INHALATION TOXICOLOGY AND TECHNOLOGY

Basil K. J. Leong

ANN ARBOR SCIENCE

Proceedings of the INHALATION TOXICOLOGY AND TECHNOLOGY Symposium

Sponsored by
The Upjohn Company

Kalamazoo, Michigan
October 23–24, 1980

Edited by
Basil K. J. Leong
Senior Research
Industrial Toxicologist
The Upjohn Company

ANN ARBOR SCIENCE
PUBLISHERS INC / THE BUTTERWORTH GROUP

230 Collingwood, P.O. Box 1425, Ann Arbor, Michigan 48106

Library of Congress Catalog Card Number 81-67510
ISBN 0-250-40414-1

Butterworths, Ltd., Borough Green, Sevenoaks, Kent TN15 8PH, England

Welcoming Address

R. H. DENLINGER
Manager, Pathology and Toxicology Research
The Upjohn Company
Kalamazoo, Michigan 49001

It is a pleasure to welcome you to The Upjohn Company and to have you participate in The Symposium on Inhalation Toxicology and Technology. This Symposium was planned in concert with the opening of a brand new inhalation toxicology facility which we are very proud to show to you. The history of Inhalation Toxicology at The Upjohn Company goes back a number of years, although this new facility represents the first major advance in the area.

The need for inhalation toxicology was recognized in the development of agricultural, chemical, and pharmaceutical products and in evaluation of potential hazards of the work-place environment. In 1967 Dr. Richard Johnston organized a group of people to visit several laboratories to determine the state-of-the-art of the field of inhalation toxicology and bring such technology into the company.

In 1968 a small laboratory was developed for acute inhalation studies. A plan was adopted to expand the capability in acute inhalation toxicology; to develop capability of chronic inhalation studies; to generate data for safety evaluation by Occupational Health and Safety; and to familiarize others in the company of the merits of inhalation technology.

In 1976, a new 7-story, multimillion dollar research building was constructed here at The Upjohn Company. Only part of the total floor space was allocated to be completed at that time. Additional floor space was planned for completion over the next several years to coincide with the growth of research and development activities. As the number of governmental regulations began to proliferate, we saw the need to move ahead rapidly to develop a new, inhalation

toxicology facility. In December, 1978, we were very fortunate to have Dr. Basil Leong join our staff. Many of you know him personally, since he has spent his entire professional career in the field of inhalation toxicology. He was given the responsibility to coordinate the efforts in designing the facility and developing a program in Inhalation Toxicology. The personnel from the Inhalation Toxicology Unit, the Facilities Planning and Environmental Regulatory Affairs Unit and the Engineering Division worked together closely in designing and constructing the facility that you will be seeing later today.

The new laboratory was opened last week, so the animal rooms and exposure chambers have not yet been occupied by animals on studies. However, the equipment is in place and is operational to demonstrate their functions for you on the tour. You will also see the operation of two new devices - a new dust generator and new inhalation exposure chambers. Patents have been filed for both so that discussion and demonstration of these instrument and equipment are possible.

We are happy to have so many people attend this Symposium and to help us celebrate the opening of what we consider a top notch facility. I was told that this is probably the first time that such a large group of Inhalation Toxicologists have convened. Most of the major laboratories doing work in this field are represented either in the audience or as speakers. Again, I say welcome. If there is anything that I can do to make your visit more pleasant, please feel free to let me, or anyone else from the Upjohn staff, know.

Opening Remarks

B. K. J. LEONG
Industrial Toxicology Laboratory
The Upjohn Company
Kalamazoo, Michigan 49001

In inhalation toxicological investigations, experimenters tend to develop exposure techniques and equipment to meet their needs for animal studies of airborne toxicants, which may be gas, vapor, mist or dust. Consequently, the "art" of inhalation toxicology is in a state of continuous evolution of inhalation technology. The purpose of this Symposium is to review the state-of-the-art of this dynamic discipline and to extend the dialogue between investigators on the recent achievements and the existing problems. Hopefully, through gentle persuasion or vigorous discussions, the usefulness of some new techniques and apparatus may be recognized and the frontier of knowledge may be pushed a little distance in the right direction.

It is a great pleasure to acknowledge those who made this meeting possible. First and foremost, the contributors who agreed to take an active part, not only in their presentations at the Symposium, but also in the preparation of the manuscripts; The Upjohn Company whose support makes this meeting a pleasant reality; and last but not least, those who assisted in the administrative preparation of the Symposium and the subsequent publication of the Proceedings of the Symposium.

CONTENTS

AEROSOL TECHNOLOGY

INHALATION TOXICOLOGY

Hazard Containment in an Inhalation Toxicology Laboratory

W.B. REID
Facility Planning and Environmental Regulatory Affairs

J.R. KLOK
Client Engineering
Pharmaceutical Research and Development

B.K.J. LEONG
Industrial Toxicology Laboratory

The Upjohn Company
Kalamazoo, Michigan 49001

ABSTRACT

The design of an inhalation toxicology laboratory required consideration of hazard containment. Effective planning required complete communication between the inhalation toxicologist and the engineers on the philosophy, regulatory requirements and economic impact of conducting inhalation experiments. After this exchange of ideas, the toxicologist and the engineers discussed the technical details and visited other established inhalation laboratories.

The final design incorporated as much as possible the latest technology in floor plan design for proper isolation of functional areas, ventilation, and most important of all, the containment and elimination of chemical and animal wastes.

INTRODUCTION

Until recently the pharmaceutical industry was concerned primarily with protecting drugs intended for human consumption from contamination by employees during the manufacturing process. However, the industry is increasingly aware that workers should be protected from the possible harmful effects of overexposure to drugs. The Occupational Health and Safety Act of 1970 made a safe environment for the workers a legal obligation of the employer.

The Upjohn Company's standing policy and practice has been to comply with the law and to minimize the environmental impact of drug manufacturing on employees and the

surrounding community. For the evaluation of hazards and toxic effects from exposure to drugs and chemicals in the workplace, the company built an industrial toxicology laboratory with the most up-to-date facilities for conducting inhalation toxicology studies.

PLANNING

Before the drawings for the inhalation toxicology laboratory were started, the effects of working with potentially hazardous materials had to be considered (Steere, 1971; Sansone, 1980). First, The Upjohn Company engineering staff, already quite experienced with the unique requirements of designing pharmaceutical laboratories, and the inhalation toxicology personnel had to establish communications. The inhalation toxicologist explained to the engineers the philosophy of inhalation toxicology and reviewed the techniques for testing gases, liquid aerosols and dust generation and procedures for performing inhalation experiments. The detailed explanation was in terms that people outside the field readily understood.

The design team visited several inhalation laboratories, discussed their function with the scientists using them, the problems encountered and the changes the scientists would make. The latest technology and planning were incorporated in the layout drawings. Following careful review and discussion between the inhalation toxicologist and the design team, the design approved for field work was developed.

HAZARD CONTAINMENT

Floor Plan

The inhalation toxicology laboratory suite was built in an isolated corner of a research building. The building's general traffic pattern is outside the suite which has only one entrance, and yet other facilities like the building ventilation system, utility service shafts, animal waste disposal and cage-washing are convenient. Furthermore, a floor-to-floor dimension of 14 1/2 feet in this section of the building permits all service conduits or cables to be installed overhead, keeping the floor traffic and work area free of obstacles.

Traffic flows from the clean to the contaminated parts of the suite (Figure 1). The clean areas include rooms for animal quarantine before experiments begin, office space,

AC = Acute Exposure Chamber

S = Subchronic Exposure Chamber

C = Chronic Exposure Chamber

H = Animal Holding Room

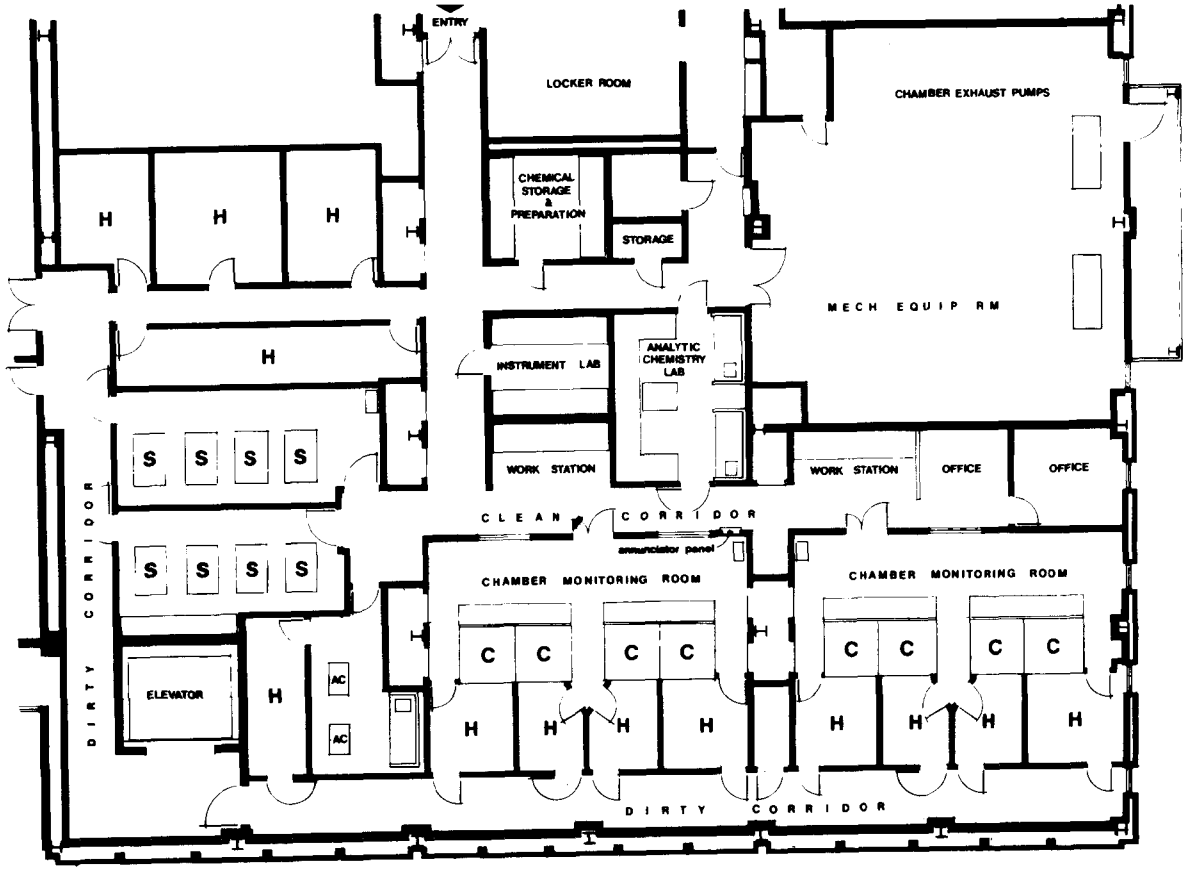


Figure 1. Floor plan of The Upjohn Company Inhalation Laboratory

the rooms housing analytical equipment for exposure chambers and the corridor that connects the suite with the rest of the building. The dirty areas include the exposure chambers, the postexposure animal-holding rooms and the corridor connecting the holding-rooms with the elevator to the waste disposal and cage-washing areas on the floor below.

The animal exposure facilities follow the one-room one-experiment and the double-corridor concepts (Leong, 1977; Sansone & Losikoff, 1979). Animals from each exposure chamber can be isolated in separate holding-rooms after each daily treatment. The temperature and humidity of each holding room are controlled by zone thermostats and humidistats.

LABORATORY VENTILATION

One air-conditioning unit serves the inhalation toxicology laboratory. Air drawn from the outside of the research building is filtered and regulated to 74° $\pm$ 2° dry bulb and rehumidified to 50% $\pm$ 5% relative humidity before being distributed to other sections of the laboratory. All animal holding-rooms are provided with 20 air changes per hour. A pressure gradient is created so that all air flows from clean to dirty areas in a one-pass system (Figure 2). Within the laboratory suite in the rooms designed for handling and preparing chemicals, conditioned air flows through the perforated ceiling toward the laboratory benches. All the air entering from the ceiling is exhausted through hoods equipped with two-stage filtration systems consisting of bag-out filter housings. The first-stage filter is 90 to 95% efficient according to the ASHRAE (American Society of Heating, Refrigerating, and Air Conditioning Engineers) test, and the second-stage filter is 95% efficient according to the DOP (dioctyl phthalate test).

All exhaust hoods also have airflow-sensitive alarm systems which are activated when the linear velocity of airflow across the face of the hood drops below a specified ft/sec value (Witheridge, 1967). Exhaust hoses which we fondly call "elephant trunks" are provided for local removal of waste gases generated by analytical instruments such as gas chromatographs and chemical storage cabinets.

The air exhausted from the laboratory suite is discharged into the central exhaust system. Then it passes through the heat exchanger for energy recovery before being released outside.

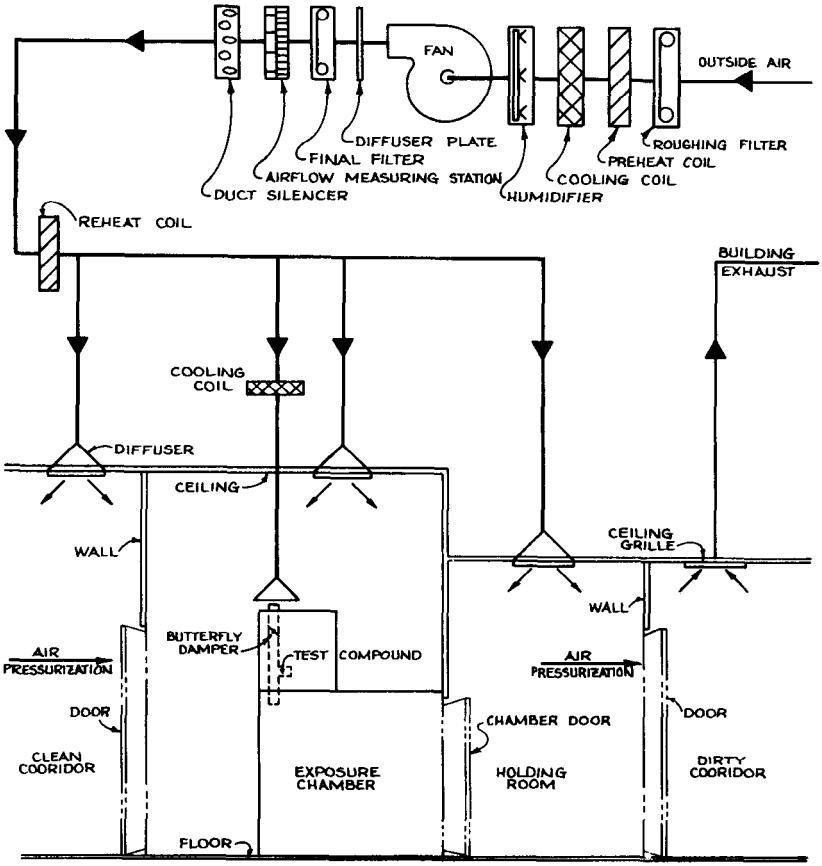


Figure 2. Schematic diagram showing the direction of airflow within the Inhalation Toxicology Laboratory.

EXPOSURE CHAMBER VENTILATION

Air from the laboratory air-conditioning system is drawn through branching ducts into individual chambers. At each branch, an additional heating and cooling system permits further adjustment of temperature and humidity to meet the needs of individual experiments (Figure 3). The design temperature points are 55°F dry bulb temperature for the supply air, 54°F wet bulb for the cooling coil and 75°F for the reheating coils. Temperature in the chamber is monitored by a high and low thermostat connected to an automatic pneumatic controller with manual override.

If the temperature varies from the range selected for a particular experiment, a signal is sent to the microprocessor which triggers an alarm in the work and office areas. The light flashing on a panel indicates the chamber which

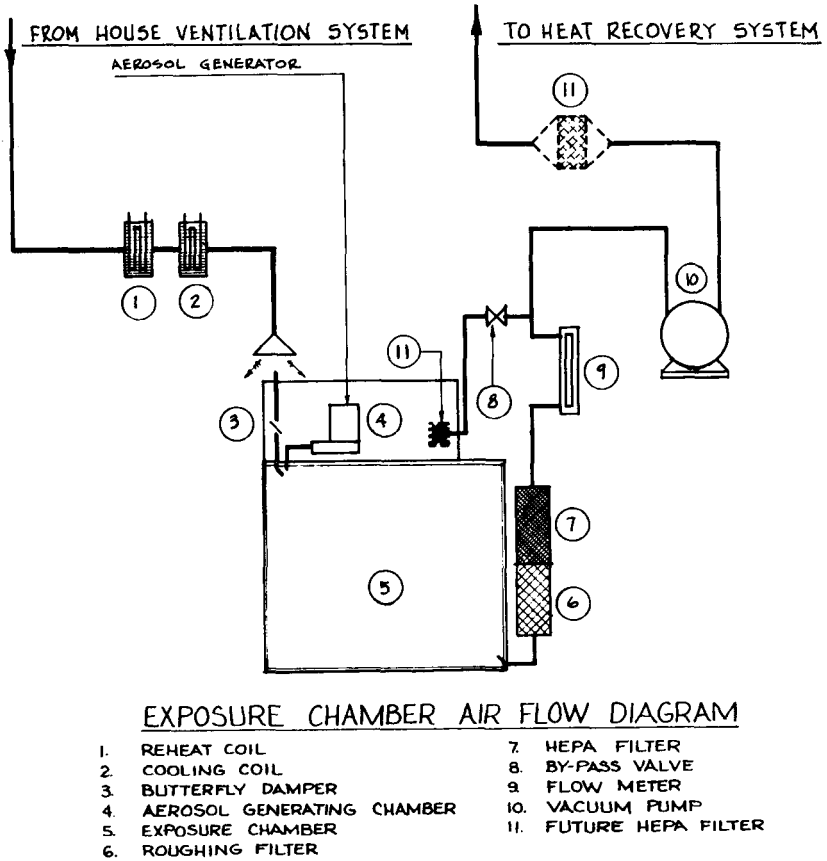


Figure 3. Schematic diagram showing the air supply and exhaust for an exposure chamber.

caused the alarm. While the alarm can be silenced by pushing the silence button, the pilot light will continue to flash until the problem has been corrected. During the silence, failure of another chamber will sound the alarm as before.

CHAMBER PRESSURE CONTROL

All chambers operate under dynamic air flow at a negative pressure of 0.1 to 0.2 inches of water. This is accomplished by restricting the supply air entering the chamber by throttling the butterfly damper in the chamber air inlet. The total chamber airflow equals the sum of the volume of air ejected from an aerosol or dust generator and the volume

of air drawn into the chamber to make a specified concentration of test compound. Airflow is read on the flow meter and adjusted to the proper rate (cubic feet per minute) by throttling the manual bypass valve. Two differential pressure switches (DPS) within the chamber monitor the pressure. The first DPS is wired to the microprocessor alarm system. If, for any reason, the chamber is not properly sealed and the negative pressure is not within the proper limits, the first DPS will sound a local alarm within 30 seconds, depending on the specified program (Figure 4). If a pump fails, a back-up pump can be switched on manually to restore airflow and the slightly negative pressure in the chamber.

CHAMBER EXHAUST PUMPS

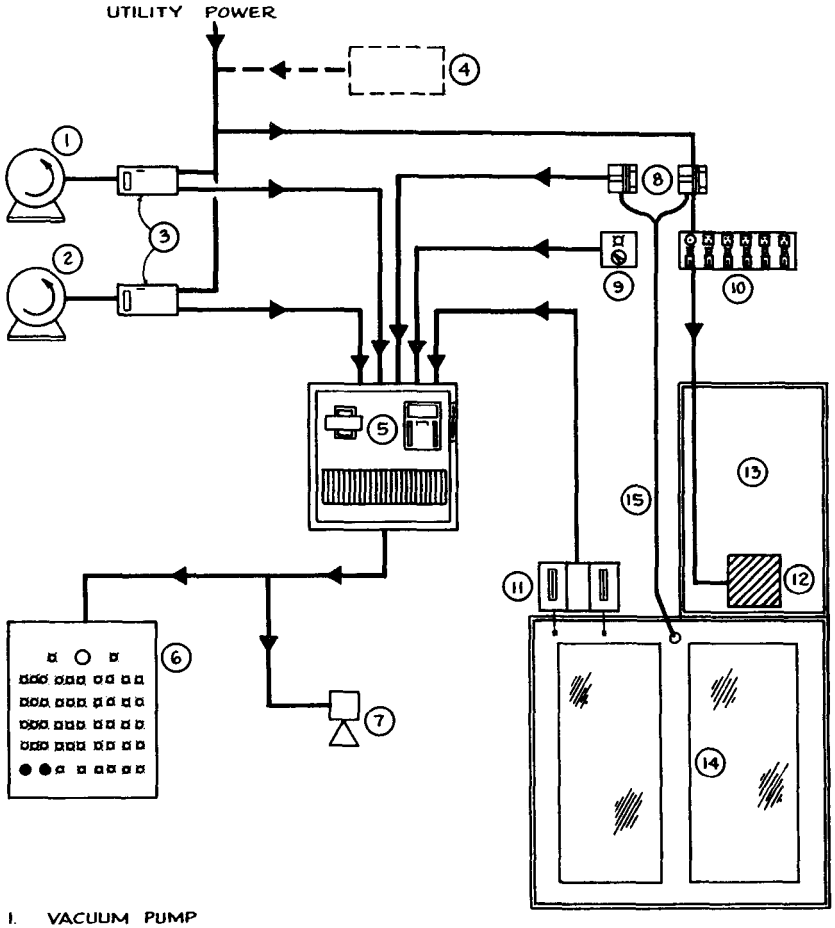
Rotary sliding-vane pumps (Furtado, 1978) with the capacity to create various vacuums exhaust the animal exposure chamber atmosphere. This type of exhaust pump has a stable volumetric efficiency over a wide range of vacuum pressure and, therefore, reliably maintains a constant airflow in each chamber. The pump is also durable for continuous operation for a long period of time. One pump is used for each chamber so that the chamber airflow can be individually regulated.

EXPERIMENTAL ATMOSPHERE GENERATION

A compartment at the top of the chamber houses all vapor or aerosol-generating equipment. The compound to be tested is added to the air stream entering the air inlet at an upper corner of the specially designed chamber (Leong, 1981). This compartment also operates under a slightly negative pressure relative to the ambient pressure to ensure total containment of the test compound. A DPS connected to the exposure chamber controls the power supply to the generating equipment. All generating equipment operates only when the chamber atmosphere reaches a specified negative pressure. Thus, the hazard from accidental dispersion of airborne toxicants can be eliminated.

CONTAMINANT AND WASTE CONTROL

For ease of decontamination, the wall and ceiling finishes in the animal and chamber rooms are coated with epoxy paint. The floors are made of inlaid epoxy. All



1. VACUUM PUMP
2. VACUUM PUMP (STAND-BY)
3. PUMP CONTROLLER
4. FUTURE EMERGENCY GENERATOR
5. MICRO PROCESSOR
6. ANNUNCIATOR PANEL
7. LOCAL ALARM
8. DIFFERENTIAL PRESSURE SWITCH
9. REMOTE START/STOP VACUUM PUMP SWITCH
10. EQUIPMENT OUTLETS FOR AEROSOL GENERATING CHAMBER
11. HIGH - LOW THERMOSTAT
12. AEROSOL GENERATOR
13. AEROSOL GENERATING CHAMBER
14. EXPOSURE CHAMBER
15. PRESSURE SENSOR PROBE

Figure 4. Schematic diagram of chamber temperature and pressure monitoring-alarm system.