

than occurring in the general population.<sup>53</sup> Consequently, the severity of health effects observed in controlled human exposure studies evaluating the effects of PM should be expected to be less than observed in epidemiologic studies. Nonetheless, that effects are observed in relatively healthy individuals participating in controlled exposure studies serves as an indicator that PM is initiating health responses and that more severe responses may reasonably be expected in a more diverse population.

It should also be noted that there is a small body of toxicological evidence demonstrating mortality in rodents exposed to PM (e.g., Killingsworth et al. 1997). Overall it is not surprising that lethality is not induced in more toxicological research, as these types of studies do not readily lend themselves to this endpoint. Epidemiological studies have observed associations between PM and mortality in communities with populations in the range of many thousands to millions of people. Clearly, it is not feasible to expose hundreds (if not thousands) of animals to ambient PM (potentially over many years) in a laboratory setting to induce enough lethalties to distinguish between

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<sup>53</sup> For example, the EPA excludes from its controlled human exposure studies involving exposure to PM<sub>2.5</sub> any individual with a significant risk factor for experiencing adverse effects from such exposure. Thus, the EPA excludes *a priori* the following categories of persons: those with a history of angina, cardiac arrhythmias, and ischemic myocardial infarction or coronary bypass surgery; those with a cardiac pacemaker; those with uncontrolled hypertension (greater than 150 systolic and 90 diastolic); those with neurogenetic diseases; those with a history of bleeding diathesis; those taking beta-blockers; those using oral anticoagulants; those who are pregnant, attempting to become pregnant, or breastfeeding; those who have experienced a respiratory infection within four weeks of exposure; those experiencing eye or abdominal surgery within six weeks of exposure; those with active allergies; those with a history of chronic illnesses such as diabetes, cancer, rheumatologic diseases, immunodeficiency state, known cardiovascular disease, or chronic respiratory diseases; smokers. The EPA “Application for Independent Review Board Approval of Human Subjects Research: Cardiopulmonary Effects of healthy Older GSTM1 Null and Sufficient individuals to Concentrated Ambient Air Particles (CAPTAIN)”, Nov. 9, 2011, p. 9.