9
Ozone

This chapter summarizes relevant epidemiologic and toxicologic studies of ozone. Selected chemical and physical properties, toxicokinetic and mechanistic data, and inhalation exposure levels from the National Research Council (NRC) and other agencies are also presented. The committee considered all that information in its evaluation of the Navy's current and proposed 1-h, 24-h, and 90-day exposure guidance levels for ozone. The committee's recommendations for ozone exposure guidance levels are provided at the conclusion of the chapter with a discussion of the adequacy of the data for defining them and the research needed to fill remaining data gaps.

PHYSICAL AND CHEMICAL PROPERTIES

Ozone is a highly reactive atmospheric gas whose molecule consists of three atoms of oxygen. At ambient temperatures, it is a pale blue gas that is a powerful oxidizer (Wojtowicz 1996). It is very reactive, and all phases (gas, liquid, and solid) are combustible and explosive. Some describe ozone as having a pungent odor that is detectable at 0.01 ppm (Wojtowicz 1996). Others describe it as having a "pleasant, characteristic" odor at concentrations below 0.2 ppm but as "irritating" at concentrations above 0.2 ppm

(Budavari et al. 1989). Selected physical and chemical properties are summarized in Table 9-1.

OCCURRENCE AND USE

Ozone is widely used in water treatment because of its ability to disinfect; to eliminate taste, odor, and color; to lower turbidity; to remove iron and manganese; and to degrade a variety of organics, including detergents, pesticides,

TABLE 9-1 Physical and Chemical Data on Ozone

Synonyms	Triatomic oxygen
CAS registry number	7782-44-7
Molecular formula	O_3
Molecular weight	48.00
Boiling point	–111.9°C
Melting point	–193°C
Flash point	NA
Explosive limits	NA
Specific gravity	2.144 g/L at 0°C
Vapor pressure	NA
Solubility	49 mL/100 mL water at 0°C; soluble in alkaline solvents and oils
Conversion factors	1 ppm = 1.96 mg/m^3; 1 mg/m^3 = 0.51 ppm

Abbreviations: NA, not available or not applicable.
Sources: Solubility data from HSDB 2005; all other data from Budavari et al. 1989.

and proteins (Wojtowicz 1996). It is used to treat drinking water, industrial process streams, and municipal wastewater effluents and to treat water in cooling towers, swimming pools, and spas. It is also used for pulp delignification and bleaching and in the production of specialty organic chemicals

and intermediates.

Ozone occurs naturally in the stratosphere at concentrations of 1-10 ppm and shields Earth from biologically damaging ultraviolet (UV) radiation (Wojtowicz 1996). In the stratosphere, short-wave UV radiation directly splits molecular oxygen (O_2) into atomic oxygen (O·) that rapidly combines with O_2 to form ozone. In the troposphere, "ground-level" ozone is generated predominantly by a series of complex reactions involving nitrogen oxides, oxygen, and sunlight. Nitrogen dioxide (NO_2) absorbs longer-wavelength UV radiation, and this results in the generation of O· and nitric oxide (NO). O· then combines with O_2 to form ground-level ozone. NO_2 is regenerated by the reaction of NO with the newly formed ozone. In the absence of volatile organic compounds (VOCs), that reaction would approach a steady state with no buildup of ozone. However, atmospheric VOCs react with O· to produce oxidized compounds and free radicals that react with NO to form more NO_2. Consequently, the NO scavenging of ozone is upset, and this results in increased ozone concentrations.

In urban areas—such as Los Angeles, California—with high motor-vehicle traffic that emits large amounts of VOC-containing exhaust and with intense midday sunlight, complex atmospheric reactions are common place and result in what is termed photochemical smog. Ozone, the principal oxidant pollutant in photochemical smog, is considered both an environmental and a public-

health concern and is classified by the U.S. Environmental Protection Agency (EPA) as a criteria pollutant. EPA has established an 8-h national ambient air quality standard (NAAQS) concentration of 0.08 ppm for ozone (EPA 1996). In 1999, an estimated 90 million residents of the United States lived in areas where ambient ozone concentrations exceeded the NAAQS. Average background concentrations in the United States, in the absence of local anthropogenic emissions, are estimated to range from 0.02 to 0.04 ppm in the afternoon and are highest during spring (Fiore et al. 2003).

Ozone concentrations in airliner cabins on some flights may exceed the Federal Airline Administration and EPA NAAQS. Increased concentrations of ozone are expected primarily on aircraft without ozone converters or with malfunctioning converters that fly at high altitudes (NRC 2002).

According to federal airline regulations, ozone in the cabin may not exceed 0.25 ppm at any time during a flight and may not exceed an average of 0.1 ppm during a 3-h flight above 27,000 feet. Mean ozone concentrations on aircraft have been reported to range from 0.022 ppm (Nagda et al. 1989) to 0.20 ppm (Waters 2001).

Potential sources of ozone in a submarine include motors, vent-fog precipitators, copying machines, and laser printers (Crawl 2003). No measurements of ozone concentrations onboard submarines have been reported in the literature.

SUMMARY OF TOXICITY

The toxicity of inhaled ozone has been extensively reviewed (EPA 1996). Numerous studies of controlled acute exposure have been conducted in human and laboratory animals. Study results have demonstrated that ozone is a potent irritant to the upper and lower airways that, when inhaled, results in impairments in pulmonary function and increased airway hyperresponsiveness with concurrent airway tissue injury and inflammation. The following is a brief review of important toxicologic studies in the scientific literature that were relevant to the committee's discussion and determination of appropriate guidance levels for ozone.

Effects in Humans

Accidental and Occupational Exposure

In an occupational setting, pulmonary congestion was reported in welders who used an inert-gas shielded-arc process that generated ozone at concentrations as high as 9 ppm (Kleinfeld and Giel 1956). Similar effects have been reported in welders exposed to ozone concentrations below 2 ppm (Challen et al. 1958). The effects were not observed when exposure concentrations were near 0.2 ppm. An accidental human exposure for 2 h to a high concentration of ozone (1.5 ppm) caused a 20% reduction in timed vital capacity of the lung and other effects (Chambers et al. 1957).

Experimental Studies

The harmful effects of inhaled ozone have been studied extensively in healthy and high-risk human subjects and in laboratory animals (EPA 1996); however, only the studies that are most relevant to the safety of submarine crew members (healthy men) are discussed in this report. Several well-designed studies have been conducted to investigate the pulmonary responses of healthy, non-smoking human subjects acutely exposed to near ambient concentrations of ozone in environmentally controlled inhalation chambers. Those acute ozone exposures have resulted in pulmonary-function alterations, such as a decrease in inspiratory capacity; mild bronchoconstriction; rapid, shallow breathing during exercise; and symptoms of cough or pain on inspiration. Ozone exposure has been shown to result in airway hyperresponsiveness (as demonstrated by increased physiologic response to a nonspecific bronchoconstrictor, such as methacholine) and airway injury and inflammation (as assessed with bronchoalveolar lavage [BAL] or bronchial biopsy). An ozone-induced decrease in inspiratory capacity results in a decrease in forced vital capacity (FVC) and total lung capacity (TLC) and, in combination with mild bronchoconstriction, contributes to a decrease in the forced expiratory volume in 1 sec (FEV_1). The response of healthy adults to inhalation of ozone occurs in three phases: a delay phase in which no response to ozone is detected, an onset phase during which breathing frequency begins to increase, and a response phase during which breathing frequency stabilizes at a new higher level (Schelegle et al. 2007). Table 9-2 provides a summary of controlled ozone-exposure studies in humans that are discussed further below.

DeLucia and Adams (1977) exposed subjects to ozone at 0, 0.15, and 0.30 ppm for 1 h, while they were at rest and exercising continuously at three workloads, from light to heavy, with minute ventilation (VE) of 28-66 L/min. Significant time-dependent increases in breathing frequency and decreases in FEV_1 and forced midexpiratory flow (FEF25-75%) were observed in subjects after exposure at 0.30 ppm but only during heavy exercise. In another study, Folinsbee et al. (1978) exposed four groups of subjects (10 per group) to ozone at 0, 0.3, and 0.5 ppm for 2 h. One group was exposed at rest, and the other groups were exposed during intermittent

exercise at levels requiring VE of 30, 50, or 70 L/min. They found that there were decrements in pulmonary function, such as FEV_1, even in resting subjects at 0.5 ppm and at 0.3 ppm with exercise. Horvath et al. (1979) also examined changes in pulmonary function during resting exposure to ozone at 0, 0.25, 0.50, and 0.75 ppm. In this study, resting 2-h exposure at 0.75 and 0.50 ppm caused significant mean decrements in FVC of 10% and 5%, respectively. However, ozone at 0 and 0.25 ppm induced no pulmonary decrements. On the basis of the studies of Folinsbee et al. (1978) and Horvath et al. (1979), which investigated the effects of ozone exposure on sedentary, healthy, young adults, the lowest concentration of ozone causing significant

TABLE 9-2 Controlled Exposure of Healthy Human Subjects to Ozone and Observed Effects on Pulmonary Function

Concentration (ppm)	Exposure Duration and Activity	Subjects and Effects	Reference
0.15, 0.30	1 h at rest and light to heavy workloads	6 men, 22-42 years old Mean FEV_1 decrements of 14% and 6.1% at 0.30 ppm with moderate and heavy exercise, respectively	DeLucia and Adams 1977
0.5	2 h at rest	40 men, 18-28 years old Decrease in mean FEV_1 (7%) and FVC (6%)	Folinsbee et al. 1978
0.25, 0.50, 0.75	2 h at rest	8 men and 5 women, 21-22 years old Mean FVC decrements of 5% and 10% at 0.50 and 0.75 ppm, respectively	Horvath et al. 1979
0.20, 0.30, 0.40	30-80 min with light to heavy exercise	8 men, 22-46 years old Decrease in FEF with heavy exercise with an effective dose of 0.2-0.3	Adams et al. 1981

0.12, 0.18, 0.24, 0.30, 0.40	2.5 h, IE	20-29 men per group, 18-30 years old Decrease in FVC, FEV_1 and FEF at 0.12 ppm	McDonnell et al. 1983
0.10, 0.15, 0.20, 0.25	2 h, IE	20 men, 21-29 years old Decrease in FEV_1 (>5%) and specific airway conductance (>15%) at 0.15 ppm	Kulle et al. 1985
0.12, 0.18, 0.24	1 h, heavy workload (competitive exercise)	10 men, 19-29 years old Decrease in FVC and FEV_1 at 0.18 ppm	Schelegle and Adams 1986
0.12	6.6 h, IE	10 men, 18-33 years old Mean FEV_1 decrements of 13% after 6.6 h and FVC of 8.3%; cough and discomfort increased with exposure; airway responsiveness to methacholine doubled after ozone exposure	Folinsbee et al. 1988
0.08, 0.10	6.6 h, IE	38 men, mean age 25 years Mean FEV_1 decrements of 8.4% at 0.08 ppm and 11.4% at 0.10 ppm; cough and discomfort increased with exposure	McDonnell et al. 1991
0.08, 0.10, 0.12	6.6 h, IE	22 men, 18-33 years old Decreased FVC and FEV_1 throughout exposure; mean FEV_1 decrements of 7.0%, 7.0%, and 12.3%, respectively	Horstman et al 1990
0.12	6.6 h/day, IE 5 consec-	17 men, mean age 25.4 years Mean FEV_1 decrements of 12.8%, 8.7%, 2.5%, 0.6%, and improvement of 0.2% on days 1-5,	Folinsbee et al. 1994

	utive days	respectively; methacholine airway responsiveness increased by 100% on all exposure days; symptoms increased on first ozone day but were absent on last 3 exposure days	
0.30	1 h, CE	12 men, 18-34 years old Mean decrements of FEV_1 17.0-17.9%	McKittrick and Adams 1995
0.25	1 h, CE	32 men and 28 women, 22 ± 0.6 years old Mean FEV_1 decrements of 15.9% in men and 9.4% in women; FEV_1 decrements −0.4 to 56%	Ultman et al. 2004
0.1, 0.4	1 h, IE	12 men and 3 women, healthy, nonsmoking adults Neutrophils increased in BAL 6 h after exposure at 0.4 ppm.	Morrison et al. 2006
0.04, 0.06, 0.08	6.6 h, IE	15 men and 15 women, 22.8 ± 1.2 and 23.5 ± 3.0 years old, respectively Exposures included square-wave and triangular concentration profiles; at 0.08 ppm average, responses were observed earlier with the triangular profile (when ozone concentration was 0.15 ppm) than with the square-wave profile; no significant effects at 0.04 or 0.06 ppm	Adams 2006

Abbreviations: BAL, bronchoalveolar lavage; CE, continuous exercise; FEF, forced expiratory flow; FEV_1, forced expiratory volume at 1 sec; FVC, forced vital capacity; IE, intermittent exercise.

pulmonary function decrements has been determined to be 0.5 ppm for 2 h with average decrements of about 4% and 7% in FVC and FEV_1, respectively (EPA 1986).

Adams et al. (1981) exposed subjects to ozone at 0, 0.2, 0.3, or 0.4 ppm during continuous exercise at one of two workloads for 30-80 min. Eight trained male subjects (22-46 years old) completed 18 protocols, including

exposure via mouthpiece to filtered air and to ozone at three concentrations, while exercising continuously for 30-80 min. The ozone effective dose was significantly related to pulmonary-function impairment and exercise ventilatory-pattern alteration. Multiple regression analysis, however, substantiated the predominant importance of ozone concentration, with the threshold for ozone toxicity during exercise at a moderately heavy workload—about 65% maximal O_2 uptake ($VO_{2\ max}$)—shown to be between 0.20 and 0.30 ppm.

McKittrick and Adams (1995) conducted a study designed to determine further what effect exercise pattern has on ozone-induced pulmonary responses when the total inhaled dose of ozone at a given concentration is kept the same. They exposed 12 aerobically trained men to ozone at 0.3 ppm for 1 h during continuous exercise and 2 h during intermittent exercise with equivalent estimated total doses of ozone. The two exposure regimens led to similar pulmonary-function alterations, but symptoms were slightly less during the last rest period of the intermittent-exercise exposure than at the end of the continuous exposure.

After brief exposure to ozone at concentrations over a few tenths of a part per million, exposed people have reported discomfort in the form of headache and dryness of the throat, nasal passages, and eyes. McDonnell et al. (1983) conducted a study designed to determine the lowest ozone concentration at which group mean decrements in pulmonary function occur in heavily exercising healthy young men. Subjects (20-29 per group) were exposed at 0, 0.12, 0.18, 0.24, 0.30, or 0.40 ppm at a VE of 67 L/min for 2.5 h (15-min rest, 15-min exercise). Significant decrements in FVC, FEV_1, and FEF25-75% and an increase in cough were observed at 0.12 ppm, and there were concentration-dependent responses in all variables measured at concentrations greater than 0.24 ppm. Similar studies have also demonstrated significant decrements in pulmonary function with ozone exposures as low as 0.12 ppm (Kulle et al. 1985; Seal et al. 1993).

In a more recent study, Ultman et al. (2004) reported pulmonary responses in 60 healthy nonsmoking adults (32 men, 28 women) exposed to ozone at 0.24 ppm for 1 h with controlled exercise at a target VE of 30 L/min. They found considerable intersubject variability in FEV_1, with responses ranging from a 4% improvement to a 56% decrement. One-third of the subjects had decrements of more than 40%.

In a study directed at investigating possible mechanisms of pulmonary epithelial damage, Morrison et al. (2006) exposed six healthy nonsmoking adults to ozone at 0.1 ppm and seven similar subjects at 0.4 ppm with ^{99m}technetium-

labeled diethylene-triamine-penta-acetate (^{99m}Tc-DTPA) and performed BAL 1 or 6 h after exposure on different occasions. Five control subjects were exposed to filtered air. All study participants were exposed during intermittent exercise. Decreases in FEV_1 were observed immediately and at 1 h after exposure at 0.4 ppm. Ozone exposure did not affect ^{99m}Tc-DTPA lung clearance, but neutrophils increased in BAL fluid 6 h after exposure at 0.4 ppm. Superoxide anion release from BAL leukocytes decreased after 1 h of exposure at 0.1 ppm and after 6 h of exposure at 0.4 ppm. At 0.4 ppm, products of lipid peroxidation in BAL fluid decreased at 1 and 6 h. There was no change in antioxidant capacity of the lung epithelium or glutathione concentrations as measured after BAL at either concentration of ozone.

Controlled environmental exposure-chamber studies of longer duration have been reported (Folinsbee et al. 1988; Horstman et al. 1990; McDonnell et al. 1991). Adult volunteers were exposed for 6.6 h to ozone at 0.08, 0.10, or 0.12 ppm in whole-body chambers. Moderate exercise was performed for 50 min each hour for 3 h in the morning and afternoon. Folisbee and co-workers found that pulmonary-function decrements became greater after each hour of exposure at 0.12 ppm, with FVC declining by 8.3% and FEV_1 declining by 13% at the end of the sixth hour of exposure. Ozone exposure also caused increasing symptoms of cough and chest discomfort and increases in airway responsiveness to methacholine challenge. Similar studies were conducted to investigate the effects of ozone at 0.08 ppm on pulmonary function in exercising people (Horstman et al. 1990; McDonnell et al. 1991). Both studies found significant changes in spirometric measurements and significant increases in airway reactivity, specific airway resistance, and respiratory symptoms. At exposure concentrations of 0.08 ppm and 0.1 ppm, Horstman et al. (1990) found mean FEV_1 decreases of 7% and 8%, respectively. Likewise, McDonnell et al. (1991) found FEV_1 decreases at 0.08 and 0.1 ppm ozone of 8.4% and 11.4%, respectively. The FEV_1 response

data in that study were best fitted to a three-parameter logistic model, suggesting that the ozone pulmonary-function response relationship has a sigmoid shape. That suggests that the induced response has a plateau, which indicates that at the given ozone concentration, workload, and length of exposure, no further increase in response is predicted with increasing exposure duration.

Folinsbee et al. (1994) extended their controlled-exposure studies by exposing healthy, nonsmoking men subjects to ozone at 0.12 ppm for 6.6 h while they exercised for 50 min of every hour at a ventilation rate of 39 L/min (moderate exercise) each day for 5 consecutive days. Although spirometric performance decreased with ozone exposure on the first day, the decrease was less on the second day and returned to control values on the third day. However, airway responsiveness to methacholine challenge (a measure of airway reactivity) increased progressively from day 1 through day 5.

In reviewing data from the literature, McDonnell et al. (1997) found that acute ozone exposure-response models of changes in lung function in humans should be consistent with the following observations: (1) for exposures of less

than 8 h, the response increases with increasing concentration (C), VE, and duration of exposure (T); (2) the response is nonlinear in each of the three exposure variables, and the exposure-response curve is concave upward at low values of the three variables; (3) with increasing T, the response reaches a plateau whose magnitude is a function of the rate of exposure; (4) with increasing C, the response appears to approach a plateau; (5) people vary in their response to ozone, and this variability becomes more pronounced at higher concentrations; and (6) older adults tend to be less responsive than younger adults. Using previously published data on 485 healthy young adult men exposed for 2 h to ozone at one of six concentrations while exercising at one of three levels, McDonnell et al. (1997) identified a sigmoid model that was consistent with previous observations of ozone pulmonary-response characteristics and was found to predict the mean response accurately with independent data. They did not find that the response was more sensitive to changes in C than in VE. They found that the response to ozone decreases with age.

Adams (2006) found that chamber exposure to ozone at an average of 0.08 ppm that more closely simulated the summertime ambient pollution exposure profile, which has a triangular shape, compared with the typical chamber exposure, which is a square wave, resulted in significantly greater FEV_1 response and total symptom severity response at 4.6 h, whereas responses at 6.6 h were not significantly different.

Controlled ozone-exposure studies of subjects with mild to moderate asthma suggest that they are at least as sensitive as nonasthmatic subjects. There was a tendency toward increased ozone-induced pulmonary-function decrements in asthmatic subjects relative to nonasthmatic subjects exposed to ozone at up to 0.2 ppm for 4-8 h (Scannell et al. 1996). Similarly, Alexis et al. (2000) reported that statistically significant ozone-induced decreases in FEV_1 in mildly atopic asthmatics tended to be greater than those in healthy subjects when both were exposed at 0.4 ppm for 2 h. Horstman et al. (1995) found that people with mild to moderate asthma exposed at 0.16 ppm for a longer duration (7.6 h) had reductions in FEV_1 that were significantly greater those in healthy subjects (19% vs 10%, respectively). Information derived from ozone exposure of tobacco-smokers is more limited. The general trend is that smokers are less responsive to ozone under controlled exposure conditions (Framptom et al. 1997; Torres et al. 1997).

Lippman (1993) reviewed the relevant literature that addresses pulmonary inflammatory responses to ozone in humans under controlled exposure conditions. He reported that ozone-induced pulmonary inflammation is detectable at concentrations as low as 0.1 ppm. He did not find an apparent threshold for ozone-induced pulmonary inflammation as measured with BAL. Devlin et al. (1991) exposed nonsmoking men randomly to filtered air (no ozone) and air with ozone at 0.10 or 0.08 ppm for 6.6 h with moderate exercise (VE, about 40 L/min). BAL was performed 18 h after each exposure, and cells and fluid were

analyzed. The BAL fluid of volunteers exposed to ozone at 0.10 ppm had significantly more neutrophils (PMNs), protein, prostaglandin E2 (PGE2), fibronectin, interleukin-6 (IL-6), and lactate dehydrogenase (LDH) than BAL fluid from the same volunteers exposed to filtered air. Moreoever, there

was a decrease in the ability of alveolar macrophages to phagocytize yeast via the complement receptor; this suggested an ozone-induced impairment of lung defense mechanisms. Exposure at 0.08 ppm while exercising also resulted in significant increases in PMNs, PGE2, LDH, IL-6, alpha 1-antitrypsin and decreased phagocytosis via the complement receptor. The investigators concluded that exposure of humans to ozone at a concentration as low as 0.08 ppm for 6.6 h is sufficient to initiate an inflammatory reaction in the lung.

Epidemiologic Studies

There have been no reported epidemiologic studies of health effects in submariners exposed to onboard ozone. Numerous epidemiologic studies have examined the relationship of high ambient outdoor ozone concentrations to hospital admissions and daily morbidity and mortality. Some studies have examined the effects of sensitive populations, such as asthmatic children and the elderly; however, these groups are not relevant to the healthy male submariner population and are not further considered here.

EPA (1996) has thoroughly reviewed the epidemiologic dataset. Several studies have reported associations of adverse human health effects with exposure to increased ambient ozone (EPA 1996; Medina-Ramon et al. 2006). In one study, healthy adults had significant decrements in lung function when exercising outdoors and exposed to ambient ozone at 0.021-0.124 ppm (Spektor et al. 1988b). Similarly, healthy children attending a summer camp and exposed to ozone at the ambient concentration of 0.12 ppm had significant decrements in average FVC, FEV_1, peak expiratory flow rate, and FEF (Spektor et al. 1988a). A study of Taiwanese mail carriers indicated a reduction in peak expiratory flow rates that occurred sometime after exposure to ambient ozone at 0.006-0.096 ppm (Chan and Wu 2005). A study of adult hikers exposed to ambient ozone at 0.028-0.079 ppm while undergoing moderate exercise did not identify significant effects on lung function (Giradot et al. 2006). Several recent hospital admission and emergency-department visit studies in the United States (Peel et al. 2005), Canada (Burnett et al. 1997), and England (Anderson et al. 1998) have reported associations between an increase in ozone and an increase in risk of emergency-department visits and hospital admissions. In France, a short-

term (1-2 days) increase in ozone exposure has been correlated with acute coronary events in middle-aged adults without heart disease (Ruidavets et al. 2005). Statistical modeling of exposure-response curves for ozone concentration and mortality indicate that even low concentrations of ozone, in the range of 0.01-0.25 ppm, are associated with an increased risk of premature death in the general U.S. population (Bell et al. 2006).

Effects in Animals

Acute Toxicity

Numerous toxicologic studies of inhaled ozone have demonstrated that the respiratory tract is the principal target for toxicity in laboratory animals. Acute exposures (3-4 h) to ozone at high concentrations (greater than 2 ppm) have been shown to cause death in laboratory rodents because of severe lung injury that results in alveolar edema, congestion, and hemorrhage. Four-hour exposures of rats, mice, and hamsters resulted in LC_{50}s of 2.1-9.9 ppm for rats, 2.1-9.9 ppm for mice, and 15.8 ppm for hamsters (Saltzman and Svirbely 1957).

Acute exposures of laboratory animals to ozone at much lower, nonlethal concentrations (less than 1 ppm), some of which are near ambient concentrations commonly in urban atmospheres with photochemical smog (≤ 0.5 ppm), have been reported to cause airway epithelial injury particularly in the nasal passages and the distal conducting airways, especially in the centriacinar regions of the lung where terminal conducting airways have interfaces with the most proximal gas-exhange regions of the lung (the alveolar parenchyma). The more distal pulmonary alveoli in the deep lung of laboratory animals, including nonhuman primates, do not appear to be adversely affected by acute or chronic exposures to ozone at the low concentrations. Most of the reported morphologic studies of ozone-induced injury in laboratory animals exposed at near ambient concentrations have focused on the airway lesions in the pulmonary centriacinus. Fewer studies have been specifically designed to examine ozone-induced lesions in the upper respiratory tract, such as in the nose.

In general, the character of the airway epithelial changes induced by ozone is similar among laboratory animal species, including rodents and nonhuman primates. Some cell types in the surface epithelium lining affected airway sites are particularly susceptible to acute exposures at low concentrations and may undergo cellular degeneration or cell death. The epithelial cells most sensitive to ozone injury are ciliated cells and nonciliated cuboidal cells in the surface epithelium lining the proximal nasal airways, ciliated cells in the distal bronchiolar airways, and the alveolar type II cells lining the alveoli in the walls of respiratory bronchioles and proximal alveolar ducts. Loss of those sensitive epithelial cells due to death and exfoliation is quickly followed by reparative cellular proliferation and an abnormal increase in the numbers (hyperplasia) or size (hypertrophy) of more resistant nonciliated cells that include mucous goblet cells in the nasal passages, Clara cells in the terminal and respiratory bronchioles, and alveolar type II cells in the proximal alveolar ducts.

Several studies have investigated the time course of pulmonary inflammation after acute ozone exposure in laboratory rodents and rabbits. Maximal increases in total protein, albumin, and the number of PMNs in BAL fluid occur 8-18 h after the end of an acute exposure. Ozone-induced increases in total protein and albumin (indicators of increased permeability) and PMNs (cellular indicators of acute inflammation) depend on several factors, including species, strain,

concentration, exposure duration, and exercise during exposure. Hatch et al. (1986) investigated the acute inflammatory responses of five species (mice, guinea pigs, rats, hamsters, and rabbits) exposed to ozone at several concentrations, ranging from 0.2 to 2.0 ppm for 4 h. They found that guinea pigs were the most responsive (increased BAL fluid protein at 0.2 ppm or higher), rabbits were the least responsive (affected only at 2.0 ppm), and rats and mice were intermediate in their measured responses (effects only at 1.0 ppm or higher). Bhalla and Hoffman (1997) reported that rats exposed for 3 h at 0.5 ppm, but not 0.3 or 0.15 ppm, had increased permeability and inflammation in the lung. Dye et al. (1999) investigated strain-related differences in rats acutely exposed at 0.5 ppm and found that Wistar rats had significantly greater lung injury and inflammation than Sprague Dawley or F344 rats. The rat strain least sensitive to acute ozone

injury was the F344 rat. Several studies have indicated that as ozone exposures continue for 3-7 days, the increases in BAL fluid PMNs and protein peak in the first few days and then attenuate, returning to near pre-exposure numbers. Van Bree et al. (2002) and colleagues have shown that rats exposed to ozone for 5 consecutive days had lower levels of protein, fibronectin, IL-6, and inflammatory cells than rats exposed for 1 day.

Exercise-induced enhancement of ozone-induced lung injury has been demonstrated in rats acutely exposed at 0.3 ppm (Mautz et al. 1985). The abundance and severity of pulmonary lesions increased as exercise and exposure duration were increased. Preliminary results also indicate that bacterial endotoxin, a common contaminant of indoor air, can enhance ozone-induced metaplasia in the nonciliated epithelium of the proximal nasal airway of the rat (Harkema and Wagner 2005).

Repeated Exposure and Subchronic Toxicity

Toxicologic studies of the nasal airways in laboratory rodents and nonhuman primates exposed to ozone has been reviewed recently (Nikasinovic et al. 2003). Macaques exposed to ozone at 0.15 ppm for 6 days (8 h/day) had acute neutrophilic rhinitis with alterations to the nasal transitional and respiratory epithelium in the anterior regions of the nasal passages. The nasal epithelial lesions in the exposed monkeys consisted of ciliated-cell necrosis, degeneration of ciliated cells with few or shortened cilia, and mucous-cell hyperplasia or metaplasia (Harkema et al. 1987). Exposures of laboratory rats at 0.8 ppm, but not 0.12 ppm, for 3 or 7 days (8 h/day) caused nasal epithelial injury with increased cellular proliferation, which resulted in epithelial hyperplasia and mucous-cell metaplasia in the nasal transitional (nonciliated cuboidal) epithelium lining the proximal nasal airways (Harkema et al. 1989; Johnson et al. 1990). Those data and data from several later toxicity studies in rats suggest that the rat nasal epithelium is less sensitive to ozone injury than that of nonhuman primates (Hyde et al. 1994).

Dungworth et al. (1975) reported that macaque monkeys exposed to ozone at 0.2-0.8 ppm 8 h/day for 7 days had hyperplasia and hypertrophy of the epithelium lining respiratory bronchioles in the centriacinar regions of the

lung. The ozone-induced epithelial alterations were accompanied by accumulations of cellular debris and numerous alveolar macrophages in the affected airway lumina. The investigators stated that the threshold for the histologically detectable changes in the monkeys was below 0.2 ppm and most likely closer to 0.1 ppm. However, the ozone-induced alterations during the first 3-4 days of exposure did not increase in severity after 7 days of exposure, and they suggested cellular adaptation and apparent resistance to any further ozone-induced injury.

In later studies in the same laboratory (Harkema et al. 1987), macaques were exposed to ozone at 0.15 or 0.30 ppm for 90 days (8 h/day). After 90 days of exposure, there was ciliated cell necrosis, degenerated ciliated cells with few or attenuated cilia, and mucous-cell hyperplasia in the surface epithelium lining the proximal nasal airways. A neutrophilic inflammatory cell influx (acute rhinitis) was also present at 6 days, but not 90 days. The same ozone-exposed monkeys had moderate to marked hyperplasia of bronchiolar epithelium in the pulmonary centriacinar regions with increases in luminal macrophages (Harkema et al. 1993). There were no morphometrically determined differences in the severity of the bronchiolar epithelial lesions among the different ozone-exposed groups. The airway epithelial alterations did not appear to be concentration- or time-dependent. In contrast with the acute response to ozone in the nose, there was no evidence of epithelial-cell necrosis or inflammatory-cell influx (other than an increase in macrophages) accompanying the epithelial hyperplasia in the respiratory bronchioles of monkeys exposed for 6 or 90 days.

A small amount of work has been completed in studying the effects of ozone on the central nervous system. Groups of 10 male Wistar rats were exposed to air or ozone at 0.25 ppm 4 h/day for 15 or 30 days (Pereyra-Munoz et al. 2006). Motor activity measured over a 5-min period for both ozone-exposed groups was significantly decreased, to comparable degrees, after 15 and 30 days of exposure. Lipid peroxidation measured in the striatum of six rats per group was increased in a time-dependent manner in both ozone-exposed groups. The remaining four rats per group were used in histochemical preparations and for morphologic study. Increases were observed in the expression of dopamine and adenosine 3',5'-monophosphate-regulated phosphoprotein of 32 KD in the striatum after 30 days of exposure and in the expression of inducible nitric oxide syn-

thase and copper-zinc superoxide dismutase in both the striatum and substantia nigra after 15 and 30 days of exposure. The number of neurons in the substantia nigra (stained with the Klüver-Barrera technique or histochemically for tyrosine hydroxylase) was reduced in a time-dependent manner in the ozone-exposed groups. There are no reports in the scientific literature demonstrating that exposure of humans to ozone results in neurotoxicity.

Chronic Toxicity

Long-term exposures (more than 90 days) to ozone have been conducted in laboratory rodents and macaques (Catalano et al. 1995; Chang et al. 1992; Tyler et al. 1988). Chang et al. (1992) exposed rats to a background concentration of 0.06 ppm 13 h/day, 7 days/week for 1, 3, 13, and 78 weeks with a sole daily 9-h spike (5 days/week) that rose to 0.25 ppm. The integrated concentration of the daily exposure with the spike was 0.19 ppm. The investigators found that in the terminal bronchioles, cilia were lost (at 78 weeks) and the surface area of Clara cells was decreased (at 1, 3, 13 and 78 weeks). There was also a progressive increase in epithelial hyperplasia, fibroblast proliferation, and thickening of the interstitial matrix from 13 to 78 weeks. There was a general postexposure recovery from the pulmonary lesions except the fibrotic interstitial changes, which were still apparent 17 weeks after the end of the chronic exposure. Pulmonary-function alterations consistent with restrictive lung disease and fibrotic lesions were also found in similarly exposed rats (Costa et al. 1995).

Tyler et al. (1988) exposed young monkeys (7 months) and rats to ozone at 0.25 ppm 8 h/day, 5 days/week over an 18-month period. Some animals were exposed throughout the entire 18-month period, and others were exposed only during alternate months (total of 9 months of exposure). At the end of the exposure, monkeys in both groups had developed respiratory bronchiolitis, increased volume density of respiratory bronchioles, and alterations in lung growth. The monkeys that received ozone exposures only during alternate months had for the most part pulmonary alterations equivalent to those in the group receiving ozone exposures throughout the entire 18-month period and in some cases greater alterations, such as

greater collagen deposition. In the rat study, there were no significant differences between the two exposure groups; both groups had more bronchiole-alveolar duct junctions as determined by morphometric analyses.

A comprehensive study of F344 rats exposed at 0.12, 0.5, or 1.0 ppm 6 h/day, 5 days/week for 3 or 20 months has been summarized by Catalano et al. (1995). Detailed morphometric examinations of the noses and lungs of the animals were conducted by a team of investigators in several institutions (Chang et al. 1995; Harkema et al. 1994; Pinkerton et al. 1995; Stockstill et al. 1995). Adverse effects were found in the nasal, tracheobronchial, and pulmonary centriacinar airways. Rats chronically exposed at 0.5 and 1.0 ppm, but not 0.12 ppm, had marked alterations in the nasal airways consisting of chronic rhinitis, turbinate atrophy, epithelial hyperplasia, and mucous-cell metaplasia or hyperplasia. Chronic exposure to ozone at all concentrations caused epithelial alterations in the centriacinar regions of the lung. Similar nasal and pulmonary lesions have been reported in mice exposed at 0.5 or 1.0 ppm for 2 years (Herbert et al. 1996). The lesions were shown to persist with an additional 6 months of exposure.

Although it is well documented that the nasal and pulmonary alterations in all laboratory animals are similar, the concentrations at which ozone-induced

lesions are observed differ among rodents and nonhuman primates. After reviewing comparable acute and chronic ozone-exposure studies in rodents (rats and mice) and in macaques, Hyde et al. (1994) estimated that monkeys are about 10 times more sensitive to the development of ozone-induced nasal and pulmonary lesions.

In a more recent study, infant monkeys (30 days old) were episodically exposed to ozone at 0.5 ppm alone or with house-dust mite allergen (HDMA) 8 h/day, 5 days/week every 14 days for a total of 11 ozone episodes (Schelegle et al. 2003). The 6-month episodic exposure to ozone alone or with HDMA caused profound remodeling of the distal airways and centriacinar region and loss of bronchiolar airways.

Reproductive Toxicity in Males

There are few reports in the scientific literature on the effects of ozone on the male reproductive system. Exposure of male and female mice to ozone at 0.05-0.09 ppm before breeding did not affect pregnancy rate, the weight of live fetuses, or skeletal or soft-tissue malformations in offspring (Zhou et al. 2006). In a second study, male rats were exposed to ozone at 0.5 ppm or control air 5 h/day for 50 days (Jedlinska-Krakowska et al. 2006). The number of successful matings and the survival of pups were equivalent in the two groups. The testes of the ozone-exposed and control rats were not different with regard to morphology or motility of sperm, but sperm concentration was 17% lower in the ozone-exposed rats.

Sokol et al. (2006) retrospectively studied the relationship between air pollution and human sperm quality over a 2-year period in Los Angeles, California. A linear mixed-effects model was used to study average sperm concentration and total motile sperm count for each donation (more than 5,000 semen samples) from each study participant (48 donors). The model indicated a statistically significant negative correlation between ozone concentration 0-9, 10-14, and 70-90 days before sperm donation and average sperm concentration. Other pollution measures did not correlate with differences in sperm quality. The average daily ozone concentration during the study was 0.022 ± 0.009 ppm. Bonde (2007) indicated that welders who have an occupational exposure to ozone have been reported not to have lower sperm counts.

Immunotoxicity

The immune system is a sensitive target for ozone-induced toxicity (Gilmour et al. 1993a; Gilmour et al. 1993b; Gilmour and Selgrade 1993; Ryan et al. 2002; Selgrade et al. 1988). Ozone exposures at high ambient concentrations (0.08-0.22 ppm) have been shown to induce adverse effects on the local airway mucosal and systemic immune systems in laboratory animals and in humans. The most sensitive effects include inhibition of bacterial phagocytosis by alveolar macrophages (Devlin et al. 1991; Driscoll et al. 1987; Van Loveren et al. 1988), production of proinflammatory cytokines and mediators (Balmes et al. 1996; Becker et al. 1991; Devlin et al. 1991; Driscoll et al.

1993; Driscoll et al. 1987; Jaspers et al. 1997; Scannell et al. 1996; Torres et al. 1997), and recruitment of inflammatory cells into the lung (Devlin et al. 1991; Koren et al. 1989) and the nasal airways (Graham et al. 1988; Graham and Koren 1990; Harkema et al. 1987). The ozone-induced effects could influence the development of CD4+ T_H2 lymphocytic cytokine responses in allergic airway diseases, such as asthma and allergic rhinitis. Mice exposed to ozone at 0.13 ppm had enhanced allergic sensitization (Osebold et al. 1988), and atopic asthmatic human subjects exposed at 0.12 ppm had increased bronchial responsiveness to allergens (Molfino et al. 1991). In that regard, epidemiologic studies support the experimental findings (Bascom 1996). Asthmatic children living in the inner city of Atlanta had more emergency-room visits on days when ozone concentrations were greater than 0.11 ppm (White et al. 1994).

Genotoxicity

Several in vitro and in vivo studies have been conducted to investigate the genotoxicity and mutagenicity of ozone (Victorin 1996). The research includes in vitro mutagenicity tests in a variety of cell types (bacteria, yeast, plants, human cell lines, and other mammalian cells) and in vitro assays for chromosomal alterations in cells from laboratory animals exposed to ozone at higher than ambient concentrations. Some of the studies have shown that ozone is genotoxic and mutagenic. Collectively, the data from the genotoxicity studies suggest that ozone is at most a weak mutagen, but more data are needed to draw definitive conclusions. However, the reactive, gaseous, and toxic nature of ozone makes it difficult to conduct interpretable studies in those test systems.

Carcinogenicity

In a National Toxicology Program chronic bioassay study, male and female rats and mice were exposed to filtered air or ozone at 0.12, 0.5, or 1.0 ppm 6 h/day, 5 days/week for 2 years or a lifetime (Boorman et al. 1994; Herbert et al. 1996). The results in male and female F344/N rats showed no evidence of carcinogenic activity. In male B6C3F1 mice, there was equivocal evidence of carcinogenic activity. There was some evidence of carcinogenic activity in female B6C3F1 mice only at the highest concentration (1.0

ppm). Other lung-tumor development studies that exposed rats, hamsters, or mice chronically to ozone at up to 0.8 ppm for less than their lifetime were either negative or ambiguous for ozone-induced carcinogenicity (Hassett et al. 1985; Ichinose and Sagai 1992; Last and Warren 1987; Witschi et al. 1993). Thus, ozone has been

shown to be a weak pulmonary carcinogen only in female mice at one concentration and in only one long-term inhalation study. EPA and the International Agency for Research on Cancer have not provided any classification regarding ozone's carcinogenic potential.

TOXICOKINETIC AND MECHANISTIC CONSIDERATIONS

Because ozone is a highly reactive gas, it has a negligible half-life, and its uptake is limited to the air-liquid interface lining the mucosal membranes of the respiratory tract. In resting subjects, 40-50% of inhaled ozone is absorbed in the nasopharyngeal airways with nasal breathing or in the mouth and pharynx with oral breathing. The conducting airways remove 90% of the remainder of the inhaled ozone that reaches the lower respiratory tract. Therefore, about 95% of the total inhaled ozone is removed in the respiratory tract (Asplund et al. 1996; Gerrity et al. 1995; Gerrity et al. 1988; Hu et al. 1992a; Hu et al. 1992b). The efficiency of ozone uptake varies directly with concentration and inversely with breathing rate (Gerrity et al. 1988). With increased ventilation rates, there is a decrease in both upper and lower airway absorption that results in more penetration of ozone into the lung (Hu et al. 1992a; Hu et al. 1992b).

Mathematical models of ozone dosimetry in the respiratory tract have estimated that the rate or amount of ozone uptake in the lung would be greatest in the centriacinar regions. The mathematical predictions for the primary intrapulmonary site of ozone-induced toxicity (Miller et al. 1985; Overton et al. 1987) support the numerous experimental-animal studies that have identified site-specific, ozone-induced lesions in this distal region of the respiratory tract. Experimental dosimetry studies with ^{18}O-

labeled ozone have also shown that exercising humans had ^{18}O concentrations in their BAL fluid 4-5 times greater than those in the BAL fluid of similarly exposed resting laboratory rats (Hatch et al. 1994). The results of that comparative dosimetry study are consistent with pulmonary physiology studies that suggest that ozone has greater detrimental effects on the lung function of humans than in animals (Costa et al. 1989; Overton et al. 1987).

Acute responses to controlled exposures to ozone cause alterations in lung function, airway caliber, breathing pattern, respiratory symptoms, and airway inflammation. More than one biologic mechanism appears to mediate the responses to ozone exposure. Broadly categorized, the ozone-induced alteration mechanisms are due to neural or inflammatory mechanisms. Several experimental studies in animals and humans have shown that the reduction in pulmonary function with acute ozone exposure is mediated through the parasympathetic system. Ozone stimulates vagal afferents, including C fibers and rapidly adapting receptors, and this results in vagal reflexes that cause increases in airway resistance and frequency of respiration, symptoms of respiratory irritation, and a decrease in tidal volume (Beckett et al. 1985; Gertner et al. 1983a; Gertner et al.

1983b; Gertner et al. 1983c; Lee et al. 1979; Passannante et al. 1998; Schelegle et al. 2001; Schelegle et al. 1993).

Airway inflammation caused by inhaled ozone is a secondary response to toxicant-induced damage to the epithelial cells lining the luminal surface of the respiratory tract. The extreme reactive nature of ozone with the fluid lining the respiratory tract (epithelial lining fluid, or ELF) makes it unlikely that it passes unreacted into the airway lining cells and causes direct cytotoxicity (Pryor 1992). Ozone is more likely to react with lipids high in unsaturated fatty acids in the ELF or in the outer epithelial cell membranes (lipid peroxidation). Ozonation in the airway lumen, which also has high water content, produces aldehydes, hydroperoxides, and small amounts of ozonides (Driscoll et al. 1993; Frampton et al. 1999a; Frampton et al. 1999b; Leikauf et al. 1993; Pryor et al. 1995a; Pryor et al. 1995b). The ozonation products stimulate airway epithelial cells to release a variety of proinflammatory agents, including eicosanoids, platelet-activating factor, reactive oxygen species, and inflammatory cytokines (Leikauf et al. 1995a; Leikauf et

al. 1995b; Pryor et al. 1995a; Schelegle et al. 1989). Ozone-exposed epithelial cells release inflammatory mediators, such as IL-6, IL-8, and fibronectin (Devlin et al. 1994). Cytokines and chemokines released from the injured epithelium recruit neutrophils and monocytes and macrophages into the airways. The activated inflammatory cells release additional mediators that may amplify the inflammatory response and promote later airway structural and functional alterations. Ozone-induced inflammation may directly amplify oxidative damage to the airway tissues due to ozone. It takes several hours for the inflammatory cascade to develop after the start of acute exposure when initial pulmonary function and respiratory symptoms may have abated (Blomberg et al. 1999; Foster et al. 2000; Schelegle et al. 1991). The presence of inflammatory cells, such as PMNs, and inflammatory mediators in the BAL fluid of exposed subjects are important indicators of acute airway injury (Balmes et al. 1996; Foster and Stetkiewicz 1996; Koren et al. 1989).

INHALATION EXPOSURE LEVELS FROM THE NATIONAL RESEARCH COUNCIL AND OTHER ORGANIZATIONS

A few organizations have established or proposed acceptable inhalation exposure limits or guidelines for ozone. Selected values are summarized in Table 9-3.

COMMITTEE RECOMMENDATIONS

The committee's recommendations for EEGL and CEGL values for ozone are summarized in Table 9-4. The current and proposed U.S. Navy values are provided for comparison.

TABLE 9-3 Selected Inhalation Exposure Levels from the NRC and Other Agencies[a]

Organization	Type of Level	Exposure Level	Reference

Occupational			
ACGIH	TLV-TWA (heavy work)	0.05 ppm	ACGIH 2001
	TLV-TWA (moderate work)	0.08 ppm	
	TLV-TWA (light work)	0.10 ppm	
	TLV-TWA (2-h, all work types)	0.2 ppm	
NIOSH	REL-Ceiling	0.1 ppm	NIOSH 1997
OSHA	PEL-TWA	0.1 ppm	29 CFR 1910.1000
Submarine			
NRC	EEGL		NRC 1984
	1-h	1 ppm	
	24-h	0.1 ppm	
	CEGL		
	90-day	0.02 ppm	

[a]The comparability of EEGLs and CEGLs with occupational-exposure and public-health standards or guidance levels is discussed in Chapter 1 ("Comparison with Other Regulatory Standards or Guidance Levels"). Abbreviations: ACGIH, American Conference of Governmental Industrial Hygienists; CEGL, continuous exposure guidance level; EEGL, emergency exposure guidance level; NIOSH, National Institute for Occupational Safety and Health; NRC, National Research Council; OSHA, Occupational Safety and Health Administration; PEL, permissible exposure limit; REL, recommended exposure limit; TLV, Threshold Limit Value; TWA, time-weighted average.

TABLE 9-4 Emergency and Continuous Exposure Guidance Levels for Ozone

Exposure Level	U.S. Navy Values (ppm)		Committee Recommended Values (ppm)
	Current Values	Proposed Values	

EEGL			
1-h	1	0.3	0.5
24-h	0.1	0.1	0.1
CEGL			
90-day	0.02	0.02	0.02

Abbreviations: CEGL, continuous exposure guidance levels; EEGL, emergency exposure guidance level.

1-Hour EEGL

There is a preponderance of strong dose-response data in the scientific literature on short-duration ozone exposure (hours) in human populations of similar age and sex as submariners, and the committee derived the 1-h EEGL from the weight of evidence from the controlled human studies. Clinical research has demonstrated that healthy young men (18-34 years old) at rest (Folinsbee et al. 1978; Horvath et al. 1979) or performing moderate to heavy intermittent exercise (DeLucia and Adams 1977; Folinsbee et al. 1978; McDonnell et al. 1983) or continuous exercise (Adams et al. 1981; Adams and Schelegle 1983; Folinsbee and Horvath 1986) will develop marked decrements in pulmonary function and symptoms of breathing discomfort, such as chest tightness and cough, when exposed to ozone at less than 1 ppm for 1-2.5 h. Collectively, the studies of exercising healthy men have clearly demonstrated that 1 h of continuous exercise or 2-2.5 h of intermittent exercise increases the deleterious pulmonary-function responses to acute ozone exposure. However, in determining the 1-h EEGL for ozone, the committee assumed that most submariners would have VE equivalents closer to "rest" than to the "moderate-to-heavy" exercise paradigms used in the experimental studies and protocols reviewed here because of the confined conditions on the submarine. The lowest ozone concentration at which modest reductions in FVC and FEV_1 have been reported in nonexercising young men after 2 h of controlled exposures is 0.5 ppm (Folinsbee et al. 1978; Horvath et al. 1979). A concentration of 0.5 ppm was used by the committee as the starting point for the derivation of the

1-h EEGL. Because the controlled human studies used short exposure durations and age classes of interest, no further adjustments to the 1-h EEGL were needed for these specific areas. Variability in sensitivity to low ozone concentrations for that short exposure in low to moderate activity was assumed to be minimal, and an intraspecies adjustment was not considered to be warranted. Therefore, the committee determined that a 1-h exposure to ozone at 0.5 ppm would not impair a submariner's ability to conduct normal or emergency activities.

24-Hour EEGL

There have been no human studies of controlled ozone exposures for 24 h. The committee's determination of a recommended 24-h EEGL was based on the weight of evidence from the controlled human studies at low ozone concentrations (0.08-0.12 ppm) for durations of 4-8 h with a range of exercise loads (Folinsbee et al. 1988; Horstman et al. 1990; McDonnell et al. 1991). In those studies, ozone exposures caused dose-dependent symptoms of cough and chest discomfort, increases in airway responsiveness to methacholine challenge, and consistent but transient decrements in pulmonary function, such as FEV_1 and FVC. Further analysis of the data suggests that the ozone-pulmonary response

relationship plateaus after a 6.6-h exposure protocol. Therefore, further decrements in respiratory function of functional and operational significance with an extended exposure up to 24 h are not expected, and the committee did not consider that a time adjustment factor was warranted. The committee acknowledged that the response database exhibits population variability in ozone-induced changes in respiratory function. However, it concluded that the observed degree of change would be clinically or operationally insignificant for low to moderate activity in a submariner population. Therefore, response variability in sensitivity to the low ozone concentrations in submariners in low to moderate exercise for a 24-h exposure was assumed to be low, and no intraspecies adjustment was applied. The committee concluded that exposure to ozone at 0.1 ppm during a 24-h period should not impair a healthy submariner from conducting normal or emergency activities.

90-Day CEGL

There have been no 90-day controlled human exposures to ozone. However, the 90-day exposure study of macaques conducted by Harkema and colleagues (Harkema et al. 1987; Harkema et al. 1993) demonstrated that exposures at 0.15 and 0.30 ppm (6 h/day, 5 days/week) resulted in conspicuous morphologic but subclinical airway injury and remodeling in the nose and lung. Although the reversibility of the airway lesions in monkeys has not been determined, similar nasal airway lesions induced by ozone in laboratory rats have been shown to persist, although markedly attenuated, at least 3 months after the end of a 90-day exposure (Harkema et al. 1999). Therefore, the committee used a concentration of 0.15 ppm as a starting point for deriving the recommended 90-day CEGL. Because the morphology of the upper and lower respiratory tract of the macaque closely resembles that of humans (Tyler 1983), an interspecies uncertainty factor of 1 was used in the committee's determination. An uncertainty factor of 10 was used to adjust from a lowest observed-adverse-effect level to a no-observed-adverse-effect level. That resulted in a recommended 90-day CEGL for ozone of 0.02 ppm, which is well below the EPA NAAQS concentration of 0.08 ppm and within estimated background concentrations of outdoor ozone in the United States.

DATA ADEQUACY AND RESEARCH NEEDS

There is a lack of data on personal exposure of submariners to ozone and other oxidant gases. The committee suggests that the Navy consider conducting exposure studies designed to determine the personal exposure of submariners to ozone during their short- and long-term tours of duty.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2001. Ozone in Documentation of the Threshold Limit Values and Biological

Exposure Indices, 7th Ed. American Conference of Governmental Industrial Hygienists, Cincinnati, OH.

Adams, W.C. 2006. Comparison of chamber 6.6-h exposures to 0.04-0.08 ppm ozone via square-wave and triangular profiles on pulmonary responses. Inhal. Toxicol. 18(2):127-136.

Adams, W.C., and E.S. Schelegle. 1983. Ozone and high ventilation effects on pulmonary function and endurance performance. J. Appl. Physiol. 55(3):805-812.

Adams, W.C., W.M. Savin, and A.E. Christo. 1981. Detection of ozone toxicity during continuous exercise via the effective dose concept. J. Appl. Physiol. 51(2):415-422.

Alexis, N., B. Urch, S. Tarlo, P. Corey, D. Pengelly, P. O'Byrne, and F. Silverman. 2000. Cyclooxygenase metabolites play a different role in ozone-induced pulmonary function decline in asthmatics compared to normals. Inhal. Toxicol. 12(12):1205-1224.

Anderson, H.R., A. Ponce de Leon, J.M. Bland, J.S. Bower, J. Emberlin, and D.P. Strachan. 1998. Air pollution, pollens, and daily admissions for asthma in London 1987-92. Thorax 53(10):842-848.

Asplund, P.T., A. Ben-Jebria, M.L. Rigas, and J.S. Ultman. 1996. Longitudinal distribution of ozone absorption in the lung: Effect of continuous inhalation exposure. Arch. Environ. Health 51(6): 431-438.

Balmes, J.R., L.L. Chen, C. Scannell, I. Tager, D. Christian, P.Q. Hearne, T. Kelly, and R.M. Aris. 1996. Ozone-induced decrements in FEV1 and FVC do not correlate with measures of inflammation. Am. J. Respir. Crit. Care Med. 153(3):904-909.

Bascom, R. 1996. Environmental factors and respiratory hypersensitivity: The Americas. Toxicol. Lett. 86(2-3):115-130.

Becker, S., M.C. Madden, S.L. Newman, R.B. Devlin, and H.S. Koren. 1991. Modulation of human alveolar macrophage properties by ozone exposure in vitro. Toxicol. Appl. Pharmacol. 110(3): 403-415.

Beckett, W.S., W.F. McDonnell, D.H. Horstman, and D.E. House. 1985. Role of the parasympathetic nervous system in acute lung response to ozone. J. Appl. Physiol. 59(6):1879-1885.

Bell, M.L., R.D. Peng, and F. Dominici. 2006. The exposure-response curve for ozone and risk of mortality and the adequacy of current ozone regulations. Environ. Health Perspect. 114(4):532-536.

Bhalla, D.K., and L. Hoffman. 1997. Time course of airway epithelial and inflammatory changes in rats exposed to moderate levels of ozone. Inhal. Toxicol. 9(9):829-842.

Blomberg, A., I.S. Mudway, C. Nordenhall, H. Hedenstrom, F.J. Kelly, A.J. Frew, S.T. Holgate, and T. Sandstrom. 1999. Ozone-induced lung function decrements do not correlate with early airway inflammatory or antioxidant responses. Eur. Respir. J. 13(6):1418-1428.

Bonde, J.P. 2007. Ozone and semen quality. Environ Health Perspect 115(4):A185.

Boorman, G.A., R. Hailey, S. Grumbein, B.J. Chou, R.A. Herbert, T. Goehl, P.W. Mellick, J.H. Roycroft, J.K. Haseman, and R. Sills. 1994. Toxicology and carcinogenesis studies of ozone and ozone 4-(N-nitrosomethylamino)-1-(3-pyridyl)-1-butanone in Fischer-344/N rats. Toxicol. Pathol. 22(5): 545-554.

Budavari, S., M.J. O'Neil, A. Smith, and P.E. Heckelman, eds. 1989. Ozone. P. 6936 in Merck Index: An Encyclopedia of Chemicals, Drugs, and Biologicals, 11th Ed. Rahway, NJ: Merck.

Burnett, R.T., J.R. Brook, W.T. Yung, R.E. Dales, and D. Krewski. 1997. Association between ozone and hospitalization for respiratory diseases in 16 Canadian cities. Environ. Res. 72(1):24-31.

Catalano, P.J., L.Y. Chang, J.R. Harkema, D.A. Kaden, J.A. Last, P.W. Mellick, W.C. Parks, K.E. Pinkerton, B. Radhakrishnamurthy, L.M. Ryan, and J.L Szarek. 1995. Consequences of Prolonged Inhalation of Ozone on F344/N rats: Collaborative Studies. Part XI. Integrative Summary. Research Report No. 65-XI. Health Effects Institute, Boston, MA.

Challen, P.J., D.E. Hickish, and J. Bedford. 1958. An investigation of some health hazards in an inert-gas tungsten-arc welding shop. Br. J. Ind. Med. 15(4):276-282.

Chambers, L.A., S.S. Griswold, and H.L. Motley. 1957. Report of a case of exposure to high ozone concentrations for two hours. AMA Arch. Ind. Health 15(2):108-110.

Chan, C.C., and T.C. Wu. 2005. Effects of ambient ozone exposure on mail carriers' peak expiratory flow rates. Environ. Health Perspect. 113(6):735-738.

Chang, L.Y., Y. Huang, B.L. Stockstill, J.A. Graham, E.C. Grose, M.G.

Menache, F.J. Miller, D.L. Costa, and J.D. Crapo. 1992. Epithelial injury and interstitial fibrosis in the proximal alveolar regions of rats chronically exposed to a simulated pattern of urban ambient ozone. Toxicol. Appl. Pharmacol. 115(2):241-252.

Chang, L.Y., B.L. Stockstill, M.G. Menache, R.R. Mercer, and J.D. Crapo. 1995. Consequences of Prolonged Inhalation of Ozone on F344/N Rats: Collaborative Studies. Part VIII. Morphometric Analysis of Structural Alterations in Alveolar Regions. Research Report No. 65-VIII. Health Effects Institute, Boston, MA.

Costa, D.L., G.E. Hatch, J. Highfill, M.A. Stevens, and J.S. Tepper. 1989. Pulmonary function studies in the rat addressing concentration versus time relationships of ozone. Pp. 733-743 in Atmospheric Ozone Research and Its Policy Implications: Proceedings of the 3rd U.S.-Dutch International Symposium, 9-13 May 1988, Nijmegen, The Netherlands, T.L. Schneider, S.D. Lee, G.J.R. Wolters, and L.D. Grant, eds. Amsterdam: Elsevier.

Costa, D.L., J.S. Tepper, M.A. Stevens, W.P. Watkinson, D.L. Doerfler, T.R. Gelzleichter, and J.A. Last. 1995. Restrictive lung disease in rats exposed chronically to an urban profile of ozone. Am. J. Respir. Crit. Care Med. 151(5):1512-1518.

Crawl, J.R. 2003. Review/Updating of Limits for Submarine Air Contaminants. Presentation at the First Meeting on Emergency and Continuous Exposure Guidance Levels for Selected Submarine Contaminants, January 23, 2003, Washington, DC.

DeLucia, A.J., and W.C. Adams. 1977. Effects of O3 inhalation during exercise on pulmonary function and blood biochemistry. J. Appl. Physiol. 43(1):75-81.

Devlin, R.B., W.F. McDonnell, R. Mann, S. Becker, D.E. House, D. Schreinemachers, and H.S. Koren. 1991. Exposure of humans to ambient levels of ozone for 6.6 hours causes cellular and biochemical changes in the lung. Am. J. Respir. Cell Mol. Biol. 4(1):72-81.

Devlin, R.B., K.P. McKinnon, T. Noah, S. Becker, and H.S. Koren. 1994. Ozone-induced release of cytokines and fibronectin by alveolar macrophages and airway epithelial cells. Am. J. Physiol. 266(6 Pt 1):L612-L619.

Driscoll, K.E., T.A. Vollmuth, and R.B. Schlesinger. 1987. Acute and sub-

chronic ozone inhalation in the rabbit: Response of alveolar macrophages. J. Toxicol. Environ. Health 21(1-2):27-43.

Driscoll, K.E., L. Simpson, J. Carter, D. Hassenbein, and G.D. Leikauf. 1993. Ozone inhalation stimulates expression of a neutrophil chemotactic protein, macrophage inflammatory protein 2. Toxicol. Appl. Pharmacol. 119(2):306-309.

Dungworth, D.L., W.L. Castleman, C.K. Chow, P.W. Mellick, M.G. Mustafa, B. Tarkington, and W.S. Tyler. 1975. Effect of ambient levels of ozone on monkeys. Fed. Proc. 34(8):1670-1674.

Dye, J.A., M.C. Madden, J.H. Richards, J.R. Lehmann, R.B. Devlin, and D.L. Costa. 1999. Ozone effects on airway responsiveness, lung injury, and inflammation. Comparative rat strain and in vivo/in vitro investigations. Inhal. Toxicol. 11(11):1015-1040.

EPA (U.S. Environmental Protection Agency). 1986. Air Quality Criteria for Ozone and Other Photochemical Oxidants, Vols. I-V. EPA-600/8-84-020aF-eF. Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, U.S. Environmental Protection Agency, Research Triangle Park, NC.

EPA (U.S. Environmental Protection Agency). 1996. Air Quality Criteria for Ozone and Related Photochemical Oxidants, Vol. I-III. EPA/600/P-93/004aF, EPA/600/P-93/004bF, EPA/600/P-93/004cF. National Center for Environmental Assessment, Office of Research and Development, U.S. Environmental Protection Agency, Research Triangle Park, NC [online]. Available: http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=2831#Download [accessed June 20, 2007].

Fiore, A., D.J. Jacob, H. Liu, R.M. Yantosca, T.D. Fairlie, and Q. Li. 2003. Variability in surface ozone background over the United States: Implications for air quality policy. J. Geophys. Res. 108(D24):4787. doi:10.1029/2003JD003855

Folinsbee, L.J., and S.M. Horvath. 1986. Persistence of the acute effects of ozone exposure. Aviat. Space Environ. Med. 57(12 Pt.1):1136-1143.

Folinsbee, L.J., B.L. Drinkwater, J.F. Bedi, and S.M. Horvath. 1978. The influence of exercise on the pulmonary function changes due to exposure to low concentrations of ozone. Pp. 125-145 in Environmental Stress: Individual Human Adaptations, L.J. Folinsbee, J.A. Wagner, J.F. Borgia, B.L.

Drinkwater, J.A. Gliner, and J.F. Bedi, eds. New York: Academic Press.

Folinsbee, L.J., W.F. McDonnell, and D.H. Horstman. 1988. Pulmonary function and symptom responses after 6.6-hour exposure to 0.12 ppm ozone with moderate exercise. JAPCA 38(1):28-35.

Folinsbee, L.J., D.H. Horstman, H.R. Kehrl, S. Harder, S. Abdul-Salaam, and P.J. Ives. 1994. Respiratory responses to repeated prolonged exposure to 0.12 ppm ozone. Am. J. Respir. Crit. Care Med. 149(1):98-105.

Foster, W.M., and P.T. Stetkiewicz. 1996. Regional clearance of solute from the respiratory epithelia: 18-20 h postexposure to ozone. J. Appl. Physiol. 81(3):1143-1149.

Foster, W.M., R.H. Brown, K. Macri, and C.S. Mitchell. 2000. Bronchial reactivity of healthy subjects: 18-20 h postexposure to ozone. J. Appl. Physiol. 89(5):1804-1810.

Frampton, M.W., P.E. Morrow, A. Torres, K.Z. Voter, J.C. Whitin, C. Cox, D.M. Speers, Y. Tsai, and M.J. Utell. 1997. Effects of Ozone on Normal and Potentially Sensitive Human Subjects. Part II. Airway Inflammation and Responsiveness to Ozone in Nonsmokers and Smokers. Reseach Report No. 78. Health Effects Institute, Boston, MA.

Frampton, M.W., W.A. Pryor, R. Cueto, C. Cox, P.E. Morrow, and M.J. Utell. 1999a. Aldehydes (Nonanal and Hexanal) in Rat and Human Bronchoalveolar Lavage Fluid After Ozone Exposure. Reseach Report No. 90. Health Effects Institute, Boston, MA.

Frampton, M.W., W.A. Pryor, R. Cueto, C. Cox, P.E. Morrow, and M.J. Utell. 1999b. Ozone exposure increases aldehydes in epithelial lining fluid in human lung. Am. J. Respir. Crit. Care Med. 159(4 Pt. 1):1134-1137.

Gerrity, T.R., R.A. Weaver, J. Berntsen, D.E. House, and J.J. O'Neil. 1988. Extrathoracic and intrathoracic removal of O3 in tidal-breathing humans. J. Appl. Physiol. 65(1):393-400.

Gerrity, T.R., F. Biscardi, A. Strong, A.R. Garlington, J.S. Brown, and P.A. Bromberg. 1995. Bronchoscopic determination of ozone uptake in humans. J. Appl. Physiol. 79(3):852-860.

Gertner, A., B. Bromberger-Barnea, A.M. Dannenberg, Jr., R. Traystman, and H. Menkes. 1983a. Responses of the lung periphery to 1.0 ppm ozone. J. Appl. Physiol. 55(3):770-776.

Gertner, A., B. Bromberger-Barnea, R. Traystman, D. Berzon, and H.

Menkes. 1983b. Responses of the lung periphery to ozone and histamine. J. Appl. Physiol. 54(3):640-646.

Gertner, A., B. Bromberger-Barnea, R. Traystman, and H. Menkes. 1983c. Effects of ozone on peripheral lung reactivity. J. Appl. Physiol. 55(3):777-784.

Gilmour, M.I., and M.K. Selgrade. 1993. A comparison of the pulmonary defenses against streptococcal infection in rats and mice following O3 exposure: Differences in disease susceptibility and neutrophil recruitment. Toxicol. Appl. Pharmacol. 123(2):211-218.

Gilmour, M.I., P. Park, D. Doerfler, and M.K. Selgrade. 1993a. Factors that influence the suppression of pulmonary antibacterial defenses in mice exposed to ozone. Exp Lung Res. 19(3):299-314.

Gilmour, M.I., P. Park, and M.K. Selgrade. 1993b. Ozone-enhanced pulmonary infection with Streptococcus zooepidemicus in mice. The role of alveolar macrophage function and capsular virulence factors. Am. Rev. Respir. Dis. 147(3):753-760.

Girardot, S.P., P.B. Ryan, S.M. Smith, W.T. Davis, C.B. Hamilton, R.A. Obenour, J.R. Renfro, K.A. Tromatore, and G.D. Reed. 2006. Ozone and PM2.5 exposure and acute pulmonary health effects: A study of hikers in the Great Smoky Mountains National Park. Environ. Health Perspect. 114(7):1044-1052.

Graham, D.E., and H.S. Koren. 1990. Biomarkers of inflammation in ozone-exposed humans. Comparison of the nasal and bronchoalveolar lavage. Am. Rev. Respir. Dis. 142(1):152-156.

Graham, D., F. Henderson, and D. House. 1988. Neutrophil influx measured in nasal lavages of humans exposed to ozone. Arch. Environ. Health 43(3):228-233.

Harkema, J.R., and J.G. Wagner. 2005. Epithelial and inflammatory responses in the airways of laboratory rats coexposed to ozone and biogenic substances: Enhancement of toxicant-induced airway injury. Exp Toxicol. Pathol. 57(Suppl. 1):129-141.

Harkema, J.R., C.G. Plopper, D.M. Hyde, J.A. St George, D.W. Wilson, and D.L. Dungworth. 1987. Response of the macaque nasal epithelium to ambient levels of ozone. A morphologic and morphometric study of the transitional and respiratory epithelium. Am. J. Pathol. 128(1):29-44.

Harkema, J.R., J.A. Hotchkiss, and R.F. Henderson. 1989. Effects of 0.12 and

0.80 ppm ozone on rat nasal and nasopharyngeal epithelial mucosubstances: Quantitative histochemistry. Toxicol. Pathol. 17(3):525-535.

Harkema, J.R., C.G. Plopper, D.M. Hyde, J.A. St George, D.W. Wilson, and D.L. Dungworth. 1993. Response of macaque bronchiolar epithelium to ambient concentrations of ozone. Am. J. Pathol. 143(3):857-866.

Harkema, J.R., K.T. Morgan, E.A. Gross, P.J. Catalano, and W.C. Griffith. 1994. Consequences of Prolonged Inhalation of Ozone on F344/N Rats: Collaborative Studies. Part VII. Effects on the Nasal Mucociliary Apparatus. Research Report No. 65. Health Effects Institute, Boston, MA.

Harkema, J.R., J.A. Hotchkiss, E.B. Barr, C.B. Bennett, M. Gallup, J.K. Lee, and C. Basbaum. 1999. Long-lasting effects of chronic ozone exposure on rat nasal epithelium. Am. J. Respir. Cell. Mol. Biol. 20(3):517-529.

Hassett, C., M.G. Mustafa, W.F. Coulson, and R.M. Elashoff. 1985. Murine lung carcinogenesis following exposure to ambient ozone concentrations. J. Natl. Cancer Inst. 75(4):771-777.

Hatch, G.E., R. Slade, A.G. Stead, and J.A. Graham. 1986. Species comparison of acute inhalation toxicity of ozone and phosgene. J. Toxicol. Environ. Health 19(1):43-53.

Hatch, G.E., R. Slade, L.P. Harris, W.F. McDonnell, R.B. Devlin, H.S. Koren, D.L. Costa, and J. McKee. 1994. Ozone dose and effect in humans and rats. A comparison using oxygen-18 labeling and bronchoalveolar lavage. Am. J. Respir. Crit. Care Med. 150(3):676-683.

Herbert, R.A., J.R. Hailey, S. Grumbein, B.J. Chou, R.C. Sills, J.K. Haseman, T. Goehl, R.A. Miller, J.H. Roycroft, and G.A. Boorman. 1996. Two-year and lifetime toxicity and carcinogenicity studies of ozone in B6C3F1 mice. Toxicol. Pathol. 24(5):539-548.

Horstman, D.H., L.J. Folinsbee, P.J. Ives, S. Abdul-Salaam, and W.F. McDonnell. 1990. Ozone concentration and pulmonary response relationships for 6.6-hour exposures with five hours of moderate exercise to 0.08, 0.10, and 0.12 ppm. Am. Rev. Respir. Dis. 142(5):1158-1163.

Horstman, D.H., B.A. Ball, J. Brown, T. Gerrity, and L.J. Folinsbee. 1995. Comparison of pulmonary responses of asthmatic and nonasthmatic subjects performing light exercise while exposed to a low level of ozone. Toxicol. Ind. Health. 11(4):369-385.

Horvath, S.M., J.A. Gliner, and J.A. Matsen-Twisdale. 1979. Pulmonary func-

tion and maximum exercise responses following acute ozone exposure. Aviat. Space Environ. Med. 50(9):901-905.

HSDB (Hazardous Substances Data Bank). 2005. Ozone (CASRN: 10028-15-6). TOXNET, Specialized Information Services, U.S. National Library of Medicine, Bethesda, MD [online]. Available: http://toxnet.nlm.nih.gov/cgi-bin/sis/htmlgen?HSDB [accessed March 14, 2007].

Hu, S.C., A. Ben-Jebria, and J.S. Ultman. 1992a. Longitudinal distribution of ozone absorption in the lung: Quiet respiration in healthy subjects. J. Appl. Physiol. 73(4):1655-1661.

Hu, S.C., A. Ben-Jebria, and J.S. Ultman. 1992b. Simulation of ozone uptake distribution in the human airways by orthogonal collocation on finite elements. Comput. Biomed. Res. 25(3):264-278.

Hyde, D.M., R.P. Bolender, J.R. Harkema, and C.G. Plopper. 1994. Morphometric approaches for evaluating pulmonary toxicity in mammals: Implications for risk assessment. Risk Anal. 14(3): 293-302.

Ichinose, T., and M. Sagai. 1992. Combined exposure to NO2, O3 and H2SO4-aerosol and lung tumor formation in rats. Toxicology 74(2-3):173-184.

Jaspers, I., E. Flescher, and L.C. Chen. 1997. Ozone-induced IL-8 expression and transcription factor binding in respiratory epithelial cells. Am. J. Physiol. 272(3 Pt. 1):L504-L511.

Jedlinska-Krakowska, M., Z. Gizejewski, J.G. Dietrich, K. Jakubowski, J. Glogowski, and A. Penkowski. 2006. The effect of increased ozone concentrations in the air on selected aspects of rat reproduction. Pol. J. Vet. Sci. 9(1):11-16.

Johnson, N.F., J.A. Hotchkiss, J.R. Harkema, and R.F. Henderson. 1990. Proliferative responses of rat nasal epithelia to ozone. Toxicol. Appl. Pharmacol. 103(1):143-155.

Kleinfeld, M., and C.P. Giel. 1956. Clinical manifestations of ozone poisoning: Report of a new source of exposure. Am. J. Med. Sci. 231(6):638-643.

Koren, H.S., R.B. Devlin, D.E. Graham, R. Mann, M.P. McGee, D.H. Horstman, W.J. Kozumbo, S. Becker, D.E. House, W.F. McDonnell, and P.A. Bromberg. 1989. Ozone-induced inflammation in the lower airways of human subjects. Am. Rev. Respir. Dis. 139(2):407-415.

Kulle, T.J., L.R. Sauder, J.R. Hebel, and M.D. Chatham. 1985. Ozone response relationships in healthy nonsmokers. Am. Rev. Respir. Dis. 132(1):36-41.

Last, J.A., and D.L. Warren. 1987. Synergistic interaction between nitrogen dioxide and respirable aerosols of sulfuric acid or sodium chloride on rat lungs. Toxicol. Appl. Pharmacol. 90(1):34-42.

Lee, L.Y., C. Dumont, T.D. Djokic, T.E. Menzel, and J.A. Nadel. 1979. Mechanism of rapid, shallow breathing after ozone exposure in conscious dogs. J. Appl. Physiol. 46(6):1108-1114.

Leikauf, G.D., Q. Zhao, S. Zhou, and J. Santrock. 1993. Ozonolysis products of membrane fatty acids activate eicosanoid metabolism in human airway epithelial cells. Am. J. Respir. Cell Mol. Biol. 9(6):594-602.

Leikauf, G.D., L.G. Simpson, J. Santrock, Q. Zhao, J. Abbinante-Nissen, S. Zhou, and K.E. Driscoll. 1995a. Airway epithelial cell responses to ozone injury. Environ. Health Perspect 103(Suppl. 2): 91-95.

Leikauf, G.D., Q. Zhao, S. Zhou, and J. Santrock. 1995b. Activation of Eicosanoid Metabolism in Human Airway Epithelial Cells by Ozonolysis Products of Membrane Fatty Acids. Research Report No 71. Health Effects Institute, Boston, MA.

Lippmann, M. 1993. Health effects of tropospheric ozone: Review of recent research findings and their implications to ambient air quality standards. J. Expo. Anal. Environ. Epidemiol. 3(1):103-129.

Mautz, W.J., T.R. McClure, P. Reischl, R.F. Phalen, and T.T. Crocker. 1985. Enhancement of ozone-induced lung injury by exercise. J. Toxicol. Environ. Health 16(6):841-854.

McDonnell, W.F., D.H. Horstman, M.J. Hazucha, E. Seal, Jr., E.D. Haak, S.A. Salaam, and D.E. House. 1983. Pulmonary effects of ozone exposure during exercise: Dose-response characteristics. J. Appl. Physiol. 54(5):1345-1352.

McDonnell, W.F., H.R. Kehrl, S. Abdul-Salaam, P.J. Ives, L.J. Folinsbee, R.B. Devlin, J.J. O'Neil, and D.H. Horstman. 1991. Respiratory response of humans exposed to low levels of ozone for 6.6 hours. Arch. Environ. Health 46(3):145-150.

McDonnell, W.F., P.W. Stewart, S. Andreoni, E. Seal, Jr., H.R. Kehrl, D.H. Horstman, L.J. Folinsbee, and M.V. Smith. 1997. Prediction of ozone-induced FEV1 changes. Effects of concentration, duration, and ventilation. Am. J. Respir. Crit. Care Med. 156(3 Pt. 1):715-722.

McKittrick, T., and W.C. Adams. 1995. Pulmonary function response to equivalent doses of ozone consequent to intermittent and continuous exercise. Arch. Environ. Health 50(2):153-158.

Medina-Ramon, M., A. Zanobetti, and J. Schwartz. 2006. The effect of ozone and PM10 on hospital admissions for pneumonia and chronic obstructive pulmonary disease: A national multicity study. Am. J. Epidemiol. 163(6):579-588.

Miller, F.J., J.H. Overton, Jr., R.H. Jaskot, and D.B. Menzel. 1985. A model of the regional uptake of gaseous pollutants in the lung. I. The sensitivity of the uptake of ozone in the human lung to lower respiratory tract secretions and exercise. Toxicol. Appl. Pharmacol. 79(1):11-27.

Molfino, N.A., S.C. Wright, I. Katz, S. Tarlo, F. Silverman, P.A. McClean, J.P. Szalai, M. Raizenne, A.S. Slutsky, and N. Zamel. 1991. Effect of low concentrations of ozone on inhaled allergen responses in asthmatic subjects. Lancet 338(8761):199-203.

Morrison, D., I. Rahman, and W. MacNee. 2006. Permeability, inflammation and oxidant status in airspace epithelium exposed to ozone. Respir. Med. 100(12):2227-2234.

Nagda, N.L., M.D. Fortmann, M.D. Koontz, S.R. Baker, and M.E. Ginevan. 1989. Airliner Cabin Environment: Contaminant Measurements, Health Risks, and Mitigation Options. DOT-P-15–89–5. NTIS/PB91–159384. Prepared by GEOMET Technologies, Germantown, MD, for the U.S. Department of Transportation, Washington DC.

Nikasinovic, L., I. Momas, and N. Seta. 2003. Nasal epithelial and inflammatory response to ozone exposure: A review of laboratory-based studies published since 1985. J. Toxicol. Environ. Health B Crit. Rev. 6(5):521-568.

NIOSH (National Institute for Occupational Safety and Health). 1997. NIOSH Pocket Guide to Chemical Hazards. DHHS (NIOSH) Publication No. 97-140. National Institute for Occupational Safety and Health, Centers for Disease Control and Prevention, U.S. Department of Health and Human Services, Public Health Service, Cincinnati, OH.

NRC (National Research Council). 1984. Ozone. Pp. 99-106 in Emergency and Continuous Exposure Limits for Selected Airborne Contaminants, Vol. 1. Washington, DC: National Academy Press.

NRC (National Research Council). 2002. The Airliner Cabin Environment

and the Health of Passengers and Crew. Washington, DC: National Academy Press.

Osebold, J.W., Y.C. Zee, and L.J. Gershwin. 1988. Enhancement of allergic lung sensitization in mice by ozone inhalation. Proc. Soc. Exp. Biol. Med. 188(3):259-264.

Overton, J.H., R.C. Graham, and F.J. Miller. 1987. A model of the regional uptake of gaseous pollutants in the lung. II. The sensitivity of ozone uptake in laboratory animal lungs to anatomical and ventilatory parameters. Toxicol. Appl. Pharmacol. 88(3):418-432.

Passannante, A.N., M.J. Hazucha, P.A. Bromberg, E. Seal, L. Folinsbee, and G. Koch. 1998. Nociceptive mechanisms modulate ozone-induced human lung function decrements. J. Appl. Physiol. 85(5):1863-1870.

Peel, J.L., P.E. Tolbert, M. Klein, K.B. Metzger, W.D. Flanders, K. Todd, J.A. Mulholland, P.B. Ryan, and H. Frumkin. 2005. Ambient air pollution and respiratory emergency department visits. Epidemiology 16(2):164-174.

Pereyra-Munoz, N., C. Rugerio-Vargas, M. Angoa-Perez, G. Borgonio-Perez, and S. Rivas-Arancibia. 2006. Oxidative damage in substantia nigra and striatum of rats chronically exposed to ozone. J. Chem. Neuroanat. 31(2):114-123.

Pinkerton, K.E., M.G. Menache, and C.G. Plopper. 1995. Consequences of Prolonged Inhalation of Ozone on F344/N Rats: Collaborative Studies. Part IX. Changes in the Tracheobronchial Epithelium, Pulmonary Acinus, and Lung Antioxidant Enzyme Activity. Research Report No. 65-IX. Health Effects Institute, Boston, MA.

Pryor, W.A. 1992. How far does ozone penetrate into the pulmonary air/tissue boundary before it reacts? Free Radic. Biol. Med. 12(1):83-88.

Pryor, W.A., G.L. Squadrito, and M. Friedman. 1995a. The cascade mechanism to explain ozone toxicity: The role of lipid ozonation products. Free Radic. Biol. Med. 19(6):935-941.

Pryor, W.A., G.L. Squadrito, and M. Friedman. 1995b. A new mechanism for the toxicity of ozone. Toxicol. Lett. (82-83):287-293.

Ruidavets, J.B., M. Cournot, S. Cassadou, M. Giroux, M. Meybeck, and J. Ferrieres. 2005. Ozone air pollution is associated with acute myocardial infarction. Circulation 111(5):563-569.

Ryan, L.K., L.R. Copeland, M.J. Daniels, E.R. Costa, and M.J. Selgrade. 2002.

Proinflammatory and Th1 cytokine alterations following ultraviolet radiation enhancement of disease due to influenza infection in mice. Toxicol. Sci. 67(1):88-97.

Saltzman, B.E., and J.L. Svirbely. 1957. Ozone toxicity and substances associated with its production. AMA Arch. Ind. Health 15(2):111-118.

Scannell, C., L. Chen, R.M. Aris, I. Tager, D. Christian, R. Ferrando, B. Welch, T. Kelly, and J.R. Balmes. 1996. Greater ozone-induced inflammatory responses in subjects with asthma. Am. J. Respir. Crit. Care Med. 154(1):24-29.

Schelegle, E.S., and W.C. Adams. 1986. Reduced exercise time in competitive simulations consequent to low level ozone exposure. Med. Sci. Sports Exerc. 18(4):408-414.

Schelegle, E.S., W.C. Adams, S.N. Giri, and A.D. Siefkin. 1989. Acute ozone exposure increases plasma prostaglandin F2 alpha in ozone-sensitive human subjects. Am. Rev. Respir. Dis. 140(1):211-216.

Schelegle, E.S., A.D. Siefkin, and R.J. McDonald. 1991. Time course of ozone-induced neutrophilia in normal humans. Am. Rev. Respir. Dis. 143(6):1353-1358.

Schelegle, E.S., M.L. Carl, H.M. Coleridge, J.C. Coleridge, and J.F. Green. 1993. Contribution of vagal afferents to respiratory reflexes evoked by acute inhalation of ozone in dogs. J. Appl. Physiol. 74(5):2338-2344.

Schelegle, E.S., M.F. Alfaro, L. Putney, M. Stovall, N. Tyler, and D.M. Hyde. 2001. Effect of C-fiber-mediated, ozone-induced rapid shallow breathing on airway epithelial injury in rats. J. Appl. Physiol. 91(4):1611-1618.

Schelegle, E.S., L.A. Miller, L.J. Gershwin, M.V. Fanucchi, L.S. Van Winkle, J.E. Gerriets, W.F. Walby, V. Mitchell, B.K. Tarkington, V.J. Wong, G.L. Baker, L.M. Pantle, J.P. Joad, K.E. Pinkerton, R. Wu, M.J. Evans, D.M. Hyde, and C.G. Plopper. 2003. Repeated episodes of ozone inhalation amplifies the effects of allergen sensitization and inhalation on airway immune and structural development in Rhesus monkeys. Toxicol. Appl. Pharmacol. 191(1):74-85.

Schelegle, E.S., W.F. Walby, and W.C. Adams. 2007. Time course of ozone-induced changes in breathing pattern in healthy exercising humans. J. Appl. Physiol. 102(2):688-697.

Seal, E., Jr., W.F. McDonnell, D.E. House, S.A. Salaam, P.J. Dewitt, S.O. Butler, J. Green, and L. Raggio. 1993. The pulmonary response of white and black

adults to six concentrations of ozone. Am. Rev. Respir. Dis. 147(4):804-810.

Selgrade, M.K., J.W. Illing, D.M. Starnes, A.G. Stead, M.G. Menache, and M.A. Stevens. 1988. Evaluation of effects of ozone exposure on influenza infection in mice using several indicators of susceptibility. Fundam. Appl. Toxicol. 11(1):169-180.

Sokol, R.Z., P. Kraft, I.M. Fowler, R. Mamet, E. Kim, and K.T. Berhane. 2006. Exposure to environmental ozone alters semen quality. Environ. Health Perspect. 114(3): 360-365.

Spektor, D.M., M. Lippmann, P.J. Lioy, G.D. Thurston, K. Citak, D.J. James, N. Bock, F.E. Speizer, and C. Hayes. 1988a. Effects of ambient ozone on respiratory function in active, normal children. Am. Rev. Respir. Dis. 137(2):313-320.

Spektor, D.M., M. Lippmann, G.D. Thurston, P.J. Lioy, J. Stecko, G. O'Connor, E. Garshick, F.E. Speizer, and C. Hayes. 1988b. Effects of ambient ozone on respiratory function in healthy adults exercising outdoors. Am. Rev. Respir. Dis. 138(4):821-828.

Stockstill, B.L., L.Y. Chang, M.G. Menache, P.W. Mellick, R.R. Mercer, and J.D. Crapo. 1995. Bronchiolarized metaplasia and interstitial fibrosis in rat lungs chronically exposed to high ambient levels of ozone. Toxicol. Appl. Pharmacol. 134(2):251-63.

Torres, A., M.J. Utell, P.E. Morow, K.Z. Voter, J.C. Whitin, C. Cox, R.J. Looney, D.M. Speers, Y. Tsai, and M.W. Frampton. 1997. Airway inflammation in smokers and nonsmokers with varying responsiveness to ozone. Am. J. Respir. Crit. Care Med. 156(3 Pt 1):728-736.

Tyler, W.S. 1983. Comparative subgross anatomy of lungs. Pleuras, interlobular septa, and distal airways. Am. Rev. Respir. Dis. 128(2 Pt. 2):S32-S36.

Tyler, W.S., N.K. Tyler, J.A. Last, M.J. Gillespie, and T.J. Barstow. 1988. Comparison of daily and seasonal exposures of young monkeys to ozone. Toxicology 50(2):131-144.

Ultman, J.S., A. Ben-Jebria, and S.F. Arnold. 2004. Uptake Distribution of Ozone in Human Lungs: Intersubject Variability in Physiologic Response. Research Report No. 125. Health Effects Institute, Boston, MA.

van Bree, L., J.A. Dormans, H.S. Koren, R.B. Devlin, and P.J. Rombout. 2002. Attenuation and recovery of pulmonary injury in rats following short-term, repeated daily exposure to ozone. Inhal. Toxicol. 14(8):883-900.

Van Loveren, H., P.J. Rombout, S.S. Wagenaar, H.C. Walvoort, and J.G. Vos. 1988. Effects of ozone on the defense to a respiratory Listeria monocytogenes infection in the rat. Suppression of macrophage function and cellular immunity and aggravation of histopathology in lung and liver during infection. Toxicol. Appl. Pharmacol. 94(3):374-393.

Victorin, K. 1996. Genotoxicity and carcinogenicity of ozone. Scand. J. Work Environ. Health 22(Suppl. 3):42-51.

Waters, M. 2001. Cabin Air Quality Exposure Assessment Presented to the NRC Committee on Air Quality in Passenger Cabins of Commercial Aircraft, January 3, 2001, Washington, DC.

White, M.C., R.A. Etzel, W.D. Wilcox, and C. Lloyd. 1994. Exacerbations of childhood asthma and ozone pollution in Atlanta. Environ. Res. 65(1):56-68.

Witschi, H., M.A. Breider, and H.M. Schuller. 1993. Failure of Ozone and Nitrogen Dioxide to Enhance Lung Tumor Development in Hamsters. Research Report No. 60. Health Effects Institute, Boston, MA.

Wojtowicz, J.A. 1996. Ozone. Pp. 953-994 in Kirk-Othmer Encyclopedia of Chemical Technology, 4th Ed., Vol. 17. New York: John Wiley and Sons.

Zhou, Z.J., Z.S. Zhou, and B.Z. Tang. 2006. General reproductive toxicity assessment in mice exposed to low-level ozone [in Chinese, abstract in English]. Zhong Nan Da Xue Xue Bao Yi Xue Ban 31(3):450-452.