APPENDIX A
CONSIDERATIONS IN SELECTING PARTICLE SIZE CUT POINT FOR FINE PARTICLES

An important decision relating to the choice of indicator is the choice of measurement which in a sense serves as an operational definition of fine particles. The CD concludes that the minimum of mass between the fine and coarse modes lies between 1 and 3 μm, and that the scientific data support a cut point to delineate fine particles in this range (CD, Chapter 3-5). Because of the overlap of fine and coarse particles in this intermodal region, specific cut points are only an approximation of fine particles. Thus, the decision within this range is largely a policy judgement. Although most fine particle (accumulation mode) mass is below 1.0μm, some hygroscopic particles in conditions of high relative humidity may gain water and grow above this size. However, energy considerations normally limit coarse mode particle sizes to greater than 1.0 μm in diameter (CD, 3.1.2).

The main policy choice centers on two options: $PM_{2.5}$ and PM_1. Staff recommend the three primary factors to consider in selecting a cut point are consistency with health data, potential for intrusion of mass from the other mode, and availability of monitoring technology.

From a public health perspective, use of a $PM_{2.5}$ cutpoint will result in the capture of all of the potential agents of concern in the fine fraction. For example, the cutpoint of $PM_{2.5}$ captures most sulfates, acids, fine particle metals, organics, and ultrafine particles and accounts for most of surface area, and particle number. Although the CD outlines some conditions (e.g., relative humidity near 100 percent) under which it is possible that hygroscopic particles may grow above 2.5μm, use of the $PM_{2.5}$ cutpoint is still better at capturing the constituents of concern than PM_1.

$PM_{2.5}$ has been measured directly in many health studies as described in the CD and Chapter V, Section F above. Significant associations have been reported between $PM_{2.5}$ concentrations and mortality, hospital admissions, cough, upper respiratory infection, lower respiratory infection, asthma status, and pulmonary function changes.

$PM_{2.5}$ measurement technologies are widely available and have been in routine use in the field since the early 1980s. For example, the EPA AIRS database contains $PM_{2.5}$ data from the Inhalable Particle Network (1982-1984), the IMPROVE network (1987 - present), and the NESCAUM network (1988- present). In addition, the California Air Resource Board (CARB) dichotomous sampler network has been collecting $PM_{2.5}$ data routinely since 1980, and many other special studies measuring $PM_{2.5}$ have been conducted across the country. Furthermore, dichotomous samplers allow the coincident measurement of PM_{10} and $PM_{2.5}$, increasing the certainty of comparability between the two measurements.

Measurement of fine particle mass using a 1 μm (PM_1), on the other hand, has not been used in health studies primarily due to lack of available monitoring data. Comparisons between PM_1 and other measurements that were used in the health studies (e.g., PM_{10}) are also not widely available due to lack of available PM_1 monitoring data. Furthermore, PM_1 may not capture as much of the hygroscopic substances such as sulfates which health studies report as having statistically significant associations between sulfate measurements and endpoints including increased mortality and hospital admissions.

PM_1 sampling technologies have been developed and some limited validated data are available from locations such as Phoenix, Arizona. However, the PM_1 samplers have not been widely field-tested to date.

Proponents of the PM_1 option are concerned that the intrusion of particles generated by grinding or crushing (i.e., coarse mode particles) into the daily $PM_{2.5}$ measurement could create spurious NAAQS exceedances. Given the lack of PM_1 data currently available, it is difficult to determine how much intrusion might occur or what areas might be affected during the implementation of a $PM_{2.5}$ NAAQS. The available data show that typically only 5-15 percent (on the order of 1 to 5 $\mu g/m^3$) of the $PM_{2.5}$ mass is attributable to soil-type sources even in dusty areas such as San Joaquin Valley, California, and Phoenix, Arizona. However, this percentage may increase during events such as high winds.

The staff judges that in typical urban areas, the potential for this type of intrusion may be smaller, but without sufficient data these determinations remain very uncertain. A sharper inlet for the Federal Reference Method may help to minimize the intrusion of coarse mode

particles into the $PM_{2.5}$ measurement. Although intrusion of coarse mode particles into daily $PM_{2.5}$ measurements is not anticipated to be significant in most situations, if in light of more data a problem is identified, this issue might be better addressed on a case-by-case basis in the monitoring and implementation programs.

Finally, the staff concludes that $PM_{2.5}$ measurements are more appropriate than some of the measurements historically used in the epidemiological studies (e.g., BS, CoH) although these measurements have been useful in advancing the state of scientific knowledge of particle effects. British Smoke (BS) readings vary more with darkness of particles (i.e., carbon content) than with mass, making associations with mass highly site- and time-specific. The BS method emphasizes control of primary elemental carbon emissions; however, elemental carbon is a minor contributor to fine and total mass in current U.S. atmospheres. Furthermore, lack of consistent relationships between BS reflectance and PM mass measurements diminishes one of the major advantages: BS is not related to the available quantitative health data from U.S. cities with as much certainty as the $PM_{2.5}$ mass measurements although BS is used in many other countries. Using a similar principle to BS, the principle of coefficient of haze (COH) is that visible light is transmitted through (or reflected from as in the case of BS) a section of filter paper before and after ambient air is drawn through it. Thus, COH associations with mass are also highly site- and time-specific.

Thus, because of the consistency with health data, small potential for intrusion, and availability of monitoring technology and existing air quality database, the staff judges that the $PM_{2.5}$ measurement is more appropriate for regulatory purposes than PM_1, or historical measurements such as BS or COH.

APPENDIX B

MEASUREMENT METHODS FROM EPIDEMIOLOGY STUDIES

The CD and Chapter V of this Staff Paper summarize health studies which have reported associations between various indicators of PM and health effects. The main mass concentration indicators are TSP, PM_{10}, and $PM_{2.5}$. In addition to $PM_{2.5}$ mass measurements, fine particles have been measured in the U.S. and abroad using a variety of techniques including British or black smoke (BS), coefficient of haze (COH), carbonaceous material (KM), and estimates from visibility measurements (CD, Section 4.2.8).

Studies have also reported associations between health effects and exposure to fractions found predominantly in the fine fraction such as sulfate ($SO_4^=$) and strong acidity (H^+). The CD describes measurement techniques in detail; this section highlights relevant information about other indicators of fine particles (i.e., BS, COH, and KM).

In the past, it was noted that visibly black plumes were emitted by industrial sources; thus, light absorption was adopted as a measure of PM pollution (Chow, 1995). Measurements of the optical properties of particles may be related to gravimetric mass measurements on a site- and time-specific basis with on-site calibrations.

BS preferentially measures elemental carbon particles found in the fine fraction (CD, Section 4.2.8; Baily and Clayton 1980). In addition, the BS inlet design, taken together with its other operating parameters, restricts the size of particles that are sampled. For example, it has been shown in wind tunnel tests that the best estimate of the cut point for BS is 4.5 µm (CD, page 4-52; Waller, 1980; McFarland, 1979). Most particles larger than the cut point of 4.5 µm are either rejected at the inlet or lost in the inlet line (U.S. EPA, 1982a). Furthermore, the BS reading varies more with darkness of particles (i.e., carbon content) than with mass, thus making associations with mass highly case-specific. Because elemental carbon is found predominantly in the fine mass (less than 1.0 µm range), variations in BS are more closely related to fine mass and unlikely to be sensitive to coarse mode particles (NAS, 1980; U.S. EPA, 1982b).

Using a similar principle to BS, COH measures visible light transmitted through (compared to reflected from in the case of BS) a section of filter paper before and after

ambient air is drawn through it. The amount of light transmitted is measured by a photocell (Chow, 1995; Fairley, 1990). In addition, this sampler uses a funnel inlet and a small diameter transport tube nearly identical to the BS sampler. Although the two samplers operate at different flow rates, the particles reaching the filter tape could be expected to have a size range similar to that of the BS instrument (U.S. EPA, 1982a, see Figure 3A-12).

Prior to the 1980s, PM was measured in California by optical reflectance of particles collected on a sample tape (KM). Similar in principle to BS, KM has been shown to be closely related to elemental carbon content in Los Angeles (Kinney and Özkaynak, 1990). Similar to BS, KM is also a fine particle measurement.

Visibility measurements can also be used as a reasonable surrogate to estimate fine particle concentrations because the extinction coefficient is directly related to fine particle mass (CD, page 6-216).

APPENDIX C

PM_{10} NATIONAL CONCENTRATION MAPS AND DEFINITIONS OF REGIONS

Current U.S. PM_{10} levels are illustrated in Figures C-1 and C-2. Figure C-1 shows the fourth highest 24-hour PM_{10} concentration recorded in a county and Figure C-2 depicts highest annual mean PM_{10} concentration using 1992 to 1994 AIRS data in each county for which data completeness criteria were met. Counties not represented with a monitor are left blank.

The following methods were used to calculate the values depicted in the maps. The current single exceedance form of the PM_{10} daily standard allows for an average of one exceedance per year over a three-year period. Thus, the fourth highest concentration is of interest because this value is used to determine attainment with the current daily standard. Seven hundred and twelve counties met the data completeness criterion of at least 75 percent complete data for the period 1992 to 1994. For these counties, all daily concentrations were ordered largest to smallest and the fourth highest PM_{10} concentration was determined for each site. If a county had only one site, then the fourth highest concentration for that site was reported. If a county had more than one site, the site with the maximum fourth highest concentration was used to represent the county.

Figure C-2 shows the maximum annual mean concentration in each county over the three-year period using an average weighted by calendar quarter. Three hundred and eighty counties met the 75 percent data completeness criterion by quarter for 1992 to 1994. Means were calculated for all four calendar quarters for each year in the 3-year period and annual values were calculated based on the quarterly means. The three yearly means were then averaged to obtain one value for each site. If a county had only one site, then the annual mean for that site was reported. If a county had more than one site, the site with the maximum annual mean was used to represent the county.

Figure C-3 shows the regions of the country used in some air quality analyses. Note that state boundaries were used except that California and Texas were split.

Figure C-4 illustrates that a total of 87 different sites reported $PM_{2.5}$ data to AIRS from 1983 to 1993. Over the 11 year period, less than 50 sites reported data to AIRS in any given year. Additional special studies have also monitored $PM_{2.5}$, but these data are not reported in AIRS.

Figure C-1.

Figure C-2.

Figure C-3. Regions Used in Air Quality Analyses in this Staff Paper

APPENDIX D

I. HYPOTHETICAL MECHANISMS OF ACTION FOR PM

1. Dosimetric Considerations

Dosimetric considerations formed the principle basis of the approach used for selecting PM_{10} as the indicator of the current standard (pp.23-39, U.S. EPA, 1982b). Exposure can be described, in the context of regulating PM, as the concentration of particles available in the ambient air that a human or animal breathes over a relevant period of time. Dose is the amount of this material that is inhaled and available for deposition at various target sites (e.g., regions of respiratory tract) (CD, p. 10-1). It is the dose that the target site or organ receives upon which manifestation of toxicity depends. The amount of particles deposited or retained in each region of the respiratory tract is governed by exposure concentration, particle diameter and distribution, physico-chemical properties of the inhaled particle (e.g. hygroscopy and solubility), and duration of relevant exposure. In the previous review, such dosimetric considerations, health effects of concern, and aerosol physico-chemical characteristics prompted the Staff with CASAC concurrence to determine that the major risk of commonly occurring outdoor PM was presented by particles of 10 micron or less aerodynamic diameter. Particles of this size are able to penetrate the presumptive targets of PM (tracheobronchial and alveolar regions of the human respiratory tract) (CD, Chapter 10).

The human respiratory tract can be divided into three main regions: (1) extra-thoracic, (2) tracheobronchial, and (3) alveolar regions as shown in Table 10-5 of the CD. They differ markedly in structure, function, size, and sensitivity or reactivity to deposited particles (U.S. EPA, 1982b). Disposition and retention of initially deposited particles depends on clearance and translocation mechanisms that vary with each region of the respiratory tract. Coughing, mucociliary transport, endocytosis by macrophages or epithelial cells, and dissolution and absorption into the blood or lymph are important mechanisms of clearance in the tracheobronchial region. Endocytosis by macrophage or epithelial cells and dissolution of absorption into the blood or lymph are the dominant mechanisms of clearance in the alveolar region.

In essence, ambient particles of 10 μm diameter or less deposit with varying efficiencies in tracheobronchial and alveolar regions of the respiratory tract. Simulations of deposition show that alveolar deposition is fairly uniform for particle between 0.5 and 4.0 μm diameter. Table V-1 of Chapter V is derived from Tables 10-21 and 10-23 of the CD and shows the deposition patterns in the human lung for typical particle distributions found the cities of Philadelphia and Phoenix. This table represents the general population of adult males with normal breathing. The table shows not only do all size fractions below 10 μm diameter have the potential for some deposition in both tracheobronchial and alveolar regions but deposition patterns of the types of particles found in urban areas can be similar in these lung regions under specific conditions.

In regard to sensitive sub-populations, increased deposition and altered clearance may play a role in susceptibility to PM. A detailed discussion of these individuals is presented in section 5-D. Model simulations have suggested that deposition efficiency of particles will be increased in people with COPD and asthma (Anderson, 1990; Miller et al., 1995; Svartengren et al., 1994). Kim et al (1988) demonstrated much greater particle deposition in COPD patients using aerosol re-breathing tests. A compromised lung with greater deposition has a greater probability of interaction of PM with potential targets of PM toxicity and thus increased effects. However, the contribution of such differential deposition of particles to mortality and morbidity has not been elucidated or quantified.

Similarly, differences in dosimetry between animals and humans may be a contributing factor for the apparent differences in animals and human study results. Rodents have a greater deposition of particles in the upper respiratory tract than humans. In addition, models show that humans retain a greater fraction of particles deposited in the alveolar region than do rats or mice. Thus, the differences in deposition patterns of particles between species and between susceptible and nonsusceptible subpopulations could be a contributing factor for the necessity of using relatively high concentrations of larger diameter particles to elicit effects seen in experimental animal studies (CD, Chapter 10).

2. Possible Mechanisms of Action for Health Effects Associated with Ambient Levels of PM Exposure

This discussion focuses on more specific possible mechanisms by which airborne particles may be exerting their effects. Upon deposition, substantial uncertainty still exists as to how particles, alone or in combination with other atmospheric pollutants, produce physiological and ultimately pathological effects. Because both the population affected and PM are heterogenous, the mechanism(s) of action may also be diverse. As shown in the CD (Chapter 13), exposure to particulate matter has been identified as causing a variety of health effects including respiratory symptoms, mechanical changes in lung function, alteration of mucociliary clearance, pulmonary inflammatory responses and morphological alteration in the lung. In addition, from epidemiological studies PM has been reported to be associated with increases in respiratory illness, hospital admissions, and daily mortality.

Consequently, the increasing body of community epidemiological studies finding associations between PM and mortality and morbidity in recent years have prompted a number of authors to advance potential mechanisms of PM toxicity. One major area of interest is pulmonary inflammation. Potential mechanisms for induction of an inflammatory response have been described for: (1) aerosol acidity (Lippmann, 1989a), (2) presence of ultrafine particles (Seaton et al., 1995), and (3) transition metal ions (Tepper et al., 1994). A second area of renewed interest includes examination of the ways particles may affect individuals with preexisting conditions. Frampton et al. (1995) list potential causes of PM induced mortality as being: (1) premature death (i.e., hastening of death for individuals near death within hours or days); (2) increased susceptibility to infectious disease; and (3) exacerbation of chronic underlying cardiac or pulmonary disease. Also of significant interest are new approaches for controlled exposures to particles which are closest to those found under ambient conditions than have been possible in past toxicologic studies (Sioutas et al., 1995). The opportunity to study such particles may be particularly valuable in studying the effects from and potential mechanisms of action for PM exposure. The issue of discrepancies between experimental doses and ambient PM in terms of composition and magnitude of administer dose may be resolved. However, early results of such studies while promising are preliminary and may be

valuable for future reviews. A brief summary of potential mechanisms of toxicity is discussed below. Further discussion is provided in Chapters 11 and 13 of the CD.

The most serious effects associated with community studies of PM appear to be found in individuals who have preexisting conditions. Even in the London episodes, the total amount of inhaled PM by mass eliciting a response in humans was small. Therefore, it is likely that the effect of PM exposure is amplified in conjunction with preexisting conditions that increase risk for PM effects. Given that immunological responses can be quite rapid, consistent with the period between increased PM exposure and an acute effect such as mortality, it is plausible that inflammatory processes can amplify and spread the response from small amounts of PM.

Preexisting inflammation (e.g., from an ongoing infection) of the lung can amplify the inflammatory response to residual fly ash in emphysemic rats (Costa et al., 1995). Indeed, several of the risk factors for PM toxicity involve inflammatory response (e.g., asthma, COPD, and infection). A similar profile of susceptibility may be shown by the only animal deaths recorded during the London Fog of 1952 linked to the fog. These were prize show cattle which suffered from both shipping fever and emphysema. Thus, the cattle which shared susceptibility to the London fog with humans may also share some of the same pre-existing conditions (e.g., COPD and inflammation). A commonly offered explanation of the susceptibility of the show cattle was that they were kept in cleaner stalls and thus had much lower waste ammonia present that might serve to neutralize the high levels of acid aerosol portions of the fog and thus decrease their toxicity. The original report by the Ministry of Health (MOH, 1954), however, also reported cattle death in previous fogs with ordinary stall maintenance and therefore high ambient levels of ammonia that could neutralize acid particles.

Seaton et al., (1995) has proposed the hypothesis that the mechanism of PM involves production of an inflammatory response by ultrafine particles (< 0.02 μm diameter) in the urban particulate cloud. As a result, mediators may be released capable of causing exacerbation of lung disease in susceptible individuals and increased coagulability of the blood. Thus a rationale is provided for the observed increase in cardiovascular deaths associated with urban pollution episodes. Several hematological factors, including plasma viscosity, fibrinogen, factor VII, and plasminogen activator inhibitor are not only known to be predictive

of cardiovascular disease (Lowe, 1993) but to also rise as a consequence of inflammatory reactions. Low grade inflammation has been hypothesized to be particularly important in altering the coagulability of blood as a result of activation of mononuclear cells in the lung (MacNee and Selby, 1993). Activated white cells may initiate and promote coagulation (Helin, 1986) via the final clotting pathway (Ottaway et al., 1984). Alveolar inflammation may also cause the release of interleuken - 6 from macrophages and thus stimulate hepatocyte to secrete fibrinogen (Akira and Kishimoto, 1992). Crapo et al., (1992) has suggested that activation of lung macrophages in the absence of recruited neutrophils leads to acute damage of capillary endothelial cells as well as alveolar lining cells, resulting in intracellular edema, hemorrhage and fibrin deposition.

In support of Seaton's proposed mechanisms is the observation that ultrafine particles cause greater inflammation (assayed by broncho-alveolar lavage) than larger particles of the same substance (Chen et al., 1992; Oberdörster et al., 1992). Fine particles have been shown to be taken up by lung epithelial cells (Stringer et al., 1995) and lung macrophages (Godleski et al., 1995). They have also been shown to produce inflammation *in vitro* (Dye et al., 1995) and *in vivo* (Kodavanti et al., 1995). In addition, metals have been shown to increase the toxicity of particles. Intertracheal instillation of residual oil fly ash into rats also produces an inflammatory response (Jaskot et al., 1995) with Dreher et al., (1995) linking such inflammation to soluble vanadium, iron, and nickel compounds on the particles. Ferric sulfate has been shown to alter pulmonary macrophage function (Skornik and Brain, 1983). In support of an inflammatory component to PM toxicity are several recent reports involving diesel particles which have ascribed observed inflammatory/tumor promoting effects to carbon cores rather than adsorbed organic (CD, Chapter 11, Section 11.5.5). Thus, under this proposed mechanism of PM effect, toxicity may involve a response to PM which involves inflammation.

Aggravation of underlying conditions (chronic cardiopulmonary disease in particular) has been observed in epidemiologic studies as increased hospital admissions for such conditions and decreases in pulmonary function. Aggravation of severity of these conditions has also been hypothesized to explain increases in daily mortality and longitudinal increases in

mortality. Under such a scenario individuals experience more frequent and severe symptoms of their preexisting disease or a more rapid loss of function.

Airflow obstruction could result from laryngeal constriction or broncho-constriction secondary to stimulation of receptors by PM in the extrathoracic or intrathoracic airways. In addition, stimulation of mucous secretion could contribute to mucous plugging in small airways. In pre-existing airway diseases, which feature localized airway narrowing or obstruction, the increased accumulation of PM may lead to hypoxia in the respiratory regions of the lung served by the obstructed airways. In tandem under such condition, there also may be an increased particle deposition and adverse effects on the non-obstructed areas of the lung (CD, p. 11-184). Finally, effects on the surfactant layer in the alveoli by PM may cause increased leakiness in the pulmonary capillaries leading to interstitial edema. Experimentally, acid aerosols have been shown to cause acute effects on pulmonary function among some sensitive individuals. They may induce hyper-reactive airways after 75 $\mu g/m^3$ H_2SO_4 for 3 hours (El Fawal and Schlesenger, 1994). Therefore, the elderly with debilitating disease such as asthma may be stressed by the fine acid aerosols.

In regard to particle size, Thurston et al., (1994b) have reported that hospital admissions for asthma were more strongly associated with fine rather than coarse fraction particles. Aggravation of asthma symptoms has also been reported for fine particles (Ostro et al., 1991; Perry et al., 1983). In studies of cellular and immunological injury with PM inhalation, Kleinman et al. (1995) reports that in eliciting responses 0.2 µm diameter SO_4^{-2} is greater than 0.6 µm diameter NO_3^-, which in turn is greater than 4µm diameter resuspended road dust. Measures of alveolar cord length and cross sectional area were most reduced with the fine sulfate particles which could result in a decrease in compliance or "stiffening" of the lung and smaller inflation volume.

Related to the potential for aggravation of underlying disease by PM is the issues of whether increases in mortality reported to be associated with PM are a result of hastening of imminent death. While this is a plausible and reasonable suggestion, other evidence suggests that it may not explain the full effects of PM on mortality. For example, in interviews with the family members of victims of the London pollution episode of 1952, while some of those

victims were reported to having chronic pre-existing conditions and some having infections, several were reported to have no indication of a life threatening disease process (Ministry of Health, 1954). As reported by the CD (Chapter 13), it appears likely that life shortening from PM exposure is highly variable and could range from days to years. The CD concludes that duration life shortening, lag times, and latent periods of PM-mediated mortality are almost certainly distributed over long time periods. However, confident quantitative determination of specific estimates of years lost to ambient PM exposure is not possible at this time.

There are several potential targets for PM throughout the respiratory tract which may involve stimulation of airway neurological receptors to elicit observed health effects (e.g., bronchoconstriction and mucous secretion). The tracheal bronchial tree has been described as the dominating site for vagal reflexes affecting the airways and most definitely associated with common conditions such as asthma and chronic bronchitis (Widdicombe, 1988). However, respiratory receptors which can effect cardiac as well as other pulmonary effects are distributed through the respiratory tract. For example, "irritant" receptors reside in the epithelium from trachea to respiratory bronchiole, that produce bronchoconstriction and reflex contraction of constrictor muscles of the larynx as well as secretion of tracheal mucous (Widdecombe, 1988). "C" receptors are distributed throughout the tracheobronchial tree and in the alveolar wall, and probably also in the laryngeal mucosa (Sant' Ambrogio, 1982; Coleridge and Coleridge, 1986). They have some of the same actions as "irritant" receptors and are activated by the same group of stimuli (Widdicombe 1988). Most of the lung inflammatory and immunologic conditions such as asthma and chronic bronchitis would probably activate C and irritant receptors, which would interact to cause augmented airway responses (Widdecombe 1988). "J" receptors, which reside in the alveolar wall, can elicit a powerful constriction of the larynx as well as bronchoconstriction. The main activation of these receptors occurs in pathological changes in pulmonary circulation and the alveolar wall rather physiological conditions (Widdcombe, 1974, 1988). Lung pathologic conditions (e.g., edema, pulmonary congestion, pneumothorax, microembolisms and anaphylaxis) as well as various irritant gases (e.g., cigarette smoke, sulfur dioxide, and ammonia) and a wide range of

mediators (e.g., prostaglandins and histamine) have been shown to stimulate lung "irritant" receptors. Irritant gases have been shown to stimulate both lung "irritant" and "J" receptors (Widdecombe 1974, 1988).

Cessation of cardiac activity is often the terminal event in life. Pulmonary responses to PM exposure may include hypoxemia, broncho-constriction, apnea, impaired diffusion, and production of inflammatory mediators that can contribute to cardiovascular perturbation (CD, p. 13-71). For example, hypoxia can precipitate cardiac arrhythmias and other cardiac electrophysiologic responses that may lead to ventricular fibrillation and ultimately cardiac arrest. In addition stimulation of many respiratory receptors have direct cardiovascular effects such as bradycardia and hypertension (C-fibers, nasal receptor or pulmonary J-receptor, and laryngeal receptors) and arrythmia, apnea and cardiac arrest (laryngeal receptors) (CD, p. 13-72).

Particles that may deposit in the lung over time may induce an inflammatory response that could lead to pulmonary fibrosis and impaired pulmonary function. With repeated cycles of acute lung injury by PM and subsequent repair, fibrosis may develop. Persistence of toxic particles may also promote a fibrotic response (CD, p. 13-72). Large lung burdens of particles of even relatively low inherent toxicity have been shown to cause lung cancer in rats (Mauderly et al., 1994). While there is difficulty in elucidating how long-term particle accumulation can induce acute mortality, it may be a factor for the elderly who have been chronically exposed to PM in the work place, those who have resided in heavily industrialized cities before effective control of PM, or smokers. As reported in the previous section, sensitive subpopulations with obstructive pulmonary diseases may have focalized particle accumulation in their lungs due to ventilation abnormalities. However, the mechanism by which prior exposure to particulate could predispose an individual to acute PM effects is unknown.

Impaired respiratory defense has also been proposed as a contributing factor to PM toxicity. Patients with pneumonia have increased risk of mortality and morbidity from PM exposure. Cough, bronchitis, and lower respiratory illness have been reported to be associated with increased ambient particle concentrations (CD, Chapter 12, see below).

Both mucociliary transport and macrophage function are critical to host defense against inhaled pathogens. Potentiation of inflammation and infection from biologically active particles (e.g., spores, fungi, and bacteria) may result from effects on clearance and macrophage function by the acid aerosol component of PM (CD, p. 13-75). Increased risk of infection has been associated with changes in mucociliary clearance (e.g., excessive mucus secretion into the airways can cause airway blockage and reduced clearance). Alveolar macrophages are the primary defense cells of lungs and impairment of their function would also be expected to increase risk of infection. Clearance and macrophage function have been shown experimentally to be affected by constituents of PM, notably fine acid aerosols.

H_2SO_4 and trace metals have been shown to have direct effects on alveolar macrophages in animal experiments (CD, p. 13-75). Kleinman et al. (1995) also reported in their study of cellular and immunological injury by PM that antigen binding to receptors in and respiratory burst activity by macrophages was depressed by exposure to fine (0.2µm diameter) SO_4^{-2} particles. H_2SO_4 has also been shown to affect mucociliary transport and, in combination with ozone, resistance to bacterial infection. However, these effects have been shown at concentrations which are much higher than those reported in the recent epidemiological studies for which PM effects have been reported. Effects mediated through clearance, in particular, would be expected to be manifested over an extended period of exposure rather than a few days. While impaired host defense may not be plausible as a mechanism for mortality associated with short-term fluctuations of PM level, it may contribute to the long-term exposure mortality. In addition, the lag-time reported between PM concentration elevations and general indicators of morbidity (e.g., missed school and work loss days) is consistent with an increased susceptibility to infection which may precipitate respiratory symptoms (see discussion in section V.C).

II. EXTRAPOLATION OF RESULTS FROM LABORATORY STUDIES TO THOSE OF EPIDEMIOLOGIC STUDIES: STRENGTH AND LIMITATIONS OF CONTROLLED HUMAN AND ANIMAL STUDIES

As discussed above, the adverse effects of particulate matter exposure have been shown to be consistent between historical and more recent studies. The effects can be severe and tend to be concentrated in sensitive sub-populations who have pre-existing conditions or characteristics that tend to make them vulnerable to respiratory insult (the very young and old, asthmatics, COPD patients, patients with pneumonia etc). The additional risk of reported mortality and morbidity from particulate matter exposure is relatively small in terms of the whole population. Therefore, large numbers of people must be exposed before effects can be discerned in studies. The question arises as to how to elucidate the mechanism of action of particulate matter in humans. What are the considerations that must be taken into account when an analysis of the body of human clinical data and experimental animal work is done in order to infer a plausible mechanism for particulate matter effects?

1. Numbers of Individuals Affected

An issue of primary concern is that of statistical power. The nature of the effect described in epidemiological work is consistent, and serious, but occurring in a relatively small fraction of the total population (1 in a million increased risk for daily mortality). Therefore, theoretically a relatively large number of animals would be needed to mimic the frequency of response at similar doses. The use of a similar number of animals to mimic the frequency of response to ambient air concentrations of particles which have been associated with effect in humans is impractical. Therefore, in many experimental paradigms, relatively large concentrations are often given investigate the response from a limited number of animals. However, the questionable relevancy and sensitivity of such paradigms limits their use in the determination of the mechanism of action of relatively low changes in concentrations of inhaled particulate matter.

2. Heterogeneity of Human Population

The human population for which the effects are most demonstrable are a sub-population from a genetically heterogenous group. Furthermore, consistency of response is highly variable among the population at risk (e.g., a relatively small group of asthmatics have aggravation of symptoms and not all patients with pneumonia or COPD die as a result of an increase in inhaled particle concentration). The CD suggests that for clinical studies involving asthmatics, differences among subjects may explain in part the differing results between laboratories who study effects of acid aerosols. As an example of differential susceptibility to a respiratory insult, a minority of individuals (3-5%) who are exposed to etiologic agents responsible for hypersensitivity pneumonitis (allergic alveolitis) will develop disease. Determinants of susceptibility for that disease have been described as both the genetic constitution of the individual and the presence of preexisting lung disease. Similar factors probably play a role in susceptibility to inhaled particulate matter effects.

By contrast experimental animals are bred as much as possible to be homogenous genetically so as to give great consistency in response. They are also usually studied in their prime in regard to age and general health. Presence of disease is generally considered to be a confounding factor to be stringently controlled in most animal paradigms. As stated above, those segments of the general population most affected from PM_{10} exposure are the sick, the very young, and the old. Therefore the sensitivity of studies using relatively small numbers of healthy, genetically homogenous, laboratory animals who are in their prime is diminished in exploring mechanism of particulate matter effects.

3. Heterogeneity of PM_{10} Composition

Another key element helps to frame the discussion of the relevance of human clinical studies and experimental animal work to establish a mechanism of action of particulate matter in humans. That is the issue of heterogeneity of both the composition of and exposure to particulate matter. Particulate matter is a broad class of physically and chemically diverse substances (as described in Chapter IV). The PM_{10} fraction is composed of two distinct sub-fraction of particle: fine and coarse particles. PM_{10} samplers collect all of the fine particles

and a portion of the coarse ones. There is a fundamental uncertainty regarding which components or properties of particulate matter is essential to the observed effects in humans.

Coarse particles are typically composed of re-suspended dusts from fields and streets and may contain metal oxides of silica, aluminum, magnesium, titanium, and iron. Coal and oil fly ash, calcium carbonate, sodium chloride, sea salt, small pollen, mold spores, and plant parts may also be present. Fine particles are generally composed of sulfate, nitrate, hydrogen ion, elemental carbon, organic compounds, biogenic organic compounds such as terpenes, and metals such as iron, lead, cadmium, vanadium, nickel, copper, and zinc. Some materials which are more typically found in the coarse fraction, may be also found the fine fraction. Similarly, some materials typically found in the fine fraction may also be in the coarse fraction due to particle growth in conditions of high relative humidity (e.g., sulfates). Additionally, the properties of PM_{10} vary greatly from place to place because of differences in source mixes and atmospheric conditions.

Thus unlike a typical experimental paradigm, where the agent to be studied is isolated and the effects of exposure described in well controlled studies, the heterogeneity of the PM_{10} entity forces a different experimental approach. Typically constituents of the fraction are tested individually to see if effects similar to those observed in humans are reproduced. Consequently, animal studies are further weakened in regard to ability to establish a mechanism of action of particulate matter and to either refute or validate epidemiological observation of effect in humans.

4. Dosimetric Heterogeneity

Finally, dosimetric comparisons between laboratory animals and humans, show that there are significant differences in the respiratory architecture and ventilation of the two which adds additional complication to comparisons of experimental and observed data. Ventilation differences coupled with differences in upper airway respiratory tract structure and size, branching pattern, and structure of the lower respiratory tract occur between species as well as between healthy versus diseased states. These differences may result in significantly different patterns of airflow affecting particle deposition patterns in the respiratory tract (CD, Chapter 13). Additionally, inter-species variability in regard to cell morphology, numbers, types,

distribution, and functional capabilities between animal and human respiratory tracks, leads to differences in clearance of deposited particles which may in turn affect the potential for toxicity. (CD, Chapter 13). Consequently the difficulty of using experimental animal data to investigate particulate matter effects is further defined.

5. Lack of Distinct Disease Pathology

The background levels of cardiopulmonary disease as the cause of death for the general population is very high. Given that COPD and heart diseases are frequent causes of death, it is difficult to discern those who die from the additional effects of particulate matter from those already dying from such diseases and to do autopsy to identify a specific pathology associated with particulate matter caused mortality. Even in historical studies involving higher levels resulting in more pronounced effect it is hard to get an adequate characterization of pathology related to particulate matter effects. Thus without such a characterization of the pathology of particulate matter induced mortality, development and validation of appropriate models to study such effects are more difficult.

6. Lack of Appropriate Equivalents to Epidemiological Endpoints

Animal toxicological equivalents of such epidemiological endpoints as hospital admissions and emergency room visits as an indication of morbidity cannot be obtained. Although mortality can be recreated in a laboratory setting, the relevance of mechanism is currently an issue. In addition, there is question as to what the most appropriate measure of particulate matter is in regard to its toxicity. Specifically is it the inhalable mass which is the most relevant metric of the toxic quantity of particulate matter or is it the number of particles which reaches specific targets? Particles may have low inherent toxicity at one size, yet greater potency at another (CD, Chapter 11). A recent study by Chen et al. (1995) confirmed that the number of particles in the exposure atmosphere not just total mass concentration is an important factor in biological responses following acidic sulfate inhalation (CD, Chapter 11). Specifically, ultrafine particles with a diameter of 20 μm have an approximately 6 order of magnitude increased number than a 2.5 μm diameter particle of the same mass concentration (CD, Section 11). Comparisons of particle number and size are shown in Table 11-1 of the CD.

In addition to considerations of dose (inhalability and appropriate metric), the nature of the response to particles and correlations of the appropriate response to susceptible population are yet to be resolved. Thus, identification of the dosimeter which induces mortality and morbidity has not been elucidated with consequent difficulty interpretation and design of controlled animal and human studies.

Appendix E

CONCENTRATION-RESPONSE RELATIONSHIPS FOR MODEL SENSITIVITY ANALYSIS IN RISK ASSESSMENT

The interpretation of specific concentration-response relationships is understood to be one of the most problematic issues at this time for the assessment of health risks associated with exposure to ambient PM. The approach to addressing this issue taken in the risk assessment discussed in Chapter VI and in the technical support documents (Abt Associates, 1996a,b) is to consider alternative concentration-response models through a sensitivity analysis. The sensitivity analysis is intended to develop ranges of estimated risks, without attempting to develop any single best estimate of health risks. One of the elements needed to frame such a sensitivity analysis is the development of alternative PM concentration ranges over which reported concentration-response functions would be applied. Alternative approaches to identifying appropriate PM concentration cut-points which define the lower end of such ranges are discussed below. The application of these approaches to a number of epidemiological studies using PM_{10} and $PM_{2.5}$ indices of exposure for mortality, hospital admissions, and respiratory effects in children is also presented.

A. Alternative Approaches to Defining Concentration Cutpoints

The characterization and interpretation of observed PM concentration-response relationships are of particular importance in adequately assessing risks from ambient PM. Varying degrees of uncertainty exist concerning the PM concentration-response relationship. Such uncertainties may limit the ability to discriminate between a range of plausible alternative concentration-response relationships, and this in turn weakens the ability to estimate potential risks associated with exposure to PM, especially at low ambient concentrations[1]. Key issues for consideration include: 1) what tests and procedures have been done to examine the possibility of linear versus nonlinear dose-response relationships; 2) to what degree do statistical uncertainty and inadequate power preclude exclusion of different alternative concentration-response

[1] The terminology of "low" or "lower" concentrations is used to simply refer to observed PM concentrations generally within the lower half to twenty-five percentile of the reported observations, rather than any concentrations "lower" than those observed.

functions; and 3) how factors such as measurement error or copollutants may potentially obscure an underlying concentration-response relationship substantially different and possibly less linear than the reported apparently linear relationship.

Epidemiological investigations of PM generally have taken several approaches to addressing the shape of the concentration-response relationship. A number of investigators have addressed possible non-linearity in this relationship by the use of categorical variables (CD, p. 12-18). Using categorical variables (e.g., quintiles, quartiles) disaggregates the PM concentration spectrum into discrete ranges, and allows risk estimates to be generated independently for each interval. This may increase the likelihood for detecting those ranges of PM concentrations that may be associated with little risk from those associated with substantially higher risk. However, by partitioning the PM data into smaller groups, this procedure may increase the impact of measurement error and reduce the statistical power of the analyses. (CD, p.12-18). More recent studies (1993-on) have used various nonparametric approaches--locally estimated smoothing, cubic splines, etc.-- applicable in Generalized Additive Models to allow better assessment of nonlinearities in the PM concentration-response relationships, as well as control for confounders such as weather, season, and time trends (CD, p. 12-19). In addition, potential nonlinearity in these nonparametric concentration-response models are often assessed through statistical tests as well.

In the base case risk analyses described in Chapter VI, reported linear concentration-response functions have been applied across the range of reported PM concentrations, when available, with estimated risk never being quantified below estimate of PM background concentrations. However, given the uncertainty concerning PM concentration-response relationships, especially at lower concentrations, alternatives to the base case assumptions are examined through a sensitivity analysis. Of particular interest is the possibility of substantial nonlinearity -- i.e., a less steep or zero slope in PM concentration-response relationships at lower concentrations. To address such possibilities, concentration-response information from key studies can be assessed to determine for which concentrations it may be most reasonable to posit a reduced or zero slope in the concentration-response relationship.

Several approaches to determine possible cutpoint PM concentrations of particular interest for use in modeling alternative concentration-response relationships are discussed below. Staff recognizes that no consensus exists on the best approach to identify, test, or interpret the effect of such cutpoints on concentration-response information. Detailed evaluation of concentration-response relationships is made more difficult by a lack of information on data densities and confidence intervals (CD, 12-310-311). Given these circumstances, alternative approaches are used to generate a range of potential cutpoints, with no attempt to identify the best or most appropriate cutpoint for risk assessment purposes.

The overall approach taken here is to evaluate the extent to which detailed concentration-response information from key studies suggests statistical limitations or nonlinearities in PM concentration-response relationships over the range of PM concentrations observed in the studies. This evaluation focuses on lower concentrations ranges, given that several concerns raised about PM concentration-response relationships center on whether reported linear functions may be disguising flat or essentially flat relationships (i.e., show no increase in risk) in the lower portions of the concentration-response relationship. Three approaches, identified as "lower limit of detection," "minimum mean concentration," and "visual interpretation" are defined below. These approaches have been used to identify reasonable cutpoint concentrations for the concentration-response model sensitivity analysis.

- Lower Limit of Detection: A number of studies present concentration-response information which suggests a generally monotonic increase in response as PM increases (CD, p. 12-23, 12-309). Even if such studies for which the concentration-response information does not suggest a substantially nonlinear relationships across the range of data, the ability to detect any potential effects thresholds or other nonlinearities is limited by the data (CD, p. 12-309-311). For example, plots of RR as a function of the quantile PM concentrations are inherently not able to detect any nonlinearities that may be present within the lowest quantile (CD, p.12-309-310). Thus, for studies that only present concentration-response information in quantile plots and do not show apparent nonlinearities, the maximum concentration (the 20th or 25th percentile value for quintile

and quartile plots, respectively) of the lowest quantile can be considered to be the lower limit of detection of possible nonlinearities.

Reported concentration-response relationships using nonparametric smoothed curves allow a much better assessment of nonlinearities in the concentration-response model (CD p.12-19). Statistical tests can be performed to indicate whether any fluctuations seen in these smoothed curves reflect a substantially nonlinear overall relationship that is statistically discriminable from a linear relationship . Limited numbers of air quality observations can reduce the power of this test, however, and even the visual presentations of smoothed curves are not able to discriminate nonlinearities in regions where there are not enough data points to obtain a stable curve shape (CD, p. 12-310). For studies in which an overall linear relationship cannot be statistically rejected and substantial nonlinearities are not evident, the lower limit for detection of nonlinearity may be considered to be around the 10th percentile. Use of the 10th percentile reflects the greater sensitivity of these smoothing methods compared to quantile analyses to examine whether an observed linear relationship appears to hold toward the lower end of the range of observed concentrations.

- Minimum Mean Concentration: The second approach considered is to use a central tendency concentration as the cutpoint of interest, which is generally available for all studies. The mean (or median) concentration may serve as a reasonable cutpoint of increased PM health risk since at this point there is generally the greatest confidence (i.e., the smallest confidence intervals) in the association and the reported RR estimates. The mean concentration considered by staff as most informative to test implications of potential alternative concentration-response functions is the minimum mean concentration associated with a study or studies reporting statistically significant increases in risk across a number of study locations, provided that the monitoring data is sufficient and representative of the area to which the RR estimate is applied. Alternatively, averages of mean concentrations across a group of locations or studies may be more appropriate if location-specific data are inadequate.

- Visual Interpretation: Concentration-response relationships reported by some studies sometimes visually suggest that nonlinearities may exist within the range of the data, even when PM concentrations are significantly associated with health effects in a linear model. Caution is warranted in any visual interpretation of available PM concentration-response information, given the limited information provided and the amount of measurement error that often is involved (CD, p.12-309-311). Use of quantiles can exacerbate this problem as it might increase the likelihood of identifying an apparent nonlinearity in the effect estimate entirely due to increased uncertainty in each quantiles' smaller sample size.

In conjunction with the use of these methods to identify cutpoints for estimating adjusted concentration-response functions, consideration is given to adjustments to the slope of the reported concentration-response relationship. If an underlying nonlinearity is present, the reported slope of a linear concentration-response relationship would change both below the cutpoint concentration (where the reported slope would be too high) and above the cutpoint concentration (where the reported slope would be too low). Adjustments to the slopes of such segments in concentration-response relationships used in this sensitivity analysis are described in the technical support documents (Abt Associates, 1996a,b).

B. Concentration Cutpoints from Key Studies

The three methods described above were applied where appropriate to the studies used in the risk assessment (Table VI-2 in section VI.B of this Staff Paper), including both PM_{10} and $PM_{2.5}$ studies where applicable, for mortality, hospital admissions, and respiratory symptoms effects. As outlined below, judgments are necessary to apply such methods, and staff recognizes that other judgments could reasonably be made. However, staff believes that the approach taken here is reasonable and results in selected cutpoints that are useful for the purpose of defining sensitivity analyses that help to address uncertainties in the quantitative assessment of risks based on the available epidemiological evidence. Following the identification of a number of potential cutpoints from these alternative approaches, summarized in Tables E-1 and E-3, the last section condenses this information into a few selected cutpoints, for use in the sensitivity analyses presented in section VI.C of this Staff Paper.

1. Concentration-Response Relationships Associated with Short-Term PM Exposures

The potential concentration cutpoints identified in the following discussion of short-term exposure studies are summarized in Table E-1 for both PM_{10} and $PM_{2.5}$ studies.

a. PM_{10} Mortality Studies

The five studies, conducted in ten locations, included in Table IV-2 which reported PM_{10} mortality relationships were examined.

Lower Limit of Detection: This method was applied to the two studies (Birmingham, Schwartz 1993a; Utah Valley, Pope et al., 1992 and Pope and Kalkstein, 1995) which reported concentration-response relationships between mortality and PM_{10} concentrations. Although some nonlinearity may be evident in the nonparametric smoothed curve reported by Schwartz (1993a; 1994g) in the central portion of the range, from approximately 40 - 60 $\mu g/m^3$ (Fig E-1), these are concentrations at which mortality risk is elevated (Samet et al., 1995). Tests failed to indicate the overall PM-mortality relationship could be statistically discriminated from a possible linear relationship (p value of 0.7 for rejecting linearity). The 10th percentile concentration in Birmingham was reported to be 21 $\mu g/m^3$ (Schwartz, 1993a). The nonparametric smoothed curve reported in Pope and Kalkstein's (1995) reanalysis of Utah Valley mortality (Fig. E-2) was also reported as not significantly different from linear ($p>0.5$). In this study, the 10th percentile concentration was not directly reported but is likely to be approximately 20 $\mu g/m^3$, the approximate midpoint of the lowest quintile reported for Utah Valley by Samet et al. (1995). These concentrations are consistent with the lower limit of detection for nonlinearities of 20 $\mu g/m^3$ PM_{10} identified in the CD discussion of PM mortality exposure-response functions (CD, 12-310).

Minimum Mean Concentration: The lowest mean PM_{10} concentration reported in these mortality studies was 30 $\mu g/m^3$, from Schwartz et al. (1996a). This combined mean, averaged across the cities in the study, rather than the lowest mean concentration from any one city in this study, was judged to be appropriate to use for this purpose, since the single monitors used to characterize air quality for each city were sited in locations that may underestimate the average

concentrations experienced across the cities as a whole. The mean concentrations in the three cities in which statistically significant results were reported ranged from 24 - 32 $\mu g/m^3$.

Visual Interpretation: A quintile analysis of a Utah Valley study provided by Pope et al., (1992) suggests that any increased risk associated with the second quintile may be less than the increases associated with the three higher concentration quintiles (Fig. E-3). Alternatively, Samet et al. (1995), using quintiles in a slightly different approach, reported that mortality appeared to increase in the two highest quintiles only (Table E-2). This information would suggest a possible cutpoint of interest in the range of 37 (midpoint of quintile showing reducing increased risk in Fig. E-3) to 42 $\mu g/m^3$ (maximum concentration of quintile showing no increase in risk in Table E-2). The staff judges that the weight given these observations should take into consideration the more recent Utah Valley results discussed above, given the greater sensitivity of the nonparametric methods that have been subsequently been applied to the Utah Valley data.

Various analyses have been done on data from Philadelphia examining PM-mortality relationships using TSP as the measure of PM. Table E-1 also contains converted PM_{10} "cutpoint equivalents" from the TSP findings of these studies that examined TSP concentration-response relationships when associated copollutants were included in the model. There are substantial uncertainties both in interpreting this TSP data in relation to smaller particle indicators (PM_{10}, $PM_{2.5}$) (CD, p. 243), especially when evaluation between copollutants is attempted, and inherent in converting TSP findings into estimates of $PM_{2.5}$. The method and issues involved in deriving these PM_{10} "cutpoint equivalents" are discussed in Section C.

b. PM_{10} Hospital Admissions Studies

Studies conducted in seven locations included in Table IV-2 reporting respiratory and cause-specific hospital admissions relationships with PM_{10} were examined.

Lower Limit of Detection: Nonparametric smooth curves of the concentration-response relationships between PM_{10} and pneumonia (Fig. E-4) and COPD hospital admissions in the elderly in Birmingham have been reported by Schwartz (1994e). No apparent nonlinearities are observed, and the relationships are not statistically distinguishable from linearity ($p \geq 0.25$). The 10th percentile concentration is approximately 19 $\mu g/m^3$. A quartile plot of an analysis of cardiac

hospital admissions for the elderly in Detroit (Schwartz and Morris, 1996) displays increased risk at and above the second quartile (Fig. E-5), with a 25th percentile concentration of 30 $\mu g/m^3$.

Minimum Mean Concentration: The year-long study with the lowest mean PM_{10} concentration, 36 $\mu g/m^3$, reporting significant associations was the Schwartz (1994f) study of COPD and pneumonia hospital admissions among the elderly in Minneapolis. This compares closely to the mean concentration was reported by Thurston et al. (1994) in their study of summertime hospital admissions in Toronto, with a PM_{10} mean concentration of 33 $\mu g/m^3$ averaged across three summers.

Visual Interpretation: The quartile plot of Schwartz (1994d) for elderly pneumonia hospital admissions in Detroit (Fig. E-6) indicates that pneumonia risk may not increase as sharply for the second quartile of PM concentrations as for subsequent quartiles. The midpoint concentration of this second quartile is 37 $\mu g/m^3$.

c. PM_{10} Respiratory Symptoms Studies

The two studies listed in Table VI-2 reporting PM_{10} associations with respiratory symptoms were examined.

Lower Limit of Detection: The Six City study (Schwartz et al., 1994) provides nonparametric smoothed plots for PM_{10} associations with cough (Fig. E-7) and lower respiratory symptoms (Fig. E-8). Statistical tests of deviations from linearity for these associations are not significant. However, the ability to detect nonlinearities is not likely to extend below the 10th percentile concentration of 13 $\mu g/m^3$ PM_{10}.

Minimum Mean Concentration: The Six City study (Schwartz et al., 1994) reports the lower mean PM_{10} concentration of 30 $\mu g/m^3$.

d. $PM_{2.5}$ Mortality Studies

There is less available information concerning $PM_{2.5}$ concentration-response relationships for mortality in comparison to PM_{10}. However, the Harvard Six Cities study (Schwartz et al., 1996a) reports significant associations between $PM_{2.5}$ and mortality in a combined analysis of six cities, as well as associations in individual cities, that indicate that $PM_{2.5}$ mortality associations were relatively consistent in magnitude and statistically significant for three locations (Boston, St. Louis, and Knoxville) with mean concentrations ranging from approximately 16 to 21 $\mu g/m^3$

$PM_{2.5}$ No concentration-response curves were provided, precluding any visual interpretation of results presented in terms of $PM_{2.5}$.

Lower Limit of Detection: For this Six City study, a potential cutpoint could be chosen at the 25th percentile concentration, 9 $\mu g/m^3$, consistent with similar interpretations of studies reporting results in terms of quartile plots.

Minimum Mean Concentration: The $PM_{2.5}$ mean of the combined results from this Six Cities study is 18 $\mu g/m^3$.

Visual Interpretation: Consistent with the approach used above for PM_{10} mortality and discussed more fully in Section C, Table E-1 also gives potential $PM_{2.5}$ "cutpoint equivalents" based on conversions of recent reanalyses of TSP/copollutant concentration-response relationships.

e. $PM_{2.5}$ Hospital Admissions Studies

Minimum Mean Concentration: The only study to examine respiratory hospital admissions directly in terms of $PM_{2.5}$ (Thurston et al., 1994) reported mean concentrations for three summers ranging from approximately 16 to 22 $\mu g/m^3$, with an overall average of approximately 19 $\mu g/m^3$. This is roughly consistent with the more uncertain estimate obtained from the Burnett et al. (1995) study of sulfates and respiratory and cardiac admissions. The mean sulfate concentration of 4.4 $\mu g/m^3$ in that study roughly corresponds to an estimated $PM_{2.5}$ concentration of 15 $\mu g/m^3$.

Lower Limits of Detection: The only study to which this approach can be applied is the Burnett et al. (1995) sulfate study which reports that the respiratory and cardiac hospital admissions from the third quartile were statistically significantly higher than those from the first two quartiles combined. The maximum concentration associated with the bottom two quartiles was approximately 3.0 $\mu g/m^3$ sulfate, the 50th percentile value for the nine Ontario monitoring sites used in the study. To express this finding in terms of a potentially relevant $PM_{2.5}$ cutpoint of interest, a site-specific conversion between SO4 and $PM_{2.5}$ was made using conversion factors for the three largest cities in the study (Toronto, Ottawa, and Windsor), resulting in a $PM_{2.5}$ concentration of roughly 13 $\mu g/m^3$.

f. $PM_{2.5}$ Respiratory Symptoms Studies

Lower Limit of Detection: The Six City respiratory symptoms study (Schwartz et al., 1994) found significant relationships between $PM_{2.5}$ and cough and lower respiratory symptoms in children, although it did not provide either separate quantile or nonparametric smoothed plots for $PM_{2.5}$. Consistent with the approach taken for $PM_{2.5}$ mortality, a potential cutpoint could be chosen at the 25th percentile concentration of 12 $\mu g/m^3$ for this study.

Minimum Mean Concentration: The $PM_{2.5}$ mean concentration for this study (Schwartz et al., 1994) was 18 $\mu g/m^3$.

2. Concentration-Response Relationships Associated with Long-Term PM Exposures

The potential concentration cutpoints identified in the following discussion of short-term exposure studies are summarized in Table E-3 for both PM_{10} and $PM_{2.5}$ mortality studies.

Lower Limit of Detection: The Dockery et al. (1993) Six City study provides plots of long-term mean fine particle concentrations versus adjusted mortality risk for PM_{10} and $PM_{2.5}$. For PM_{10}, increased risks from particles may extend as low as 24 $\mu g/m^3$, the mean concentration for Watertown, which shows an increase in relative risk compared to Portage (Fig. E-9). For $PM_{2.5}$, increased risks may extend as low as 12.5 $\mu g/m^3$, the mean $PM_{2.5}$ concentration for Topeka, which shows a slight increase in relative risk compared to Portage (Fig. E-10).

Minimum Mean Concentration: The mean PM_{10} concentration for the Six City study (Dockery et al., 1993) as a whole was 30 $\mu g/m^3$. The mean $PM_{2.5}$ concentration for the Six Cities study (Dockery et al., 1993) and the mean of the median $PM_{2.5}$ concentrations for each city in the ACS study (Pope et al., 1995) were both reported as 18 $\mu g/m^3$.

Visual Interpretation: For PM_{10}, a case might be made from visually inspecting the results of the Six City study (Dockery et al., 1993) that risk consistently increases only beginning with St. Louis, with a long-term PM_{10} mean of approximately 32 $\mu g/m^3$. For $PM_{2.5}$, a similar case might be made that risk consistently increase beginning with Watertown, with a long-term $PM_{2.5}$ mean of approximately 15 $\mu g/m^3$. Such comparisons, however, are limited by the small number of cities in the study. The ACS study (Pope et al., 1995) provides concentration-response information for $PM_{2.5}$ which appears to more consistently increase at concentrations above the median $PM_{2.5}$ concentration of approximately 15 $\mu g/m^3$ (Fig E-11).

C. Potential Effects of Copollutants or PM Measurement Error on Concentration- Response Relationships

The approach carried out in the sections above for assessing whether underlying nonlinearities exist in PM concentration-response relationships (e.g., resulting from the presence of biological thresholds) uses existing reported concentration-response relationships. The large majority of these relationships were derived considering ambient PM concentrations alone (e.g., without simultaneous inclusion of copollutants). As discussed in Section V.E., several commentors have raised the issue that if the observed concentration-response relationship reflect PM-health effects relationships in which PM is serving as a proxy for other non-considered factors (e.g., the effects of coassociated pollutants, or of total personal exposure to particles) that may causally give rise to health effects, then analyses of observed concentration-response data that do not fully take into account the potential role of these other factors may fail to reveal a genuine underlying nonlinear relationship between ambient PM and health effects. The failure to consider these factors, if they have a genuine causal role, may potentially serve to "disguise" nonlinear concentration-response relationships, and might result in an apparently linear PM concentration-response relationship in cases in which a genuine nonlinear relationship existed.

The two factors advanced as issues of particular concern to consider in this regard have been the influence of coassociated pollutants (Samet et al, 1995; Samet et al., 1996b; Moolgavkar et al., 1995b; Moolgavkar and Luebeck, 1996; Cifuentes and Lave, 1996; Lipfert and Wyzga, 1995b), and the potential influence of different types of measurement error. Measurement error in this context includes concerns over the potential implications that measurements of ambient PM may not accurately reflect total personal exposures to particles, either exposures to all particles or at a mininum a subset of particles including particles of nonambient origin (e.g., from indoor combustion sources). In both the case of potential effects of copollutants and of measurement error, concerns have been raised that available concentration-response relationships may create erroneous estimates of PM-health effects relationships for risk analyses purposes by failing to consider the possibility that these unacknowledged factors may alter the shape of the estimated PM concentration-response relationship.

1. Potential Effects of Copollutants on Determining Effects Thresholds

Several authors have evaluated concentration-response relationships for particles while simultaneously including other combustion source copollutants as variables in the health effects concentration-response regression. Samet et al. (1995) reanalyzed information from Philadelphia for 1973-1980 simultaneously considering SO_2 in the model. One form of presentation they give to their results leads to the question of whether potential TSP effects thresholds exist when copollutants are considered simultaneously. Figure 11 of their report appears to indicate a linear response between mortality and TSP only for TSP > 100 $\mu g/m^3$ (all ages) or TSP > 60 $\mu g/m^3$ (age 65+) (CD, p. 12-311). However, the CD also acknowledges that other approaches undertaken by Samet et al. (1995), such as nonparametric smoothed surfaces simultaneously displaying TSP and SO_2 relationships (CD, pp. 335-344), differs significantly from the simple threshold model shown in their Figure 11 (CD, p. 12-311).

Cifuentes and Lave (1996) analyzed a later period in Philadelphia simultaneously considering two copollutants in the model, SO_2 and O_3. They presented a number of results from several different approaches investigating potential thresholds. The CD finds that Cifuentes and Lave (1996) provides no precise estimate of a change point in the TSP mortality relationship, with the lower portion of a potential cutpoint relationship not showing significance below 60 $\mu g/m^3$ and showing general significance at 90 $\mu g/m^3$ and above (CD, p. 301; Figure 12-32). The study's authors particularly call out the concentration of 78 $\mu g/m^3$ as a concentration below which "the effects of TSP decreased significantly," a concentration representing roughly the midpoint of the range identified by the CD. Although as pointed out by the CD, the methods applied by Cifuentes and Lave do not necessarily imply a slope of zero below the tested cutpoints (CD, pp. 301-302), this central value of 78 $\mu g/m^3$ TSP will be used to summarize the results of their findings in the cutpoint sensitivity analyses for the risk analysis, which does presume a slope of zero below the cutpoint (Appendix F).

To enable the general findings of Samet et al (1995) and Cifuentes and Lave (1996) to be considered in the risk analysis, conversion of their TSP cutpoint findings to fine particles ($PM_{2.5}$) were carried out. Such an approach involves substantial uncertainties both in determining both an appropriate conversion factor to express TSP results as $PM_{2.5}$ as well as the possibility that

substantially different results may have been obtained in the copollutant models if $PM_{2.5}$ data had been available for inclusion in the model rather than the less robust surrogate measure of TSP, especially when discriminations between the particle measure and an associated copollutant are attempted simultaneously in the health model. As indicated by the CD, there is less basis for assuming that analogous results would be obtained for other PM indices, such as PM_{10} or $PM_{2.5}$ (CD, p. 343).

With these concerns in mind, conversion factors were derived from information in Table 6-13 of the CD to allow rough estimates of the potential impacts of application of cutpoints based on the TSP-copollutant analyses of Samet et al. (1995a) and Cifuentes and Lave (1996) to be considered. The Samet et al. (1995) findings were represented by converting the all mortality and elderly 2-D nonparametric smoothed plot findings (reported in Figure 11 of their report) to $PM_{2.5}$ by using the $PM_{2.5}$/TSP ratio (for TSP > 80 $\mu g/m^3$) of 0.36 for the Inhalable Particle Network (IPN), 1979-1983, which provided a rough central estimate $PM_{2.5}$/TSP ratio of 0.36 (CD, Table 6-13). The Cifuentes and Lave (1996) findings were converted to an estimated $PM_{2.5}$ concentration by using the $PM_{2.5}$/TSP ratio available from a site reported to AIRS, 1987-1990 (CD, Table 6-13). Applying these conversions, the Samet et al. (1995) findings could be interpreted as suggesting potential cutpoints in the range of 22 - 36 $\mu g/m^3$ for elderly and all age mortality, respectively, and the Cifuentes and Lave (1996) findings could be interpreted as suggesting the potential for a cutpoint of roughly 29 $\mu g/m^3$ for all age mortality.

Comparable conversions based on Table 6-13 also can be done for PM_{10} , although some additional concern exists for deriving a PM_{10} /TSP conversion factor for Samet et al. (1995) in that the IPN dataset that overlapped the period of study provided information only in terms of PM_{15}. Use of a single monitor operating two years after the study (1982-1983), which was not used in determining the $PM_{2.5}$ conversion factor for Samet et al. (1995) presented previously because the earlier, more extensive network was available, would provide a PM_{10} /TSP conversion factor of approximately 0.57. Use of this factor and a PM_{10} /TSP conversion factor of 0.53 for the AIRS 1987-1991 site provides possible PM_{10} cutpoint concentrations of approximately 34 - 57 $\mu g/m^3$ for the Samet et al. (1995) findings and approximately 43 $\mu g/m^3$ for the Cifuentes and Lave (1996) findings.

For the purposes of sensitivity analyses for the risk analyses, the various cutpoints findings from Samet et al. (1995) and Lave and Cifuentes were represented with a cutpoint of 30 $\mu g/m^3$ $PM_{2.5}$. Given the following considerations: (1) that the Lave and Cifuentes, Samet et al. (1995) findings for the elderly, and the central tendency of the findings for the elderly and all mortality for the two studies combined suggest PM_{10} cutpoints at or below the range of 40 - 45 $\mu g/m^3$, (2) the increased uncertainty in estimating PM_{10} cutpoint equivalents for the Samet et al. (1995) study, and (3) the emphasis of the alternative standards portion of the risk analysis on $PM_{2.5}$, it was judged that there was not a sufficient need to add a separate PM_{10} cutpoint to the sensitivity analyses above 40 $\mu g/m^3$, a concentration that also summarizes the upper end of the analyses of reported concentration-response relationships in Table E-1 (see Summary Section D).

2. Potential Effects of Measurement Error on Determining Effects Thresholds

Another issue to consider in estimating PM concentration-response relationships is the potential effects of measurement error. As discussed in Chapter V, the term measurement error in the broadest sense refers to errors or mis-estimation of several forms that can arise from the use of outdoor monitors to indicate exposure. Measurement error includes both errors resulting from errors in the direct measurement of ambient concentrations, and inaccuracies in the ability of central measurements to proxy for individual exposures, either to ambient pollutant concentrations or potentially the more broad array of particulate pollution from both indoor or outdoor sources to which an individual is personally exposed.

The potential of ambient exposure measurement error (i.e., either error in the direct measurement of ambient concentrations or in the ability of a central monitor to proxy for an individual's exposure to ambient pollutants) to give rise to an apparent more linear-seeming relationship that can disguise an underlying nonlinear relationship has been discussed to some extent in the air pollution and statistics literature (e.g.,Yoshimura, 1990). However, some evidence exists suggesting that the extent of such error may not serve to have large practical significance for current ambient particle concentration-response relationships. As discussed in Section V.E., Schwartz et al. (1996a) reported that statistical relationships between ambient $PM_{2.5}$ concentrations and mortality were observed even when the analysis was restricted to

only days with $PM_{2.5}$ concentrations of 25 μg/m^3 or below. A number of other studies (Pope, 1991; Schwartz et al.,1993a; Schwartz, 1994d; Schwartz, 1994e; Schwartz, 1994f) have excluded higher PM concentrations (e.g., PM_{10} concentrations above 150 μg/m^3). The similar or slightly larger relative risks observed in these studies when days with high concentrations are excluded from the analysis suggests that it is unlikely that measurement error is serving to disguise a nonlinear relationship that extends far into the range of observed concentrations. These studies also suggest that any "personal exposure measurement error" (errors in the ability of a central monitor to proxy for an individual's total exposure to indoor and outdoor particles, or some relevant subset of total exposure such as, exposures to all outdoor and indoor combustion sources), if present, may be affecting reported ambient $PM_{2.5}$ concentration-response relationships to only a limited extent. If ambient particle exposures are associated with mortality risk at 25 μg/m^3 $PM_{2.5}$ or below, it seems unlikely that a nonlinear concentration-response relationship with little or no risk for ambient particles may be being "disguised" by the unacknowledged role of other particle exposures, since relationships between ambient $PM_{2.5}$ and health effects, in general, would not be expected to be influenced by exposures to nonambient indoor sources, which are largely independent of ambient exposures (CD, p.1-10).

To allow for assessment of the potential effects on the risk analysis if measurement errors were found to be substantially affecting the shape of reported concentration-response relationships, cutpoint concentrations and slope adjustments of the type described in Chapter VI can be used to remodel ambient concentration-relationships to reflect hypothetical measurement error. For this purpose, although they were originally derived using the results from other lines of investigation, the cutpoint levels effects selected in Section D of this Appendix, which provide cutpoints across a substantial portion of the lower range of ambient concentrations, can be used to also model the possibility that measurement errors might be obscuring a nonlinear ambient concentration response function with little or no risk in this lower range of concentrations. For example, the possibility that exposure error might be obscuring ambient concentration-response nonlinearities at cutpoints of 10, 18 and 30 μg/m^3 $PM_{2.5}$ can be examined. Although the very issue raised by concerns about measurement error

is that these reported functions may "disguise" nonlinearity through the operation of errors in measurement of exposure, the results of the analyses in Sections A - C.1 above generated generate a set of potential cutpoints that include substantial PM concentrations, and thus for practical purposes can be used to examine of the potential impacts of substantial measurement error as well.

D. Summary

Staff believes that it is most appropriate to combine the potential concentration cutpoints summarized in Tables E-1 and E-3 into a few cutpoints for the purpose of doing sensitivity analyses. Combining information across studies, effects, and alternative approaches avoids giving undue weight to any particular study or approach. From these efforts, the following specific cutpoints judged of use for illustrating the sensitivity of risk analyses results have been identified:

- Short-term PM_{10} studies: 20, 30, 40 $\mu g/m^3$
- Short-term $PM_{2.5}$ studies: 10, 18, 30 $\mu g/m^3$
- Long-term PM_{10} studies: 24, 30, 32 $\mu g/m^3$
- Long-term $PM_{2.5}$ studies: 12.5, 15, 18 $\mu g/m^3$

These cutpoints were derived for the purposes of obtaining a reasonable range of possible cutpoints for the purposes of investigating the potential sensitivity of the risk analyses results to alternative concentration-response relationships reflecting alternative interpretations of reported relationships, potential changes in the concentration-response relationships from the consideration of copollutants, and/or potential effects of different types of measurement error. The material in Appendix E is not intended to be a critical or rigorous assessment of relative weight of evidence for any particular cutpoints from the available literature.

Appendix F

SENSITIVITY ANALYSES OF KEY UNCERTAINTIES IN THE RISK ASSESSMENT

As indicated in Chapter VI, a number of assumptions are involved in conducting a quantitative risk analysis of the effects of ambient PM, and any such effort involves a number of significant uncertainties. Sensitivity analyses are one approach that can provide insight into the potential effects of uncertainties and selection of alternative input assumptions on the risk analyses results. The results of a number of sensitivity analyses for the risk analyses are presented below. A more detailed discussion of the sensitivity analyses conducted for the PM health risk assessment can be found in the technical support document (Abt Associates, 1996b).

A. Sensitivity Analyses of Key Air Quality Uncertainties

1. Sensitivity Analysis of Alternative Background Concentrations

An important uncertainty concerning the air quality information used in the risk analysis involves estimates of background concentrations (see Table IV-3 for range of estimated background PM_{10} and $PM_{2.5}$ concentrations based on Chapter 4 of the CD). For the base case PM risk estimates, effects were quantified across the range of observations in the original study or to background concentrations, whichever was higher. For the base case risk analysis results reported in Chapter VI, the midpoint of the range of estimated annual background concentrations has been used. Tables F-1A and F-1B show the sensitivity of the risk estimates to using either the low end of the annual background concentration range identified in the CD (5 $\mu g/m^3$ PM_{10} and 2 $\mu g/m^3$ $PM_{2.5}$ in the eastern U.S.) or the high end of the annual background concentration range identified in the CD (11 $\mu g/m^3$ PM_{10} and 5 $\mu g/m^3$ $PM_{2.5}$ in the eastern U.S.) as the estimate for background concentrations rather than the midpoint of the range.

One important point from Table F-1A and F-1B is that the estimates of mortality and bronchitis risks associated with long-term exposure to PM do not change as a result of alternative background concentrations. Because these long-term studies relate health effects to annual mean concentrations, and the lowest observed annual mean concentration (the limit used for quantification of risk) is well in excess of current estimates of background (e.g., the range of concentrations observed for the cities in the ACS study (Pope et al., 1995) was 9.0 - 33.4 $\mu g/m^3$

$PM_{2.5}$), the estimates of health risks associated with these endpoints do not change in relation to estimates of background concentrations in the ranges used here (e.g., 2 -5 $\mu g/m^3$ $PM_{2.5}$).

2. Sensitivity of Health Risks Estimates to Alternative Rollback Methods for Simulating Attainment of Alternative Standards

In addition to uncertainties concerning "as is" air quality, there is inherent uncertainty concerning any effort to estimate air quality distributions that would occur upon attaining standards at some future date. In the risk analysis, such uncertainties are introduced both in efforts to model health risks upon attainment of the current standard (Chapter VI, Table VI-8) and upon attainment of alternative $PM_{2.5}$ standards (Chapter VI, Tables VI-12a -13b). The base case analysis assumes that proportional reductions would be observed in air quality concentrations as an area attained either a controlling annual mean or 24-hr standard. A sensitivity analysis was conducted to examine the sensitivity of risk reduction estimates associated with alternative $PM_{2.5}$ standards to an alternative assumption concerning the pattern of air quality rollbacks and the resulting air quality distribution that might be observed in reaching attainment of $PM_{2.5}$ standards (Table F-2). Because $PM_{2.5}$ standards do not currently exist, information on past air quality rollbacks in response to $PM_{2.5}$ standards is not available. However, monitoring information for $PM_{2.5}$ can be examined, although it is uncertain how much of the variation observed between years in the air quality distribution at a location reflects actual control strategies versus more general year-to-year variability. In a preliminary examination of changes in the distribution of $PM_{2.5}$ concentrations from sites with multiple years of data (from AIRS and CARB data sets), Abt Associates found that proportional rollback reasonably approximated the central tendency of variations in $PM_{2.5}$ air quality distributions, however, considerable variation could be observed in this relationship across time and location (see Abt Associates, 1996b for more information).

An attempt to bound the potential effects of alternative PM air quality reduction patterns has been examined in a sensitivity analysis of PM-associated risks by choosing alternative assumptions for modeling $PM_{2.5}$ rollbacks. Table F-2 shows the sensitivity of risks reduction estimates associated with alternative $PM_{2.5}$ standards to the rollback assumption in which the upper 10% of the $PM_{2.5}$ 24-hr air quality concentrations are reduced by a larger amount (a ratio of 1.6) than in the remaining 90% of the distribution of PM air quality concentrations. This

alternative rollback case is intended to model a control strategy that preferentially targets peak $PM_{2.5}$ levels. The proportion of preferential reduction in peak concentrations (a 1.6 ratio in reduction for the upper 10% of concentrations) is based on empirical observation of the 99th percentile of observed year-to-year variation in $PM_{2.5}$ air quality among site-years for all available $PM_{2.5}$ monitoring sites with multiyear data from the AIRS or CARB $PM_{2.5}$ datasets.

Table F-2 shows for both a proportional rollback and the preferential peak reduction rollback the amount of reduction in $PM_{2.5}$ concentrations necessary to reach alternative standards (for simplicity, the annual and daily standards are considered alone) and the air quality distribution (summarized as the annual mean and 2nd daily max concentration) that is projected to occur upon attainment. In this example, the annual standard provides less of a change in total incidence of health effects, but this is simply a consequence of the annual standard chosen (15 $\mu g/m^3$) being less controlling than the daily standard chosen (50 $\mu g/m^3$) for Philadelphia County (Chapter VI, Table 11b).

More important to consider are the PM-associated risk reductions and resulting air quality observed when the operation of the same standard (annual or daily) is modeled under the two rollback cases rather than any comparison of total incidence reduction between the two standards. The important observation is that estimated changes in incidence of health effects provided by attainment of annual standards are less sensitive to deviation from the base case assumption on rollback than estimated reductions in health effects incidence risk resulting from attainment of a daily standard. For instance, the results in Table F-2 indicate that for a controlling annual standard, past patterns of air quality change would suggest the reduction in health effects from short-term exposures, as represented by mortality from short-term exposures, could potentially vary more than 35% with a controlling 24-hr standard (mean change in total incidence of 70 versus 110), compared to approximately 25% with a controlling annual standard. For mortality from long-term exposures, this contrast is greater. For example, under a controlling short-term standard estimated risk reduction could potentially vary 30%, while under an annual standard there would be no change in estimated risk reduction. This is a result of the fact that mortality from long-term exposures are related to central estimate air quality measures such as annual mean concentration in the reported concentration-response relationships, thus the distribution of 24-hr

concentrations associated with this annual mean concentration does not influence the estimated health risk reduction as long as the same annual mean (in this case, 15 $\mu g/m^3$) is achieved under both rollback conditions.

Figure F-1 illustrates some of the characteristics of the integration of current air quality distributions and reported concentration-response relationships as used to predict the total risk from ambient particle exposures across a year. Figure F-1 shows the relative contribution of different portions of the ambient $PM_{2.5}$ concentration distribution for Philadelphia County to the "as is" mortality health risk from short-term exposures. The Figure shows in bar graph form the proportion of total observed PM-2.5 concentrations across the year (in groups of 4 $\mu g/m^3$ per bar), with the number of days out of the whole year (361 observations) that concentrations fell within each concentration range shown on the left-hand Y axis. On top of this frequency distribution has been overlaid the proportion of "as is" mortality risk under base case assumptions associated with each 4 $\mu g/m^3$ concentration range (Since "as is" mortality risk from short-term exposures was calculated using a two-day mean averaging time, the averaging time used at the largest number of mortality study locations, the proportion of "as is" mortality risk is calculated for each two-day mean interval of 4 $\mu g/m^3$). This Figure shows that for base case assumptions, concentrations in the range of 16-20 $\mu g/m^3$ contribute the largest amount to the estimated mortality risk on an annualized basis for Philadelphia County. Even though concentrations in the range of 44 $\mu g/m^3$ $PM_{2.5}$ and above clearly contribute more mortality per day for these concentrations, the much larger number of days within the 16-20 $\mu g/m^3$ range results in this interval being associated with the largest total risk. Standards with

Figure F-1. Distribution of $PM_{2.5}$ Concentrations and of Estimated Mortality Risks from Short-Term Exposures in Philadelphia County

a 24-hr averaging time are traditionally based on peak air quality statistics, concentrations for which the risk on an individual day is highest, but, as a result of the ambient air quality distribution and the $PM_{2.5}$ concentration-response functions that have been observed, appear to contribute a relatively small amount of the total health risk compared to the distribution as a whole. The annual mean statistic contains information about the aggregate total of all the air quality concentrations, a quantity similar to the quantity of all air quality concentrations minus estimated background that contributes to estimates of annualized mortality risk in the base case risk analysis.

The difference between the air quality distribution as a whole and that estimated to contribute to aggregate annualized health risk will be more pronounced if assumptions about a substantial cutpoint concentration are made. However, even in these cases, the aggregate annualized risk will be a function of the concentrations across a wide portion of the upper end of the $PM_{2.5}$ air quality distribution. Since reducing high concentration days can provide a greater microgram reduction in $PM_{2.5}$ annual average mass for a lesser percentage reduction in air quality, an annual standard will still favor reducing high concentration values. In contrast to the 24-hr standard, however, an annual standard is less likely to allow areas whose air quality concentrations are substantially above those necessary for attainment to reduce concentrations in a fashion that might not result in meaningful risk reduction (e.g., by reducing just a few high peak values). In so doing, an annual controlling standard might be expected to lead to less variation in the risk reduced in different geographic areas having similar initial air quality that reduce PM concentrations to attain a set of $PM_{2.5}$ alternative standards.

Table F-2 conveys this point in a related fashion. Table F-2 shows that under the preferential peak reduction rollback considered, the lower 90% of air quality concentrations are reduced only 18% versus the 30% reduction observed if the entire distribution is reduced evenly. Because the lower 90 percent of the air quality values contribute so substantially to the aggregate annualized risk (Figure F-1), a lesser reduction across this wide range of concentration values leads to less total $PM_{2.5}$ reduction [as reflected by the higher annual mean upon attainment of a daily standard of 50 $\mu g/m^3$ in which lower concentrations have been less substantially reduced

(13.6 $\mu g/m^3$) than when concentrations have been reduced evenly (12.6 $\mu g/m^3$)], and thus less total annual health risk being reduced.

Absent information that allows the possibility to be excluded that PM concentrations through a wide portion of the air quality distribution may contribute to risk, an annual controlling standard is likely to be less sensitive to alternative rollback assumptions. This is in large part because the standard employs an air quality measure (the annual mean) that inherently captures more information reflective of the concentrations across the bulk of the air quality distribution. In general, annual standards would be expected to decrease uncertainty in risk reductions observed for areas that might undergo different air quality rollbacks to reach attainment of $PM_{2.5}$ alternative standards relative to comparably stringent controlling 24-hr standards.

For the special case of modeling the "attainment of current PM_{10} standards" case for Los Angeles County, since the current daily PM_{10} standard is controlling in Los Angeles, it is relevant to consider the potential effects of variations from a proportional rollback for PM_{10} on the risk estimates for alternative $PM_{2.5}$ standards. Variations in the PM_{10} rollback that would result in attainment of the current standards from the proportional rollback assumed could either increase or decrease the amount of risk associated with PM remaining to be affected by alternative $PM_{2.5}$ standards. In addition, the risk estimate for the "attainment of the current standards" case in Los Angeles has an important additional source of uncertainty relating to patterns of reductions. If control strategies to meet the current PM_{10} standards preferentially reduce the coarse fraction of PM_{10} in relation to the fine fraction of PM_{10}, risks associated with $PM_{2.5}$ as an indicator of PM under the "attain current standards" case could be higher and, thus, proportions of estimated risk reduced under the alternative $PM_{2.5}$ standards also would be greater. Alternatively, if control strategies to meet the current standards preferentially reduce the fine fraction, then risks associated with $PM_{2.5}$ as an indicator of PM would be less under the "attain current standards" and the proportion of estimated risks reduced under the alternative $PM_{2.5}$ standards would be less.

B. Sensitivity Analyses of Key Concentration-Response Uncertainties

The area of the risk analysis with the largest number of uncertainties amenable to sensitivity analyses involves the application of PM concentration-response relationships in the risk analysis. The sensitivity of risk estimates for "as is" air quality in Philadelphia has been analyzed to determine the potential impact of alternative analytic approaches to addressing uncertainty in the concentration-response relationships. The following sensitivity analyses about concentration-response relationships are summarized in this Section:

- The effect of alternative assumptions concerning the shape of the concentration-response relationships, especially concerning the effect of cutpoint concentrations below which variations in PM concentration are not associated with increases in risk, is analyzed. Alternative assumptions about the slope of the concentration-response relationship above any presumed cutpoints also is addressed.

- The effect of pooling studies to combine information from a number of studies to apply to the two risk analysis locations is examined. The sensitivity of short-term mortality risk estimates is analyzed, especially with respect to the effects of combining studies that are heterogenous in averaging time.

- The effect of using coefficients for PM obtained simultaneously with other copollutants in the regression model is addressed.

- The effect of alternative assumptions concerning the potential role of air quality previous to that monitored in studies of the effects on mortality associated with long-term exposure is examined.

All of these sensitivity analyses are conducted using "as-is" air quality in Philadelphia County. Further sensitivity analyses are provided in the technical support document (Abt Associates, 1996b).

1. Sensitivity Analyses of Alternative Cutpoint Concentrations

Tables F-3A-E present the results from sensitivity analyses of different alternative cutpoint concentrations for short-term and long-term exposures to PM. The concentrations chosen as cutpoints for these sensitivity analyses were selected from the analysis of potential cutpoints of interest described in Appendix E and summarized in Chapter VI. For the base case analysis, no cutpoint has been assumed. In the sensitivity analyses, various cutpoint concentrations have been examined, and no health risks associated with PM are estimated for any days whose 24-hr concentrations are below the specified cutpoint concentration. In addition, the slope of the

relationship above the cutpoint has been remodeled using one of two approaches. For both approaches, the relationship is assumed to begin at zero increased risk at the cutpoint concentration, and to extend upward with an increased slope compared to the original reported relationship (see Fig. VI-6). In Approach 1 it is assumed that the new slope would increase to an extent where the increased health risk predicted at the highest concentration is increased proportional to the proportion of the range of original concentrations that fall below the cutpoint. While this adjustment produces a slope resembling those generally posited to result in a model incorporating a cutpoint (e.g., Fig VI-6), there is no clear guidance on how to most appropriately model changes in slope for purposes such as the PM risk analysis (where, for instance, primary datasets are not readily available).

In light of this uncertainty, a second approach, involving a more minimal adjustment to slope (labeled "Approach 2" on Figure VI-6) also has been carried out as a potential lower bound for an adjusted slope. In Approach 2, the concentration-response relationship has been remodeled to begin at zero at the cutpoint and intersect with the same health risk estimated at the highest concentrations observed in the original relationship. As cutpoints are chosen that exclude successively larger number of observations, it is expected that the milder degree of increased slope represented by Approach 2 would be less likely to be observed.

Figure F-2 suggests that relatively mild increases in slope may be observed for some TSP concentration-response relationships compared to a linear model meta analysis from the CD. However, other TSP concentration-response relationships which examined cutpoints well within the range of data observed a pattern of increased slope more like that modelled in Approach 1 (Philadelphia 1983-88, which included SO_2 and O_3 in the analysis, compared with a meta analysis of PM coefficients from models including copollutants).

As might be expected, Tables F-3A - D indicate that the two slope adjustment approaches agree mostly closely at the lowest cutpoint concentration. In addition, these tables suggest that the method of adjusting the slope of the remaining relationship is less important to the estimates of health risk than the choice of cutpoint concentration itself. The higher the cutpoint, the greater the proportion of observations for each city that is associated with no increase in risk. Depending on judgments concerning the weight to be given the estimates at

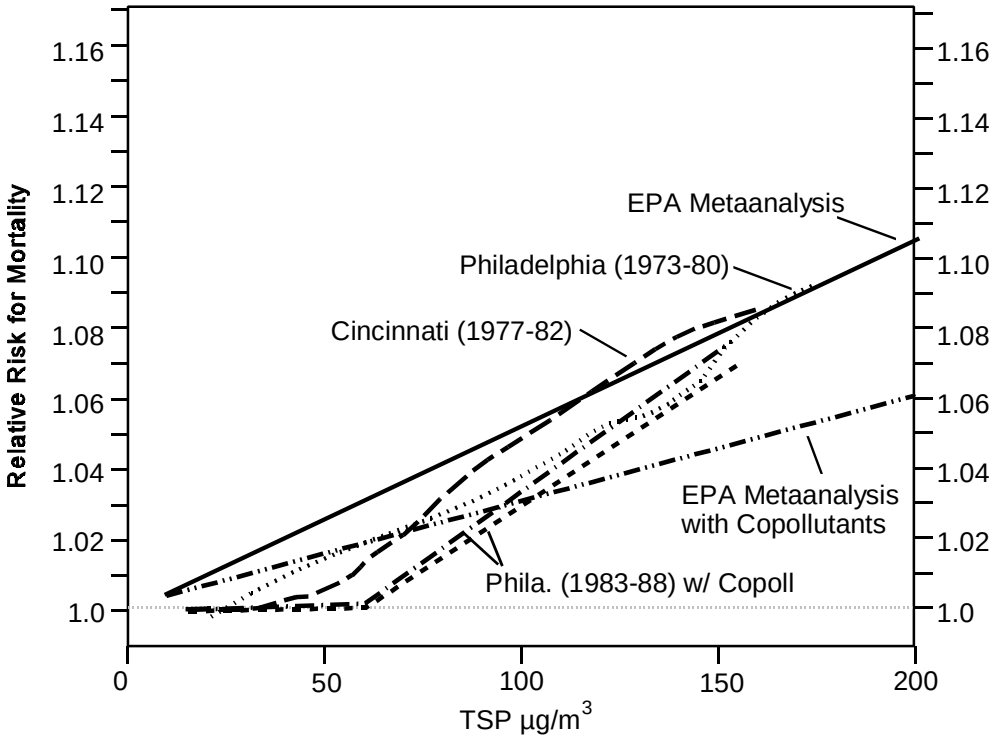

Figure F-2. Comparison of Smoothed Nonlinear and Linear Mathematical Models for Relative Risk of Total Mortality Associated with Short-Term TSP Exposure (CD, Figure 13-6). Curves show smoothed nonparametric models for Philadelphia (based on Schwartz 1994b) and for Cincinnati (based on Schwartz, 1994a), and piecewise linear models for Philadelphia (based on Cifuentes and Lave, 1996). Solid curve shows linear model from EPA metaanalysis using studies with no copollutants, dash-dot curve shows linear model from EPA metaanalysis using studies with SO_2 as a copollutant (described in CD Chapter 12).

higher cutpoint concentrations, assumptions concerning cutpoint concentrations can make a substantial difference in the estimates of risks associated with PM.

For the concentration-response relationship of mortality from long-term exposures (Table F-3E), the upper cutpoint eliminates estimated risk for Philadelphia County because Philadelphia County's annual mean concentrations are below 18 $\mu g/m^3$. For health risks both from short-term and long-term exposures, the sensitivity of estimates of risks would be expected to vary with location, especially for locations with substantially different overall PM air quality (e.g., Los Angeles County).

2. Effect on Pooled Concentration-Response Analyses Using Studies with Different Averaging Times

In their review of the PM mortality literature, the CD pointed out that heterogeneity in averaging time is an important factor to consider in assessing results (CD, p.12-72). In the PM risk analysis estimates from a number of studies have been pooled for several endpoints. For the mortality pooled analysis, studies that used averaging times ranging from 1 to 5 day mean PM concentrations have been included. Table F-4 disaggregates the pooled analysis to examine the effect of restricting the estimates of mortality risk to those studies using only the same averaging time (with the exception of the three-day and five-day mean studies, which were combined). Results vary considerably over averaging times. In the base case analysis, two-day mean air quality concentrations were used to estimate mortality, since the largest number of functions used that averaging time. Table F-4 indicates that using two-day mean concentrations to represent Philadelphia County PM_{10} concentrations results in an increase in the risk estimates predicted by the single study that reported results related to a one-day mean concentration (Kinney et al., 1995), and a slight increase in the risk predicted for the set of two studies using three- to five-day mean concentrations (Schwartz, 1993 and Pope et al., 1992). However, the Table also indicates that applying an alternative averaging time, such as one-day or five-day mean concentrations, results in no apparent difference in estimated risk from the base case two-day mean assumption.

3. Effect of Using Concentration-Response Relationships Simultaneously Considering Copollutants

PM is part of a mix of combustion source pollutants originating from a variety of stationary and mobile sources and, thus generally occurs along with other pollutants generated by combustion sources (e.g., sulfur oxides, nitrogen oxides, volatile organic compounds) or produced through the transformation of these pollutants (e.g., O_3). Such copollutants could either serve as potential confounders of the observed PM-health associations or as effect modifiers that influence the magnitude of PM associated effects. The studies used in the risk analysis provide PM coefficients from areas with widely varying levels of copollutants. One approach to controlling for the potential effects of copollutants is to include copollutants simultaneously in the model with PM when estimating the PM coefficient for a health endpoint. However, this method may be limited by collinearity in the pollutants of interest (Samet et al., 1996b). (For a fuller treatment of copollutants, potential confounding, and the significance of observed variations across study locations, see Chapter V and CD, Chapters 12 and 13).

The base case analysis used concentration-response relationships estimated without inclusion of copollutants, and it is not possible to directly estimate the sensitivity of the base case results taking into account the effect of simultaneous inclusion of copollutants, since not all the studies used for the base case examined copollutants in this manner. As an alternative, the sensitivity of individual study estimates in relationship to inclusion of copollutants is examined in Tables F-5A and F-5B. Table F-5A provides a comparison of the coefficients for studies that reported PM coefficients both with and without inclusion of copollutants, and Table F-5B provides the risk estimates obtained from applying those coefficients to Philadelphia County in the risk analysis. The results in these two tables provide a more general sense of how much of an effect inclusion of copollutants typically has on the magnitude of the health risk estimates and, thus, potentially on the base case results. The results for many, but not necessarily all, of the studies are consistent with the assessment in the CD that PM effect sizes and their statistical uncertainty in most studies showed little sensitivity to the adjustment for copollutants (CD, p.13-55).

Two substantial uncertainties remain concerning copollutants and the method of controlling for their effects through simultaneous inclusion in the health risk model. First, to what degree is it possible that the associated copollutant does not have a bona fide independent

effect on mortality separate from PM? If the copollutant does not have an independent effect on mortality, then changes in the PM coefficient resulting from inclusion of the second pollutant may just be the results of collinearity between the pollutants and may not accurately reflect the underlying PM coefficient. Second, if the changes seen with inclusion of copollutants actually do reflect a bona fide improvement in the estimate of the PM effect, then is it possible simultaneous inclusion of additional copollutants would further reduce the coefficient? As pointed out by Samet et al. (1996b) and in Chapter V, examination of effects within a single location may often be limited by collinearity between pollutants and comparison across geographic areas may be required for a fuller assessment of the potential effects of copollutants on reported PM concentration-response relationships.

4. Sensitivity Analysis Concerning Reduction in the Slope of Concentration-Resposer Relationships for Risks from Long-Term Exposures

Two major concerns have been raised concerning whether the slope of the concentration-response relationships from recent studies of mortality from long-term exposures (Dockery et al., 1993, Pope et al., 1995) may be misestimated. One major uncertainty concerning the studies of health risks associated with long-term exposures to PM for adults is the potential relevance of air quality concentrations previous to the period of monitoring in the study. If long-term air quality concentrations previous to the period being monitored: 1) are relevant for a substantial portion of the population for the endpoint being studied, and 2) are substantially different than concentrations monitored during the study, then the actual long-term concentration-response relationship may be substantially different than that observed in the reported study (CD, p.13-34). The second major uncertainty relates to whether inadequate control of potential confounders may substantial alter the reported concentration-response relationships (CD, pp. 12-140-43, 12-165, 12-176-178).

The question of the degree to which previous (from years to decades) air quality exposures might have affected mortality risk is complex.[1] In addition, quantitative information

[1] Judging the extent to which previous air quality may be a significant concern for the estimates of risk from long-term exposures requires consideration of both of past air quality variability *and* of the relevant exposure period that might be expected to affect mortality risk for a substantial portion of the cohort population. The CD notes that a detailed investigation of temporal relationships has not been attempted in the cohort studies, but also notes that if

on the levels of previous air quality concentrations is difficult to ascertain, especially for $PM_{2.5}$. The CD reports that for the monitoring data reported in the Six City mortality study, downward trends in $PM_{2.5}$ mass are evident for four of the six cities (CD, p. 13-14).

Given these uncertainties in developing a quantitative basis for a sensitivity analyses concerning historical air quality, Table F-6 simply shows the potential impact of mortality risk estimates associated with long-term exposures if one assumes that previous air quality concentrations reduce the observed slope of the PM concentration-response relationship by 33% (modeling the case if relevant previous $PM_{2.5}$ concentrations averaged approximately 50% higher than that monitored in the study period) and by 50% (modeling the case if relevant previous $PM_{2.5}$ concentrations were twice as high). As expected, positing that the most important $PM_{2.5}$ concentrations in regards to effects on mortality risk occurred before the study monitoring period leads directly to similarly proportional reductions (approximately 33% and 50%) in the estimates of long-term mortality risk. To the extent that the estimates of mortality risks from long-term exposure reflect the net sum of acute events that take place over that year (which will occur when increases in daily death rates associated with acute events are not subsequently canceled by decreases ("harvesting") (CD p.12-139), this component of mortality risk from long-term exposures risk is not sensitive to assumptions about previous air quality.

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responses reflect primarily the last few years of integrated exposure then the concurrent average monitoring data would be reasonably predictive (CD, p. 12-171, 12-181). Some findings from air pollution epidemiology suggest recent exposures may be of primary importance. The reduction in mortality incidence observed with a reduction in PM concentrations for 14 months in Utah Valley suggests that a significant amount of the mortality of substantial prematurity associated with particles in that location did not appear dependent on exposures over the span of years, since changes in mortality rates could be observed with a relatively brief temporal change (a 14 month period of reduced concentrations) in long-term average PM pollution.

Observations of the temporal relationship of exposure to mortality risk for a large portion of cardiovascular mortality (deaths from myocardial infarction) and for lung cancer from cohort studies on active cigarette smoke exposure suggest that elevated risks for myocardial infarction generally return to close to baseline nonsmoking relative risks within three to ten years (Rosenberg et al., 1985; 1990) and that much of the lung cancer risk is reduced close to the risk for never smokers (compared to the marked elevation in relative risk for lung cancer among current smokers) within 10-15 years after cessation of smoking (USEPA, 1992, Table 4-6 and 4-7). The significance of these findings to air pollution effects cannot be assumed, since quite distinct mechanisms for cigarette smoking and particular matter exposure and mortality from cardiovascular and lung cancer causes may be likely. However, the smoking cohort studies show that in one area in which the temporal relationship of exposure to mortality risk from cardiovascular and lung cancer causes has been examined, evidence suggests recent exposures may be substantially more important than less recent exposures.

Similar slope reductions can also serve to model concerns about uncontrolled confounding. The CD provides as an example how inclusion of additional ecological variables can attentuate the PM2.5-mortality relationship observed in a initially simply age- and race-adjusted dataset. The direction and extent of change in slope that might be observed by control of such confounders in a prospective cohort design, which features individual data for some risk factors is not certain (CD, pp. 12-176-77), however for the purposes of sensitivity analyses reductions in slope of 33-50% for the long-term studies will be assumed appropriate appropriate to reflect the viewpoint that exhibits substantial concerns about residual uncontrolled confounding in these studies. These would result in the same proportional reductions of approximately 33-50% in the estimates of long-term mortality risk (relative to base case assumptions) as when this slope reduction was considered as a sensitivity analysis for the potential effects of previous air quality.

Appendix G

MEASURES OF VISIBILITY IMPAIRMENT AND LIGHT EXTINCTION

Several atmospheric optical indices and approaches can be used for characterizing visibility impairment and light extinction. The CD discusses several indicators that could be used in regulating air quality for visibility protection, including: 1) light extinction (and related parameters of visual range and deciview) calculated from measurements of fine particle constituents and their associated scattering and absorption; 2) light extinction measured directly by transmissometer; 3) light scattering by particles, measured by nephelometer; 4) fine particle mass concentration; 5) contrast transmittance (CD, 8-125).

In conjunction with the National Park Service, other Federal land managers, and State organizations, EPA has supported since 1986 a monitoring protocol utilizing a combination of the first four measurements. This long-term visibility monitoring network is known as IMPROVE (Interagency Monitoring of PROtected Visual Environments. The following discussion briefly describes the IMPROVE protocol and provides rationale supporting use of the light extinction coefficient, derived from both direct optical measurements and measurements of aerosol constituents, for purposes of implementing air quality management programs to improve visibility.

IMPROVE provides direct measurement of fine particles and precursors that contribute to visibility impairment at more than 40 mandatory Federal Class I areas across the country. The IMPROVE network employs aerosol, optical, and scene measurements. Aerosol measurements are taken for PM_{10} and $PM_{2.5}$ mass, and for key constituents of $PM_{2.5}$, such as sulfate, nitrate, organic and elemental carbon, soil dust, and several other elements. Measurements for specific aerosol constituents are used to calculate "reconstructed" aerosol light extinction by multiplying the mass for each constituent by its empirically-derived scattering and/or absorption efficiency. Knowledge of the main constituents of a site's light extinction "budget" is critical for source apportionment and control strategy development. Optical measurements are used to directly measure light extinction or its components. Such measurements are taken principally with either a transmissometer, which measures total light extinction, or a nephelometer, which measures particle scattering (the largest human-caused component of total extinction). Scene characteristics are recorded 3 times daily with 35 millimeter photography and are used to

determine the quality of visibility conditions (such as effects on color and contrast) associated with specific levels of light extinction as measured under both direct and aerosol-related methods. Because light extinction levels are derived in two ways under the IMPROVE protocol, this overall approach provides a cross-check in establishing current visibility conditions and trends and in determining how proposed changes in atmospheric constituents would affect future visibility conditions.

The light extinction coefficient has been widely used in the U.S. for many years to describe visibility conditions and the change in visibility experienced due to changes in concentrations of air pollutants. As noted earlier, the extinction coefficient can be defined as the fraction of light lost or redirected per unit distance through interactions with gases and suspended particles in the atmosphere. Direct relationships exist between measured ambient pollutant concentrations and their contributions to the extinction coefficient. The contribution of each aerosol constituent to total light extinction is derived by multiplying the aerosol concentration by the extinction efficiency for that aerosol constituent. Extinction efficiencies vary by type of aerosol constituent and have been obtained through empirical studies. For certain aerosol constituents, extinction efficiencies increase significantly with increases in relative humidity.

In addition to the optical effects of atmospheric constituents as characterized by the extinction coefficient, lighting conditions and scene characteristics play an important role in determining how well we see objects at a distance. Some of the conditions that influence visibility include whether a scene is viewed towards the sun or away from it, whether the scene is shaded or not, and the color and reflectance of the scene (NAPAP, 1991). For example, a mountain peak in bright sun can be seen from a much greater distance when covered with snow than when it is not.

One's ability to see an object is degraded both by the reduction of image forming light from the object caused by scattering and absorption, and by the addition of non-image forming light that is scattered into the viewer's sight path. This non-image forming light is called path radiance (CD, 8-23). A common example of this effect is our inability to see stars in the daytime due to the brightness of the sky caused by Rayleigh scattering. At night, when the sunlight is not being scattered, the stars are readily seen. This same effect causes a haze to appear bright when looking at scenes that are generally towards the direction of the sun and dark when looking away

from the sun.

Though these non-air quality related influences on visibility can sometimes be significant, they cannot be accounted for in any practical sense in formulation of national or regional measures to minimize haze. Lighting conditions change continuously as the sun moves across the sky and as cloud conditions vary. Non-air quality influences on visibility also change when a viewer of a scene simply turns his head. Regardless of the lighting and scene conditions, however, sufficient changes in ambient concentrations of PM will lead to changes in visibility (and the extinction coefficient). The extinction coefficient integrates the effects of aerosols on visibility, yet is not dependent on scene-specific characteristics. It measures the changes in visibility linked to emissions of gases and particles that are subject to some form of human control and potential regulation, and therefore can be useful in comparing visibility impact potential of various air quality management strategies over time and space (NAPAP, 1991).

By apportioning the extinction coefficient to different aerosol constituents, one can estimate changes in visibility due to changes in constituent concentrations (Pitchford and Malm, 1994). The National Research Council's 1993 report *Protecting Visibility in National Parks and Wilderness Areas* states that "[P]rogress toward the visibility goal should be measured in terms of the extinction coefficient, and extinction measurements should be routine and systematic." Thus, it is reasonable to use the change in the light extinction coefficient, determined in multiple ways, as the primary indicator of changes in visibility for regulatory purposes.

Visual range is a measure of visibility that is inversely related to the extinction coefficient. Visual range can be defined as the maximum distance at which one can identify a black object against the horizon sky. The colors and fine detail of many objects will be lost at a distance much less than the visual range, however. Visual range has been widely used in air transportation and military operations in addition to its use in characterizing air quality. Because it is expressed in familiar units and has a straightforward definition, visual range is likely to continue as a popular measure of atmospheric visibility (Pitchford and Malm, 1994). Conversion from the extinction coefficient to visual range can be made with the following equation (NAPAP, 1991):

$$\text{Visual Range} = 3.91/b_{ext}$$

Another important visibility metric is the deciview, which describes changes in uniform atmospheric extinction that can be perceived by a human observer. It is designed to be linear with respect to perceived visual changes over its entire range in a way that is analogous to the decibel scale for sound (Pitchford and Malm, 1994). Neither visual range nor the extinction coefficient has this property. For example, a 5 km change in visual range or 0.01 km^{-1} change in extinction coefficient can result in a change that is either imperceptible or very apparent depending on baseline visibility conditions. Deciview allows one to more effectively express perceptible changes in visibility, regardless of baseline conditions. A one deciview change is a small but perceptible scenic change under many conditions, approximately equal to a 10% change in the extinction coefficient. The deciview metric also may be useful in defining goals for perceptible changes in visibility conditions under future regulatory programs. Deciview can be calculated from the light extinction coefficient by the equation:

$$dv = 10\log_{10}(b_{ext}/10\ Mm^{-1})$$

Figure G-1 graphically illustrates the relationships among light extinction, visual range, and deciview.