

# Toxicology of Fine Particulate Matter (PM<sub>2.5</sub>)

## Issue Brief



### Background

Several approaches can be used to investigate the health effects of fine particulate matter (PM<sub>2.5</sub>). Air pollution epidemiology studies typically compare health events in population(s) (e.g., hospital admissions or deaths) over time or over geographic areas, and relate the patterns in health events to measures of air pollution. If a statistically significant positive association is observed, this is taken as indicative—though not causative—of a potential PM effect. Toxicology, or controlled exposures in the laboratory, is another approach for investigating air pollution and health effects.

Numerous epidemiological studies have indicated that exposure to PM<sub>2.5</sub> is associated with a wide range of adverse health effects, including mortality, increased numbers of emergency room or physician visits for

asthma or respiratory infections, cardiovascular problems such as myocardial infarctions (heart attacks) and alterations of heart rhythm, and decreases in lung function. However, while epidemiology studies are extremely valuable in generating hypotheses and developing associations, toxicology plays a critical role in testing these hypotheses and establishing biological plausibility.

### What is Toxicology?

Toxicological studies are generally conducted in the laboratory and allow a high level of control of exposure conditions to better determine cause and effect. Typically, animals or cell cultures are exposed to certain pollutants or mixtures of pollutants in a highly controlled setting, with a corresponding control group of animals that is exposed only to filtered air but is otherwise treated identically. Because the animals used, generally mice or rats, are inbred strains, the inter-individual differences are much smaller than in a human population. Also, there are no issues of confounding, since all animals have had the same treatment from birth. Toxicology is very helpful in answering questions such as:

- Which component(s) of PM cause health effects?
- Are the statistical associations between PM and health effects observed in epidemiological studies biologically plausible?
- What are the mechanisms of effect?

### How Do We Study PM Health Effects Using Toxicology?

Several toxicological approaches can be taken. The simplest type of exposure is to individual PM components (e.g., sulfate, elemental carbon, specific

metals). However, this approach does not take into account the complexity of the atmosphere and the fact that there are likely to be interactions between the various pollutants/components. Studies can be conducted using collected industrial PM (e.g., coal fly ash from an electrostatic precipitator) or from the ambient atmosphere (using a high-volume sampler to collect large amounts of material on a filter). This material, because it is collected in bulk and is difficult to re-aerosolize, cannot typically be used for inhalation exposures and rather must be instilled directly into the lungs of the animals. Studies using intratracheal instillation have typically employed higher doses of material delivered to the lung than with inhalation exposures. Because of this dose issue, as well as the unrealistic delivery method, it is a challenge to determine health risk potential using this method. However, much insight can be gained about the mechanism of effect in these types of studies. In fact, we owe much of our knowledge of the effects of metals in PM to studies using ROFA (residual oil fly ash), a surrogate PM that is enriched in transition metals such as nickel and vanadium. Another approach is to carry out studies focused on whole emissions from specific sources. For example, we can expose animals directly to coal combustion emissions, vehicular engine emissions, or wood smoke, etc. These types of studies are useful because they account for the complexity of the components of a given source; however, care must be taken to ensure that the emissions are representative of those that humans would typically encounter. For example, humans do not inhale whole, un-aged coal combustion stack emissions from power plants; therefore, to accurately simulate human exposures, these emissions must be aged to form sulfate particles, as would naturally occur in the atmosphere. The final toxicological approach is the use of ambient particle concentrators. These instruments concentrate PM<sub>2.5</sub> in the atmosphere by a factor of 30 to 100, resulting in concentrations that are more likely to cause observable effects over a short period of time. Since the levels and composition of concentrated ambient particles (CAPs) vary day-to-day and place-to-place, we can apply repeated exposure and multi-site study designs to “tease out” the effects of various PM components on health. In addition, using statistically-based source apportionment methods, the contribution of different PM sources to

health effects can be estimated (for more information on source apportionment methods, please see EPRI’s Issue Brief on Receptor Models). To date, humans, mice, rats, and dogs have been exposed to CAPs using this technique. The method is particularly useful if the CAPs are thoroughly characterized to consider specific components in the analysis.

### What Kinds of Animals are used in Toxicology Studies?

Rodents are typically used in PM toxicology studies because of their ease of use and generally low cost; however, dogs and humans are also used. Human toxicological exposures differ from epidemiology studies, which are also conducted in humans, by virtue of the controlled nature of the exposures. In fact, controlled human exposures are an extremely valuable approach to assessing health risk potential, or mechanisms of effect, in the species of interest. Of course, the issue of safety becomes of paramount importance in designing human exposures, particularly with susceptible subpopulations who may already have chronic health problems.

Selection of an appropriate animal strain/type (usually called an “animal model”) is dependent upon the health endpoint that one wishes to evaluate. For example, guinea pigs are excellent models for assessing airway hyperresponsiveness, since they innately have a high level of responsiveness and we therefore have increased power to observe more subtle effects. We also select animal models based on the population we may be trying to represent. Some examples are aged animals (to simulate the elderly), spontaneously hypertensive rats (to simulate individuals with high blood pressure), a chronic bronchitic rat model, diabetic rats, rats and dogs with surgically-induced ischemic heart disease or myocardial infarction, “asthmatic” mice, and certain types of “knockout” animals that have been bred to lack certain genes (e.g., the cystic fibrosis mouse model lacks the a specific type of gene).

### What Have We Learned Through Toxicology About the Relative Toxicity of Different PM Components?

Below is a brief summary of our current state of knowledge on the health effects attributable to different

PM components:

- *Sulfate and acid aerosols.* There is little evidence for sulfate-related health effects except at high concentrations (in the mg/m<sup>3</sup> range, several orders of magnitude higher than ambient concentrations), where some effects on pulmonary function have been noted. Some strong acids (eg. H<sub>2</sub>SO<sub>4</sub>) can cause pulmonary effects, but again, in the mg/m<sup>3</sup> concentration range.
- *Metals.* Recent research has showed pulmonary, systemic, and cardiovascular effects being associated with several metals, including iron, zinc, vanadium, and nickel. Such research suggests a role for metal-containing PM in alterations in heart rate and heart rate variability, and in the development of arrhythmias.
- *Ultrafine particles (particles with a diameter <100 nm).* The evidence is inconclusive; although some toxicology studies indicate that ultrafines have adverse health effects and that they are more toxic on a mass basis than fine PM; however, the epidemiological literature does not support this.
- *Diesel exhaust particles (DEPs).* These particles have been shown to have adverse health effects and affect a variety of systems (e.g., pulmonary, cardiovascular, etc.). Current research is focusing on the specific component(s) of DEPs; recent studies have shown that the gases, organic particle constituents, or particle core are responsible for the observed toxicity.
- *Organic compounds.* Clearly some specific organics can have adverse health effects (e.g., polycyclic aromatic hydrocarbons – PAHs – are mutagenic); recent studies utilizing source apportionment methods have suggested that the organic fraction is associated with a number of biological responses, including lipid peroxidation and oxidative stress, cytokine release, elevated plasma fibrinogen, and changes in blood pressure/vasculature.

### What PM Toxicology Research is EPRI Currently Undertaking?

EPRI currently has two large-scale field toxicology efforts underway, along with a number of smaller, ancillary projects. The **TERESA Study** (Toxicological Evaluation of Realistic Emissions of Source Aerosols) is a unique project being performed at several power plants to investigate the health effects of the secondary particles formed downwind of coal-fired plants. Power plant emissions are “aged” in a mobile laboratory in an effort to simulate what happens in the atmosphere, and a number of atmospheric scenarios are simulated (e.g., oxidized, neutralized, with and without the addition of secondary organic aerosol). Laboratory rats are exposed to the aged mixtures and a number of biological effects are evaluated. The research, co-funded by the U.S. Department of Energy’s National Energy Technology Laboratory (DOE-NETL), is being carried out at 3 locations in the eastern U.S. In addition, an important component of TERESA, co-funded by the EPA through the Harvard-EPA PM Research Center, is the replication of the study using a vehicular traffic source which will enable us to compare the relative toxicity of coal combustion versus mobile source emissions.

The Tri City Concentrated Ambient Particle Study (**Tri City CAPS**) is another novel research project. In this study, a mobile ambient particle concentrator is stationed at three locations in the U.S. (Detroit, MI; Steubenville, OH; and a state park in NW PA). This project represents the first time a mobile concentrator has been used to carry out inhalation exposures to CAPs in different regions. Each of these locations has a different PM compositional profile, which is further enhanced by seasonal differences. Laboratory rats are exposed to CAPs during two seasons at each location, and heart rate and rhythm parameters, along with other endpoints, are evaluated. Importantly, comprehensive characterization

of the CAPs allows us to carry out source apportionment analyses to link specific PM sources with health effects. This research is also co-funded by DOE-NETL.

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