IMPROVED INHALATION TECHNOLOGY FOR SETTING SAFE EXPOSURE LEVELS FOR WORKPLACE CHEMICALS

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ABSTRACT

Threshold Limit Values recommended as allowable air concentrations of a chemical in the workplace are often based upon a no-observable-effect-level (NOEL) determined by experimental inhalation studies using rodents. A "safe level" for human exposure must then be estimated by the use of generalized safety factors in attempts to extrapolate from experimental rodents to man. The recent development of chemical-specific physiologically-based toxicokinetics makes use of measured physiological, biochemical, and metabolic parameters to construct a validated model that is able to "scale-up" rodent response data to predict the behavior of the chemical in man. This procedure is made possible by recent advances in personal computer software and the emergence of appropriate biological data, and provides an analytical tool for much more reliable risk evaluation and airborne chemical exposure level setting for humans.

INTRODUCTION

The Brookhaven National Laboratory (BNL), located in Upton, NY, has reactivated its Inhalation Toxicology Facility (ITF), under the auspices of a five-year collaborative research agreement with ManTech Environmental Technology, Inc. (ManTech Environmental), Research Triangle Park, NC. Coordinated under legislation set forth in the Technology Transfer Act of 1988, ManTech Environmental with Brookhaven National Laboratory will utilize these facilities and its resources for the conduct of toxicological research and testing to address a national need, i.e., providing inhalation biology studies to set safe levels of response to workplace chemicals. The ITF and its adjoining Veterinary Services Complex-Laboratory Animal Facility (VSC) are integral components of the BNL Medical Department.

The ITF, located in the eastern corner of the Medical Department complex (Figure 1), in its renovated configuration, encompasses a dual corridor system, to expose, monitor, and test virtually any gas, vapor phase, or aerosolized chemical of concern from a human health standpoint. BNL has conducted a variety of studies at the ITF on behalf of several governmental sponsors in the past, including the Department of Energy (DOE), the Department of Defense (DOD), and the National Institutes of Health/National Institute of Environmental Health Sciences (NIEHS) and the National Toxicology Program (NTP). The ITF/VSC performs toxicological research and testing of chemicals of interest to a variety of sponsors, including both regulatory and non-regulatory governmental agencies, civilian agencies, DOD, as well as sponsors from the private sector.

FACILITY DESCRIPTION

A complete description of existing and newly renovated areas of the ITF and supporting VSC are provided in this section. Supporting floor diagrams, flow charts, and equipment utilization plans also are included in order to better present this detailed information for review.

Floor Plans

A detailed floor plan of the ITF and VSC are shown in Figure 2. The 6,500-ft^2 ITF building is located at the eastern corner of the Medical Department and has a 1,800-ft^2 basement. The basement is devoted entirely to mechanical equipment to support the facility. New heating, ventilation, and air handling/air conditioning (HVAC) systems ensure that clean air flows out of the clean corridor at all access points (Figure 3). The ITF is divided into three areas: (1) access corridors (clean and dirty), (2) regulated inhalation exposure areas, and (3) the actual chambers and other equipment designed for containment. Two barriers are created between the access corridors and potential airborne hazardous chemicals in the chambers by maintaining the air pressure in

the chambers at 5 mm water less than the pressure in the inhalation exposure area, which is in turn maintained about 5 mm less than the pressure in the clean access corridor.

The general access (non-regulated) area contains two offices, two laboratories, an electron microscopy suite, a glassware washing room, and several closets all opening from the "dirty" corridor. Two windows allow observation of the regulated exposure laboratories from the non-regulated access corridor.

The regulated inhalation exposure area consists of the clean corridor; two large inhalation exposure laboratories (A and B); generation, preparation, and analytical laboratories; cage and rack washing areas (air lock "A" and "B"); and two general purpose exposure rooms for acute and subchronic inhalation studies. The regulated area is separated easily into two distinct areas by locking a normally closed door in the hallway connecting the two chamber rooms. A hazardous material preparation laboratory, cage washing facilities, rack wash-down facilities, and the necropsy room open into Chamber Room A. An analytical laboratory, the necropsy room, and the general purpose exposure rooms open into Chamber Room B. The corridor outside these exposure rooms connects directly to the VSC clean corridors of the Medical Department. The installation of two air locks in the rack wash-down areas serving Chamber Rooms A and B ensures directional air flow and equipment flow toward the dirty corridor, but also prevents any airborne test material from escaping into the dirty corridor. As a standard operating procedure, all personnel must shower prior to entering the clean corridor and must shower out before exiting the laboratory into the dirty corridor using the two separate locker facilities connected to the air locks adjacent to Chamber Rooms A and B.

Heating, Ventilation and Air Conditioning

The non-regulated area, including offices, has a single pass air-handling system (Figure 4) with a common supply and local exhaust ventilation. The 5000 CFM air supply system is located on the roof with outside air being filtered, chilled (for dehumidification), heated, humidified, and HEPA-filtered before entering the ductwork. It is reheated in the ducts before entering each room, as required. The non-regulated area is maintained at a slight pressure positive to ambient pressure.

Four separate HVAC systems supply air to the building (Figure 4A, AC-1A, AC-1B, AC-2A, AC-2B). The main exhaust is through three laboratory hoods, each with its own separate HEPA filter and exhaust blower on the roof (Figures 4A and 4B). In addition, there is local exhaust ventilation provided in the laboratories, the showers, and in the chemical storage cabinets by individual blowers on the roof.

The air supply systems for the chambers (AC1, Figure 4A) and for the inhalation exposure rooms (AC2, Figure 4A) are located in the basement. Supply for the inhalation exposure room air is filtered through prefilters, HEPA filters, and charcoal filters. The 10,000 CFM supply is completely redundant up to the point where air enters the common air supply duct that goes up to the inhalation exposure rooms. The exhaust air from these rooms is removed through hoods and exhaust louvers in rooms (Figure 3). The air then enters a common exhaust system (E2) and is passed through HEPA filters and charcoal filters located on the roof prior to entering the environment.

The HVAC system for the inhalation chambers and glove boxes (AC1-E1, Figure 4A) is also redundant with supply and exhaust fans interlocked. Chamber exhaust air is cleaned immediately after exiting the chambers before entering the exhaust duct. This system also has backup filtration with both HEPA and charcoal filters on the roof in the event of an accident or a malfunctioning chamber filter. The supply air system (AC4, Figure 4B) for the clean corridor and the ITF is located on the roof. This system also provides air supply for the animal quarantine area and bedding storage. The supply systems and exhaust systems are completely redundant.

Electrical

Emergency power is available to all the HVAC systems associated with the inhalation exposure area and the chambers and glove boxes. Each room in the building has a single light fixture and an outlet (marked by a red cover) on emergency power.

Fire Protection

The building has sprinklers located throughout, and heat sensors are located in the supply air ducts. The building is constructed of foam sandwich panels on exposed steel (noncombustible universal building code type II-N). Ceilings in the inhalation exposure area are made of sealed plasterboard supported by a steel grid. Ceilings in the non-regulated area are made of fiber tile. Interior partitions are constructed of gypsum board

on metal studs in the non-regulated area and of concrete block painted with epoxy coating in the inhalation exposure area.

Physical Design Features

Containment

The primary containment system in this facility consists of Chamber Rooms A and B, the analytical laboratory, the hazardous material preparation laboratory, the necropsy room, inhalation chambers, and glove boxes serviced by the AC1-E1 HVAC systems.

The HVAC system for the chambers and glove boxes is redundant with supply and exhaust fans interlocked. Filtered, conditioned air supplied at +8 cm water pressure (wg) is available in two ducts along the wall in each chamber room. Chamber air is exhausted through one of four high pressure (-30 cm wg) continuous welded stainless steel ducts, also located on the walls of the chamber rooms. Chamber air is cleaned immediately after exiting the chambers before entering the exhaust ducts. The air-cleaning devices are selected for the specific chemical under study. Each filter holder has provision for a HEPA filter and an appropriate vapor absorber. Vapors or gases are absorbed on charcoal, which is changed when necessary. Aerosols can be removed on HEPA filters. If other prefiltering devices are required, they will be installed in the chamber and the common exhaust system. This system also has backup filtration with both HEPA and charcoal filters on the roof in the event of an accident or a malfunctioning chamber filter. In the event of a failure of one system, the backup system will come on automatically within 5 sec, and an alarm will be sounded. The start-up also is accomplished with time delay relays to establish exhaust negative pressure first, in order to prevent the inhalation chambers from going positive with respect to the chamber room. All generation equipment is configured with "normally closed" solenoid valves that immediately terminate the flow of test chemical into the chambers in the event of power failure.

Under normal operations, no toxic or potentially carcinogenic chemicals will be airborne outside the primary containment system. All chemical standardization, generator loading, sample preparation, and chemical storage will take place inside the primary containment system. Whenever a chemical is handled in the secondary containment space or in the non-regulated area, it will be doubly contained in nonbreakable containers.

The secondary containment is the regulated area which is serviced by air supply and exhaust systems AC2-E2. Air for the regulated area is filtered through prefilters, HEPA filters, and charcoal filters. The 10,000 CFM supply is completely redundant up to the point where air enters a common air supply duct that goes up to the regulated area. The exhaust air from the regulated area is removed through hoods located in the Test Material Preparation Room (Figure 3) and the two air-lock exhaust systems serving chamber rooms A and B (Figure 3). The air then enters a common exhaust system (E2) and is passed through HEPA filters and charcoal filters located on the roof prior to entering the environment. The exhaust air-cleaning system consists of six sets of 2000 CFM HEPA-plus charcoal filters. Each set of filters can be isolated from its exhaust fan with manually controlled dampers for filter change-out. The exhaust fans, also in duplicate, are interlocked to the supply fans to form two independent systems. If any part of one system fails, the entire system shuts down and the backup system starts up independently of the other system. Start-up is arranged with time delay relays such that the exhaust system comes on before the supply system to prevent the regulated space from becoming positive. When a failure occurs, alarms are triggered to indicate that the primary system failed and that the backup system is now in operation An analog pressure sensor detects the differential air pressure and controls the supply air to maintain the required pressure gradient.

If the gradient falls below a set point, alarms (visual and audible) are activated. Alarms also are sounded when the differential pressure across the exhaust filters indicates that they should be changed, when the supply or exhaust damper is at a minimum, and when the supply duct air pressure falls below a set point. All alarms indicating a malfunction are sent to the local police headquarters which relays the alarm to the HVAC watch unit staffed 24 h/day.

Inhalation Chamber Operation

Conventional inhalation exposure chambers are usually square in cross section and have pyramidal tops and bottoms (Figure 4A). Air is introduced at the top and removed at the bottom. Windows are provided and one side usually consists of a door that allows animals to be introduced into or removed from the chamber. Such systems can be safely used to expose animals to chemical vapors (and to some aerosol particles) when certain precautions are taken. At 15 air changes/hour (the flow rate normally used), the chamber concentration will

reach 1% of its equilibrium concentration less than 20 minutes after generators of test chemical vapors or gases are shut down. A possible problem is the potential for the animals to exhale some of the vapors or gases of test chemical that had previously been inhaled. This outgassing is investigated on a chemical by chemical basis.

These conventional systems are being used to expose animals to test chemical vapors such DMES (dimethylethoxysilane), styrene oxide, etc. Specific operational protocols are developed for each test chemical.

Exposure of rodents to potentially toxic test chemicals in the form of particulate aerosols is a more complex problem. Even after the concentration is no longer detectable by air sampling, the internal chamber surfaces including the cages and the coats of the animals themselves may be contaminated by the test chemical. If not properly controlled, handling the animals and cages could present an opportunity for skin contamination or the inhalation by technicians of any particles reentrained into the air. For this reason, inhalation exposures to hazardous particulate test chemicals must be done using nose-only exposure chambers. Such systems enable investigators to expose animals to potentially hazardous test chemical aerosols while constantly maintaining a physical barrier between the exposed animal and the personnel operating the system, and virtually eliminates test chemical contamination of the coats of the animal. This system is available in the ITF, as is shown schematically in Figure 4B. Exposures are carried out in a chamber that can expose up to 50 rodents via the nose only. Aerosol generators are located above the chamber, and the atmospheric clean-up takes place in filters or activated charcoal purifiers located in the exhaust stream. All exhaust air is filtered once more through absolute filters for secondary air purification. Chamber exhaust air cleaning may include electrostatic precipitation or air scrubbing as the primary clean-up procedure backed up by HEPA filtration.

Monitoring for test chemicals will be specific for the chemical in question. Many experiments will be conducted using four chambers; that is, three-dose level study plus a control. In the case of a five-dose level, four-dose level, or three-dose level study, one air analyzer, specific for the chemical in question, is used to sample the chambers consecutively. In addition, the system samples the chamber room and the common exhaust duct to verify that the room air is clean and that the air cleaning devices are functioning properly. Detectors will be chosen for their applicability to the chemical in question. Highly sensitive, dedicated instruments are available for many agents and will be used where applicable. Both gas chromatography and infrared spectroscopy are available with multiple valve switching for detecting vapors, and both techniques are capable of detecting more than one compound at a time. These instruments are calibrated with calibration gas mixtures. In addition, wet chemical methods may be used to verify the calibration.

Real-time particle analyzers incorporating optical scattering sensors are used where applicable to measure the concentration and particle size of aerosols in the chambers. Light-scattering devices can be used where deposition on internal surfaces does not interfere with calibration set points. Cascade impactor samples are taken to assess particle size at multiple points within the chamber.

By the use of such rigidly controlled test rodent exposure systems to provide much more reliable data, and computer-assisted techniques for physiologically-based toxicokinetic analyses of the data, valid determinations of allowable workplace air concentrations for specific chemicals can be obtained. As an example, the question was addressed of whether the change in workshift schedule from a standard 5-day, 8-hour/day work week to a different schedule involving longer shifts would affect the cumulative body burden of carbon tetrachloride in exposed workers. A physiological model for inhalation uptake of carbon tetrachloride in the rat was developed and then used to predict the kinetics of uptake in humans. It was found that the accumulation and removal of carbon tetrachloride in humans, based upon scaling up by the model using known biochemical and physiological parameters, followed a much slower time constant to cause greater retention of this airborne chemical at the end of the work week. This revealed that altered buildup patterns would occur with the longer work shift, requiring a longer between-shift recovery period. These techniques have also been expanded into more reliable risk estimate procedures for exposure of the general population to potentially carcinogenic volatile organics, such as methylene chloride.

ENERGY AND ENVIRONMENT PART 4: ENVIRONMENTAL TECHNOLOGIES