15.1: Pulmonary Toxicology and Disease Epidemiology

Pulmonary disease and dysfunction exact a tremendous health burden on society. In a recent survey of lung disease published by the American Lung Association in 2012, upwards of 10 million Americans were diagnosed with chronic bronchitis while over 4 million Americans had emphysema. In separate surveys of asthma prevalence, close to 9% of adults and children residing in the United States were afflicted with asthma. According to the Centers for Disease Control (CDC) in the United States, lung cancer is the leading cause of cancer death, and in 2007, it was estimated that over 200,000 adults had lung cancer, and nearly 160,000 died from it. While genetic and susceptibility factors play significant roles in pulmonary disease incidence, a vast majority of cases result from environmental, dietary, or occupational exposures to xenobiotic agents. For example, over 80% of all cases of lung cancer are due to smoking. In asthma, several inhaled protein and chemical agents can sensitize the respiratory tract and gases and particulates can trigger clinical symptoms including asthma attacks. The vulnerability of the lung to toxicants stems primarily from the fact that it is exposed to both the external environment and the entire cardiac output. The major toxicological consequence of this is that xenobiotics can enter the respiratory tract upon inhalation and directly affect lung tissue and function or enter via other routes (e.g., dietary or dermal) and reach the lung through the systemic circulation. While not the focus of this chapter, inhalation is also a major route of exposure to systemic toxicants that have extra-pulmonary targets such as carbon disulfide that when inhaled causes neurological effects including encephalopathy.

The number of known pulmonary toxicants is staggering with the toxicity potential of countless others still uncharacterized. Their study is complicated by the fact that many are ubiquitous in the environment and exist in varied mixtures. Thus, tremendous scientific and

public health efforts dating back to the early parts of the last century have been devoted to understanding toxic responses of the lung. These efforts are naturally beset by challenges owing principally to the difficulty in ascribing effects to a causative agent in part because the lung is exposed to the external environment and consequently to a plethora of foreign substances found in ambient air. The other great challenge relates to the limitations associated with human studies, both epidemiological and clinical. As a result, much of the information regarding toxic effects of chemicals is derived from animal and *in vitro* toxicological studies. This chapter will focus on lung-specific toxicity including a discussion of basic lung anatomy and physiology, the basis for pulmonary toxicity including the principles of gas and particle deposition, dosimetry and metabolism, key pulmonary toxicants and their known or hypothesized mechanisms of action, and toxicological approaches to characterizing the effects of agents with known and unknown potential for respiratory effects.

15.2: Comparative Functional Anatomy of the Lung

Ventilation and Perfusion – The most essential functions of the respiratory tract are the delivery of inspired air and the distribution of pulmonary blood flow to regions where exchange of oxygen and carbon dioxide can occur in an energy-independent process. In mammals, this exchange is dependent on an intimate association between the alveoli, which are the basic gas-exchange units of the lung and a vast capillary network, which transports the gases to and from the lung and systemically at the tissue and cellular level. The arborization (~26 bifurcations) of the bronchial tree distal to the trachea increases the total cross-sectional area, which is maximal in the alveolar region to assure adequate gas exchange. In order for this to take place, the lungs must overcome flow resistive and tissue elastic forces to bring air in from the ambient