

APPENDIX D**I. HYPOTHETICAL MECHANISMS OF ACTION FOR PM**1. Dosimetric Considerations

Dosimetric considerations formed the principle basis of the approach used for selecting PM₁₀ 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 ($< 0.02 \mu\text{m}$ 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 interleukin - 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 $75 \mu\text{g}/\text{m}^3$ 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 $0.2 \mu\text{m}$ diameter SO_4^{2-} is greater than $0.6 \mu\text{m}$ diameter NO_3^- , which in turn is greater than $4 \mu\text{m}$ 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 arrhythmia, 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 ($0.2\mu\text{m}$ 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 heterogeneous 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 homogeneous 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 homogeneous, 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.