Determinants of SFE Toxicity: Interaction of Atmospheric, Dynamic, and Physiological Responses

R. L. Carpenter[1], E. C. Kimmel[2], and E. A. Smith[1]

1. Naval Medical Research Institute Detachment (Toxicology) and 2. GEO-CENTERS, INC.

NMRI/TD, Building 433, Area B, 2612 Fifth Street,
Wright-Patterson AFB, OH 45433-7903
Telephone: (513) 255-6058 Fax: (513) 476-7094

Abstract: The physical and chemical properties of an aerosol have a direct influence upon fire suppression mechanisms and extinguishing efficacy. These same properties are also basic determinants of aerosol inhalation toxicity. To evaluate the toxicity of an aerosol, it must first be determined if the aerosol can be inspired. Particles with a median aerodynamic diameter of 1-2 μm are capable ofpenetrating deep into the human tracheobronchial tree, reaching the alveolar acini. These acini are comprised of parenchymal tissues. which are highly susceptible to damage and least protected by clearance (defense) mechanisms. Both chemical and physical properties of inhaled particulate matter combine to control aerosol toxicity. The dose to regional lung tissue depends on particle size, particle specific surface area and chemical solubility. As is true of other routes of toxic entry into the body, tissue response to dissolved material in the lung is dependent on the chemical nature of the insult. Potential toxic effects include altered pulmonary function, irritation and altered gas exchange, leading to discomfort, altered oxygen uptake, incapacitation and death. In the case of pyrotechnically generated aerosols, carbon monoxide may also be present, resulting in increased carboxyhemoglobin levels and decreased oxygen uptake leading to disorientation and possible incapacitation. Aerosol toxic effects are not limited to the lung; dissolved material can be transported from the lung to other systems throughout the body. In addition to pulmonary and systemic effects, aerosolized material can cause irritation of the skin and/or nasal and ocular mucosa. The companion papers concerning SFE toxicity in this proceedings detail the observation of these effects for SFE exposures. This paper relates our observations to the basics of inhalation toxicology and aerosol science.

Introduction

The fire extinguishing engineering community has a significant interest in dry powder and mist fire extinguishing/suppression systems. As part of improving system efficacy, agent particle size is being reduced, bringing a significant fraction of the dispersed agent into the respirable range. Water mist systems and Encapsulated Micron Aerosol Agent (SFE) are two examples of such fire fighting systems. These systems must undergo toxicity evaluation and use permitting similar in scope to that used for gaseous extinguishing systems, requiring the effects of respirable particle toxicity be evaluated. The inhalation toxicity of aerosol agents is inherently more complex than a pure gas. However, this should not be a deterrent to their development or use. The purpose of this paper is to discuss the basic determinants of aerosol toxicity, illustrating them with the

SFE data obtained by our group. It is hoped that the reader will gain some working insight into the physicochemical basis for understanding aerosol toxicity.

The Respiratory System

One must recognize that the respiratory system is both a portal of entry into the body and a target organ for toxicity in its own right. For example, inhalation of many halogenated hydrocarbons results in little effect on the respiratory system, but the whole body response may include liver toxicity, cardiac sensitization, or anesthesia (Farber & Fisher, 1979; Mehendale, 1994; Reynolds, 1984). Inhalation of aerosols of asbestos leads to pulmonary fibrosis and respiratory system cancer (mesothelioma) while chronic inhalation of cigarette smoke leads to destruction of the lung architecture leading to emphysema . Inhalation of chlorine or phosgene lead to massive cell death, edema, inflammation and loss of blood oxygenation capability.

Effects from inhalation of particulate matter suspended in a mixture of gases which **is** commonly called an aerosol are dependent on the physicochemical nature of both gases and particles. The dose of material to the body depends on the solubility of the gases in respiratory fluids and the size distribution of the particulate matter making up the aerosol. The biological response to this inhaled material depends on the characteristics of the respiratory system and the response of its defense mechanisms to the inhaled material. It **is** important to realize that inhaled material may have the respiratory system as its target organ or the respiratory system may only be a route of entry to the body and the aerosol material may have another organ as its target.' There are numerous examples of both instances.

The normal adult processes between 10 and 20 m^3 of air per day. From the nose, air passes through 23 generations of branching ducts with a velocity ranging from 390 cm/sec to 0.32 cm/ sec. The gas exchange surface area of the human lung is about 30 m^2 in area and is perfused by about 2000 km of blood capillaries. The residence time of air ranges from 30 to 550 ms. Relative humidity ranges from ambient to 100% saturation at body temperature (37 C). Thus the environmental conditions surrounding inhaled materials vary over many orders of magnitude (Hinds, 1982).

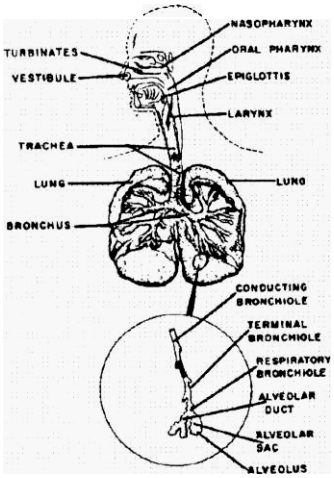

Figure 1 The Respiratory *System,* Adapted from Handbook *of* Air Pollution.

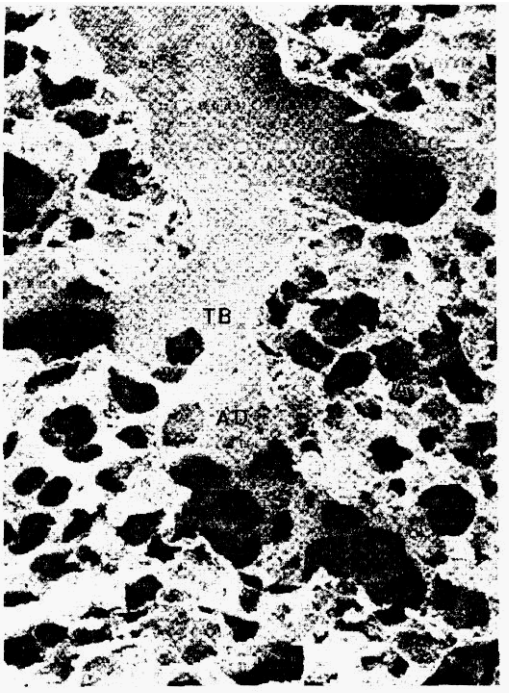

Figure 2 Rat lung pulmonary region showing a terminal bronchiole (TB) ending in branching alveolar ducts (AD) surrounded by alveoli (A).

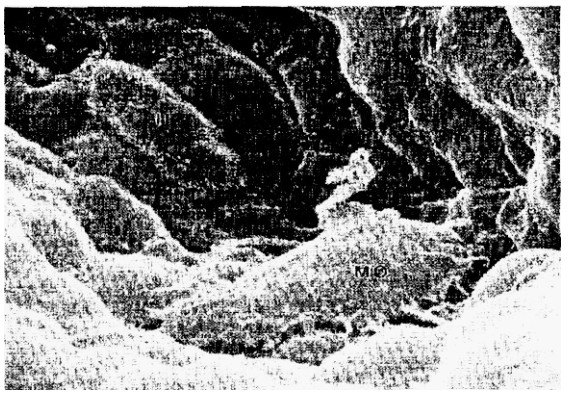

Figure 3 Rat alveolus showing alveolar macrophage (MΦ) on the surface of type I epithelial cells with a type 11 epithelial cell in the background.

The respiratory system is composed of several major subdivisions that can be defined on the basis of the differences alluded to in the previous paragraph. Figure 1 schematically illustrates these subdivisions of the respiratory system. The nasopharyngeal region is annotated to show the external nose and the nasal turbinates, the region of first contact with inhaled aerosols and the first particle filtering region of the respiratory tract. It is important to note that mouth breathing commonly seen in humans during periods of exertion bypasses this filtration region. The tracheobronchial region consists of the air conducting airways from the larynx to the terminal bronchioles. This region of the lung conducts gases to and from the gas exchange regions of the lungs and is coated with a mucous layer that acts to transport particulate material from the lower lung. The gas exchange region of the lung consists of respiratory bronchioles, alveolar ducts, and the alveolar sac or alveolus (Phalen. 1984). The following three figures illustrate the nature of the gas exchange region (Mauderly, 1996). Figure 2 is a scanning electron micrograph of the gas exchange region of a rat lung showing a terminal bronchiole ending in branching alveolar ducts and surrounded by alveoli. The interior of an alveolus is shown in Figure **3** which is a scanning electron micrograph of a rat alveolus. The close association between gas space and blood capillaries in the lung are illustrated by the bulges in the alveolar wall caused by the underlying capillaries. Gas is exchanged through the epithelial cells lining the alveolus and the capillary wall cells. The alveolar walls are shown in cross section in Figure 4. The epithelial cells (type I and type II) are shown as are macrophages which are a major immune defense cell within the lung the capability to engulf foreign particles. For many animal species, the major regions of the respiratory tract are similar overall, but differ in anatomical detail. The effects of these species differences has been studies extensively (Schum & Yeh, 1980; Martonen et al., 1995). For this reason, laboratory animal studies may be extrapolated to humans with some degree of confidence.

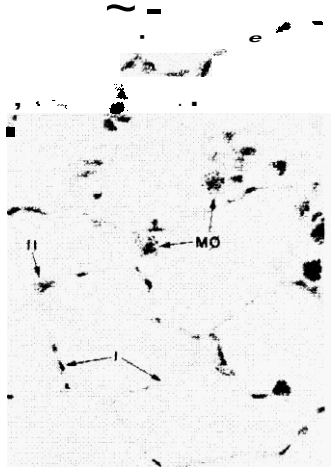

Figure 4 Cross sectional photomicrograph of rat alveoli, showing type I (I) and type II (II) epithelial cells and alveolar macrophages (MΦ).

The respiratory system provides life sustaining functions at several levels. It is a system for exchange **of** oxygen into and carbon dioxide out **of** the blood. Mechanically, the respiratory system must function to pump gases counter-currently while maintaining a relative humidity gradient without dehydration **of** tissues or the body. It must maintain a balance between oxygen and blood flow. To achieve these functions, the respiratory system actively controls its mechanical stiffness, active ventilatory volume and resistance to blood flow. It interacts with other organ systems in the body and responds to outside control signals. The respiratory system also acts to filter the inspired air and protect itself as well as the rest of the organism from particulate infections agents. The first region of filtration is at the back of the nose and removes larger particles. Smaller particles are deposited throughout the airways with the smallest particles reaching the gas exchange regions **of** the lung. Macrophages within the lung act to engulf foreign particles **of** both biological and other origins and transport them either to the mucous lined airways for removal or to the lymphatics. Many of these functions are more extensively discussed in Comroe (1974) and Phalen (1984).

Aerosol Characteristics and Deposition

An aerosol is an ensemble of small liquid or solid particles suspended in a gas. For the purpose **of** this discussion, the particulate matter may be a fire extinguishing powder and the gas air. Since aerosol toxicity depends both on the particulate and gaseous phases making up the aerosol, the quantity **of** gas absorbed by the lung and the quantity of particulate matter retained by the lung define the toxic dose. In many cases, the gas of concern is primarily air, so this discussion will focus on the aerosol particulate phase. The particles making up the solid portion of an aerosol often range over two to three orders of magnitude in size. In the particle size ranges that permit deposition in the lower respiratory tract, the particle physical and aerodynamic properties vary greatly with size. Because the quantity of solids retained by the lung is the parameter of concern in inhalation toxicity, the most relevant way to describe an aerosol is to specify the factors affecting that quantity; the mass per unit volume of particulate matter, the distribution of particle sizes, and significant effects of the suspending gas. **For** many aerosols, it is observed that the logarithm of the particle diameter is normally distributed, providing a convenient means of parameterizing the size distribution (Hinds, 1982; Raabe, 1971). Thus one speaks of a lognormal aerosol distribution having a median diameter and a geometric standard deviation (standard deviation of the log (particle diameter) distribution). Although the quantity of aerosol particles per unit diameter may be specified by a number of methods (counting particles, sieving, **or** weighing for example), the most relevant method for inhalation toxicology is determination by mass. Several well developed methods are available for these determinations and the reader is referred to texts on the subject (Hinds, **1982).**

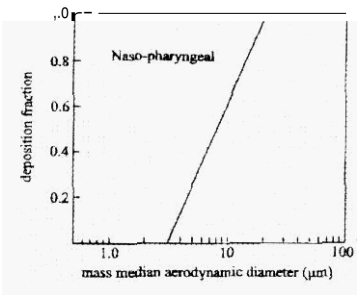

Figure 5 Fractional aerosol deposition in the nasopharyngeal region of the respiratory tract.

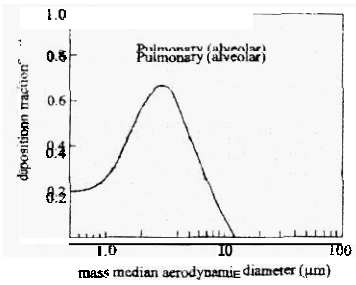

Figure 6 Fractional aerosol deposition in the pulmonary region of the respiratory tract.

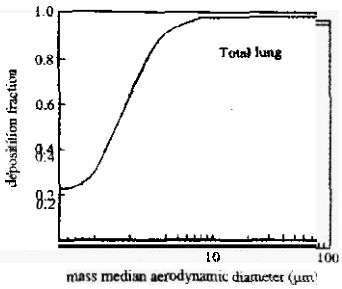

Figure 7 Fractional aerosol deposition in the total lung.

Particles small enough to remain airborne for any length of time and deposit in the lung are greatly influenced by the aerodynamic forces exerted by the fluid motion of the air exerts. This is particularly true during their transport into the respiratory system. In order to account for these effects on lung deposition, it is convenient to define particle size to include these effects (Raabe, 1976). Thus one refers to an aerosol as being of a specific mass median aerodynamic diameter (MMAD), each adjective modifying diameter having a particular significance. Mass denotes aerosol characterization by weight; median refers to the median of the size distribution; and aerodynamic denotes the fact that the interaction between the suspending gas and the particle is included as part of the measurement.

Because the environment in the respiratory tract varies so greatly from nose to alveolus, aerosol particles deposit in different regions as a function of their MMAD. This regional deposition has been experimentally determined and described with increasing theoretical accuracy (Wojciak, **1988).** Figures 5-7 show aerosol deposition fractions for the nasopharyngeal and alveolar regions of the lung as well as for the whole lung (Hatch & Gross, 1964). It should be noted that large particles (>2.5 micrometers for humans) are removed from the inhaled air by the nasal turbinates with high efficiency while very small particles are largely removed in the gas exchange regions of the lung. Thus a significant fraction of SFE aerosol, with an average MMAD of 2-2.7 micrometers will deposit significantly in the upper respiratory tract and in the alveolar spaces of the lung.

In considering the fate and effects of inhaled particulate matter, the chemical nature of the particulate matter dominates consideration after particles are deposited. The gas exchange spaces of the lungs are coated with a fluid containing many of the materials found in the fluid surrounding cells in all tissues and in addition containing a surfactant particular to the lung. The physiological purpose of this fluid is to promote uniform inflation of the active portion of the lung. Aerosol particulate solubility in this fluid is an important determinant of aerosol toxicity. If the inhaled particles are highly soluble in the fluid lining the respiratory tract, the dissolved material is highly mobile and can be transported readily into the blood for distribution throughout the body. However, if the inhaled particulate matter is poorly soluble, then general body distribution is slowed, but local response within the lung **is** probable. Thus with SFE aerosol exposures, little airway epithelium or macrophage response was seen. In contrast, after exposure for 24 months

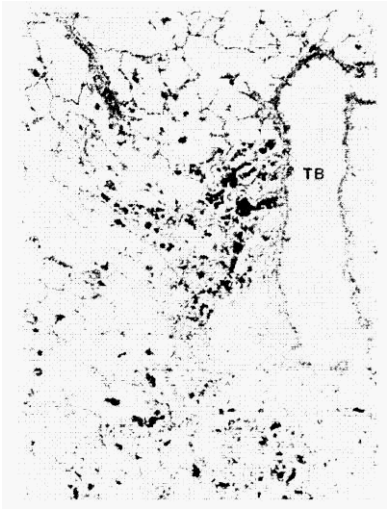

Figure 8 Alveolar accumulation of carbon particles after 24 months of repeated exposure 7 mg/cu. m of diesel soot; TB terminal bronchiole.

to 7 mg/m^3 of diesel exhaust soot, rat lungs respond as shown in Figure 8 with significant macrophage uptake of soot particles and tissue response to the macrophage contents spilled when these macrophages die (Mauderly, 1996).

Returning to consideration of the aerosol gaseous phase, it may also impact toxicity either directly or by influencing the respiratory pattern of the exposed individual. This phenomenon is observed in our SFE studies. Exposure to SFE in the absence of carbon monoxide results in interstitial edema surrounding the blood capillaries. but a similar exposure including 6675 PPM carbon monoxide leads to significant alveolar flooding due to loss of fluid impermeability by the airways (Kimmel et al., Smith et al., this publication). Furthermore, the presence of carbon dioxide leads to increased deposition of particulate matter due to changes in the volume of air inhaled per minute.

Toxic Responses of the Lung

Respiratory tract response to toxic insult is varied; depending not only on the chemical nature of the inhaled aerosol but also on the region of deposition. At the organ level, the lung may respond to toxic insult by changing its mechanical and ventilatory characteristics. The onset of an asthmatic attack and its relief by the action of pharmaceutical agents is an example of such behavior. The gas exchange portions of the lung may respond to toxic insult by a disturbance in gas exchange or blood flow arising from inability to maintain fluid barriers, such as exhibited by the lung after exposure to SFE and carbon monoxide. For soluble particles, these effects are driven by the chemical nature of the particles and the effects may persist for a short time. Resolution of the damage may result in no permanent **loss** of hnction.

At the tissue level, the respiratory system maintains cell competence and balance among its constituent cell populations (Niewoehner & Hoidal, **1982).** Destruction of specific cell populations in the respiratory system is often followed by physiologically significant failure of the respiratory tract that can be life threatening. Toxic effects such as the specific killing of alveolar Type I cells by NO and NO_2 lead to loss of liquid barrier integrity until Type I cells are replaced (Stavert et al., 1986; Postlethwait et al., 1991; Levin et al., 1989). Specific killing of secretory cells or ciliated cells in the respiratory tract leads to loss of particle clearance as a result of failure to move mucous up the conducting airways.

Lung response to a variety of tissue insults follows a common sequence **of** events, although the biochemical details may differ among insults. **If** macrophage recruitment to

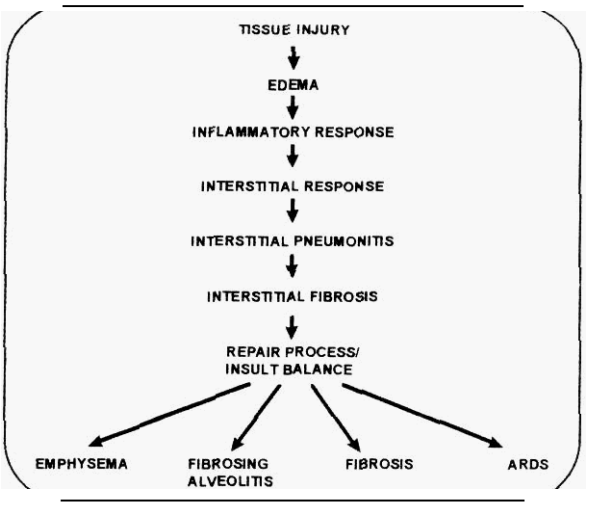

Figure 9 Commonality of pulmonary response *to* tissue injury.

deposition sites continues due to repeated exposure or loading of the lung with insoluble particles, the macrophage cellular contents will be released into regions of the lung. One hypothesis is that the continued insult of macrophage enzymes stimulates inflammation which, if not resolved, stimulates collagen formation leading to lung scarring. If this inflammatory and scamng process becomes pronounced as in adult respiratory disease, the entire lung can become involved and continued life is not possible. If these effects occur at a lower intensity. diseases such as pulmonary fibrosis and emphysema may arise. These diseases reflect the progressive stiffening of the lung due to scarring and loss of lung gas exchange due to destruction of alveolar structures. Additionally an increasing body of evidence suggests that, at least in laboratory rats, chronic high concentration exposure to insoluble aerosol materials enhances the appearance of both benign and malignant lung tumors (Mauderly, 1996).

Conclusion

This overview of inhalation toxicology and aerosol physics is intended to illustrate that aerosol toxicology issues associated with liquid droplet or particulate aerosols can be characterized and managed in the context of developing new fire extinguishing systems. Although the addition of particulate matter to a gas complicates the exposure analysis and pulmonary response, these complications are manageable. Reference has been made to several reviews of inhalation toxicology and aerosol science that are available and provide guidance on how to proceed in specific instances. Understanding that the manifestation of inhalation toxicity is controlled by the nature of the gas and particulate phases of the inhaled aerosol is necessary to managing the development of such agents. Similarly, understanding the range of pulmonary responses and their relationship to the nature of the toxic insult is key to developing rational risk assessments of potential hazard; indeed the characteristics of the respiratory system may be used to minimize the toxic effects of fire extinguishing aerosols.

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References

Comroe, J. H. **1974.** Physiology of Respiration, Year Book Medical Publishers, Chicago.

Farber, E., Fisher, M. M., eds. **1979.** Liver: Normal Function and Disease, ed. F. F Becker. New York. ***NY:*** Marcel Dekker

Hatch, T. F. and Gross, P. **1964.** Pulmonary Deposition and Retention of Inhaled Aerosols. New York ***NY:*** Academic Press

Hinds, W. C. **1982.** Aerosol Technology John Wiley & Sons, New York .

Levin, B. C., Paabo, M., Highbarger, L., Eller, N. **1989.** Synergistic Effects Of Nitrogen Dioxide And Carbon Dioxide Following Acute Inhalation Exposures In Rats. Gathersburg, MD: NIST

Martonen, T., Zhang, Z., Yang, Y. **1995.** Interspecies Modeling Of Inhaled Gases Inhalation Toxicology **7:1125-39**

Mauderly, J. L. **1996.** Lung Overload: The Dilemma and Opportunities for Resolution, Inhalation Toxicology, 8(suppl): **1-28.**

Mehendale, H. M. **1994.** Cellular And Molecular Foundations Of Hormetic Mechanisms. In Biological Effects of Low Level Exposures: Dose-Response Relationships, ed. E. J. Calabrese:111**-42.** Boca Raton, FL: Lewis Publishers

Niewoehner, D. E. **1982.** Lung Fibrosis and Emphysema: Divergent Responses to a Common Injury? Science, 217:359-360

Phalen, R. **F. 1984.** Inhalation Studies: Foundations and Techniques. Boca Raton. FL: CRC Press. **277** pp.

Postlethwait, **E.** M., Langford, **S.** D., Bidani, A. **1991.** Transfer Of NO2 Through Pulmonary Epithelial Lining Fluid. Toxicol. Appl. Pharmacol. 109:464-71

Raabe, **O.** ***G.*** **1971.** Particle Size Analysis Utilizing Grouped Data and the Log-Normal Distribution. J. Aerosol. Sci. **2;** 3:289-303

Raabe, **O.**G. **1976.** Aerosol Aerodynamic Sue Conventions for Inertial Sampler Calibration. **Air** Pollution Control Association Journal **26;** 9:856-60

Reynolds, A. **K. 1984.** On The Mechanism Of Myocardial Sensitization To Caecholamines By Hydrocarbon Anesthetics. Can. J. Physiol. Pharmacol. **62:183-98**

Schum, M., Yeh, H. C. 1980. Theoretical Evaluation Of Aerosol Deposition In Anatomical Models Of Mammalian Lung Airways. Bull. Math. Biol. **42:1-15**

Stavert, D. M., Archuleta, D. C., Holland, L. M., Lehnert, B. E. **1986.** Nitrogen Dioxide Exposure And Development Of Pulmonary Emphysema. J. Toxicol. Environ. Health. 17:249-67

USPHS, **1968.** Handbook of **Air** Pollution. Report Number **999-AP-44,** available from NTIS, Springfield, VA

Wojciak, J. F. **1988.** Theoretical **And** Experimental Analysis Of Aerosol Deposition In The Lung: Implications For Human Health Effects. Ph.D. Dissertation. University of Rochester; Rochester, New York. **387** pp.