sample is injected into a gas chromatograph.

(d) The area of the resulting peak is determined and compared with areas obtained from the injection of standards.

Range and Sensitivity

(a) The lower limit for detection of halothane on a gas chromatograph with a flame ionization detector is 1μg/sample.

(b) The upper limit value for halothane is 4.0 mg/sample. This is the estimated amount of halothane which the front section will hold before this compound breaks through to the reserve section of charcoal. If a

particular atmosphere is suspected of containing a high concentration of halothane, it is recommended that a smaller volume of air be sampled.

Interferences

(a) Halothane cannot be trapped when the amount of water in the air is so great that condensation occurs in the charcoal sampling tube.

(b) Any compound which has the same retention time as halothane with the chromatographic conditions described in this method could interfere. These can be eliminated by altering operating conditions of the gas chromatograph using a different column packing or using a selective detector, ie, electron capture.

Advantages of the Method

(a) This method provides one basic method for determining many different organic compounds.

(b) The sampling device is small, portable, and involves no liquids.

(c) The analysis of the tubes can be accomplished rapidly.

Disadvantages of the Method

(a) The amount of sample which can be taken is limited by the weight of halothane which the tube will hold before overloading.

(b) When the sample value obtained for the reserve section of charcoal exceeds 25% of that found on the front section, the possibility of appreciable sample loss exists.

(c) Other organic compounds in high concentrations may displace halothane from the charcoal.

Apparatus

(a) Gas chromatograph equipped with a flame ionization detector.

(b) Stainless steel column (6 m x 3 mm) with 10% free fatty acid polymer (FFAP) stationary phase on 80/100 mesh Chromosorb W (or equivalent), acid-washed and treated with dimethyldichlorosilane.

(c) A recorder and some method for determining peak area.

(d) Glass-stoppered microtubes of 2.5-ml capacity or 2-ml vials that can be sealed with inert caps.

(e) Microsyringe of 10-μl capacity, and convenient sizes for making standards.

(f) Pipets 0.5-ml delivery pipets or 1.0-ml pipets graduated in 0.1-ml increments.

(g) Volumetric flasks of 10-ml capacity or convenient sizes for making standard solutions.

Reagents

(a) Spectroquality carbon disulfide.

(b) Halothane, preferably chromatoquality grade.

(c) Bureau of Mines Grade A helium.

(d) Prepurified hydrogen.

(e) Filtered compressed air.

Analysis of Samples

(a) All equipment used in the analysis should be washed in detergent followed by appropriate tap and distilled water rinses.

(b) Preparation: Each charcoal tube is scored with a file in front of the first section of charcoal and broken open. The glass wool is removed and discarded. The charcoal in the first (larger) section is transferred to a small stoppered test tube. The separating foam is removed and discarded; the second section is transferred to another similar tube or vial. These two sections are analyzed separately. Prior to analysis, 0.5 ml of carbon disulfide is pipetted into each test tube to desorb halothane from the charcoal. Do not pipette by mouth.

EXTREME CAUTION MUST BE EXERCISED AT ALL TIMES WHEN USING CARBON DISULFIDE BECAUSE OF ITS HIGH TOXICITY AND FIRE AND EXPLOSION HAZARDS. IT CAN BE IGNITED BY HOT STEAM PIPES. ALL WORK WITH CARBON DISULFIDE MUST BE PERFORMED UNDER AN EXHAUST HOOD.

(c) Typical chromatographic operating conditions:

(1) 40 ml/minute (70 psig) helium carrier gas flow.

(2) 65 ml/minute (24 psig) hydrogen gas flow to detector.

(3) 500 ml/minute (50 psig) airflow to detector.

(4) 200 C injector temperature.

(5) 200 C manifold temperature (detector).

(6) 60 C isothermal oven or column temperature.

(d) Injection: The first step in the analysis is the injection of the sample into the gas chromatograph. To eliminate difficulties arising from blowback or distillation within the syringe needle, the solvent flush injection technique is employed. The 10-μl syringe is first flushed with carbon disulfide several times to wet the barrel and plunger. Three microliters of carbon disulfide are drawn into the syringe to increase the accuracy and reproducibility of the injected sample volume. The needle is removed from the carbon disulfide solvent, and the plunger is pulled back about 0.2 μl to separate the solvent flush from the sample, with a pocket of air to be used as a marker. The needle is then immersed in the sample, and a 5-μl aliquot is withdrawn, taking into consideration the volume of the needle, since the sample in the needle will be completely injected. After the needle is removed from the sample and prior to injection, the plunger is pulled back a short distance to minimize evaporation of the sample from the tip of the needle. Duplicate injections of each sample and standard should be made. No more than a 3% difference in area is to be expected.

(e) Measurement of area: The area of the sample peak is determined and preliminary sample results are read from a standard curve prepared as discussed below.

Determination of Desorption Efficiency

It is necessary to determine the percentage of halothane on the charcoal that is removed in the desorption process. This desorption efficiency is determined once for a given compound provided the same batch of charcoal is always used.

Activated charcoal, equivalent to the amount in the first section of the sampling tube (100 mg), is measured into a 2-inch long tube, with an inside diameter of 4 mm, flame-sealed at one end. This charcoal must be from the same batch used in obtaining the samples and can be obtained from unused charcoal tubes. The open end is capped with inert plastic. A known amount of the compound is injected directly into the activated charcoal with a microliter syringe, and the tube is capped with inert plastic.

A minimum of six tubes are prepared in this manner and allowed to stand at least overnight to ensure complete adsorption of halothane onto the charcoal. These six tubes will be referred to as the "desorption samples." A parallel blank tube should be treated in the same manner except that no halothane is added to it. The desorption samples and blanks are desorbed and analyzed in exactly the same manner as previously described.

Two or three desorption standards are prepared for analysis by injecting the same volume of halothane into 0.5 ml of carbon disulfide with the same syringe used in the preparation of the desorption samples. These are analyzed with the desorption samples.

The desorption efficiency equals the difference between the average peak area of the desorption samples and the peak area of the blank divided by the average peak area of the desorption standards, or

$$\text{desorption efficiency} = \frac{\text{area of sample} - \text{area of blank}}{\text{area of standard}}$$

Calibration and Standards

It is convenient to prepare standards in terms of mg halothane/0.5 ml of carbon disulfide because samples are desorbed in this amount of carbon disulfide. To minimize error due to the volatility of carbon disulfide, 20 times the weight can be injected into 10 ml of carbon disulfide. For example, to prepare a 0.3 mg/0.5 ml standard, 6.0 mg of halothane is injected into exactly 10 ml of carbon disulfide in a glass-stoppered flask. The density of halothane (1.86 g/ml) is used to convert 6.0 mg into microliters for easy measurement with a microliter syringe. A series of standards is prepared, varying in concentration over the range of interest and analyzed under the same gas chromatographic conditions and during the same time period as the unknown samples. Curves are established by plotting concentration versus average peak area.

Calculations

(a) The weight in mg corresponding to the peak area is read from the standard curve. No volume corrections are needed, because the standard curve is based on mg halothane/0.5 ml carbon disulfide, and the volume of sample injected is identical to the volume of the standards injected.

(b) Separately determine the weights of halothane on the front and reserve sections of the charcoal tube.

(c) Corrections must be made to the halothane weights determined on both the front and reserve sections for the weights of the respective sections of the blank charcoal tube.

(1) Subtract the weight of halothane found on the front section of the blank charcoal tube from the weight of halothane found on

the front section of the sample charcoal tube to give a corrected front section weight.

(2) Subtract the weight of halothane found on the reserve section of the blank charcoal tube from the weight of halothane found on the reserve section of the sample charcoal tube to give a corrected reserve section weight.

(3) Add the corrected amounts of halothane present on the front and reserve sections of the sample tube to determine the total measured halothane in the sample.

(4) Divide this total weight by the determined desorption efficiency to obtain M, the total mg/sample.

(d) Convert the liters of air sampled (V) to volume (V') at standard conditions of 25 C and 760 mmHg, as follows:

$$V' = \frac{298VP}{760(T+273)} = \frac{0.392VP}{(T+273)}$$

where:

V' = volume of sampled air in liters at 25 C and 760 mmHg

V = measured volume of sampled air in liters

P = barometric pressure in mmHg, measured at time of sampling

T = temperature of air in degrees celsius, measured at time of sampling

(e) The concentration of halothane in the sampled air can be expressed in various ways using M, the weight of halothane obtained in (c)(4), and V', the standardized sample volume, obtained in (d), as follows:

(1) mg/liter = M/V'

(2) mg/cu m = g/liter = 1,000 M/V'

(3) ppm = 124.1 M/V'

XII. APPENDIX IV

ANALYTICAL PROCEDURE FOR DETERMINATION OF ANESTHETIC GASES BY INFRARED SPECTROPHOTOMETRY

Principle of the Method

Air is passed directly through portable infrared (IR) instruments, through tubing to remote IR instruments, or air samples are collected in plastic bags, evacuated containers, or syringes and analyzed by IR. Analysis by IR is dependent on the total number of anesthetic agent molecules introduced into the sample cell.

Range and Sensitivity

(a) The lower limit for detection of gases by IR depends on the path length and volume of the gas cell.

(b) Portable IR units should have a minimum working range of 1 to at least 100 ppm for nitrous oxide and 0.05-2 ppm for halothane. Instruments with this capability are available.

Interferences

Many compounds present in operating rooms and dental suites may interfere with IR analysis of anesthetic agents if present in significant concentrations. Some interfering compounds are formal in, isopropyl alcohol, ethyl alcohol, carbon dioxide, and water vapor.

Advantages of the Method

For continuous IR monitoring, the sampling and analysis is nearly a simultaneous operation. Exposed workers and those responsible for air monitoring are given an immediate indication of control system efficiency. When operating on battery power, a great advantage of a portable IR unit is the number of areas that can be sampled. One portable unit may be used to monitor operating areas, recovery rooms, storage and pipeline areas, and other exposure areas.

Disadvantages of the Method

A continuous sampling IR system currently costs approximately $2,500. Portable IR units are also expensive but may be more feasible because of their versatility.

Apparatus

(a) Various types of infrared spectrophotometers are available. A representative sample of suppliers is listed below. Completeness of the list cannot be guaranteed and inclusion in the list does not constitute official NIOSH endorsement.

Air Products and Chemicals, Inc., P.O. Box 538, Allentown, Pennsylvania 18105

Cavitron/DKC Corporation, 1528 West Embassy Street, Anaheim, California 92802

Ohio Medical Products, P.O. Box 1319, Madison, Wisconsin 53701

Wilks, P.O. Box 449, South Norwalk, Connecticut 06856

(b) For remote monitoring, a high volume vacuum pump with a capacity of 25-30 liters/minute and sample probe lines, such as polyethylene tubing. Sampling distances up to 200 feet may use 0.5-inch I.D. tubing; greater lengths should use 3/4-inch I.D. tubing to prevent pressure drop. Tubing should be unreactive to groups of chemicals usually found where anesthetic agents are used, eg, alcohols, cleaning agents, etc.

(c) Manometer and vacuum pump (capable of reducing pressure to 1 mmHg).

(d) Gastight syringes (100μl, 500μl, 1,000μl).

(e) Gas tank regulators, connections, and needle valves for introducing dilution gas, anesthetic gas, and samples.

Reagents

(a) Spectroquality nitrous oxide, halothane, or any other frequently used inhalation anesthetic.

(b) Pure air, nitrogen, argon, oxygen, etc, to zero the instrument and prepare calibration samples.

Analysis of Samples

(a) The gas cell is connected to a manometer via a "T" connection and evacuated to approximately 1 mmHg.

(b) The sample is introduced into the cell. If a rigid sample container is used, the equilibrium pressure (Pe) must be noted and the cell filled to atmospheric pressure with the zero gas. A 15-minute waiting

period before analysis is necessary to establish equilibrium.

(c) The spectrum is scanned from 4-10 μ and the absorbance at 4.48 μ is used to determine nitrous oxide content. The absorbance at 8.8 μ is used to determine halothane or other halogenated anesthetic agent content of the samples. Absorbance is measured by the baseline technique.

Calibration and Standards

(a) The volume of the gas cell is determined by standard techniques. The simplest procedure is to evacuate the cell and then bring it to atmospheric pressure by permitting air to enter via a wet-test meter. The volume of the cell is the volume of air shown on the meter. After the volume has been determined, the cell is evacuated and known volumes of gaseous agents (eg, nitrous oxide) or samples of a known volatile agent in a zero-gas mixture (eg, halothane-nitrogen) are added using gastight syringes. Standard samples may be introduced through a rubber serum cap attached to the inlet of the cell, or through the rubber tubing which connects the gas cell with the tank of dilution gas. An alternative is to use a set of serial dilutions that span the concentrations of interest. The pressure in the cell is brought to atmospheric pressure with zero gas and the appropriate absorbance is measured.

(b) The anesthetic agent concentration is calculated from the quantity of agent added and the volume of the cell. For example, 1.0 ml nitrous oxide in a 2.5-liter cell gives a concentration of 400 ppm. With a volatile agent, such as halothane, 1.0 ml of a gas mixture known to contain 500 ppm or 0.5 μl halothane vapor, when introduced into a 2.5-liter cell, results in a cell concentration of 0.2 ppm halothane. A calibration curve

relating absorbance to concentration is prepared from a series of known volumes of an anesthetic agent introduced into the IR cell.

Calculations

(a) The concentration of the unknown is read from the calibration curve. To calculate the standard curve concentrations in parts per million (ppm), the following equation may be used:

$$\text{Sample concentration (ppm)} = \frac{V'}{V}$$

where:

V' = Volume of anesthetic gas added (μl)

V = Volume of IR cell (liter)

(b) The observed concentration from the calibration curve is corrected for the volume of the sample actually introduced into the cell. For samples introduced into the cell with syringes, the volume is readily known and the correction applied using the following equation:

$$\text{(ppm)} = C \times \frac{V}{V'}$$

where:

C = Observed concentration from the calibration curve

V = Volume of IR cell (liters)

V' = Volume of sample cell (liters)

For samples introduced from nonrigid bags with volumes greater that the IR cell, V' = V and the sample concentration = C.

(c) For samples introduced by pressure measurements, the sample concentration is calculated as follows:

$$\text{Sample concentration (ppm)} = C \times \frac{Pa}{Pa-Pe}$$

where:

C = Observed concentration from the calibration curve (ppm)

Pe = Equilibrium pressure after connecting the sample container to the IR cell

Pa = Atmospheric pressure

XIII. TABLES AND FIGURES

TABLE XIII-1

SELECTED PROPERTIES OF INHALATION ANESTHETICS

Anesthetic Agent	Common Synonyms	Molecular Formula and Weight		Boiling Point	Vapor Density (Air=1)
Diethyl ether	Ethyl ether Ether	CH3CH2 O CH2CH3	74.14	-35 C	2.6
Cyclopropane	Trimethylene	C3H6	42	-34 C	1.4
Chloroform	Trichloro-methane	CHC1 3	119.3	61 C	4.1
Nitrous oxide	Nitrous	N2 O	44	-88 C	1.5
Halothane	Fluothane	CF3CHBrC1	197.4	50 C	6.9
Trichloro-ethylene	Ethylene trichloride Trilene	CHC1CC12	131.4	87 C	4.5
Fluroxene	Fluoromar	CF3CH2 O CHCH2	126	43.2 C	4.4
Methoxy-flurane	Penthrane	CHC12 CF2 O CH3	165	104 C	5.7
Enflurane	Ethrane	CHC1FCF2 O CHF2	184.5	56 C	6.4

TABLE XIII-1 (CONTINUED)

SELECTED PROPERTIES OF INHALATION ANESTHETICS

Anesthetic Agent	Specific Gravity (Water=1)	Vapor Pressure mmHg (20 C)	Flammable (Explosive) Limits by Volume in Air	Chemical Abstract's Serial No.	Blood/Gas Partition Coefficient	M.A.C.* Vol %**
Diethyl ether	0.72	425	1.85-36.0%	000060297	15	2.5
Cyclopropane	0.68		2.4-10.3%	000075194	0.46	13
Chloroform	1.47	160	Nonflammable	000067663	10.3	0.62
Nitrous oxide	1.23		"	010024972	0.47	120
Halothane	1.87	243	"	000151677	2.3	0.74
Trichloro-ethylene	1.50	58		000079016	9.15	0.17
Fluroxene	1.13	286	4.2%	000406906	1.37	3.4
Methoxyflurane	1.42	23	7.0%	000076380	13.0	0.20
Enflurane	1.52	175		013838169	1.9	1.7

*M.A.C.= minimum alveolar anesthetic concentration
**1 vol% = 10,000 ppm

From references 1-11

TABLE XIII-2

SUMMARY OF ANESTHETIC GAS CONCENTRATIONS IN LOCATIONS WITHOUT WASTE GAS SCAVENGING

Gases Sampled	Sampling Site	Concentration, ppm Range	Mean	Reference
Nitrous oxide	General air, OR	0-448	130	131
Halothane	"	0-27	10	131
Nitrous oxide	Anesthetist, OR		6,000	132
Halothane	"		85	132
Halothane	"	0-28	8	133
Methoxyflurane	Anesthetist, OR	2-10		134
	Surgeon, OR	1-2		134
Nitrous oxide	Anesthetist, OR	330-9,700		134
	Surgeon, OR	310-550		134
Trichloro-ethylene	Anesthetist, OR	1-103		135
	Surgeon, OR	0.3-1.5		135
Halothane	Anesthetist, OR		8.6	136
Nitrous oxide	"		929	137
Halothane	"		10	137
Nitrous oxide	Personnel, OR		146	137
Halothane	"		3	137
Nitrous oxide	Anesthetist, OR	60-4,900	1,080	138
Halothane	"	3-57	11	138
Nitrous oxide	Personnel, OR	20-1,600	305	138
Halothane	"	1-8	3	138
"	Patient, RR	0.4-0.6		139
"	"	0-0.3 after 1 hr		139
"	Anesthetist, OR	14-59 (TWA)		140

TABLE XIII-2 (CONTINUED)

SUMMARY OF ANESTHETIC GAS CONCENTRATIONS IN LOCATIONS WITHOUT WASTE GAS SCAVENGING

Gases Sampled	Sampling Site	Concentration, ppm Range	Mean	Reference
Halothane	Anesthetist, OR	1-60		141
"	Nearby office	0.4-6		141
Halothane	Anesthetist, DO		23	142
"	"		25	142
"	Surgeon, DO		68	142
"	"		18	142
Trichloro-ethylene	Anesthetist, DO	25-50	25	143
Halothane	Anesthetist, OR	1-14		144
Nitrous oxide	General air, OR	0-1,300	177	145
Halothane	"	0-199	12	145
Enflurane	"	0-234	10	145
Nitrous oxide	General air, DO	94-3,000	793	145
Halothane	"	1.5-36	15.5	145
Nitrous oxide	Dentist, DO		6,767	146
	Dental assistant, DO		5,867	146
Halothane	General air, OR	0-1.6		148
"	Anesthetist, OR	0.1-14	11	149
Nitrous oxide	Personnel, OR	5-6,000	525	150,170
"	"	150-3,000	430	150,170
"	"	20-6,000		150,170
Halothane	"	0-21	3.5	150,170
"	"	0.3-7		150,170
"	"	0.4-29	1.0	150,170

OR=operating room
DO=dental office
RR=recovery room

TABLE XIII-3

SUMMARY OF ANESTHETIC GAS CONCENTRATIONS IN LOCATIONS WITH WASTE GAS SCAVENGING

Gases Sampled	Sampling Site	Concentration Mean, ppm	Waste Gas Control Method	Reference
Halothane	Anesthetist, OR	0.79	Scavenging to wall suction	136
"	"	0.73	"	136
Nitrous oxide	Anesthetist, OR	135	"	137
Halothane	"	0.85	"	137
Nitrous oxide	"	24	Scavenging to air conditioning exhaust grille	173
Halothane	"	1-2	Scavenging to wall suction	141
Nitrous oxide	General air, OR	35	Not given	145
Halothane	"	0.24	"	145
Enflurane	"	0.9	"	145
Halothane	Anesthetist, OR	0.2	Venting to pipe in floor plus 10 room air changes/hr	149
Nitrous oxide	General air, OR	15	Scavenging to	159
"	Anesthetist, OR	18	air-conditioning	159
"	Surgeon, OR	17	exhaust grille,	159
	Scrubnurse, OR	13	all leaks in	159
"	Circulating nurse, OR	14	machine repaired	
"	Dentist, DO	14	Double suction	172
	Anesthetist,DO	7	mask, mouth hook,	
	General air, DO	13	and fan	

OR=operating room
DO=dental office

TABLE XIII-4

CONCENTRATIONS OF NITROUS OXIDE IN ROOM AIR DURING ANESTHESIA WITH SCAVENGING

Anesthetic Technique	No. of Syringe Samples	Average Concentration of N20 (ppm)
Mask	75	36 ± 6.7*
Endotracheal tube	76	15 ± 2.4
Endotracheal tube with ventilator	57	34 ± 7.8
All samples	208	28 ± 3.4

*Standard error

Adapted from Whitcher et al [159]

TABLE XIII-5

COMPARISON OF NITROUS OXIDE CONCENTRATIONS
BY SAMPLE SITE WITH SCAVENGING IN USE

Sample Site	N20 Concentrations ppm ± S.E.*
Exhaust Grille	15 ± 2.7
Anesthetist Breathing Zone	18 ± 2.9
Surgeon's Breathing Zone	17 ± 5.0
Scrub Nurse	13 ± 3.2
Circulating Nurse	14 ± 2.8
Door	14 ± 2.8

*Standard error

Adapted from Whitcher et al [159]

TABLE XIII-6
CLASSIFICATION OF COMMONLY USED
INHALATION ANESTHETIC SYSTEM

(a)	Without CO2 Absorption		
	(1)	Open drop	
	(2)	Insufflation	
	(3)	Mapleson types (semi-closed)	
		(A)	Magill
		(B)	T-tube
	(4)	Nonreturn (nonrebreathing)	
(b)	With CO2 absorption		
	(1)	To-and-fro system	
	(2)	Circle system	
		(A)	Closed system
		(B)	Partial rebreathing (semi-closed)

TABLE XIII-7

HOSPITALS SURVEYED ACCORDING TO
AMERICAN HOSPITAL ASSOCIATION CATEGORIES

Institutional Category	Total Number of Hospitals Within Each Category	Number of Hospitals Surveyed
Governmental, Non-federal	526	400
Non-gov't, Not for Profit	1,963	400
Non-gov't, for Profit	170	170
Governmental-federal	206	206
Osteopathic	77	77
Total	2,942	1,253

Derived from reference 175

TABLE XIII-8

SUMMARY OF SURVEY RESPONSE RATE
BY HOSPITAL CATEGORY

Institutional Category	Total Surveys Mailed	Total Responses Received	% Responses
Governmental, Non-federal	400	302	75
Non-gov't, Not for Profit	400	344	86
Non-gov't, for Profit	170	124	72
Governmental-federal	206	182	88
Osteopathic	77	58	75
Total	1,253	1,009	80

Derived from reference 175

TABLE XIII-9

PERCENTAGE OF ALL HOSPITALS THAT REPORTED USING THE VARIOUS ANESTHETIC AGENTS ACCORDING TO HOSPITAL SIZE

Anesthetic Agents	Hospital Size (No. of Beds) 100-200	200-300	300-500	>500	Not Reported
Nitrous oxide	99.4	100	100	100	94.6
Halothane	97.1	99.5	99.5	100	91.3
Enflurane	42.9	53.6	69.0	68.5	40.9
Isoflurane	1.6	0.5	2.1	1.5	2.2
Methoxyflurane	57.5	56.2	66.3	66.2	57.0
Diethyl ether	19.8	27.9	20.9	30.0	19.4
Trichloroethylene	2.3	6.6	3.7	8.5	6.5
Cyclopropane	47.7	48.3	47.4	50.0	47.6
Chloroform	0.6	1.6	0.6	0.8	0.0
Other	17.5	16.4	20.3	23.1	15.1

Derived from reference 175

TABLE XIII-10

PERCENTAGE OF ALL CASES UTILIZING
VARIOUS ANESTHETIC AGENTS ACCORDING TO HOSPITAL SIZE

Anesthetic Agents	Hospital Size (No. of Beds) 100-200	200-300	300-500	>500	Not Reported
Nitrous oxide	91.9	97.3	92.1	89.1	84.7
Halothane	56.8	50.4	51.9	46.8	49.9
Enflurane	11.3	17.0	15.1	14.9	9.4
Isoflurane	0.4	0.1	0.1	0.2	0.1
Methoxyflurane	6.9	5.7	5.1	5.3	6.3
Diethyl ether	1.8	1.0	0.8	0.9	0.8
Trichloroethylene	0.5	0.8	0.1	0.3	0.1
Cyclopropane	3.0	2.9	3.2	4.1	2.8
Chloroform	0.1	0.5	3.2	0.0	0.0
Other	3.9	3.3	5.0	6.2	4.1

Derived from reference 175

TABLE XIII-11

AVERAGE PERCENTAGE UTILIZATION OF THE ANESTHESIA BREATHING CIRCUITS ACCORDING TO HOSPITAL SIZE

Anesthesia Breathing Circuit	Hospital Size (No. of Beds) 100-200	200-300	300-500	>500	Not Reported
Semiclosed and partial rebreathing	81.9	89.6	84.0	82.5	77.9
Nonrebreathing	9.5	10.9	8.2	7.6	10.7
To-and-fro absorption	2.4	2.2	0.9	0.3	0.1
Closed circle	2.6	1.7	2.0	5.2	2.8
Open drop	0.5	0.3	0.6	0.2	0.5

Derived from reference 175

TABLE XIII-12

AVERAGE PERCENTAGE UTILIZATION OF THE VARIOUS METHODS OF INHALATION ANESTHESIA ADMINISTRATION ACCORDING TO HOSPITAL SIZE

Method of Inhalation Anesthesia Administration	Hospital Size (No. of Beds)				Not Reported
	100-200	200-300	300-500	>500	
Insufflation	1.7	0.9	1.1	1.6	0.8
Endotracheal	54.2	58.7	61.1	65.2	65.2
Face mask (excluding open drop)	43.4	40.2	36.6	30.8	41.4
Other	1.1	0.7	1.1	1.1	1.8

Derived from reference 175

TABLE XIII-13

PERCENTAGE OF ALL HOSPITALS THAT REPORT USING WASTE ANESTHETIC GAS SCAVENGING* ACCORDING TO HOSPITAL SIZE

Hospital Size (No. of Beds)	Percentage Using Waste Anesthetic Gas Scavenging
100-200	65.0
200-300	73.8
300-500	74.9
>500	75.2
Not Reported	65.6

*Scavenging techniques considered are the use of either connections to the nonrecirculating air-conditioning system, central vacuum system, or a special duct system to vent waste gases from the operating room. Venting to the floor, if reported, was not considered waste anesthetic gas scavenging.

TABLE XIII-14

ANESTHETIC GAS INHALATION EXPOSURES AND EFFECTS ON HUMANS

Exposure Variables	Exposure Time	Effects	Reference
Trichloroethylene, 110 ppm	Two 4-hr periods	Decrements in performance ability	44
Trichloroethylene, 1,000 ppm	2 hr	Developed optokinetic nystagmus	40
Trichloroethylene, 100, 300, 1,000 ppm	"	Psychophysiologic decrements at 1,000 ppm	41
Trichloroethylene, 100, 200, 300, 500 ppm	2.5 hr	Psychophysiologic decrements at 300 and 500 ppm	42
Trichloroethylene, 265 and 211 ppm (TWA)	83 and 190 min	No effect reported	43
Trichloroethylene, 200 ppm	7 hr/d for 5 d	"	
Trichloroethylene, 110 ppm	4 hr	"	
Nitrous oxide, 500 ppm	Two 4-hr exposures	Digit-span test decrements	47
Nitrous oxide, 500 ppm plus halothane, 15 ppm	"	Psychologic performance decrements	
Nitrous oxide, 500 ppm plus enflurane, 15 ppm	4 hr	"	
Nitrous oxide, 50 ppm plus halothane, 1 ppm	2-4 hr	Memory, cognition, and psychomotor decrements	49
Nitrous oxide, 50 ppm	"	Audiovisual performance decrements	49
Diethyl ether, nitrous oxide, halothane, and other agents	During work hours (survey)	Increased headache, fatigue, nausea, spontaneous abortions	69

TABLE XIII-14 (CONTINUED)

ANESTHETIC GAS INHALATION EXPOSURES AND EFFECTS ON HUMANS

Exposure Variables	Exposure Time	Effects	Reference
Specific agents not given	During work hours (mortality study)	Increased suicide and malignancies	70
"	During work hours (survey)	Increased spontaneous abortions, premature deliveries, fewer males born	72
"	During work hours (interview and survey)	Increased spontaneous abortions	73
"	During work hours (survey)	Increased spontaneous abortions, congenital anomalies, and involuntary infertility	74
"	"	Increased incidence of cancer among nurses	75
"	"	Increased incidence of congenital anomalies	75
"	"	Increased incidences of spontaneous abortions, congenital anomalies, hepatic and renal diseases, and cancer	12 13
"	1 yr and 8 mon before and during pregnancy (survey)	Increased incidences of spontaneous abortions, congenital anomalies, and premature births	77

TABLE XIII-14 (CONTINUED)

ANESTHETIC GAS INHALATION EXPOSURES AND EFFECTS ON HUMANS

Exposure Variables	Exposure Time	Effects	Reference
Specific agents not given	During work hours (survey)	Increased spontaneous abortions, headache, fatigue, liver and kidney disorders	78
"	"	Decrease in number of male children born	79
"	"	Increased incidences of spontaneous abortions and congenital anomalies	80

TABLE XIII-15

ANESTHETIC GAS INHALATION EXPOSURES AND EFFECTS ON ANIMALS

Species	Exposure Concentration and Duration	Effects	Reference
Rats	700,000 ppm nitrous oxide 8 d	Decreased white blood cell count, alteration in RNA/DNA ratio	93
Guinea pigs	10,000 ppm halothane 1-5 times for 1 hr each	Focal hepatic lesions, hepatic necrosis	94
Rats	2,500 ppm methoxyflurane 1.5 hr	No kidney damage reported	95
"	5,000 ppm methoxyflurane 3 hr	Mitochondrial changes in kidneys	95
"	7,500 ppm methoxyflurane 6 hr	Damage to convoluted tubules in kidneys	95
"	200 ppm methoxyflurane 7 hr/d, 5 d/wk, 7 wk	Moderate hepatic fatty infiltration	96
"	500 ppm halothane 7 hr/d, 5 d/wk, 7 wk	Increased liver weight and hepatic fatty infiltration	96
"	2,000 ppm diethyl ether 7 hr/d, 5 d/wk, 7 wk	No hepatotoxic responses reported	96
Guinea pigs	200 ppm methoxyflurane 7 hr/d, 5 d/wk, 7 wk	Increased liver weight and hepatic fatty infiltration	96
"	500 ppm halothane 7 hr/d, 5 d/wk, 7 wk	Minimal to moderate central lobular hepatic fatty infiltration	96
"	2,000 ppm diethyl ether 7 hr/d, 5 d/wk, 7 wk	No hepatotoxic responses reported	96
Rabbits	200 ppm methoxyflurane 7 hr/d, 5 d/wk, 7 wk	Elevated SGOT and SGPT levels, moderate hepatic fatty infiltration	96
"	500 ppm halothane 7 hr/d, 5 d/wk, 7 wk	Minimal hepatic central lobular fatty infiltration	96

TABLE XIII-15 (CONTINUED)

ANESTHETIC GAS INHALATION EXPOSURES AND EFFECTS ON ANIMALS

Species	Exposure Concentration and Duration	Effects	Reference
Rabbits	2,000 ppm diethyl ether 7 hr/d, 5 d/wk, 7 wk	No hepatotoxic responses reported	96
Rats, mice,	15, 50, 150, 300 ppm halothane, 5 wk	Dose-related weight gain decrements and number of liver lesions	61
Guinea pigs	150, 500, 1,500 ppm isoflurane, 5 wk	Little or no increase in the number of liver lesions with dose	61
"	1,000 and 10,000 ppm diethyl ether, 5 wk	"	
Rats	10 ppm halothane 8 hr/d, 5 d/wk, 8 wk	Ultrastructural changes in neuronal tissues	97
"	500 ppm halothane 8 hr/d, 5 d/wk, 4 wk	Marked ultrastructural changes in neuronal tissues	97
"	10 ppm halothane 8 8 hr/d, 5 d/wk, 8 wk	Ultrastructural changes in liver and kidney tissues	98,99
"	500 ppm halothane 8 hr/d, 5 d/wk, 4 wk	Cellular and ultrastructural changes in liver and kidney tissues	98,99

TABLE XIII-15 (CONTINUED)

ANESTHETIC GAS INHALATION EXPOSURES AND EFFECTS ON ANIMALS

Species	Exposure Concentration and Duration	Effects	Reference
Rats	8-12 ppm halothane 8 hr/d, 5 d/wk, conception-d 60 of age	Permanent learning deficits and neuronal damage	119
"	8-12 ppm halothane 8 hr/d, 5 d/wk, after day 60 of age	No learning deficits reported	119
Pregnant rats	10 ppm halothane 8 hr/d, 5 d/wk, throughout pregnancy	Cellular and ultrastructural damage in fetal liver, kidney, and brain tissues	111 112 113
"	30, 100, or 300 ppm chloroform 7 hr/d, days 6-15 of gestation	Fetal abnormalities at 100 and 300 ppm	120
"	500,000 ppm nitrous oxide 2, 4, or 6 d	Increased fetal death rate and vertebral anomalies	108
"	700,000 ppm nitrous oxide 1 d during days 5-11 of pregnancy	Fetal skeletal anomalies, peak effect on day 9	109
"	8,000 ppm nitrous oxide 12-hr periods during pregnancy	Increased fetal sketetal malformations following exposure on day 8 or 9.5	110
Pregnant mice	10,000 or 15,000 ppm halothane 3 hr on day 12, 13, 14, or 15 of pregnancy	Increased incidence of cleft palate and limb developmental defects	121
Pregnant hamsters	600,000 nitrous oxide plus 6,000 ppm halothane 3 hr, on day 9, 10, or 11 of pregnancy	Increased fetal resorptions (abortions)	116
Pregnant rats	Halothane/nitrous oxide anesthesia 6-12 hr, 6-10 of pregnancy	Increased fetal resorption (abortion) rate with increased halothane concentration	115

TABLE XIII-15 (CONTINUED)

ANESTHETIC GAS INHALATION EXPOSURES AND EFFECTS ON ANIMALS

Species	Exposure Concentration and Duration	Effects	Reference
Pregnant rats	Halothane/nitrous oxide anesthesia, 6-12 hr during pregnancy	Increased vertebral anormalies but not proportional to halothane	115
"	100, 1,000, and 15,000 ppm nitrous oxide, 8 or 24 hr/d during pregnancy	Higher fetal death rates at 1,000 and 15,000 ppm nitrous oxide	122
Mice, M and F	16 ppm halothane 7 hr/d, 5 d/wk, 6 wk	No adverse reproductive effects reported	123
Rats, M	200,000 ppm nitrous oxide, 8 or 24 hr/d, up to 35 d	Spermatogenesis affected, reversible	124
Pregnant mice	1,000 or 5,000 ppm isoflurane during pregnancy; offspring exposed at 1,000 ppm. All 2-hr exposures	Hepatic neoplasms in males	130
Pregnant rats	1.35, 1.43, and 1.43% halothane 1 hr/d on days 1-5, 6-10, or 11-15 of pregnancy	Incomplete ossification centers in rats exposed on days 11-15; considered incidental by authors	125
Pregnant rabbits	2.16, 2.16, and 2.3% halothane 1 hr/d on days 6-9, 10-14, or 15-18 of pregnancy	Some incomplete centers of ossification found	125
Rats, M and F	1.48, 1.34, and 1.4% halothane 1 hr/d 1-5, 6-10, or 11-15 d prior to pairing	No effect on fertility	125
Pregnant rats	50, 100, 200, 800, 1,600, and 3,200 ppm halothane 8 hr/d on days 8-12 of gestation	No gross teratologic effect reported	126
"	1,600 or 3,200 ppm halothane 8 hr/d on days 1-21 of gestation	Reduction in fetal weight and crown-rump length	126

TABLE XIII-16

GAS SAMPLING AND ANALYTICAL EQUIPMENT

Equipment	Capabilities	Manufacturer/ Approximate Cost
AIR MONITORING		
Miran I Gas Analyzer (infrared)	With single filter and 1 m sampling cell, for N_2O. Variable filter models and longer sampling cells are available with increasing versatility and sensitivity.	Wilks Scientific Corp., S. Norwalk, Conn. $3050
Miran 101 Specific Vapor Analyzer (infrared)	With single filter and 5.5 m sampling cell, for N_2O, and/or halogenated anesthetics	Wilks Scientific Corp., S. Norwalk, Conn. $2950
Sensors N_2O Monitor (prototype model) (infrared)	With single filter and 5 in. sampling cell; volume 30 cc for N_2O, including 100 cc samples	Sensors, Inc., Ann Arbor, Mich. $1500
Halogen Leak Detector	Modified for continuous monitoring (under development). Continuous monitoring for halogenated anesthetics	Inficon, Inc., E. Syracuse, N.Y. $1500
SAMPLING IN GAS-TIGHT BAGS		
Snout-Type Sample Bags	Various capacities, 2 to 44 L	Calibrated Instruments, Inc., Ardsley, N.Y. $6-$14
Aquarium Pump (Hush I)	Economical method for filling sampling bags	Metaframe Aquarium Products, Maywood, N.J. $5
Bleed Valve	Standard hardware item. Choose one with an O-ring seal	Available in pet shops $1
Flowmeter (Dwyer Series VF, 0.06 to 0.5 L/min)	---	Dwyer Instruments, Inc., Michigan City, Ind. $18
SYRINGE SAMPLING INCLUDING TRACE GAS ANALYSIS		
Complete Kit	Includes sampling syringe and mailing box. Single analysis, includes all gases	Boehringer Labs., Wynnewood, Penn. $35
LEAK DETECTORS		
Ferret Industrial Leak Detector (ionizing)	For halogenated anesthetics	General Electric Co., Lynne, Mass. $1250
Halogen Leak Detector (HLD-1) (ionizing)	For halogenated anesthetics	Inficon, Inc., E. Syracuse, N.Y. $1500
N_2O Leak Detector (ionizing)	For N_2O (under development)	Inficon, Inc., E. Syracuse, N.Y. $1500

Adapted from reference 159

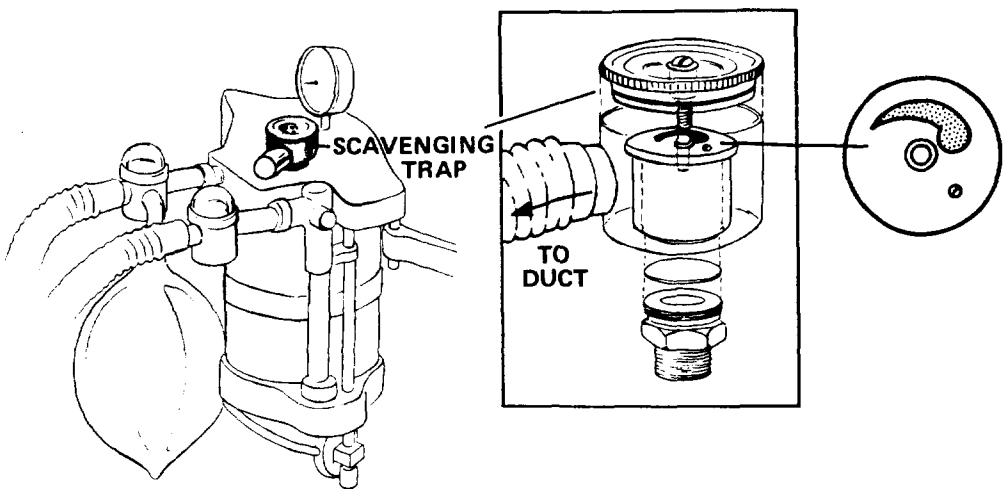


Figure XIII-1 DUPACO SCAVENGING POPOFF VALVE FOR CIRCLE ABSORBER

Adapted from reference 159

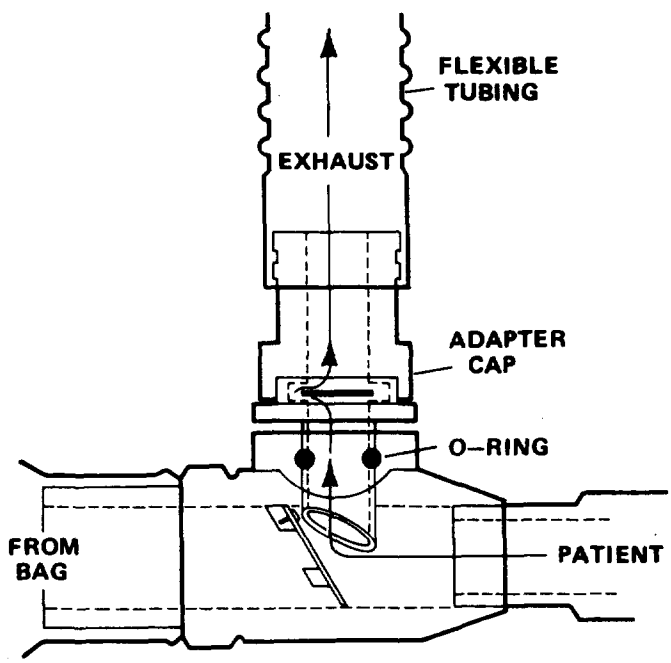


Figure XIII-2 WASTE GAS COLLECTOR FOR DUPACO NONREBREATHING VALVE

Effluent gases are captured by adapter cap.

Adapted from reference 159

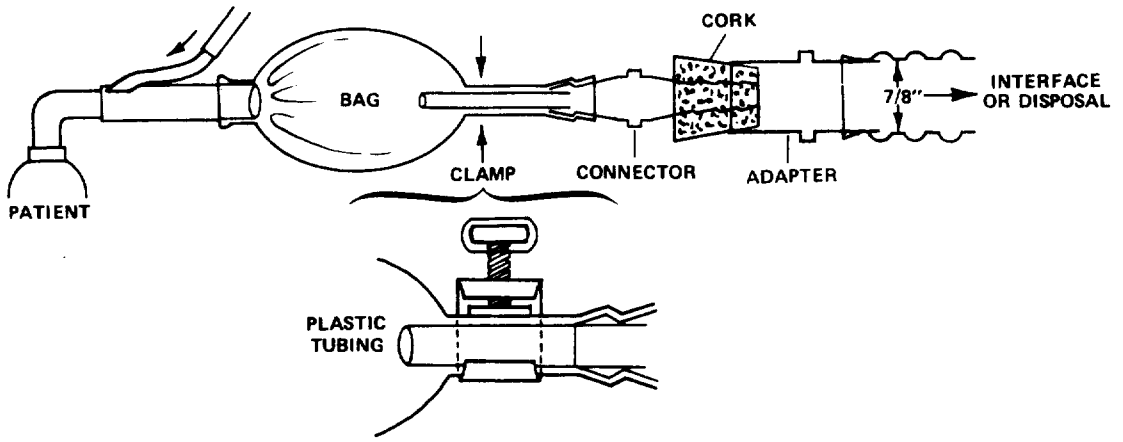


Figure XIII-3 WASTE GAS COLLECTOR FOR T-TUBE

Effluent gases are captured at tail of bag.

Adapted from reference 159

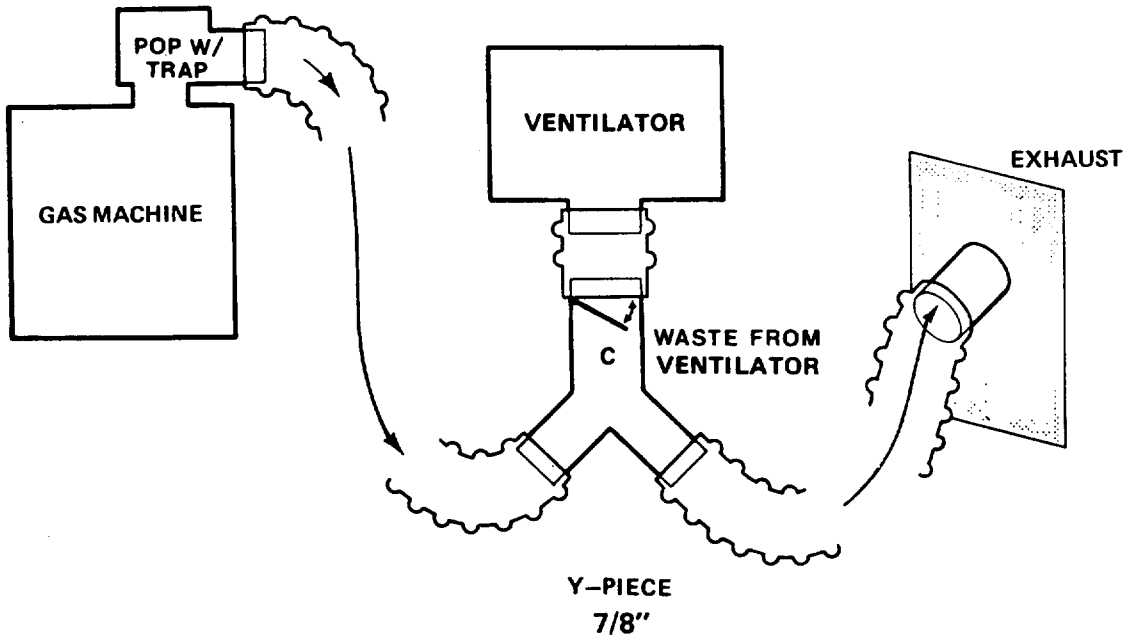


Figure XIII-4 USE OF A Y-PIECE TO COLLECT WASTE GAS FROM ABSORBER, VENTILATOR, AND CHECK VALVE (C) TO PREVENT LEAKAGE

Adapted from reference 159

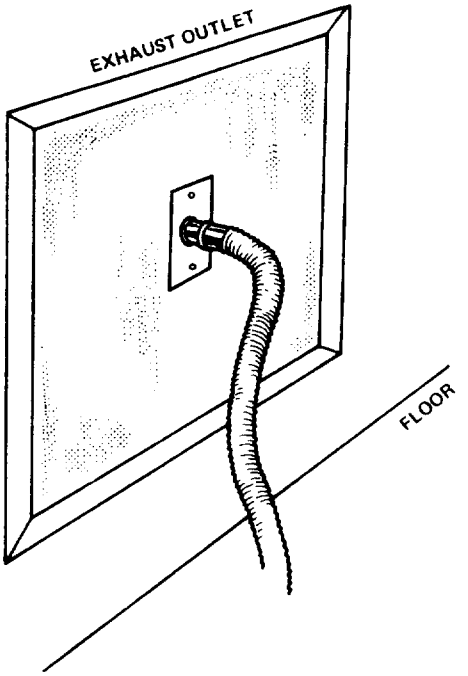


Figure XIII-5 WASTE GAS DISPOSAL INTO AIR-CONDITIONING EXHAUST SYSTEM LOCATED IN OPERATING ROOM

Adapted from reference 159

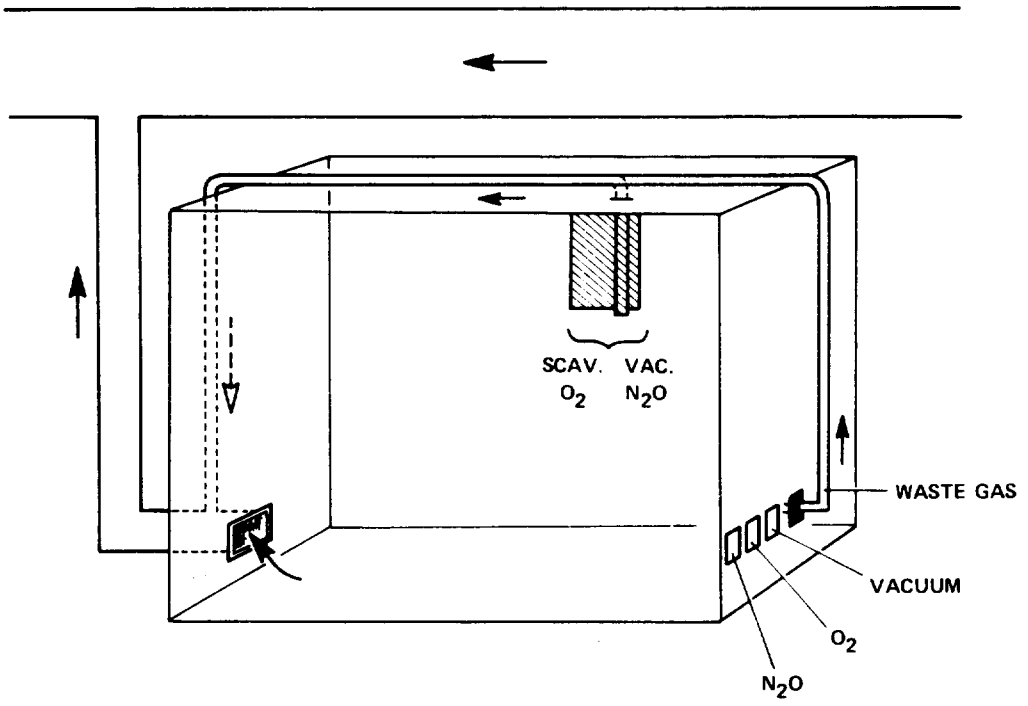


Figure XIII-6 CONCEALED ACCESS TO AIR-CONDITIONING EXHAUST

Adapted from reference 159

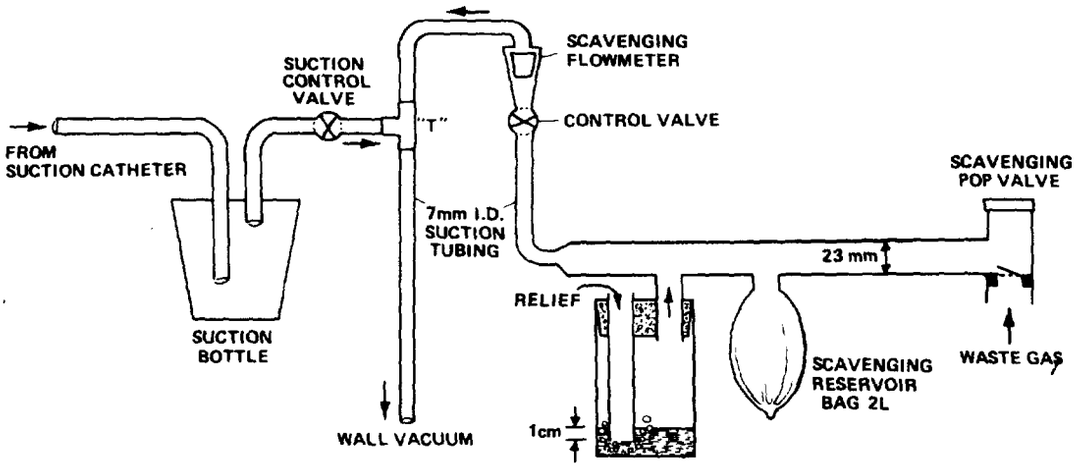


Figure XIII-7 DISPOSAL INTO WALL SUCTION - ONE OUTLET

Adapted from reference 159

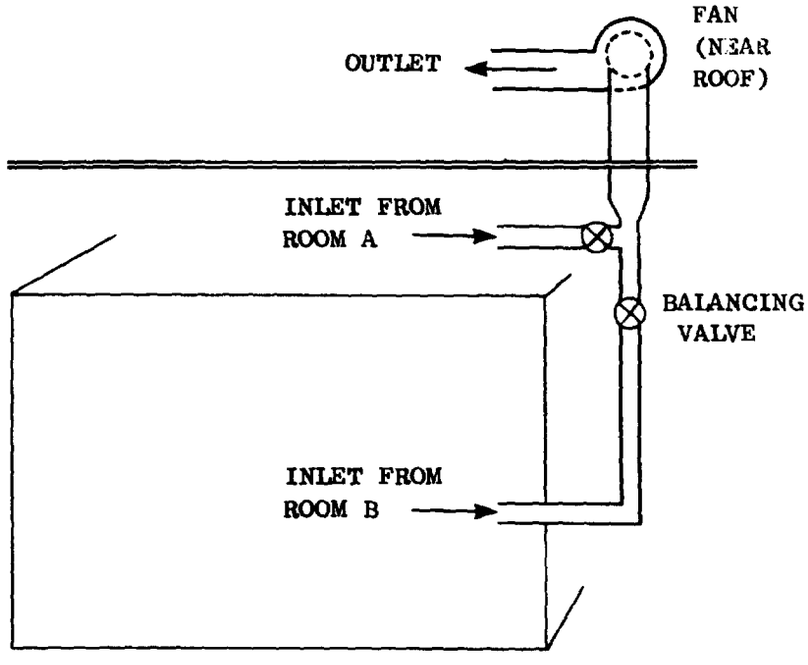
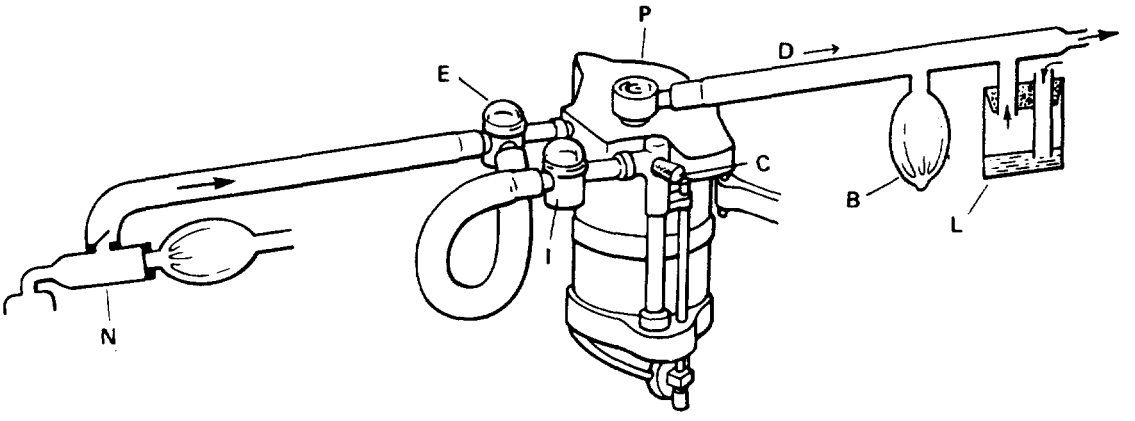


Figure XIII-8 LOW-VELOCITY DUCT SYSTEM FOR WASTE GAS DISPOSAL

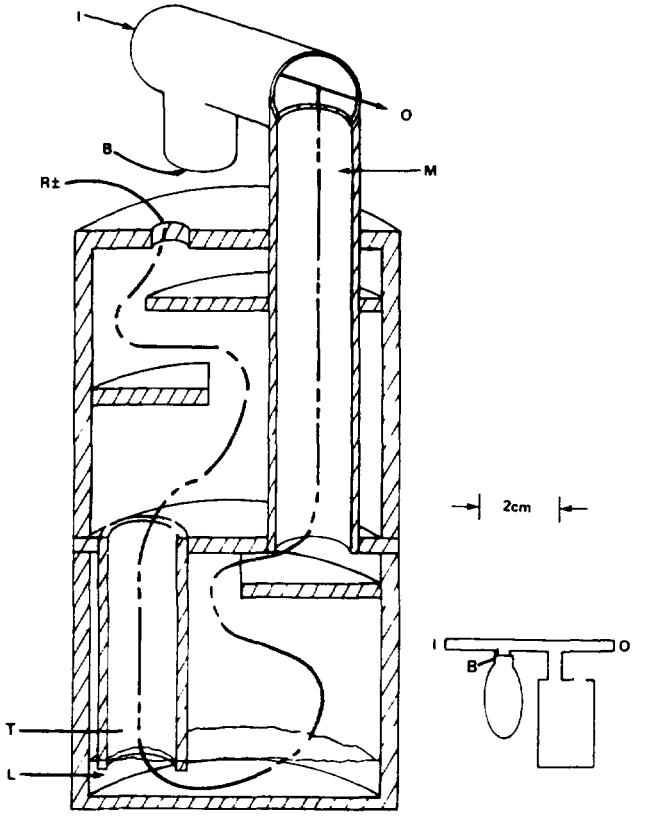
Adapted from reference 159



N = nonrebreathing valve
E = exhalation check valve
I = inhalation check valve
P = scavenging popoff valve
D = disposal tubing
C = occluded fresh gas inlet
B = scavenging reservoir bag
L = liquid-sealed interface device

Figure XIII-9 USE OF ABSORBER CIRCUIT FOR WASTE GAS DISPOSAL

Adapted from reference 159



I = inlet from breathing system

O = outlet to disposal system

M = manometer site for measurements

R± = positive/negative pressure relief opening

L = liquid level

B = scavenging reservoir bag

T = pressure limiting tube

Figure XIII-10 STANDFORD LIQUID SEALED PRESSURE LIMITING INTERFACE

Adapted from reference 159

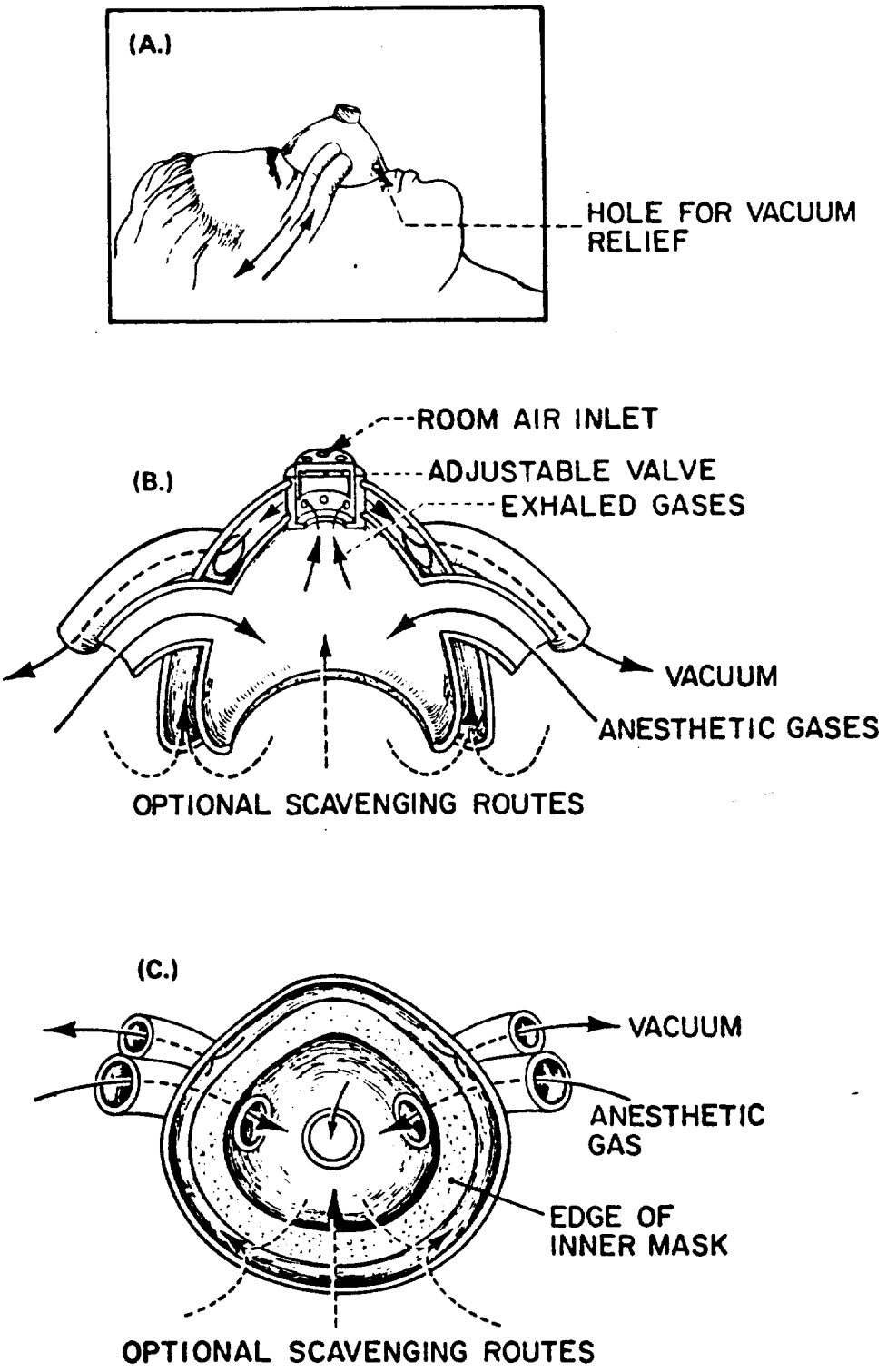


Figure XIII-11 NEWLY DEVELOPED SCAVENGING MASK

Double mask with suction in space between masks maintains low environmental concentrations of nitrous oxide.

Adapted from reference 172

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