HEALTH EFFECTS CLASSIFICATION AND ITS ROLE IN THE DERIVATION OF MINIMAL RISK LEVELS: RESPIRATORY EFFECTS

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The anatomy and physiology of the respiratory system as related to pathophysiology of the respiratory system are considered. The various toxicological end points in the respiratory system and the relative seriousness of the effects are discussed. The impact of assessing the seriousness of the effects on the derivation of health-based guidance values, with specific examples of the Agency for Toxic Substances and Disease Registry's minimal risk levels based on respiratory effects, is presented.

INTRODUCTION

To determine the levels of significant human exposure to a given chemical and associated health effects, the Agency for Toxic Substances and Disease Registry's (ATSDR's) toxicological profiles examine and interpret available toxicological and epidemiological data. The respiratory system is an important consideration from a public health standpoint because it is a primary target for hazardous substances and represents the first contact for inhaled pollutants. Respiratory effects can occur from inhalation of toxic gases, vapors, dusts, or aerosols of particulate or liquid chemicals or solutions. In addition, chemicals present in the systemic circulation from exposure by other routes can reach the lungs and elicit toxic effects therein. Respiratory tract tissue can be damaged directly by the chemical or indirectly by its metabolites, since many cells in the respiratory system are capable of xenobiotic metabolism. Many respiratory effects of toxic chemicals are due to excessive oxidative burden on the lungs, leading to chronic bronchitis, emphysema, and fibrosis, for example. ATSDR categorizes the health effects according to their seriousness and uses the highest no-observed-adverse-effect level (NOAEL) or the lowest-observed- adverse-effect level (LOAEL) in the database for minimal risk level (MRL) derivation (ATSDR, 1996a; Chou et al., 1998). This paper deals with respiratory effects and the MRLs that were based on respiratory effects in recent years.

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2. Abbreviations: ATSDR, Agency for Toxic Substances and Disease Registry; FVC, forced vital capacity; FEV_1, forced expiratory volume in one second; $FEF_{25-75\%}$, mean forced expiratory flow during the middle half of the FVC; FIV_1, forced inspiratory volume in one second; LOAEL, Lowest-observed- adverse-effect level; MRL, minimal risk level; NOAEL, No-observed-adverse-effect level; PEFR, peak expiratory flow rate; RADS, reactive airway dysfunction syndrome; RDS, respiratory distress syndrome.

3. Key words: classification of effects, minimal risk levels, respiratory effects.

Journal of Clean Technology, Environmental Toxicology, and Occupational Medicine, Vol. 7, No. 3, pp. 233–249

ISSN: 1052-1062

RESPIRATORY EFFECTS

This section consists of text regarding lung and respiratory diseases as written in *Priority Health Conditions* (ATSDR, 1993a), with additional information from Haschek and Witschi (1991) and ATSDR (1994a).

Anatomy and Physiology

The discussion of anatomy and physiology of the respiratory system refers to that of humans, with the recognition that many species differences exist between humans and animals and among various species of animals.

The major function of the respiratory system is to transfer oxygen from the atmosphere to the cells and, in turn, transfer carbon dioxide from the cells back to the atmosphere. This exchange of gases between the cells and air can be divided into four major stages: (1) pulmonary ventilation, which is the actual inflow and outflow of air between the atmosphere and the alveoli; (2) diffusion of oxygen and carbon dioxide between the alveoli and the blood; (3) transport of oxygen and carbon dioxide in the blood and body fluids to and from the cells; and (4) regulation of ventilation and other aspects of respiration.

The anatomy of the respiratory system can be divided into three functional regions: the nose and nasopharynx, the trachea and bronchi, and the respiratory bronchioles and alveoli.

The upper airway (the nose and nasopharynx) is an important component of respiratory protection. It warms and filters incoming air. As inspired air passes the highly vascular lining of the nasal turbinates, it is warmed and humidified by profuse nasal secretions. Particles of foreign matter larger than 10 micrometers (μm) are filtered out in the nasal hairs or settle in the mucus of the upper airway. Rapid breathing through the mouth during exercise or strenuous work decreases the protection that the upper respiratory tract provides. The nose and nasopharynx are so efficient that almost no particle larger than 10 μm and only 15% of those larger than 4.5 μm reach the larynx.

Beginning in the nasopharynx and continuing down to the respiratory bronchioles, airways are lined with both ciliated and mucus-producing cells that make up the mucociliary escalator. Particles larger than 2 μm get caught in the mucus and are moved up the respiratory tract until they are swallowed; only particles smaller than 2 μm are likely to reach the alveoli. Tobacco smoke and some air pollutants can interfere with the mucociliary mechanism and thus make clearance of respired particles less effective.

The respiratory tract bifurcates successively as it descends into the lungs; as a consequence, the respiratory system has a very large surface area in the bronchioles and alveoli where gas exchange takes place. Gas exchange takes place in tiny air sacs, the alveoli, where only a thin (0.4 μm) tissue barrier separates inspired air from the blood in the capillaries. Total alveolar surface area, the area available for gas exchange, is approximately 70 square meters. The volume of capillary blood in the lungs is usually only about 100 milliliters (mL). Consequently, diffusion of oxygen

and carbon dioxide occurs over a large surface covered by a very thin film of blood. At rest, the average person breathes about 8 liters of air a minute. As muscular activity increases, so does the rate of breathing, the total amount of air breathed, and consequently the dose of any toxic constituents present in the air.

Oxygen and carbon dioxide are exchanged at the level of the respiratory bronchiole and alveoli by diffusion. The layers encountered as gas goes from the alveoli to the red blood cell are the alveolar air space; pulmonary surfactant (which decreases the surface tension of the fluids lining the alveolus and prevents the alveolus from collapsing); the epithelium of the alveolus; the basement membrane; and finally the endothelium of the capillary. The average total thickness of these layers is about 0.4 μm. Pathologic processes that increase this thickness will increase the time for diffusion and thus impair gas exchange.

Inhaled particles are deposited according to their size. Particles over 10 μm are deposited largely in the nose and upper airways because of turbulent air flow; particles of 3 to 10 μm lodge in the trachea and bronchi by impaction; and smaller particles (0.5 to 3 μm) are deposited in the terminal airways and alveoli. The most dangerous particles range from 1 to 5 μm in diameter; these penetrate to the respiratory bronchioles and air spaces, where they impact or settle. The toxic potential of particles affecting the lung is influenced by the number of particles retained in the lung and airways, the size and shape of the particles, and the solubility and cytotoxicity of the particles. Highly water-soluble gases such as sulfur dioxide or formaldehyde go into solution in the nasal fluids and are, therefore, almost completely extracted in the upper airway in resting subjects during any brief exposure.

Toxic gases must penetrate several protective and functional layers of fluids to reach the underlying lung tissue. Diffusion of inhaled toxicants into these layers depends on radial and axial diffusion of a gas and the mixtures with other nontoxic gases (such as nitrogen, oxygen, carbon dioxide, and water vapor) inhaled simultaneously. The solubility of a gas in water is the major characteristic in determining the relative toxicity of the gas. Inhaled toxicants that do not exert immediate toxic effects can pass through the lung, reach the capillaries, and be transported by the blood to other tissues where they can cause injury.

Pathophysiology

The major function of the lung is to provide a means for the exchange of oxygen and carbon dioxide; the same precise physiological parameters that allow the lung to perform this task also make this organ particularly suited for the uptake and excretion of potentially toxic volatile compounds. Also, the large surface area, the airways, and narrow separation between the air space and capillary circulation make the lung an efficient organ for the absorption of nonvolatile toxicants.

Cytotoxicity as a result of exposure of the respiratory tract to inhaled substances may be reversible or irreversible and may occur in all cells within a region or be specific to a single cell type. Ciliated cells of the respiratory epithelium or large airways and the type I epithelial and capillary endothelial cells of the alveolar region are particularly susceptible to nonselective damage by

virtue of the large surface area presented to airborne or bloodborne toxic substances. In addition, exposure to extremely toxic or caustic chemicals could result in nonspecific damage to all cells that are encountered. Conversely, chemical-specific damage depends on the nature of the chemical and its interaction with specific cell types. For example, Clara cells, which contain high levels of cytochrome P-450 enzymes, would be targets for chemicals that require metabolic activation.

Repair processes usually occur after initial respiratory injury regardless of the affected cell type. Repair involves proliferation of stem cells and inflammation. Proliferation can occur in resident cells of the injured tissue or by migration of inflammatory cells into the lung. Cellular necrosis is an example of the injury by which resident cell proliferation occurs as a regenerative process. Although repair by cell proliferation maintains tissue integrity, it can also lead to hyperplasia and neoplasia if proliferation is excessive. Thus, mild epithelial cell damage may be repaired by simple cellular regeneration; however, if damage is severe (basement membrane damage, severe inflammation, persistence of toxic agent), eliciting a significant inflammatory component may be followed by tissue destruction or fibrosis. Persistence of a toxic agent, such as beryllium or silica, may lead to the formation of granulomatous disease (pneumoconiosis).

A vast array of substances are capable of producing lung disease. The pathologic responses of the lung to toxic agents can be divided into the general categories of irritation, inflammation, necrosis, edema, emphysema, fibrosis, allergic responses, and cancer. However, ATSDR's Division of Toxicology considers allergic responses as immunological effects when classifying critical end points for derivation of MRLs, and, by definition, MRLs are based on noncancer health effects only and do not reflect a consideration of carcinogenic effects. Therefore, allergic responses and carcinogenic effects in the respiratory system are not considered further in this paper on systemic respiratory effects.

Irritation

The most common effect of chemical substances on the respiratory tract is irritation. Toxicity can result from the irritant and/or corrosive properties of a chemical, with effects ranging from minor irritations that are relatively reversible to extensive damage resulting in permanent disability or death. It can occur in any of the three anatomical divisions of the lung. Examples of irritant gases include chlorine, sulfur dioxide, ozone, nitrogen dioxide, and ammonia. The extent of damage depends on the nature of the chemical, as well as the duration and concentration of the exposure.

The nose and nasopharynx can be affected by a number of substances that irritate the mucosa causing rhinitis, cough, sore throat, or loss of the sense of smell. Exposure to inhaled chemicals can also irritate the lining of the sinus cavities. The resulting inflammation can cause increased mucus secretion and ultimately sinusitis. Severity can range from simple postnasal drainage of mucus to sinusitis with secondary infection. Symptoms include headache, facial pain, local tenderness, and fever.

A substance that irritates the trachea and bronchi can cause tracheitis or bronchitis, resulting in an increase in both the size and number of mucus-producing glands. Cough and increased sputum production are frequent symptoms of bronchitis; secondary infection can occur. Cigarette smoke is the most common irritant of the bronchi.

Irritant substances can also reach the peripheral portion of the lung, causing inflammation. An important feature of chronic interstitial pneumonia is continued inflammation of the alveolar wall. Ozone and nitrogen dioxide are two gases that reach distal parts of the lung. Damage can result in nonimmunological airway hyperresponsiveness, a condition in which a wide variety of substances, such as histamine, methacholine, or cold air, cause exaggerated airway narrowing.

Acute bronchitis can be caused by dusts, fumes from certain organic compounds, and environmental irritants. It is characterized by the presence of blood in the mucous membranes (hyperemia), followed by edema and leukocytic infiltration of the submucosa. Increased mucus secretion as a result of exposure to some agents may result from direct irritation.

Chronic bronchitis due to exposure to toxic chemicals is characterized by a dramatic increase in the number of mucous cells. Hypersecretion accompanied by an increased glycoprotein content from submucosal glands may affect the viscosity of mucus. An irritating effect of excessive mucus on sensory nerve endings may trigger the cough reflex. In cases of chronic exposure, persistence of mucous cell hyperplasia or metaplasia can lead to blockage of mucous glands and ducts, airway obstruction, and alveolar damage. Accumulation of debris can incite an inflammatory response. Damage to the basement membrane may result in migration of fibroblast precursors from the ulcerated airway wall into the lumen, resulting in intraluminal fibrosis. In the presence of severe inflammation, the airway wall may be destroyed or abscessed. Sufficiently impaired clearance may lead to bronchoconstriction, hypoxic vasoconstriction, alveolar injury, and emphysema.

Chronic alveolar irritation is characterized by proliferation and persistence of type II epithelial cells, interstitial thickening due to fibrosis, and accumulation of mononuclear cells. Intraalveolar exudate composed of macrophages may be present.

Acute inhalation injury or reactive airway dysfunction syndrome (RADS) is an asthma-like syndrome that may develop after a single high environmental irritant exposure. Previously well subjects then develop wheezing and shortness of breath when exposed to a variety of airborne irritants, similar to typical asthma. These symptoms can persist for years. Chlorine, hydrogen sulfide, sulfur dioxide, and phosgene are examples of gases that are thought to cause this syndrome.

Inflammation

Inflammation is also referred to as alveolitis or interstitial pneumonia and results from diffuse or patchy damage to alveolar septa caused by inhalation of toxic agents. Granulomatous diseases and pneumoconiosis also have an inflammation component, but the fibrotic component is prominent when the disease is well established. Inflammation may occur following hyperoxia or may manifest pulmonary hypersensitivity. Acutely, damage to capillary endothelial and alveolar

epithelial cells results in serofibrinous exudate flooding of alveoli. Lining of the airspaces with membranes composed of fibrin, serum protein, and cell debris occurs in severe cases, followed by infiltration of leukocytes into the alveolar lumina and interstitial area. Proliferation of stem cells and resolution of the inflammation component can lead to repair, but if inflammation persists and regeneration is inhibited, more severe chronic effects are characterized by intraalveolar accumulation of mostly macrophages; proliferation and persistence of increased type II cell numbers; and accumulations of lymphoid cells, fibroblast proliferation, and collagen deposition that result in nonreversible and progressive fibrosis. Extensive tissue destruction may also occur.

Necrosis

A variety of materials can cause cellular damage, also known as necrosis. In the nasal cavity, cell necrosis with exfoliation, accompanied by inflammation of the respiratory epithelium, is characteristic of severe damage to the respiratory epithelium. More severe damage includes segmental loss of basal lamina or ulceration in squamous epithelium, which can lead to damage of underlying lamina propria, bone, or cartilage. An exudate containing inflammatory cells (rhinitis) may cover the affected area. These lesions may undergo repair if exposure is acute, but squamous metaplasia, occasionally with extensive keratinization, may result if exposure is repeated. If keratinization is excessive, obstruction of the nasal cavity may result. Unrepaired damage may lead to fibrosis, which may gradually obliterate the nasal cavity. Thus, chemically induced injury of the nasal epithelium may be followed by complete repair, olfactory epithelial replacement by respiratory-like epithelium, squamous metaplasia, hyperplasia, or fibrosis.

In the airways, injury to nonspecific epithelial cells or to single cell types may be mild and reversible if there is minimal inflammation and complete epithelial regeneration. Irreversible damage can occur with more severe injury if necrosis induces severe inflammation and fibrosis. Impaired mucociliary clearance due to changes in mucus or injured ciliated cells is a common response of the airway epithelium to toxic agents. Effects on ciliated cells include loss of cilia or inhibition of the ciliary beat frequency. Effects on Clara cells, usually induced by agents that require metabolic activation by the cytochrome P-450 enzymes, include necrosis followed by movement of remaining bronchiolar cells to cover the denuded basement membrane and rapid proliferation of remaining Clara cells to regenerate normal epithelium. Squamous metaplasia and hyperplasia occur in the trachea and in the larynx.

Edema

Injury to endothelial cells in the alveoli results in increased vascular permeability, which allows leakage of fluid into interstitial spaces and lymphatics and eventually into alveolar spaces. With severe damage, edema and interstitial inflammation may occur. Distortion of the normal cell-cell contact by inflammation or edema may lead to interstitial fibrosis. Injury to epithelial cells in the alveoli results in acute exudative inflammation characterized by fibrin, neutrophils, and edema. Repair via proliferation of type II cells with subsequent transformation of the type II cells into type I cells and subsidence of inflammation can occur if basement membranes are intact. With more severe injury, in which the alveolar epithelium has been denuded and the basement membrane has been damaged, intraalveolar fibrosis results from the rapid movement of fibroblast precursors

into the alveolar space. Thus, altered hemodynamics or increased permeability of the air-blood barrier can result in edema by fluid leakage from the endothelium into the interstitial area and percolation to lymphatics, leading to dilated lymphatics and increased lymph flow. Interstitial edema will occur if lymphatic capacity is overwhelmed. Alveolar edema will occur if the capacity of the interstitium is overwhelmed or if alveolar epithelial cells are damaged, leading to leakage of fluid into the alveoli. Increased wet lung weight is an indication of edema. Pulmonary edema interferes with respiratory gas-exchange function of the lung, and with prolonged injury, inflammation and fibrosis may result.

Adult respiratory distress syndrome (RDS) is a descriptive term covering lung disease that results in severe arterial hypoxia and respiratory failure. The etiology of RDS includes overwhelming infections, drug effects, and aspiration, as well as inhalation of toxins and irritants. Chlorine gas, nitrogen dioxide, smoke, ozone, and high concentrations of oxygen are thought to cause this condition. These insults result in increased alveolocapillary permeability with leakage of protein leading to pulmonary edema. The subject can be without symptoms immediately after the injury, but after several hours will have an increased respiratory rate and dyspnea.

Emphysema

Emphysema is characterized as abnormal permanent enlargement of airspaces accompanied by destruction of alveolar walls, but without fibrosis. Physiologically, the features of emphysema are reduced elastic recoil and increased lung volume. Emphysema is thought to be caused by injury to elastic fibers in pulmonary connective tissue. Emphysema can also develop as a chronic consequence of fibrosis. Because of the large reserves of the lung, damage can often be extensive before dysfunction is clinically detectable. Symptoms include a slowly progressive history of dyspnea with exercise; cough and sputum production are not prominent symptoms. The pathophysiology of this disease is of chronic airway obstruction. Patients have hyperinflated chests with diminished lung sounds. Pulmonary function tests show increased lung capacity and residual volume with low flow rates. A history of smoking is important in the development of this disease. Although no specific toxicants have been linked to its development, epidemiological surveys have shown an increased prevalence of emphysema in heavily industrialized urban areas.

Fibrosis

Fibrosis is a nonspecific inflammatory response of the alveolar wall. It can be due to injuries of different types, durations, and intensities. Initially there is alveolar injury with epithelial or endothelial cell edema, or necrosis and interstitial edema. Inflammatory cells accumulate in the alveolar septae, the spaces between the alveoli, as well as in the alveoli. This is followed by a repair with type II epithelial cells replacing the damaged type I cells. Fibroblast proliferation also occurs. If there is no further injury, the lung is repaired.

Fibrosis is characterized by an increased amount of collagen, an abnormal location of the deposited collagen, and/or an abnormality in the nature of collagen itself. The major cell type involved in collagen synthesis is the fibroblast, but other cell types may synthesize collagen in response to exposure to toxic chemicals. Fibrosis is usually irreversible once mature collagen is deposited. Abnormal collagen deposition can occur within alveolar spaces, capillaries, or airways. Changes

in the relative amounts of different types of collagen or crosslinking result in abnormalities in the nature of collagen. Collagen may distribute relatively uniformly throughout the lungs following diffuse alveolar damage or may distribute multifocally throughout the lungs as a component of granulomatous disease or pneumoconiosis. Fibrosis can result when the normal repair mechanism is disrupted, and can result in a reduction of compliance and an impairment of gas diffusion. In chronic interstitial diseases, there appears to be a continuous cycle of injury, inflammation, necrosis, and repair. End-stage fibrosis is a final common pathway. Patients present with exertional dyspnea and sometimes a cough. Early in the disease, the physical examination can be normal, whereas, in late stages, bronchovesicular breath sounds and coarse crackles can be heard during auscultation in the lung bases. Resting cyanosis with a rapid respiratory rate and use of accessory muscles are signs of advanced disease. Physiological changes include a decrease in lung volume and compliance, as well as a decrease in diffusing capacity. In early interstitial disease, there is hypoxemia with exercise, while late in the disease, there can be resting hypoxemia.

Fibrotic diseases include pneumoconioses due to inorganic dust inhalation (such as silicosis, black lung disease, and asbestosis), idiopathic pulmonary fibrosis, and interstitial lung diseases due to collagen vascular diseases. Idiopathic pulmonary fibrosis is a type of interstitial lung disease that is generally fatal over a relatively short period. Injury and inflammation in the alveoli progress to fibrosis with impairment of gas exchange due to the thickened interalveolar septae. Other names for this condition include cryptogenic fibrosing alveolitis, diffuse interstitial lung fibrosis, idiopathic interstitial pneumonia, and Hamman-Rich syndrome. The cause of idiopathic pulmonary fibrosis is largely unknown, and its prevalence is difficult to ascertain. In certain industrialized regions of England, the incidence seems to be increasing; there is some evidence that the disease is linked with environmental exposure to dust.

Fibrosis can also take the form of coal workers' pneumoconiosis, silicosis, asbestosis, or berylliosis. Pneumoconioses are diseases of the lung caused by the inhalation of dust. In coal workers' pneumoconiosis, coal dust is widely distributed throughout the lungs. Asbestosis is diagnosed by the presence of asbestos bodies in the involved area. Interstitial fibrosis is common in the lower lobes of the lung. Silicosis, a result of long-term exposure via inhalation to small particles of silicon dioxide, occurs in industries such as metal mining. Berylliosis appears to be a hypersensitivity disease that occurs in about 2 percent of those persons exposed to beryllium.

Biomarkers

Effects of toxicological insult to the respiratory system can be monitored by observing clinical signs (nasal irritation, sore throat, cough, rhinorrhea, auscultatory findings, chest pain); monitoring function (breathing rate, ventilatory volume, expired volume); observing pathological signs of damage or disease (X-ray); or performing bronchopulmonary lavage.

Pulmonary function testing provides useful functional information in relation to ventilatory function or gas exchange by assessing the mechanical characteristics of ventilatory function in relation to pressures, air flow, and air volume within the lungs. Typical measures of spirometry include forced vital capacity (FVC), forced expiratory volumes (FEV_1 - forced expiratory volume

in one second), peak flow, $FEV_1/FVC\%$, mean forced expiratory flow during the middle half of the FVC ($FEF_{25-75\%}$), forced inspiratory volumes (FIV_1), and peak expiratory flow rate (PEFR). These tests can distinguish between minor decrements in these components, emphysema, chronic obstructive pulmonary disease, and restrictive disease. Lung diffusion tests can determine effects on alveolar-capillary gas exchange. An application of the pulmonary function testing measures the depression of respiratory rate in mice to assess the sensatory irritation of an inhaled chemical.

Bronchopulmonary lavage can be performed, and aspirated fluid can be analyzed for the cellular profile, protein content, enzyme, and lipids. Cell damage in airways and lung tissue can be indicated by increased activity of lactic hydrogenase, alkaline phosphatase, or acid phosphatase. Pulmonary edema can be indicated by increased serum albumin. The presence of inflammatory cells and enzymes involved in collagen metabolism may indicate more chronic changes, such as fibrosis.

Mrls Based on Respiratory Effects

As of January 1998, ATSDR has derived 32 MRLs based on respiratory effects. The basis for and description of the derivations of these MRLs are published in the respective ATSDR toxicological profiles for the substances of concern, as indicated in Table 1.

TABLE 1. MRLs Bases on Respiratory Effects

Substance Name	Route	Duration	MRL value	UF	Critical Effect	Critical Study	Reference
Acrolein	Inhalation	Intermediate 13 wk, 5 d/wk, 6 hr/d	9×10^{-6} ppm	1000	LOAEL in rats for metaplasia in lung epithelial cells	Feron et al., 1978	ATSDR, 1990a (Final)
Ammonia	Inhalation	Acute 2 hr	0.5 ppm	100	LOAEL in humans for urge to cough, irritation to nose and throat	Verbeck, 1977	ATSDR, 1990b (Final)
Ammonia	Inhalation	Chronic 15 yr, 5 d/wk, 8 hr/d	0.3 ppm	10	NOAEL in humans for pulmonary function	Holness et al., 1989	ATSDR, 1990b (Final)
Bis (chloromethyl) ether	Inhalation	Intermediate 6 mo, 5 d/wk, 6 hr/d	0.0003 ppm	100	NOAEL in rats for histology in lungs	Leong et al., 1981	ATSDR, 1989a (Final)

TABLE 1. MRLs Bases on Respiratory Effects (cont'd)

Substance Name	Route	Duration	MRL value	UF	Critical Effect	Critical Study	Reference
Chromium, Hexavalent	Inhalation	Intermediate 0.2–23.6 yr (2.5 yr average) 5 d/wk, 6 hr/d	2×10^{-5} mg/m^3	10	NOAEL in humans for nasal mucosa atrophy and decreased pulmonary function	Lindberg and Hedenstierna, 1983	ATSDR 1993b (Final)
Chromium, Hexavalent	Inhalation	Chronic 0.2–23.6 yr (2.5 yr average) 5 d/wk, 6 hr/d	2×10^{-5} mg/m^3	10	NOAEL in humans for nasal mucosa atrophy and decreased pulmonary function	Lindberg and Hedenstierna, 1983	ATSDR, 1993b (Final)
Cobalt	Inhalation	Intermediate 13 wk, 5 d/wk, 6 hr/d	3×10^{-5} mg/m^3	1000	LOAEL in rats for larynx metaplasia	NTP, 1991	ATSDR, 1992a (Final)
Cresol, meta	Oral	Acute Gd 6–18	0.05 mg/kg/d	100	NOAEL in rabbits for audible respiration	BRRC, 1988	ATSDR, 1992b (Final)
Formaldehyde	Inhalation	Acute 2 hr	0.05 ppm	9	LOAEL in humans for itching, sneezing, nasal congestion	Pazdrak et al., 1993	ATSDR, 1997a (Public Comment)
Formaldehyde	Inhalation	Intermediate 26 wk, 7 d/wk, 22 hr/d	0.01 ppm	100	NOAEL in monkeys for hoarseness, nasal congestion, nasal discharge	Rusch et al., 1983	ATSDR, 1997a (Public Comment)
Formaldehyde	Inhalation	Chronic occupational	0.003 ppm	30	LOAEL in humans for rhinitis, nasal crusting	Edling et al., 1988	ATSDR, 1997a (Public Comment)
Hexachlorocyclo-pentadiene	Inhalation	Intermediate 14 wk, 5 d/wk, 6 hr/d	0.0001 ppm	100	LOAEL in rats for effect on Clara cells	Rand et al., 1982	ATSDR, 1997b (Public Comment)
Hexachlorocyclo-pentadiene	Inhalation	Chronic 2 yr, 5 d/wk, 6 hr/d	0.00003 ppm	300	LOAEL in rats for pigment-ation of upper respiratory tract	NTP, 1994	ATSDR, 1997b (Public Comment)

TABLE 1. MRLs Bases on Respiratory Effects (cont'd)

Substance Name	Route	Duration	MRL value	UF	Critical Effect	Critical Study	Reference
Hexamethylene diisocyanate	Inhalation	Intermediate 3 wk, 5 d/wk, 5 hr/d	3×10^{-5} ppm	30	NOAEL in rats for hemorrhage, inflammatory exudate, and epithelial changes in nasal cavity	Mobay Corporation, 1984	ATSDR, 1996b (Public Comment)
Hexamethylene diisocyanate	Inhalation	Chronic 2 yr, 5 d/wk, 6 hr/d	1 × 10-5 ppm	90	LOAEL in rats for nasal cavity epithelial hyperplasia	Mobay Corporation, 1989	ATSDR, 1996b (Public Comment)
Hydrogen sulfide	Inhalation	Acute 30 min	0.5 ppm	10	NOAEL in humans, no respiratory effects	Bhambhani et al., 1994	ATSDR, 1997c (Public Comment)
Hydrogen sulfide	Inhalation	Intermediate 17 d continuous	0.09 ppm	100	NOAEL in pigs for no respiratory effects	Curtis et al., 1975	ATSDR, 1997c (Public Comment)
Naphthalene	Inhalation	Chronic 104 wk, 5 d/wk, 6 hr/d	0.002 ppm	1000	LOAEL in mice for inflammation of nose and lung, metaplasia of olfactory epithelium, hyperplasia of respiratory epithelium	NTP, 1992	ATSDR, 1995 (Final)
Nickel	Inhalation	Chronic 2 yr, 5 d/wk, 6 hr/d	2×10^{-4} mg/m^3	30	NOAEL in rats for chronic active inflammation and fibrosis of the lungs	NTP, 1996; Dunnick et al., 1995	ATSDR, 1997d (Final)
Propylene Glycols	Inhalation	Intermediate 13 wk, 5 d/wk, 6 hr/d	0.009 ppm	1000	LOAEL in rats for nasal hemorrhaging	Suber et al., 1989	ATSDR, 1997e (Final)

TABLE 1. MRLs Bases on Respiratory Effects (cont'd)

Substance Name	Route	Duration	MRL value	UF	Critical Effect	Critical Study	Reference
Sulfur dioxide	Inhalation	Acute	0.01 ppm	30	LOAEL in humans for increased airway resistance	Sheppard et al., 1981	ATSDR, 1997f (Public Comment)
Titanium Tetrachloride	Inhalation	Intermediate 4 wk, 5 d/wk, 6 hr/d	0.01 mg/m^3	90	LOAEL in rats for mild dust cell reaction and increased lung weight	DuPont, 1979	ATSDR, 1997g (Final)
Titanium Tetrachloride	Inhalation	Chronic 2 yr, 5 d/wk, 6 hr/d	0.0001 mg/m^3	90	LOAEL in rats for tracheitis and rhinitis	EPA, 1986; Lee et al., 1986	ATSDR, 1997g (Final)
Vanadium	Inhalation	Acute 8 hr	0.0002 mg/m^3	100	LOAEL in humans for bronchial irritation	Zenz and Berg, 1967	ATSDR, 1992c (Final)
Vinyl acetate	Inhalation	Intermediate 3 mo, 5 d/wk, 6 hr/d	0.01 ppm	100	NOAEL in mice for inflammation of nasal turbinate epithelium; mild *multifocal* bronchitis	Hazleton Laboratories, 1980	ATSDR, 1992d (Final)
1-Methyl-naphthalene	Oral	Chronic 81 wk	0.07 mg/kg/d	1000	LOAEL in mice for alveolar proteinosis	Murata et al., 1993	ATSDR, 1995 (Final)
1,2-Dichloro-propane	Inhalation	Acute 2 wk, 4–5 d/wk, 6 hr/d	0.05 ppm	1000	LOAEL in rats for nasal mucosa degeneration	Nitschke and Johnson, 1983	ATSDR, 1989b (Final)
1,2-Dichloro-propane	Inhalation	Intermediate 13 wk, 5 d/wk, 6 hr/d	0.007 ppm	1000	LOAEL in rats for upper respiratory lesions	Nitschke et al., 1988	ATSDR, 1989b (Final)
1,2,3-Trichloro-propane	Inhalation	Acute 11 d, 5 d/wk, 6 hr/d	0.0003 ppm	100	NOAEL in rats for decreased thickness of olfactory epithelium	Miller et al., 1986	ATSDR, 1992e (Final)

TABLE 1. MRLs Bases on Respiratory Effects (cont'd)

Substance Name	Route	Duration	MRL value	UF	Critical Effect	Critical Study	Reference
1,3-Dichloro-propene	Inhalation	Intermediate 13 wk, 5 d/wk, 6 hr/d	0.003 ppm	100	NOAEL in rats for nasal epithelial changes	Coate, 1979	ATSDR, 1992f (Final)
1,3-Dichloro-propene	Inhalation	Chronic 2 yr, 5 d/wk, 6 hr/d	0.002 ppm	100	NOAEL in mice for nasal epithelial hyperplasia	Lomax et al., 1989	ATSDR, 1992f (Final)
1,1,2,2-Tetrachloro-ethane	Oral	Chronic 78 wk, 5 d/wk	0.04 mg/kg/d	1000	LOAEL in rats for labored respiration, wheezing, nasal discharge	NCI, 1978	ATSDR, 1996c (Final)

The MRLs are based on no-observed-adverse-effect levels (NOAELs), or in cases when NOAELs are not available, on the lowest-observed-adverse-effect levels (LOAELs) for respiratory effects observed in laboratory animals, or in humans when appropriate data are available. MRLs for respiratory effects of ammonia, bis (chloromethyl)ether, formaldehyde, hexavalent chromium, meta cresol, hexamethylene diisocyanate, hydrogen sulfide, nickel, vinyl acetate, 1,2,3-trichloropropane, 1,2-dichloropropane, and 1,3-dichloropropene are based on NOAELs for some durations of exposure. At higher doses or exposure concentrations, such respiratory effects as pulmonary function decrements or nasal mucosa atrophy in humans; hemorrhage and inflammatory exudate in the nasal cavity, epithelial changes in the nasal cavity, chronic active inflammation of the lungs, fibrosis, or decreased thickness of olfactory epithelium in rats; audible respiration in rabbits; and inflammation of nasal turbinate epithelium, nasal epithelial hyperplasia, and bronchitis in mice have been observed.

As noted previously, when NOAEL values are not available, LOAEL values are considered for derivation of the MRLs. As noted in Table 1, an MRL for ammonia was based on a LOAEL for the urge to cough and irritation of the nose and throat in humans. LOAELs for formaldehyde for rhinitis and nasal crusting or for sneezing and nasal congestion in humans, and a LOAEL for vanadium for bronchial irritation in humans were used for the drivation of MRLs. The LOAEL for sulfur dioxide is based on increased airway resistance during moderate exercise in subjects with mild asthma. In rats, LOAELs for respiratory effects that were used for derivation of MRLs included metaplasia in lung epithelial cells (acrolein), metaplasia in the larynx (cobalt), nasal cavity epithelial hyperplasia (hexamethylene diisocyanate), effects on Clara cells (hexachlorocyclopentadiene), increased lung weight, tracheitis and rhinitis (titanium tetrachloride), nasal mucosa degeneration or upper respiratory tract lesions (1,2-dichloropropane), nasal hemorrhaging (propylene glycol), and labored respiration, wheezing, and nasal discharge (1,1,2,2-

tetrachloroethane). A number of respiratory effects (inflammation of nose and lung, metaplasia of olfactory epithelium, hyperplasia of respiratory epithelium) were observed in mice at a LOAEL that was used as the basis for an MRL for naphthalene. Although pulmonary adenoma developed in the mice at a higher concentration, the effects on which the MRL was based occurred primarily in the nasal cavity, and thus were not considered to be preneoplastic.

All of the respiratory effects observed at the LOAELs just described were not considered to be serious. As discussed in the previous section on Pathophysiology, the cells and tissues of the respiratory system possess a great capacity for repair. However, if the damage is severe, serious effects such as fibrosis and emphysema can result. Thus, none of the MRLs for respiratory effects were derived from doses or exposure levels that resulted in such effects; it is ATSDR's policy not to derive an MRL based on a LOAEL value for a serious effect. Since the classification of an effect as serious or less serious may involve significant subjective bias of the risk assessor, a consensus of biomedical judgment must be reached. During the MRL derivation process, ATSDR's Division of Toxicology Health Effects Review and MRL Committees reviews the health effects and provides such a consensus for each LOAEL identified for all end points. In a later stage, a consensus on the MRLs derived is reached by ATSDR's Interagency MRL Work Group. Thus, the possibility of subjective bias in classifying a LOAEL as serious or less serious is circumvented.

ACKNOWLEDGMENTS

The author acknowledges the valuable contributions made by all MRL Workgroup members, past and present. I also thank Dr. Dennis Jones for providing critical review and comments, and Ms. Anne Olin for editing the manuscript.

REFERENCES

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1989a). "Toxicological profile for bis (chloromethyl)ether." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. TP-89-03.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1989b). "Toxicological profile for 1,2-dichloropropane." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, Ga. TP-89-12.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1990a). "Toxicological profile for acrolein." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. TP-90-01.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1990b). "Toxicological profile for ammonia." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. TP-90-03.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1992a). "Toxicological profile for cobalt." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. TP-91/10.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1992b). "Toxicological profile for cresols: o-cresol, p-cresol, m-cresol." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. TP-91/11.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1992c). "Toxicological profile for vanadium." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. TP-91/29.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1992d). "Toxicological profile for vinyl acetate." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. TP-91/30.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1992e). "Toxicological profile for 1,2,3-trichloropropane." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. TP-91/28.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1992f). "Toxicological profile for 1,3-dichloropropene." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. TP-91/15.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1993a). "Priority health conditions. An integrated strategy to evaluate the relationship between illness and exposure to hazardous substances." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1993b). "Toxicological profile for chromium." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. TP-92/08.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1994a). "A standardized test battery for lung and respiratory diseases for use in environmental health field studies." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1995). "Toxicological profile for naphthalene." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1996a). "Minimal risk levels for priority substances and guidance for derivation; republication." Agency for Toxic Substances and Disease Registry, U.S. Department of Health and Human Services. Fed. Reg. 61(125):33511–33520.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1996b). "Toxicological profile for hexamethylene diisocyanate." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. Draft for Public Comment.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1996c). "Toxicological profile for 1,1,2,2-tetrachloroethane." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1997a). "Toxicological profile for formaldehyde." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. Draft for Public Comment.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1997b). "Toxicological profile for hexachlorocyclopentadiene." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. Draft for Public Comment.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1997c). "Toxicological profile for hydrogen sulfide." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA. Draft for Public Comment.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1997d). "Toxicological profile for nickel." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1997e). "Toxicological profile for ethylene glycol and propylene glycol." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1997f). "Toxicological profile for sulfur dioxide." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

AGENCY FOR TOXIC SUBSTANCES AND DISEASE REGISTRY (ATSDR) (1997g). "Toxicological profile for titanium tetrachloride." U.S. Department of Health and Human Services, Public Health Service, Agency for Toxic Substances and Disease Registry, Atlanta, GA.

BHAMBHANI, Y., BURNHAM, R., SNYDMILLER, G., et al. (1994). "Comparative physiological responses of exercising men and women to 5 ppm hydrogen sulfide exposure." Am. Ind. Hyg. Assoc. J. 55:1030–1035.

BUSHY RUN RESEARCH CENTER (BRRC) (1988). "Developmental toxicity evaluation of o-, m-, or p-cresol administered by gavage to New Zealand white rabbits." Unpublished data by Bushy Run Research Center submitted to EPA/OTS. Fiche No. OTS0517695.

CHOU, C-H. S.J., HOLLER, J., and DE ROSA, T. (1998). "Minimal risk levels (MRLs) for hazardous substances." J. Clean Technol., Environ. Toxicol. Occup. Med. 7:1–24.

COATE, W. (1979). "Addendum to final report on the 90-day inhalation toxicity study in rats and mice - Telone II® (1,3-dichloropropene)." Hazleton Laboratories: Vienna, VA, for Dow Chemical Company, Midland, MI.

CURTIS, S.E., ANDERSON, C.R., SIMON, J., et al. (1975). "Effects of aerial ammonia, hydrogen sulfide and swine-house dust on rate of gain and respiratory-tract structure in swine." J. Anim. Sci. 41:735–739.

DUNNICK, J.K., ELWELL, M.R, RADOVSKY, A.E., et al. (1995). "Comparative carcinogenic effects of nickel subsulfide, nickel oxide, or nickel sulfate chronic exposure in the lung." Cancer Res. 55:5251–5256.

DU PONT COMPANY (1979). "Four-week inhalation study with titanium tetrachloride." Haskell Laboratory Report No. 459–479.

EDLING, C., HELLQUIST, H., and ODKVIST, L. (1988). "Occupational exposure to formaldehyde and histopathological changes in the nasal mucosa." Brit. J. Indust. Med. 45:761–765.

FERON, V.J., KRUYSSE, A., TIL, H.P., et al. (1978). "Repeated exposure to acrolein vapour: Subacute studies in hamsters, rats and rabbits." Toxicology 9:47–58.

HASCHEK, W.M. and WITSCHI, H.R. (1991). "Respiratory system." In: Handbook of Toxicologic Pathology (W.M. Haschek and C.G. Rousseaux, ed.). Academic Press, San Diego, CA. pp. 761–827.

HAZLETON LABORATORIES (1980). "Vinyl acetate: 3 month inhalation toxicity study in the mouse." U.S. EPA/OTS public files. Hazleton Labs Europe Ltd. Document no. FYI-OTS-0184-0278.

HOLNESS, D.L., PURDHAM, J.T., and NETHERCOTT, J.R. (1989). "Acute and chronic respiratory effects of occupational exposure to ammonia." Am. Ind. Hyg. Assoc. J. 50:646–650.

LEE, K.P., KELLY, D.P., SCHNEIDER, P.W., et al. (1986). "Inhalation toxicity study on rats exposed to titanium tetrachloride atmospheric hydrolysis products for two years." Toxicol. Appl. Pharmacol. 83:30–45.

LEONG, B.K.J., KOCIBA, R.J., and JERSEY, G.C. (1981). "A lifetime study of rats and mice exposed to vapors to bis (chloromethyl) ether." Toxicol. Appl. Pharmacol. 58:269–281.

LINDBERG, E. and HEDENSTIERNA, G. (1983). "Chrome plating: Symptoms, findings in the upper airways, and effects on lung function." Arch. Environ. Health 38:367–374.

LOMAX, L., STOTT, W., JOHNSON, K., et al. (1989). "The chronic toxicity and oncogenicity of inhaled technical grade 1,3-dichloropropene in rats and mice." Fundam. Appl. Toxicol. 12:418–431.

MILLER, R.R., QUAST, J.F., and MOMANY- PFRUENDER, J.J. (1986). "1,2,3-Trichloropropane: 2- week vapor inhalation study to determine the no-adverse-effect level in rats and mice." Report to Dow Chemical Co. OTS 0517055.

MOBAY CORPORATION (1984). "21-Day inhalation toxicity study with hexamethylene diisocyanate (HDI) in rats." EPA/OTS Doc #86-870001230.

MOBAY CORPORATION (1989). " Chronic inhalation toxicity and oncogenicity study (with attached appendices and cover letter)." EPA/OTS Doc #86-900000055.

MURATA, Y., DENDA, A., MARUYAMA, H., et al. (1993). "Chronic toxicity and carcinogenicity studies of 1-methylnaphthalene in B6C3F1 mice." Fundam. Appl. Toxicol. 21:44–51.

NATIONAL CANCER INSTITUTE (NCI) (1978). "Bioassay of 1,1,2,2-tetrachloroethane for possible carcinogenicity." NTIS PB277 4537GA. DHEW/PUB/NIH-78-827, 90.

NITSCHKE, K.D., JOHNSON, K.A., WACKERLE, D.L., et al. (1988). "Propylene dichloride: A 13- week inhalation toxicity study in rats, mice, and rabbits." Dow Chemical Company, Mammalian and Environmental Toxicology Research Laboratory, Midland, MI.

NITSCHKE, K.D. and JOHNSON, K.A. (1983). "Propylene dichloride: One day and two week inhalation toxicity in rats, mice, and rabbits." Dow Chemical Company, Mammalian and Environmental Toxicology Research Laboratory, Midland, MI.

NATIONAL TOXICOLOGY PROGRAM (NTP) (1991). "Cobalt sulfate heptahydrate (CAS No.10026-24-1) in F344\N rats and B6C3F$_1$ mice (inhalation studies)." U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. National Toxicology Program—Technical Report Series No. 5, NIH Publication No. 91-3124.

NATIONAL TOXICOLOGY PROGRAM (NTP) (1992). "Toxicology and carcinogenesis studies of naphthalene (CAS No. 91-20-3) in B6C3F$_1$ mice (inhalation studies)." U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. National Toxicology Program—Technical Report Series No. 410, NIH Publication No. 92-3141.

NATIONAL TOXICOLOGY PROGRAM (NTP) (1994). "Toxicology and carcinogenesis studies of hexachlorocyclopentadiene (CAS No. 74-47-7) in F344 rats and B6C3F$_1$ mice." U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. National Toxicology Program—Technical Report Series No. 437, NIH Publication No. 93-3168.

NATIONAL TOXICOLOGY PROGRAM (NTP) (1996). "Toxicology and carcinogenesis studies of nickel sulfate (CAS No. 10101-97-0) in F344/N rats and B6C3F$_1$ mice (inhalation studies)." U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health, Research Triangle Park, NC. National Toxicology Program—Technical Report Series No. 454.

PAZDRAK, K., GORSKI, P., KRAKOWIAK, A., and URSZULA, R. (1993). "Changes in nasal lavage fluid due to formaldehyde inhalation." Int. Arch. Occup. Environ. Health 63: 515-519.

RAND, G.M., NEES, P.O., CALO, C.J., et al. (1982). "The Clara cell. An electron microscopy examination of the terminal bronchioles of rats and monkeys following inhalation of hexachlorocyclopentadiene." J. Toxicol. Environ. Health 10:59–72.

RUSCH, G., CLARY, J.J., RINEHART, W.E., and BOLTE, H.F. (1983). "A 26 week inhalation toxicity study with formaldehyde in the monkey, rat and hamster." Toxicol. Appl. Pharmacol. 68:329–343.

SHEPPARD, D., SAISHO, A., NADEL, J.A., et al. (1981). "Exercise increases sulfur dioxide-induced bronchoconstriction in asthmatic subjects." Am. Rev. Respir. Dis. 123:486–491.

SUBER, R.L., DESKIN, R., NIKIFOROV, I., et al. (1989). "Subchronic nose-only inhalation study of propylene glycol in Sprague-Dawley rats." Food Chem. Toxicol. 27(9):573–584.

U.S. ENVIRONMENTAL PROTECTION AGENCY (USEPA) (1986). "Two-year inhalation study with titanium tetrachloride on rats, final report." (Vols. 1–2) U.S. Environmental Protection Agency, Washington, DC. EPA No. 8EHQ-0386-0530. Microfiche No. OTS0509697.

VERBECK, M.M. (1977). "Effects of ammonia in volunteers." Int. Arch. Occup. Environ. Health 39:73–81.

ZENZ, C. and BERG, B.A. (1967). "Human responses to controlled vanadium pentoxide exposure." Arch. Environ. Health 5:542–546.