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Health effects of World Trade Center (WTC) Dust: An unprecedented disaster with inadequate risk management

Morton Lippmann, **Mitchell D. Cohen**, and **Lung-Chi Chen**

Nelson Institute of Environmental Medicine, New York University, Tuxedo, NY, USA

Abstract

The World Trade Center (WTC) twin towers in New York City collapsed on 9/11/2001, converting much of the buildings' huge masses into dense dust clouds of particles that settled on the streets and within buildings throughout Lower Manhattan. About 80–90% of the settled WTC Dust, ranging in particle size from ~2.5 μm upward, was a highly alkaline mixture of crushed concrete, gypsum, and synthetic vitreous fibers (SVFs) that was readily resuspendable by physical disturbance and low-velocity air currents. High concentrations of coarse and supercoarse WTC Dust were inhaled and deposited in the conductive airways in the head and lungs, and subsequently swallowed, causing both physical and chemical irritation to the respiratory and gastroesophageal epithelia. There were both acute and chronic adverse health effects in rescue/recovery workers; cleanup workers; residents; and office workers, especially in those lacking effective personal respiratory protective equipment. The numerous health effects in these people were not those associated with the monitored $PM_{2.5}$ toxicants, which were present at low concentrations, that is, asbestos fibers, transition and heavy metals, polyaromatic hydrocarbons or PAHs, and dioxins. Attention was never directed at the very high concentrations of the larger-sized and highly alkaline WTC Dust particles that, in retrospect, contained the more likely causal toxicants. Unfortunately, the initial focus of the air quality monitoring and guidance on exposure prevention programs on low-concentration components was never revised. Public agencies need to be better prepared to provide reliable guidance to the public on more appropriate means of exposure assessment, risk assessment, and preventive measures.

Keywords

alkalinity; coarse particles; exposure assessment; overloading of clearance; particle resuspension; risk management; supercoarse particles; synthetic vitreous fibers; WorldTradeCenter

Introduction

The lead author has been engaged in his semi-retirement in scientific recapitulation on environmental health topics of 1) his long-term interests; 2) substantial impacts in terms of public health and concern; and 3) continuing concern and confusion in 1) the scientific literature; 2) among the regulatory agencies; and 3) the public. His two recent

Address for correspondence: Morton Lippmann, Nelson Institute of Environmental Medicine, New York University, 57 Old Forge Road, Tuxedo, NY, 10987, USA. Tel: + (914) 631-2133. morton.lippmann@nyumc.org.

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recapitulations, published in this journal, addressed 1) toxicological and epidemiological studies of effects of the cardiovascular effects of ambient air fine particulate matter (PM; $PM_{2.5}$) and its chemical components (Lippmann 2014a); and 2) toxicological and epidemiological studies of effects of airborne fibers (Lippmann 2014b). This paper, providing a holistic reappraisal on the health impacts of inhalation exposures to dust created by the collapses of the World Trade Center (WTC) twin towers on September 11, 2001, reappraises the work of many investigators, including the pioneering contributions of its co-authors, on the characterization, toxicology, and health effects of inhaled WTC Dusts. While the lead author did not get personally involved until 2014, he, like many other environmental health researchers, was surprised to see the emerging evidence in the literature that demonstrated substantial health impacts among populations exposed to WTC Dusts in Lower Manhattan. His initial doubts about major public health impacts derived from his expectation that the inhaled doses of long chrysotile asbestos fibers and of other trace-level components in the fine PM ($PM_{2.5}$) would be too small to produce measurable effects. Furthermore, he did not anticipate the unique aspects of the initial airborne dust cloud, and its subsequent resuspensions from the settled dust layers, in terms of 1) overall mass concentrations and 2) the dominance by coarse-sized particles in terms of a) alkalinity and b) high concentrations of crushed synthetic vitreous fibers (SVFs), cement, and gypsum. Finally, the initial paucity of toxicological literature on dusts having such characteristics made it difficult to envision, in advance, the toxic effects.

WTC Dust

Any adult alive today has a vivid memory of the morning of September 11, 2001, when there were impacts of two commercial airliners on the North and South Towers of the WTC in New York City (NYC). Both towers collapsed within the next few hours, and dense clouds of dust spread throughout the southern end of Manhattan Island. The bulk (about 80–90%) of the WTC Dust was generated by the successive collisions of the concrete floor slabs of the 110-story towers as they cascaded down on each lower floor, crushing the concrete, the gypsum (calcium sulfate) wallboard, and the glass- and slag-wool insulation fibers (SVFs) into a finely divided mixed powder with aerodynamic diameters ranging upward from about 2.5 micrometers (μm). The dust layers on the streets/sidewalks of Lower Manhattan (Figure 1A), and within buildings with shattered or open windows (Figure 1B) could be inches thick in the closest nearby buildings; these dusts could be readily resuspended by air currents or mechanical disturbance during the subsequent cleanup activities by 1) rescue and recovery workers and volunteers on the debris pile at what became known as Ground Zero; 2) cleanup workers for streets and building exteriors; 3) indoor cleanup workers; 4) residents (of all ages); 5) office workers; and 6) other workers within commercial buildings.

The WTC towers' collapse—a unique primary source of ambient airborne dust

Gregory Meeker of the United States Geological Survey (USGS), a participant in the early dust collection and analyses, was quoted in Chemical and Engineering News (10/20/2003) as saying "Six million ft^2 of masonry, 5 million ft^2 of painted surfaces, 7 million ft^2 of flooring, 600,000 ft^2 of window glass, 200 elevators, and everything inside came down as

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dust when the towers collapsed." The dust generated by the collapse of the WTC towers, hereafter designated herein as "WTC Dust," was unique in terms of its particle size distribution, especially in terms of its lower and upper ends. Of the total mass in the settled WTC Dust, < 1% was in the fine size range (< 2.5 in aerodynamic diameter), and > 90% was between 2.5 and 100 μm (Lioy et al. 2002, 2006, McGee et al. 2003, Yiin et al. 2006) (Figure 2), and when resuspended by Vaughan et al. (2014) for an animal inhalation study, the dust had a mass median aerodynamic diameter (MMAD) of 23 μm. Thus, virtually all of the WTC settled dust was in the coarse particle size range, and differed in sources and composition from those of fine particles, as shown in Table 1. In the more humid Eastern US, most of the ambient PM is usually smaller than 2.5 μm in aerodynamic diameter ($PM_{2.5}$), originates from both organic and inorganic vapor-phase pollutants, and is carbonaceous and/or acidic and hydroscopic. Most of the fine particles penetrate through the lung conductive airways to reach the gas exchange airways in the deep lung. In the more arid parts of the Western US, there are often more equal coarse PM mass concentrations of particles between 2.5 and 10 μm as of $PM_{2.5}$. Most particles in the 2.5–10 μm range penetrate into the conductive airways within the human and deposit in the larger lung airways. Supercoarse particles, that is, those larger than 10 μm, have high deposition efficiencies in the upper respiratory tract (URT), but can still have appreciable penetration into, and deposition within the lungs when the airborne concentrations are high, as they were of coarse and supercoarse WTC Dust in Lower Manhattan on and after 9/11/2001.

We are rarely exposed to dusts such as WTC Dust (Lioy et al. 2002, McGee et al. 2003, Yiin et al. 2006), with MMAD of 23 μm (Vaughan et al. 2014), in a form that could be resuspended by gusts of air or mechanical disturbance (McGee et al. 2003, Lee 2014). Further, WTC Dust differed substantially from typical dusts found within building construction and demolition sites, where the debris is generally composed of much larger pieces that cannot be readily resuspended into the air, or rapidly dissolved in the aqueous surface fluids of the respiratory and/or gastrointestinal (GI) tracts.

The WTC Dust was also unique in terms of its more uniform chemical composition, with 80–90% of it being a well-blended mixture of nearly equal parts of concrete, gypsum, and SVFs. Further, the WTC Dust was also unique in terms of its geographic extent of spatial dispersion, both outdoors and indoors. Pressure waves created by the collapses of the WTC Towers created hurricane-like winds that radiated out from the WTC Towers (Ground Zero; Figure 3) through the urban street canyons of Lower Manhattan, with relatively little WTC Dust reaching beyond Canal Street to the north in Manhattan or beyond the nearest parts of Brooklyn.

WTC primary dust as a secondary dust source

WTC Dust was formed on the morning of 9/11/2001, a day with an unusually low humidity. However, the potential for airborne resuspension of settled WTC primary dust deposits was quite different for the outdoor and indoor deposits, especially after September 14 and 24, when there were heavy rains. These and subsequent rains washed a lot of the outdoor WTC Dust into the storm sewers leading to the Upper New York Bay to the south, and to the Hudson and East Rivers.

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The WTC destruction on 9/11 exposed commercial buildings within ~1,000 feet of the twin Towers (One WTC and Two WTC, as shown in sampling sites denoted in Figure 3) to high levels of dust, dirt, and debris, including toxic contaminants. This WTC Dust, as suggested by Chatfield and Kominsky (2001), was unique in its propensity to become airborne, even under "passive conditions." In 2003, the RJ Lee Group (Lee 2014) undertook a study to investigate 1) the relationship between surface and airborne concentrations and to evaluate the potential for WTC Dust and WTC Hazardous Substances to be resuspended as a result of building maintenance activities in a heavily damaged building that was located near the former Towers on Liberty Street, and 2) the potential for unremediated or insufficiently remediated WTC Dust and WTC Hazardous Substances that had become attached to the WTC Dust, to become easily resuspended. They used low-velocity air pulses to resuspend dust from a variety of WTC Dust contaminated indoor surfaces into a portable vertical elutriator. Tests were conducted on concrete floors, ceiling tiles, fireproofing materials, floors and carpets, induction unit covers, and office equipment. The elutriator was sealed to the test surface with weather stripping, and used to resuspend, separate, and collect the dust particles that were resuspended from the surfaces. A standardized pulse of air 8 miles/h (mph) was used, a velocity ~1/20 was used in aggressive air leaf-blower test employed during asbestos cleanups, and within the range encountered during normal office building activities. The dust particles were collected on preweighed polycarbonate filters and analyzed by standard laboratory methods. The key findings of Lee (2014) were

- Resuspended dust was identified as WTC Dust in 75% of the sample locations;
- > 98% of resuspended PM collected by the elutriator was ≥ 10 μm in aerodynamic diameter;
- Average lead (Pb) concentration in resuspended dust from the surface was 4.90 $\mu g/m^3$; with the maximum being 42.8 $\mu g/m^3$;
- Average Pb levels increased in direct proportion with average surface wipe Pb concentrations; the correlation coefficient between the airborne respirable Pb and surface Pb being 0.99;
- The propensity of WTC Dust to aerosolize was 10–10,000 times or more than that of ordinary office building surface dust;
- Aerosolized WTC Dust contained significant quantities of respirable asbestos and Pb particles, as well as other WTC Hazardous Substances;
- There was a predictable relationship between airborne and surface concentrations of asbestos, Pb, and dust in the building. Even in spaces where the surface dust was agitated by minimal activity, there was a predictable relationship between airborne asbestos levels and surface dust loading;
- Asbestos, Pb, and beryllium (Be) concentrations in resuspended dust increased as a function of surface contamination levels, and, in these tests, respirable asbestos concentrations in the resuspended dust were 10–1,000 times higher than airborne asbestos concentrations in homes containing damaged asbestos-containing materials (ACM), and 100–10,000 times higher than airborne concentrations in public buildings containing at least one area of damaged ACM.

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Thus, the RJ Lee Group's study (Lee 2014) demonstrated that WTC Dust and WTC Hazardous Substances were resuspended into the air given a minimal amount of air movement. This meant that any WTC Dust and WTC Hazardous Substances remaining in a building, even in inaccessible areas, had the potential to be resuspended and to recontaminate occupied areas of a building that had been remediated.

In summary, the unique propensity of WTC Dust to be easily resuspended, relative to other building dust bearing ACM, was demonstrated by directly relating resuspended asbestos fibers in air and asbestos fibers in the surface dust. Both building maintenance activities and aggressive air tests resulted in the resuspension of WTC Dust and WTC Hazardous Substances from indoor surfaces into the air, evidenced by elevations in air levels of asbestos, Pb, and Be. Other studies performed in the building showed that the presence of WTC Dust reservoirs after professional abatement and WTC Dust in inaccessible areas recontaminate remediated areas and/or occupied spaces. Given the unique propensity of WTC Dusts to be easily resuspended, as demonstrated by this study, WTC Dust in the reservoirs of unremediated or incompletely remediated areas more likely than not became resuspended and recontaminated occupied spaces.

In addition, the ready resuspension of settled WTC Dust can also enhance the dose inhaled by people engaged in the cleanup of workplaces and residences whose clothing becomes contaminated. Cohen et al. (1984) demonstrated that the concentration of dust in the breathing zone of industrial workers wearing protective clothing was significantly higher than in the air outside the breathing zone, and especially for those on the worksites who were engaged in vigorous physical activity.

Inhalation exposures

WTC Dust as a source of alkaline dust exposure

Chemical leach tests were performed by USGS (2002) (1 part dust/20 parts water) and by the New York University (NYU) at 30 mg/ml (Maciejczyk et al. 2004). The WTC Dusts were chemically reactive when dispersed in water (Figure 4 for USGS tests and Figure 5 for NYU tests). The moisture that came into contact with the dusts initially became alkaline-to-caustic due to dissolution of calcium hydroxide in the crushed concrete in the particles and calcium sulfate from the gypsum wallboard in the particles. Thus, from a health perspective, there should have been concern that inhalation of the coarse particle dusts by individuals who were at/near Ground Zero could create potentially hazardous alkaline conditions in their respiratory and GI tracts.

While the rains that occurred on September 14 and 24, as well as continued reactions with atmospheric CO_2, helped to neutralize the alkalinity of the outside dusts, it is unlikely the same remediation occurred with indoor dusts protected from direct contact with rainwater.

Post-collapse human exposures to WTC Dust in Lower Manhattan, in terms of potential for inhalation exposures

In the aftermath of the WTC Towers' collapses on 9/11, there were several inhalation exposure scenarios faced by people in Lower Manhattan, that is, rescue and recovery

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workers at Ground Zero, cleanup workers, and local residents/evacuees. Moreover, these exposures varied with time post 9/11. These time-related factors included

1) During Day 1, most people living or working in Lower Manhattan were undergoing mandatory evacuation on foot to more northerly parts of Manhattan or to Brooklyn via the walkways on the Brooklyn and Manhattan Bridges over the East River. Most of the evacuees were covered with dust and had significant inhalation exposures during the exodus. Even greater inhalation exposures befell firefighters, police personnel, and volunteers who rushed to Ground Zero to engage in vigorous attempts to rescue survivors as most did so without access to, and proper use of, personal protective equipment (PPE), including respirators;

2) During Days 2 and 3, inhalation exposures of evacuees were mostly much lower than on Day 1, while an increasing number of rescue and recovery workers continued to be highly exposed as their activities resulted in resuspension of the settled dusts. Only a small fraction of the outdoor workers had respirators, and only some used them. Those that did have and use PPE often had to remove them within a few hours because the filters become clogged with dust, making the effort to breathe through them too great;

3) During succeeding days, weeks, and months, inhalation exposures of outdoor workers were much lower due to rains that removed and/or neutralized the alkalinity of the residual settled dust. Some workers and residents were engaged in indoor dust removal during the first few weeks, and their number increased over the succeeding weeks and months. Many indoor workers engaged in cleaning heavily contaminated buildings were asbestos remediation workers trained in the use negative pressure respirators and had been fit tested on their proper use. However, the indoor dusts remained highly alkaline, and the respirator filters often became clogged within the first few hours of their standard workdays. As a result, their inhalation exposures later in the workday to WTC Dust later in the workday could become high.

Exposures of the evacuees remained low, so long as they stayed away from areas surrounding Ground Zero. Most residents and workers from residential and commercial buildings were not permitted into their Lower Manhattan buildings until the sites were certified as been cleaned. For most residents, the reoccupation of their apartments took place over many weeks, while the many office workers were back at work within a few weeks (Reibman et al. 2009). However, the adequacy of the initial cleanings was often disputed, leading to many second-stage cleanings and concerns about exposures occurring between the cleanings; and

4) Actions taken/not taken to analyze and/or minimize indoor exposures to WTC Dusts: The building owners and their managers, lacking experience with such an unprecedented disaster, generally followed government agency mandates and guidelines for minimizing inhalation exposures to WTC Dust (GAO Report 2004). Unfortunately, as these agencies also lacked experience with such a

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disaster, the information they provided has, in retrospect, proved to be inadequate with respect to health protection.

Studies of health effects in people exposed to WTC Dust

Many of the government agencies listed in Table 2, from the testimony of Janet Heinrich of the U.S. Government Accountability Office (GAO) to a House Subcommittee (GAO Report 2004), were sufficiently concerned about potential health effects from exposures to WTC Dusts that they promptly mobilized teams of scientific investigators to be sent into Lower Manhattan in the first few days after 9/11/01 to collect and analyze samples of settled and airborne dusts. In addition, the National Institute of Environmental Health Sciences (NIEHS) encouraged and supported individual and collaborative on-site and laboratory-based investigations by their University-based Environmental Health Science Research Centers in the northeastern US (Table 3). These NIEHS-sponsored WTC-related studies led to numerous publications, as listed in Table 4. Table 4 also lists WTC-related health effects research studies that were supported by other sponsors. The increased incidences of health effects that have been reported in the respiratory and gastroesophageal tracts, reviewed in the next section, are the main focus of this critical review. There have also been reports of low birth weight and birth defects in children exposed *in utero* (Berkowitz et al. 2003, Lederman et al. 2004), and of post-traumatic stress disorders (PTSDs) (Fairbrother et al. 2003, Boscarino et al. 2003, Galea et al. 2003, Brackbill et al. 2009, Luft et al. 2012, Friedman et al. 2013), and there is concern about excess cancer incidence that may become evident in future years. Adverse health effects, such as birth defects, cancer, and cardiovascular responses are beyond the scope of this review.

What have we learned about WTC Dust exposures, their health risks, and how well were investigations targeted at identifying causal factors?

Unfortunately, the substantial commitments of talent and resources, both by government agencies, the University-based research centers, and by the companies and their contractors that followed agency guidance for exposure monitoring and control, were not as well conceived and/or coordinated as they could have been, and there were, over the next dozen years, substantial public health impacts of exposure to WTC Dust that had not been anticipated in terms of identifying excessive exposures to WTC Dusts, and guiding effective exposure control measures. Thus, this critical review is intended to not only provide a cautionary tale, but also demonstrate the need to carefully consider, in advance, what should be monitored, when and where measurements can be most useful in a program to protect public health, and the need for programmatic oversight to monitor progress and to suggest supplementary monitoring and toxicological studies that can address emerging concerns.

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Gaining some insights, retrospectively, on the roles of WTC Dust components in disease causation from the post-9/11/01 air quality measurements

Measurements for characterization of inhalation exposures

In the days after the September 11 attack, many Federal agencies were called on to bring their technical and scientific expertise to bear on addressing the emergency in NYC. The US Environmental Protection Agency (EPA), other federal agencies, and NYC and New York State (NYS) public health and environmental authorities initiated numerous air monitoring activities to understand the nature and extent of ongoing toxicant exposures. These efforts generated an immense amount of data. Many EPA offices and programs became involved, providing scientific, engineering, public health, and management experience to help cope with the after-effects. EPA Region 2, which includes the NYC metropolitan area in New York and New Jersey, was designated the EPA lead office for these activities, and it requested the EPA Office of Research and Development (ORD) to conduct a human health evaluation of exposure to air pollutants resulting from the WTC disaster.

The ORD evaluation, summarized in EPA (2002), relied primarily on the analyses of ambient air samples of $PM_{2.5}$ collected by fixed-site monitors that were located at the perimeter of the WTC Ground Zero and at various other sites in Lower Manhattan and the surrounding areas. It assessed the $PM_{2.5}$ inhalation exposure and potential human health risk incurred by the general population residing and working in the vicinity of the WTC. Numerous other efforts were conducted that addressed other aspects of exposure and potential risk associated with the collapse of the WTC towers, including

1) Ground Zero worker exposures on the debris pile and its disposal: EPA (2002) also reviewed data collected by the Occupational Safety and Health Administration (OSHA) and the National Institute of Occupational Safety and Health (NIOSH) that addressed the respirable WTC Dust exposures faced by fireman and other rescue workers, but it did not explicitly evaluate these exposures;

2) Indoor exposures: In addition, EPA (2002) reviewed data collected on indoor air and dust, particularly a study by the NYC Department of Health and Mental Hygiene (NYCDOHMH) and the Agency for Toxic Substances and Disease Registry (ATSDR), and provided an overview of the efforts by EPA Region 2 to clean apartments and evaluate the characteristics of indoor air and dust; and

3) Epidemiology studies: Chapter 7 of EPA (2002) provided an overview of studies that evaluated health impacts experienced by workers and others known to be in the vicinity of the WTC in the days and weeks following September 11, 2001.

The composition of the settled dust in the different particle size ranges is shown in Table 5. The ambient air $PM_{2.5}$ monitoring activities described in EPA (2002) were undertaken by federal, state, and local agencies that made their analytical results available to EPA for analysis. Most of the air quality monitors were placed, following the disaster, with the intent of characterizing outdoor levels of WTC-generated air pollutants at locations surrounding

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the WTC site at different distances. Some monitoring data for airborne PM had been collected by NYS prior to the 9/11/2001 disaster.

EPA (2002) focused on: the overall mass concentration of $PM_{2.5}$, and the concentrations of lead (Pb), chromium (Cr), and nickel (Ni) compounds, polychlorinated biphenyls (PCBs), dioxin-like compounds, asbestos, and volatile organic compounds (VOCs) within the $PM_{2.5}$, on the basis that Pb and asbestos were components of the WTC building materials; PCBs were used as dielectric fluid in transformers and capacitors; and that dioxin and VOCs were produced as a result of fuel combustion/volatilization. The assessment was limited mainly to the inhalation of airborne contaminants, although dust ingestion and dermal contact also led to exposures at and near Ground Zero. As notable as the toxicants whose airborne concentrations were monitored were those that were not monitored, especially the three WTC Dust components that contributed 80-90% of the mass of the settled WTC Dust, that is, crushed concrete, gypsum, and SVF.

The most intense period of exposure was during the collapse and the next 12 h, when Lower Manhattan was enveloped by dusts, smoke, and pollutant gases (Lioy et al. 2006). Dust and smoke were deposited on the ground and surfaces both outside and inside offices, businesses, and residential buildings. Samples were collected in October 2001 by Geyh et al. (2005), for truckers working at Ground Zero after the first 3 days; some peak total particle levels were > 15,000 $\mu g/m^3$. In 39 firefighters with significant WTC exposure, Fireman et al. (2004) found significant amounts of both fine and supercoarse particles in induced sputum (mid- and lower-airway sampling), with a size distribution and composition similar to WTC Dust.

Significant elevations of the concentrations of these contaminants that were monitored by EPA were found within and near Ground Zero for a short period of time after September 11, with elevation denoting concentrations higher by a factor of 10 or more, and often by factors of 100 or 1000, compared with other measurements of the contaminant taken after September 14 when the WTC monitoring program was initiated, and many of the elevated measurements occurred in “restricted zones,” that is, zones where access was limited to emergency management and rescue personnel and to other credentialed people. In general, the monitoring data, even within Ground Zero, indicated that ambient air $PM_{2.5}$ levels for all of these substances decreased to background ambient concentrations characteristic of pre-September 11 levels in the NYC metropolitan area by February of 2002.

EPA (2002) concluded that 1) persons exposed to the extremely high levels of ambient $PM_{2.5}$ and its components during the WTC Towers’ collapse, and for several hours afterward, were at risk for immediate acute (and possibly chronic) respiratory and other types (e.g., cardiovascular) of symptoms; 2) because the first measurements were on September 14 and those of other contaminants were not measured until September 23, and as concentrations within and near Ground Zero were highest in the few days after 9/11, exposures and potential health impacts could not be evaluated with certainty; and 3) except for exposures on September 9/11 and possibly during the next few days, persons in the surrounding community were unlikely to suffer short- or long-term adverse health effects caused by exposure to elevations in ambient air concentrations of the evaluated

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contaminants. Elevated concentrations were measured mostly within and very near Ground Zero, and lasted for 1–3 months after 9/11.

EPA (2002) also provided summaries of its findings for each contaminant or class of contaminants it had selected as a likely, or at least a possible, risk factor as follows:

Particulate matter (PM)—People caught in the initial dust/smoke cloud that encompassed Lower Manhattan after the collapse of the WTC buildings on September 11 were briefly exposed (4–8 h) to levels of airborne $PM_{2.5}$.in the mg/m^3 range, that is, thousands of μg/m^3. During the first several days after the disaster, $PM_{2.5}$ levels at the WTC perimeter exceeded the EPA daily National Ambient Air Quality Standard or NAAQS for $PM_{2.5}$ (65 μg/m^3, 24-hr); and $PM_{2.5}$ concentrations at some other nearby Lower Manhattan sites exceeded EPA's 40 μg/m^3 24-h Air Quality Index (AQI) level of concern for susceptible subgroups in the general population. The elevated PM concentrations recorded very near WTC Ground Zero during late September and early October may have increased the risks of chronic health effects for the most highly exposed individuals (e.g., persons spending extended periods of time within the WTC work zone without wearing protective respirators). By mid to late October, $PM_{2.5}$ values across Lower Manhattan had largely returned to levels typical of NYC and other US urban areas, with only a few WTC or nearby sites occasionally approaching or exceeding the AQI level of concern.

Lead (Pb)—Persons caught in the initial WTC-related dust cloud experienced brief exposures to high Pb levels based on analyses of deposited dust samples. In late September 2001, air Pb concentrations at the WTC perimeter sites reached > 1.5 μg/m^{3}on some days, that is, significantly greater than urban background levels in U.S. cities. After mid-October, airborne Pb at all sites in Lower Manhattan outside Ground Zero dropped to levels comparable with background concentrations typical of NYC and other Northeastern US urban areas.

Chromium (Cr)—Samples evaluated for total Cr at Ground Zero and at the surrounding sites never exceeded the OSHA Permissible Exposure Limit (PEL) of 1 mg/m^{3}or the ATSDR Intermediate Minimum Risk Level or MRL for Cr(VI) particles of 1.0 μg/m^3.

Nickel (Ni)—Nickel samples evaluated at Ground Zero and at the surrounding sites never exceeded the OSHA PEL of 1 mg/m^3.

The concentrations of various elements (e.g., calcium (Ca), sulfur (S), silicon (Si), and other metals) in WTC $PM_{2.5}$ particles also were above typical background levels on an episodic basis at sites on or near the WTC perimeter on some days extending into late October and November 2001.

Polychlorinated biphenyls (PCBs)—Of several hundred PCB air measurements available, only one was > 100 ng/m^3 (at 153 ng/m^3) and only three were > 50 ng/m^3. This compared with typical urban background PCB concentrations in the range of 1–8 ng PCB/m^3. After a month, nearly all readings were in the range of typical urban PCB

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concentrations or were not detected. There were no exceedances of any short-term occupational health benchmark.

Dioxins—The dioxin toxic equivalent (TEQ) levels in air near Ground Zero were up to three orders of magnitude higher than is typical for US urban areas (0.1–0.2 pg TEQ/m^3). Levels found in and near Ground Zero, starting September 23 (date of first sample taken) and continuing through late November ranged from 10 to > 150 pg TEQ/m^3. Levels measured several blocks from Ground Zero were still elevated above typical urban background, but considerably lower than sites in or near Ground Zero. Everywhere these elevations dropped rapidly; by December 2001, levels had decreased to background.

Asbestos fibers—The large majority of outside air measurements of asbestos fiber count concentrations were within the range of typical background levels. The few exceedances that occurred near September 11 were in time and close in proximity to Ground Zero. A large systematic study in November and December of 2001 suggested that indoor levels of asbestos in WTC Dusts were slightly higher near Ground Zero as compared with indoor levels in buildings further away.

Volatile organic compounds (VOCs)—Ground Zero samples of VOCs were not representative of general air quality at the site. Most samples were collected from plumes of fires and smoldering rubble in order to alert the Fire Department of New York (FDNY) and the contractors/union health/safety officers working on-site about conditions that might pose immediate health concerns. Thus, analyses of Ground Zero worker exposures to VOCs were not conducted. Eleven VOCs were evaluated at sites surrounding Ground Zero, and there were no exceedances of screening benchmarks for 1,4-dioxane, ethanol, styrene, tetrahydrofuran, and xylenes. Exceedances of screening benchmarks were seen for acetone, benzene, 1,3-butadiene, chloromethane, ethylbenzene, and toluene, but except for benzene, exceedances for these chemicals occurred only in restricted zones. Also, the exceedances were all grab samples, and 24-h samples of benzene, 1,3-butadiene, ethylbenzene, and toluene which were about three orders of magnitude (1000 times) lower. The exceedances for benzene were more frequent; some were further from Ground Zero than the other VOCs, suggesting benzene above typical background (by about a factor of 10) may have been sustained for a month or more post-September 11.

The issue of the alkalinity of WTC Dust, and its potential as a possible health concern for exposed individuals, was raised by observations by the USGS and academic researchers of high pH (>~ 10.0) values for aqueous solutions of the settled WTC Dusts that had not been leached by rainfall. After late September, indoor exposures to such dust probably warranted more concern than outdoor exposures for possible acute irritating effects or more chronic health effects. This was not only because of the basic nature of some constituent particles but also because of other unusual features of the materials, such as the presence of slender microscopic glass fibers with sharp ends, and with toxic materials attached to them.

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Occupational and indoor exposures

Extensive data sets regarding occupational exposures at Ground Zero were made available to EPA by OSHA and NIOSH on occupational exposures at Ground Zero after 9/11/01. Many of these samples were collected using personal air $PM_{2.5}$ monitors. According to EPA (2002), the vast majority of samples in both data sets were below occupational standards and guidelines, including OSHA PELs and NIOSH Recommended Exposure Limits or RELs.

The ATSDR completed a study of residential apartments (NYCDOHMH/ATSDR 2002). As summarized in EPA (2002), testing occurred between November 4 and December 11, and included 57 apartments in Lower Manhattan as well as five comparison apartments. For all the tested sites, airborne fibers were not detected above background levels. However, bulk dust samples showed there was asbestos in 16% of the apartments in Lower Manhattan, and none in the more distant comparison sites. Further, SVFs (i.e., slag wool or fibrous glass) were found in both indoor and outdoor samples in Lower Manhattan. Another study sampling indoor air and dust on September 18, in two locations very near Ground Zero, found asbestos in both air and dust, as well as low background concentrations of dioxin, PCBs, and metals.

There were, and remain, key problems with the interpretation of the WTC-related air quality monitoring. These included, in the first few years, issues with the protocols selected for characterizing exposures related to indoor cleanup operations, and documentation of the exposure and health risks to other people in Lower Manhattan buildings. A main problem, associated with these assessments, was a failure to first adequately consider 1) the unique particle size distribution and chemical composition of the WTC Dust; 2) the likelihood of excessive inhalation exposures; and 3) the optimal means for preventing and/or controlling excessive exposures. Most importantly, there was “tunnel vision” by all parties that focused excessively on known toxicants that were present as small mass fractions. These known toxicants, collectively, made up only a small percentage of the WTC Dust and of the $PM_{2.5}$ in the air samples that were analyzed; with nearly all of the WTC Dust consisting of > 2.5 μm particles, with most of the mass being in particles > 10 μm in diameter. Further, little consideration was given to the potential of toxic effects from inhaling PM containing three major mass components in the particles larger than 2.5 μm, for example, crushed concrete, gypsum, and SVFs, each of which is a known irritant. These three major mass components made up 80–90% of the settled WTC Dust and were assumed, incorrectly, to be nuisance dusts when resuspended into the air that people in Lower Manhattan were breathing.

These problems were compounded by the intense initial focus in the public media on asbestos fibers as the index toxicant for WTC Dust, and in technical guidance of exposure monitoring and control. There was a secondary focus on other trace components that were considered to pose health risks, that is, metals, molds, polyaromatic hydrocarbons (PAHs), PCBs, and dioxins. While there was some chrysotile asbestos insulation within the first 20 floors of the WTC North Tower, there was none in the other 80 floors, or in the South Tower, and no amphibole asbestos fibers in either building. Prolonged exposures to chrysotile fibers longer than 20 μm can cause lung cancer (Lippmann 2014a); the current occupational exposure limit of 0.01 fibers/ml of air as a long-term average is based on counts of asbestos fibers longer than 5 μm. Very few of the many airborne asbestos fiber

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measurements in the EPA WTC database exceeded this conservative fiber count limit, even in the first few days when the fiber concentrations were highest. The measured concentrations of the trace metals, mold, PAHs, and PCBs—as summarized by Lorber et al. (2007), and described in greater detail in EPA (2002)—were also almost all lower than current occupational exposure limits.

Since we know that many people developed respiratory and gastroesophageal illnesses after exposure to WTC Dusts, and we also now know that established occupational and ambient air exposure limits had seldom, and only briefly, been exceeded in the $PM_{2.5}$ samples, it is clear, at least to the authors of this review, that exposure components that had not been measured (such as the coarse alkaline particles and SVFs) were the ones most likely responsible for the observed increased incidence of adverse health effects in people exposed to WTC Dusts. We are not the first to question the lack of attention to the coarse particles. Lioy et al. (2006) reported that "the particles in greatest abundance (mass) in the (WTC) dust were the unregulated supercoarse (> 10 μm diameter) particles." They also noted that "Given the health effects, one issue that should have been obvious, after 9/11, was the need for a rapid characterization of the total (alkaline) dust." It is indeed unfortunate that their on target and reasonable concerns were ignored.

The next section reviews our broader review of the exposure factors not initially considered that, if they had been addressed in a mid-course reconsideration of ongoing monitoring and guidance, could have led to a minimization of at least some of the adverse health effects that did occur.

Technical topics influencing adverse WTC Dust exposures

Ease of resuspension of WTC Dusts

Figure 1A illustrates that thick deposits of WTC Dust covered outdoor surfaces in Lower Manhattan during the first day after the attack on September 11, 2001. WTC Dust covered indoor surfaces for much longer periods of time (Figure 1B). To characterize the chemical composition, particle size distribution, and potential for resuspension of the settled dust particles into human breathing zones, Chen et al. at NYU size-fractionated seven WTC settled dust samples that were collected by NYU personnel in Lower Manhattan on September 12 and 13, 2001, as reported in Yiin et al. (2006). Aliquots of these samples were sieved through a 53-μm mesh screen mounted on a shaker. The PM_{53} fraction passing through the screen was then aerosolized into a vertical elutriation chamber and passed through a size-selective air sampler inlet with a 10-μm aerodynamic diameter cut to remove particles in the 10–53 μm range, thereby isolating the PM_{10} fraction. The PM_{10} fraction was then passed through a cyclone cut at 2.5 μm to remove the coarse fraction ($PM_{10–2.5}$). The $PM_{2.5}$ fraction was collected on Teflon filters. Each individual size-fractionated sample was then subjected to physical and chemical analyses. Most of their key findings, summarized in Table 1, have previously been described (Lioy et al. 2002, McGee et al. 2003, Yiin et al. 2006). Similar work on elutriation and chemical and physical analyses was performed on settled indoor WTC Dust samples that were collected in June of 2002 for a private client (Lee personal communication, Dec. 2014). Key elements of the Lee findings were

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summarized earlier in this review. There were substantial commonalities in the findings of the two teams of independent investigators.

Dosimetry of WTC Dusts in humans

The WTC Dust, as summarized in the "Introduction" section, differed greatly from conventional airborne dusts encountered in occupational and community settings in terms of particle size distribution and chemical composition. Therefore, it is important to discuss the special circumstances of WTC Dusts in terms of the dosimetry of the inhaled dusts.

Conventional review of PM deposition in, and clearance from, the lung

The penetration of inhaled particles into the thorax is limited by their deposition in the URT during inspiration, which varies with particle size distribution; flow rate and tidal volume; the fraction passing through the oral pathway; and *in vivo* airway dimensions. All of these factors are quite variable from person-to-person, depending on age, transient illness, cigaret smoke exposure, and other short-term toxicant exposures that cause transient airway constriction, as well as elements of occupational histories associated with loss of lung function or cumulative injury.

Figure 6 shows experimental data on particle penetration through the oral pathway of healthy human adults as a function of particle aerodynamic diameter. It also shows the sampler acceptance criterion for size-selective thoracic coarse particle inlets that precede the sampling filters, as specified by the American Conference of Governmental Industrial Hygienists (ACGIH), the International Standards Organization (ISO), and the European Economic Community (CEN). The EPA variant of the thoracic coarse particle acceptance criterion is for PM_{10}, which is essentially the same for particles up to 5 μm, but has a steeper decline for larger-sized particles. The EPA fine particle ($PM_{2.5}$) sampler acceptance criterion is shown in Figure 7.

For inhaled particles that penetrate into the lower respiratory tract (LRT), that is, the airways within the thorax, the deposition patterns and efficiencies within the thoracic conductive airways (trachea, bronchi, and bronchioles) by impaction and sedimentation, and those of particles that deposit in the smaller gas-exchange airways by diffusion, are also highly variable and dependent on particle size, flow rate, and tidal volume, and on *in vivo* airway dimensions (Lippmann and Albert 1969).

Some inhaled particles remain airborne during the tidal breath inhalation and exhalation phases of a tidal breath and are exhaled without having been deposited. There is a deposition minimum of ≈ 15% for particles between 0.1 and 1.0 μm that have little intrinsic mobility, as they are too large to deposit efficiently by diffusion and too small to deposit efficiently by impaction on the surface coatings of larger airway branchings, or to deposit efficiently by sedimentation along the smaller conductive airways. In fact, the tidal flow in the airways is not completely reversible, with ≈ 15% of the inhaled air remaining in the deep lung over multiple breaths and a corresponding volume of residual lung air being exhaled. The laminar flow in the smaller airways leads to deeper penetration of particles near the airway axis than nearer the airway walls, and a flatter flow profile during exhalation, with more of the flow

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nearer the airway walls being exhaled residual lung air that is depleted of particles, and therefore with much lower particle deposition during exhalation than during inhalation (Briant and Lippmann 1992, 1993).

Particles (or aggregates of particles) larger than ≈ 1 μm in aerodynamic diameter deposit in the conductive airways. Those components that are insoluble or poorly soluble on the mucous layer of the airway lining fluid are carried proximally toward the larynx within 1 day, swallowed, pass through the GI tract, and are excreted in the feces. Particles that deposit within oral passages and ciliated nasal passages of the URT are also swallowed and pass through the GI tract where they could contribute to gastroesophageal reflux disease symptoms (GERS) and gastroesophageal disease (GERD). Soluble particles, components of particle aggregates, and insoluble particles with diameters < 0.1 μm can all gain access to the bloodstream and be transported to more distal sites, where their chemical composition determines any long-term retention and toxic potential (Lippmann 2014b).

Non-hygroscopic insoluble particles < 1 μm and hygroscopic particle < ~2.5 μm that grow in the ambient air and within the airways can deposit in the non-ciliated deep lung airways, where their soluble components can then rapidly enter the bloodstream. Most of the insoluble particles and particulate components > 0.1 μm that reach the non-ciliated deep lung airways are phagocytosed by alveolar macrophages (AMs); within the few weeks that the macrophages are resident on airway surfaces. These surface macrophages, and the particles within them, are drawn into the terminal bronchioles due to the high surface tension of the lining fluid, and then cleared from the lung conductive airways by mucociliary clearance (Lippmann and Chen 2007).

Aspiration of airborne particles into the human respiratory tract is highly particle size dependent. The penetration of inhaled particles into the tracheobronchial tree is different for inhalation via the nose versus the mouth, with the extent of the greater particle penetration of the oral pathway varying with the cross section of the pathway. Most particles with aerodynamic diameters < 2.5 μm that originate from fossil fuel combustion sources can reach the respiratory bronchioles and alveoli. By contrast, few WTC Dust particles—having much larger sizes—penetrate that far. The particle-size-dependent differences in deposition sites within the lung airways strongly affect the residence times of the particles at the deposition sites, and their pathways and rates of clearance to other sites within the body.

In summary, for conventional occupational and ambient air PM, most of the particles with size between 2.5 and 10 μm deposit in the ciliated larger thoracic airways, where they can elicit bronchoconstriction and bronchospasm that can lead to bronchitis and exacerbations of asthma (discussed in the next section). By contrast, most particles < 2.5 μm that deposit within the thorax are deposited in the more distal non-ciliated gas exchange region where they are more likely to dissolve or be translocated to distal body sites wherein they can then exert organ-system-related toxicities, including cardiovascular, hepatic, renal, and nervous systems damage.

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WTC Dust deposition in, and clearance of WTC Dusts, and other PM, from the lung

Studies of effects on deposition of PM can provide a basis for understanding how the inhaled WTC Dusts were deposited in/cleared from the lungs of exposed individuals. WTC Dust contained much more of its PM in the coarse thoracic size range ($PM_{10–2.5}$), and even greater mass fractions in the $PM_{10–53}$ and PM $_{>53}$ size ranges. Further, the alkalinity of the PM in the larger size ranges was greater than in the $PM_{2.5}$ particles. As a result, because deposition of highly alkaline particles in the URT and in the tracheobronchial airways in the LRT represents a unique challenge to the ability to clear the airways without eliciting adverse effects (such as erosion and death of epithelial cells at airway surfaces), normal defense mechanisms in the larger airways could have been overloaded in individuals who inhaled the WTC Dusts.

The concept of lung overload was invoked by Morrow (1988) with respect to lung cancer in the small airways of rats exposed to 7 mg diesel exhaust PM/m^3 interfering with the capacity of AM-mediated particle clearance from the small airways. In humans, Lippmann and Timbrell (1990) demonstrated that particle clearance from small airways could be severely disrupted by occupational exposure to amphibole asbestos fibers. Overloading of the capacity of the ciliated epithelium for short-term dust clearance by irritants such as cigaret smoke and for sulfuric acid aerosol exposures has previously been described for the larger conductive airways in humans and donkeys (Albert et al. 1969a,b, 1975, Schlesinger et al. 1978b, Leikauf et al. 1981, 1984, Lippmann et al. 1982, Spektor et al. 1985), for long-term exposures to cigaret smoke in humans and donkeys (Albert et al. 1969a,b, Bohning et al. 1975), and for cigaret smoke in donkeys by Schlesinger et al. (1978b). Disruption of the lung capacity for mucociliary clearance of the tracheobronchial airways by chemical irritants could explain the excess incidences of cough and diseases of the respiratory and GI regions to populations exposed to elevated concentrations of the large-diameter WTC Dust particles that were highly alkaline and capable of damaging or disrupting epithelial cell function.

Very high acute exposures and/or lower levels of chronic exposure to chemical irritants can not only disrupt clearance function, but also destroy ciliated and mucus-secreting epithelial cells within the tracheobronchial airways, as has been seen for long-term cigaret smokers, leading to increased retention of all kinds of PM within the lungs, and not just the irritant particles themselves (Schlesinger and Lippmann 1978a). There is also some evidence that human exposure to WTC Dust can cause disruption of mucociliary particle clearance (McMahon et al. 2011). They reported unusual ultrastructural ciliary abnormalities in 3 WTC response workers that corresponded to their respiratory and ciliary functional abnormalities. Each patient had respiratory cilia biopsies that were evaluated for motility and ultrastructural changes. Impaired ciliary motility was seen in 2 of the 3 patients, and each of the patients showed monomorphic ultrastructural abnormalities. Two of them showed identical triangular disarray of axonemal microtubules with peripheral doublets 1, 4, and 7 forming the corners of the triangle and doublet 9 always more medially displaced than doublets 2, 3, 5, 6, and 8. Two workers had cilia in which axonemes were replaced by homogeneously dense cores. One also had cilia with triangular axonemes. The other had cilia with a geometric triangular to pentagonal shape. These ciliary abnormalities may represent a new class of primary ciliary dyskinesia in which abnormalities may have a

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genetic basis and a phenotypic expression that is prompted at the cellular level by local environmental exposures. Also, there is some evidence that large particles were able to reach deep in the lung, as demonstrated by the electron micrographs of material that was obtained from a firefighter's lung after bronchoalveolar lavage (Rom et al. 2010).

In view of the unique particle size distributions and high alkalinity of the WTC Dusts, the standard dosimetry models and data tabulations have proven to be of little value in describing either the acute or cumulative WTC Dust dosages received by individuals or the distributions of doses of population groups who have had inhalation exposures to WTC Dusts in Lower Manhattan. The airborne levels of WTC Dust were highly variable both temporally and spatially, with localized hotspots of exposure being related to human activities causing WTC Dust resuspension. Furthermore, the particle size distribution of the two original WTC Dust clouds from first the South Tower, and then the North Tower, changed with distance due to more rapid settling of the largest particles, and due to the different paths of the high velocity of the airflow radiating out from Ground Zero through the surrounding buildings.

Further dose variations were caused by application of respiratory protection to capture the inhalable particles; even gauze masks and handkerchiefs were used to reduce dust penetration into the respiratory tract over the first few hours and days. After the first few days, those people having, and using, well-fitting negative-pressure respirators could avoid inhaling most of the dust in their breathing zone for as long as the dust layer on the filter caused minimal air path clogging. However, those filters worn by indoor cleanup workers often clogged during the course of a 10-h day of cleanup, and replacement cartridges were not always available.

Other factors affecting the human dosimetry of inhaled WTC Dusts

1) Oro-nasal Breathing and Airway Anatomy

Humans differ from almost all other mammals in terms of being able to inhale via the oral passages as well as through the nose, and in having nearly dichotomous bronchial airway branchings within the lungs rather than the highly asymmetric branching in nearly all other mammals. Both of these differences contribute to enhanced tracheobronchial airway particle deposition in humans (Lippmann 1977). The greater flow resistance through the nasal pathway leads adult humans to switch to oral breathing when engaged in strenuous physical activity at inspiratory flow rates > 40 L/min. When wearing a respirator with its own breathing resistance, there is likely to be a switchover to at least partial oral breathing (oronasal breathing) at a lower flow rate, especially as the respirator filter begins to clog. Partial or total inhalation via the oral passage increases particle penetration into the lungs. The asymmetric branching of the human bronchial airways results in enhanced particle deposition, especially by impaction on the airway bifurcations within them than is characteristic in animals with more asymmetric airway branching (Lippmann and Schlesinger 1984).

2) Enhanced Deposition of Fibers by Interception

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Fibers, by definition, are particles > 3–5 times longer than they are thick. In the turbulent flow within the larger lung airways their ends are more likely to touch an airway surface and be deposited than a more compact particle of the same aerodynamic diameter, and this enhanced deposition becomes statistically significant for fibers longer than 10 μm (Sussman et al. 1991).

3) Clearance Pathways for Deposited Compact Particles and Fibers

The insoluble particles that deposit on the ciliated mucosal surfaces in the nasal and bronchial airways are carried along the surface mucus toward the larynx, where they are swallowed and pass into the GI tract (Albert et al. 1969a). This is the pathway for SVFs within the WTC Dust that deposit within the nasal and oral pathways and the tracheobronchial airways during the first few days after their inhalation. For the cement and gypsum in the WTC Dust, which are soluble within the epithelial surface liquids, they added alkalinity to the mucus as it moved toward the larynx. As such, both the WTC Dusts and the alkaline mucus were likely swallowed and passed into the GI tract.

4) Laceration of Epithelia by SVFs

It has long been established that people handling fibrous glass in production facilities and at installation sites can develop dermatitis on exposed skin (Siebert 1942, Enterline et al. 1983, ATSDR 2004). Stokholm et al. (1982) reported that workers exposed to SVF in the form of rockwool had more eye symptoms, and changes in the cellular and mucous conjunctival fluid, breakup time of the precorneal film, the number of microepithelial defects, and the number of dead and degenerated cells on the cornea and bulbar conjunctiva than control workers. One would expect that crushed SVFs within the WTC Dust had a much greater proportion of SVF shards and sharp ends than SVFs handled by production workers and insulation installers. The sharp ends of the SVF fibers and the shards resulting from the crushing of the vitreous fibers could lacerate phagocytic and epithelial cells in and on the lung and GI epithelia, subsequently leading to release of digestive enzymes and further epithelial damage.

5) High pH of Surface Fluids on Airway and Gastroesophageal Tract Epithelia

The combination of chemical irritation by the highly alkaline mucus that can damage the ciliated cells of the conductive airways, and the physical irritation caused by the sharp ends of the SVFs, as well as their interactions is a highly likely causal factor for the excess respiratory and GI tract disorders documented in WTC Dust-exposed individuals.

Evidence of associations between WTC Dust inhalation and human health effects

The extensive peer-reviewed literature discussed in this section documents excesses in both acute and chronic health effects in both 1) rescue and recovery workers and volunteers who were heavily exposed to WTC Dust out-of-doors during the first few days after 9/11; and 2) in residents and local workers, many of whom were heavily exposed to WTC Dust from the

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initial dust clouds while evacuating, and subsequently from more chronic exposures from resuspended dusts and fumes in the outside streets and from indoor exposures over much longer periods of time. Thus, the people having adverse health effects associated with their exposures to WTC Dust included groups with quite different amounts and temporal patterns of exposure. In spite of their differences in exposure pattern and intensity, the still growing literature on associations of excess clinical disease and dysfunction with known exposure to WTC Dust demonstrates similarities in the effects that they have experienced, and in their causality.

The population groups with the highest disease incidence and the most severe responses include those presumed to have been exposed to quite high WTC Dust concentrations and scant use of respirators during the initial rescue and recovery phases, specifically the 1) occupational groups exposed at Ground Zero, many of whom were included in the cohorts studied at Mount Sinai School of Medicine (MSSM); 2) FDNY Employees (Firefighters and Emergency Medical Technicians) studied at the NYU Langone Medical Center; and 3) The World Trade Center Day Laborer Medical Monitoring Project at Queens College, for building cleanup workers who did not work at Ground Zero, or live near Ground Zero, but were engaged in cleaning contaminated office/residential buildings in Lower Manhattan.

While the incidence rates and severity were generally lower among people going about routine activities in Lower Manhattan, they still had statistically significant excesses in some of the same adverse health responses. Less is known about the local residents and workers; however, dose–response relationships for adverse health effects have been shown for these populations as well (Lin et al. 2007, Maslow et al. 2012). There were also clinical examinations of additional population groups who were presumed to have had exposures to lesser concentrations of WTC Dust initially, but whose periods of exposure extended into subsequent months. These groups included 1) residents and office workers in Lower Manhattan studied at NYU; and 2) the NYC Department of Health and Mental Hygiene health registry of over 71,000 people for long-term follow-up studies to document medical problems of NYC responders and volunteers (WTC Health Registry 2012). In addition, there were a variety of population groups that were not given clinical examinations whose exposures to WTC Dusts were less well defined, and whose adverse effects were elicited by questionnaires.

Despite different temporal patterns of WTC Dust exposure, and different frequencies of disease expression, both in terms of short-term and longer-term responses, all of these population groups exhibited quite similar clusters of specific disease categories within three specific anatomic regions, that is, the 1) upper respiratory; 2) lower respiratory; and 3) GI tracts. One of the clear early results of working in indoor or outdoor areas where WTC Dust contamination was substantial was a persistent cough, called “WTC cough” (Chen and Thurston 2002). This “cough” was accompanied by bronchial hyper-reactivity and respiratory distress (Prezant et al. 2002) in 8% of the highly exposed firefighters examined at NYU. Of the 332 firefighters having “WTC cough,” 95% had symptoms of shortness of breath; 87% had GERD; and 54% had nasal symptoms. The different population groups also had elevated incidences of chronic diseases that developed in the same three anatomic regions, as discussed below.

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The World Trade Center Health Program (WTCHP) was mandated to identify health conditions linked by epidemiology and health research studies to occupational exposures to WTC Dusts (Howard 2014). It is considered an authoritative source for judging what health problems suffered by WTC workers and volunteers are eligible to receive medical care. Further, the WTCHP developed its list of aerodigestive illnesses based on epidemiological research findings published in the peer-reviewed literature that could be linked to exposure to WTC Dust exposure: asthma, chronic cough syndrome, chronic laryngitis, chronic nasopharyngitis, chronic respiratory disorder, chronic rhinosinusitis, GERD, interstitial lung diseases, reactive airways dysfunction syndrome (RADS), sleep apnea, upper airway hyperreactivity, and WTC-exacerbated chronic obstructive pulmonary disease (COPD).

Groups with results based on clinical observations

In this section, we summarize the health effects reported for people exposed to WTC Dust in Lower Manhattan. In doing so, we focused on the objective findings of adverse health effects in the literature to a greater extent than on the conclusions of the authors of the published reports on the basis that they were often narrowly focused on the specific population being studied, and on the limited statistical power of the study.

Occupational groups exposed to WTC Dust at Ground Zero with clinical examinations

The MSSM established a clinically based research center in NYC to measure the health risks among workers and volunteers post-WTC Tower collapse on September 11, 2001, that is, the WTC Worker and Volunteer Medical Screening Program (The WTC Worker and Volunteer Medical Screening Program (WVMS) provided free, standardized medical assessments, clinical referrals, and occupational health education for workers and volunteers exposed to hazards during the WTC rescue and recovery effort). It provided free, standardized medical assessments, clinical referrals, and occupational health education for workers and volunteers exposed to hazards during the WTC rescue and recovery effort.

Levin et al. (2004) reported that during July 16, 2002 to August 6, 2004, the WVMS evaluated 11,768 non-FDNY workers and volunteers. Data analyzed from a subset of 1,138 of the 11,768 participants evaluated at MSSM during July 16 to December 31, 2002 indicated that a substantial proportion of participants experienced new-onset or worsened preexisting lower and upper respiratory symptoms, with frequent persistence of symptoms for months after their WTC work stopped. 46% of them worked on September 11, 2001, and 84% worked or volunteered during September 11–14, when exposures were greatest. During that period, 21% reported using respiratory protection (i.e., full- or half-face respirators). The median length of time worked on the WTC effort was 966 (range: 24–4,080) h. Of the 610 examinees present in Lower Manhattan on September 11, 51% reported being directly in the cloud of dust created by the collapse of the WTC buildings, and an additional 31% reported exposure to substantial amounts of dust. WTC-related lower respiratory symptoms were reported by 60%, and 74% reported WTC-related upper respiratory symptoms: 40% had WTC-incident lower respiratory symptoms that persisted to the month before screening, and 50% reported WTC-incident and persistent upper respiratory symptoms. Among the 851 participants who reported persistent WTC-related symptoms, an average of 32 (range: 7–63)

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weeks had elapsed since they stopped working at the site or the end of May 2002. Of all the participants, 46% had nasal mucosal inflammation, but other respiratory abnormalities (e.g., abnormal nasal turbinates or sinuses, rhonchi, and wheezing) were less common. Landrigan et al. (2004) studied the health of 183 workers at MSSM, and 32.8% of them experienced new cough after starting WTC Dust cleanup; 24% had new phlegm production; and 17.5% had *de novo* wheezing.

Skloot et al. (2004) studied 96 male ironworkers from the MSSM study group, including their exposures, medical histories, physical examinations, spirometry, and chest radiographs. The average age was 43 years, 83% were White, and 65% were current or former smokers. Cough was the most common symptom, upper and lower pulmonary complaints were common among almost half of the men, and 41 subjects wore no respiratory protection; 19 workers had abnormal radiographs. Cough was more common among those who began work on 9/11 compared with those who arrived later, 78% versus 54%. Spirometry did not differ between smokers and non-smokers, and those who wore respiratory protection seemed to have less respiratory symptoms than those who did not. They found a significant OR between cough and exposure during 9/11, OR = 3.64, 95% confidence interval (CI) of 1.35–9.83. Lung function tests were not associated with exposure duration or onset.

Herbstman et al. (2005) studied 183 WTC cleanup and recovery workers, mostly truck drivers, carpenters/mechanics, dock workers, and supervisors/laborers. Most of the participants were male, 65% White, 50% truck or heavy equipment operators, 91% reported wearing a respirator some of their working time, and an equal fraction were current or never smokers ≈ 36%. They divided the group according to whether they had respiratory symptoms (64 subjects or 35%) or not (119 subjects or 65%) when they began working at the WTC site. They reported that 31% and 34% of the groups with existing illnesses and symptom free developed new cough; 23% and 24% developed new phlegm; and 16% and 19% developed *de novo* wheeze. New-onset cough among those without pulmonary symptoms was the only symptom that followed an exposure–response pattern with those with the greatest number of days having the highest prevalence. Those with extant respiratory symptoms had a greater prevalence of new upper respiratory conditions (such as nasal congestion, sore throat, and hoarseness). Smoking seemed to play no apparent role in the findings. They noted that cough receptors were located in the larynx and larger airways, and the complex of large-sized PM and alkalinity accounted for cough being so prominent a symptom.

Herbert et al. (2006) gathered background information for later epidemiology studies of chronic respiratory diseases resulting from exposures to WTC Dust. They helped to create a clinical center at MSSM to study the health of workers not covered by other medical programs such as those of the FDNY, federal employees, and NYS rescue workers. The MSSM program drew patients from several other clinics in New York and New Jersey, and all agreed to follow the same protocol. Eligible workers or volunteers had to have worked 4 h on September 11, 24 h during September 2001, or 80 h any time within the September–December time frame. All were examined clinically, completed a standardized medical questionnaire and a pulmonary function assessment, and provided responses about their health before and after 9/11. Of the 9,442 study participants, 86.7% were male, 65.7%

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White, 86% union members, and most were construction (34.0%) or law enforcement workers (29.4%). There were also 258 cleaning and maintenance workers (2.7%). All subjects had fewer lower or upper respiratory symptoms before than after 9/11. These symptoms tended to clearly show a greater risk for those whose exposures to WTC Dust happened in the first few weeks. However, even subjects who arrived after October 1, 2001 had a prevalence of 41% for lower respiratory symptoms (~ 3 times greater than prior to 9/11) and a prevalence of 59% for upper respiratory conditions (nearly 2 times the percentage prior to 9/11). When pulmonary function was assessed, they had low FVC. Among the 4,641 never smokers, there was more than twice the prevalence of lowered pulmonary function tests (PFTs) compared with US White males (27% vs. 13%). Time of arrival was correlated with reduced forced vital capacity (FVC), with those arriving on 9/11 having much poorer FVC than those arriving October 1 or later.

Buyantseva et al. (2007) studied 1,588 NYC police officers categorized as having heavy, moderate, or light exposure to WTC Dust based on their assigned duties after 9/11. Prior to 9/11, there was 4.8% prevalence of cough compared with 43.5% after 9/11. They showed that both the odds ratio (OR), and the race- and sex-adjusted OR rose for both health interview as well as follow-up telephone assessment for chronic cough. Among police officers who had no respiratory symptoms prior to 9/11, there was both a significant rise in early onset resolved cough ($p = 0.02$) and of persistent cough ($p = 0.04$) that rose by exposure group.

de la Hoz et al. (2008) studied the links between GERD and respiratory illnesses in 42 WTC workers in the MSSM group. They were predominately male (73.8%), average age: 49.1 years, 45.2% English speaking, nearly 55% laborers, 46.5% present at Ground Zero within the first 48 h, and 40% former or current smokers. All subjects had heartburn at least once per week; 71.4% had a dry cough, 69% had shortness of breath, 73.8% had upper respiratory ailments, and 40.5% had lower respiratory conditions. Workers with GERD were more likely to have reduced FVC, and they were more likely to have lower airway health status.

Bowers et al. (2010) examined health consequences of the WTC collapse in terms of incident sarcoidosis, a multisystem inflammatory disorder of unknown etiology characterized pathologically by non-caseating granulomas. They described two cases of sarcoidosis in rescue workers with significant exposure from the WTC collapse and who presented with extrapulmonary rheumatologic manifestations. The first case involved a 33-year-old white NYC male detective found to have sarcoidosis following an evaluation of diffuse joint pain. The second case involved a 40-year-old African American male NYC officer who presented with uveitis and was subsequently diagnosed with sarcoidosis. These two cases extended the spectrum of disorders resulting from the WTC disaster.

Kleinman et al. (2011a,b) compared pulmonary function since the 2001 WTC disaster, with pre-exposure function data, in a NYC Police Department (NYPD) Emergency Responder cohort, without history of repetitive respiratory exposures. For the 206 unit members who reported arrival time, exposure location, duration, smoking history, respirator mask usage, and respiratory symptoms, and who underwent clinical evaluation and follow-up spirometry in 2002 and 2007 there was a mean long-term decline in FVC of 190 ml (3.7%) 1-year post-

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exposure in 2002, and 330 ml (6.4%) in 2007, compared with baseline data. FEV_1 was not significantly changed in 2002 but declined 160 ml (3.9%) after five further years of follow-up. Conclusions: Abnormal spirometry was observed in (5.3%) of subjects, particularly individuals experiencing higher exposure intensity, duration, or respiratory symptoms. The small number of smokers and subjects failing to wear protective respiratory masks showed greater declines. In 2002, 11 of 206 subjects (5.3%) exhibited mild pulmonary dysfunction (60–80% of predicted; 95% CI: 3.0-9.4%). Upon reevaluation in 2007, abnormalities had resolved in 4 of 11 affected individuals (36.4%), whereas 6 individuals (54.5%) continued to exhibit mild pulmonary dysfunction; 1 did not return for testing.

Li et al. (2011) examined new-onset GERS following 9/11 that persisted up to 5–6 years in relation to 9/11-related exposures among the WTC Health Registry enrollees, and potential associations with comorbid asthma and PTSD for 37,118 adult enrollees (i.e., rescue/recovery workers [RRWs], local residents, area workers, and passersby in Lower Manhattan on 9/11) who reported no pre-9/11 GERS and who participated in two Registry surveys 2–3 and 5–6 years after 9/11. Post-9/11 GERS (new onset since 9/11) reported at first survey, and persistent GERS (post-9/11 GERS reported at both surveys) were analyzed using log-binomial regression. The cumulative incidence was 20% for post-9/11 GERS and 13% for persistent GERS. Persistent GERS occurred more often among those with comorbid PTSD (24%), asthma (13%), or both (36%) compared with neither of the comorbid conditions (8%). Among enrollees with neither asthma nor PTSD, the adjusted risk ratio (aRR) for persistent GERS was elevated among workers arriving at the WTC pile on 9/11 (aRR = 1.6; 95% CI: 1.3–2.1) or working at the WTC site > 90 days (aRR = 1.6; 1.4–2.0); residents exposed to the intense dust cloud on 9/11 (aRR = 1.5; 1.0–2.3), or who did not evacuate their homes (aRR = 1.7; 1.2–2.3); and area workers exposed to the intense dust cloud (aRR = 1.5; 1.2–1.8). Thus, disaster-related environmental exposures may contribute to the development of GERS. GERS may be accentuated in the presence of asthma or PTSD.

Wisnivesky et al. (2011) described the cohort of more than 50,000 people who participated in the rescue and recovery work that followed the 9/11/2001 attacks on the WTC, reported on the incidence and prevalence rates of physical and mental health disorders during the 9 years since the attacks, examined their associations with occupational exposures, and quantified the physical and mental health comorbidities. They gathered data from 27,449 participants in the WTC Screening, Monitoring, and Treatment Program. The study population included police officers, firefighters, construction workers, and municipal workers. They used the Kaplan–Meier procedure to estimate cumulative and annual incidence of physical disorders (asthma, sinusitis, and GERD), mental health disorders (depression, PTSD, and panic disorder), and spirometric abnormalities. Incidence rates were also assessed by level of exposure (days worked at the WTC site and exposure to the dust cloud). The 9-year cumulative incidence of asthma was 27.6% (number at risk: 7027), sinusitis was 42.3% (5870), and GERD was 39.3% (5650). In police officers, cumulative incidence of depression was 7.0% (number at risk: 3648), PTSD was 9.3% (3761), and panic disorder was 8.4% (3780). In other rescue and recovery workers, cumulative incidence of depression was 27.5% (number at risk: 4200), PTSD was 31.9% (4342), and panic disorder was 21.2% (4953). 9-Year cumulative incidence for spirometric abnormalities was 41.8% (number at risk: 5769); three-quarters of these abnormalities were low FVC. Incidence of

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most disorders was highest in workers with the greatest WTC exposure. Extensive comorbidity was reported within and between physical and mental health disorders. Thus, 9 years after the 9/11 WTC attacks, rescue and recovery workers continued to have a substantial burden of physical and mental health problems.

Kim et al. (2012) studied the risk of asthma among 20,834 participants in the MSSM WTC Medical Monitoring and Treatment program between July 2002 and December 2007. They calculated the lifetime prevalence and standardized morbidity ratios (SMRs) by comparing the asthma risk among WTC responders with those from the National Health Interview Survey (NHIS). In this ongoing research study, the average age was 43 years, 85% male, 59% white, with 42% working in protective services, and 25% working in construction. The study subjects underwent a baseline clinical examination, with follow-up every 12–18 months from 2002 to 2007. Rates of asthma in the NHIS served as a comparison group for the WTC responders. Positive responses to the question, “have you ever been told by a doctor you had asthma?” were used to calculate lifetime asthma. If the respondents said they had an asthma attack in the past 12 months, they were used to serve as a control group for annual asthma risk. There was a major increase in lifetime asthma prevalence. Prior to September 11 it was 2.9%, and rose to 12.8% in 2002, and 19.4% in 2007, a > 6-fold increase. WTC Responders had age-standardized lifetime asthma SMR prevalence of 1.6 (95% CI = 1.6, 1.7) after 9/11 for all years of follow-up. In addition, the age-adjusted 12-month SMR was increased in the 2002–2005 time frame; it was 1.7 (95% CI = 1.6, 1.8). By contrast, the 12-month lifetime SMR was 0.3 (95% CI = 0.3, 0.4) for the year 2000. The increasing trend from 2002 on was the same for both women and men; it increased for all ages, with the highest being for 40- to 49-year-old group. The SMRs were elevated for all occupational groups: with protective services having a SMR of 1.5 (95% CI = 1.5, 1.6); and installation, maintenance, and repair workers having a SMR of 2.0 (95% CI = 1.8, 2.2). Acute asthma SMRs were elevated for all professions, with a 1.6 risk for transportation and material moving (95% CI = 1.2, 2.2) and a 2.3-fold risk for installation, maintenance, and repair jobs (95% CI = 1.9, 2.8).

Employees with clinical examinations (firefighters/emergency medical technicians)

The studies on FDNY workers, who had a pre-9/11 health baseline, provided an ideal benchmark for judging the impacts of WTC Dust on any employed group. As noted earlier in this review, one of the clear early results of working in indoor or outdoor areas where WTC Dust contamination was substantial was a persistent cough, called “WTC cough” (Chen and Thurston 2002). “WTC cough” was accompanied by bronchial hyperreactivity and respiratory distress (Prezant et al. 2002) in 8% of the highly exposed firefighters who were examined at NYU. Of the 332 firefighters having “WTC cough,” 95% had symptoms of shortness of breath, 87% had GERD, and 54% had nasal symptoms.

Banauch et al. (2002) reported injuries and illnesses among FDNY rescue workers responding to the WTC disaster. During the 48 h after the buildings collapsed, ≈ 90% of 10,116 FDNY rescue workers exposed at the WTC site reported an acute cough, often accompanied by nasal congestion, chest tightness, or chest burning, but only three of them required hospitalization. Compared with the numbers of service-connected, respiratory

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medical leave incidents (n = 393) during the 11 months preceding the attacks, the number of respiratory medical leave incidents (n = 1,876) increased 5-fold during the 11 months after the attacks. During February 2002, the incidence of new respiratory illness requiring either medical leave or light duty began to decrease and during May 2002 began to approach pre-attack incidence.

Banauch et al. (2002) also reported that during the 6 months after the disaster, 332 firefighters and one EMS worker had WTC-related cough severe enough to require > 4 consecutive weeks of medical leave. Despite treatment of upper and lower aerodigestive tract irritation (i.e., sinusitis, GERS, and/or asthma), 173 (52%) of 333 showed only partial improvement of WTC-related cough and remain either on medical leave or light duty or are pending a disability retirement evaluation. As of August 28, 2002, a total of 358 firefighters and five EMS workers remained on medical leave or light duty assignment because of respiratory illness that occurred after WTC exposure. On the basis of applications for respiratory disability retirement benefits during the preceding 6 months, an estimated 500 FDNY firefighters (4% of 11,336 total FDNY firefighter workforce) might eventually qualify for disability retirement because of persistent respiratory conditions. The high incidence of respiratory problems and related medical leave among FDNY rescue workers demonstrates the need for adequate respiratory protection. During the collapse, 52% of workers did not wear respirators, and 38% did not wear respirators for the rest of the first day. In addition, most of those reporting the use of a respirator during the first day used only a disposable paper dust mask that was neither NIOSH certified nor fit tested. However, despite widespread acknowledgment that rescue workers at future disasters be provided with respiratory protection as soon as possible, such plans will be successful only if barriers to use, such as supply, heat stress and discomfort, communications, training, compliance, and supervision, are resolved.

Banauch et al. (2003) conducted a prospective study of a representative sample of 179 FDNY fire/rescue workers to examine links between WTC Dusts and pulmonary hyperreactivity and WTC cough at 1, 3, or 6 months after 9/11. Subjects in both the highly and moderately exposed group showed significant declines in FVC, forced expiratory volume in 1 s (FEV_1), and FEV_1/FVC, when contrasted with control workers. Bronchial hyperreactivity showed a dose–response trend at 1, 3, or 6 months follow-up. For the highest exposure group, the median methacholine (Mch)-induced rise at 6 months was 46% for the median at 1 month, and a worsening of bronchial hyperreactivity over 5 months. After adjusting for smoking and airflow obstruction, highly exposed workers at 1 month were 7.3 times more likely (95% CI: 1.5, 34.1) to have hyperreactive airways than controls. For moderately exposed workers at 1 month, the risk was 6.3 times (95% CI: 1.7, 23.5); at 6 months, it was 6.8 times (95% CI: 1.8, 25.2). Among subjects who had hyperreactive airways at 6 months, respiratory symptoms were more frequent (p = 0.049); medical leave for respiratory illnesses was significantly longer (p = 0.022); it was found that medical leave days among hyperreactive subjects was 45 versus 12 days in non-reactive workers; and FEV_1 < 80% predicted was 18% versus 3% (p = 0.032) in comparison to non-reactive subjects. Compared with non-reactive workers, workers with hyperreactive airways at 1 or 3 months were 7.3 times more likely (95% CI: 2.6, 20.5) to develop WTC cough. A presence

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of hyperreactive airways is indicative of chronic and acute asthma. This research study began the process of seeing asthma as one of the WTC Dust respiratory hallmarks—one of the conclusions arrived at later by Guidotti et al. (2011).

Banauch et al. (2005a,b) reviewed aerodigestive inhalation lung injuries resulting from WTC Dust exposure and the persistence of non-specific bronchial hyperreactivity (Mch PC20 < 8 mg/ml) in a representative sample of 179 FDNY rescue workers stratified by exposure intensity (according to arrival time). They underwent challenge testing at 1, 3, 6, and 12 months post-collapse. Aerodigestive tract inflammatory injuries, such as declines in pulmonary function, RADS, asthma, reactive upper airways dysfunction syndrome (RUDS), GERD, and rare cases of inflammatory pulmonary parenchymal diseases, were documented in WTC RRWs and volunteers. In FDNY rescue workers, there was persistent hyperreactivity associated with exposure intensity, independent of airflow obstruction. At 1 year post-collapse, 23% of highly exposed subjects were hyperreactive as compared with only 11% of moderately exposed workers and 4% of the controls. At 1 year, 16% met the criteria for RADS.

Banauch et al. (2006) did a longitudinal study of pulmonary function in 12,079 FDNY rescue workers employed on or before 09/11/2001. Between 01/01/1997 and 09/11/2002, 31,994 spirometries were obtained and the FEV_1 and FVC were analyzed for differences according to estimated WTC Dust exposure intensity. Adjusted average FEV_1 during the first year after 09/11 was compared with the 5-year period before the disaster. Median time between 09/11/2001 and a worker's first spirometry afterward was 3 months; 90% were assessed within 5 months. WTC Dust-exposed workers experienced a substantial reduction in adjusted average FEV_1 during the year after 09/11/2001 (372 ml; 95% CI = 364–381 ml; $p < 0.001$). This exposure-related FEV_1 decrement equaled 12 years of aging-related FEV_1 decline. Moreover, exposure intensity assessed by initial arrival time at the WTC site correlated linearly with FEV_1 reduction in exposure intensity–response gradient ($p = 0.048$). Respiratory symptoms also predicted a further FEV_1 decrease ($p < 0.001$). Similar findings were observed for adjusted average FVC.

Weiden et al. (2010) studied the FDNY cohort and examined 1,720 subjects who were sent for pulmonary medicine evaluations, which included 919 PFT, 122 for Mch challenge tests, and 982 computerized tomography (CT) scans. For the subjects who had PFT before 9/11, there were significant declines in median FEV_1 and the ratio of FEV_1/FVC, and 59% had obstructive airways disease (OAD) based on a variety of factors. When adjusted for age, race, gender, height, weight, and smoking, the decline in FEV_1 was significantly correlated with predicted residual volume % and response to bronchodilators. This set of findings is consistent with injury to the airways, including bronchial wall thickening of the large airways, which was seen in CT scans. They proposed the presence of air trapping in the lung, rather than interstitial lung disease, with the cause being exposure to alkaline dusts and other pollutants from the WTC collapse.

Rom et al. (2010) reported that FDNY firefighters had significant respiratory symptoms characterized by cough, dyspnea, gastroesophageal reflux, and nasal stuffiness with a significant 1-year decline in FVC and FEV_1. Bronchial hyperreactivity measured by Mch

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challenge correlated with bronchial wall thickening on CT scans. Compared with the NHANES III data for FVC and FEV_1, 32% of 2,000 WTC Dust-exposed residents and cleanup workers were below the lower 5th percentile. The most common abnormality was a low FVC pattern, a finding similar to that also described for individuals in rescue and recovery activities. Among those complaining of respiratory symptoms with normal spirometry, almost half had abnormalities detected with impedance oscillometry consistent with distal airways disease.

Webber et al. (2011) examined physician-diagnosed asthma and other respiratory ailments in the prospective NYU cohort of FDNY firefighters. They studied 14,314 firefighters and emergency medical service (EMS) providers who were also employed by FDNY. After exclusions, there were 9,715 male firefighters and 1,228 male EMS workers studied, and their median age was 40 years. There were also 863 retired firefighters (7.9% of the 10,943 total), who had returned to assist the rescue efforts. It is worth noting that subjects with a history of OAD (such as asthma, COPD, and emphysema) were excluded from employment in FDNY, and furthermore they had to have a FEV_1 of at least 80% of predicted (70% for EMS workers). Thus, in this group, there were only 85 asthma cases diagnosed prior to 9/11 and no cases of emphysema. Exposure category was determined according to the time the firefighters arrived at WTC site: Group 1 arrived the morning of 9/11; Group 2 arrived in the afternoon of 9/11; Group 3 arrived after 9/12; and Group 4 arrived between Days 3 and 14 after 9/11. They also dichotomized duration of exposure to WTC Dust into 1–3 months, and 4–11 months.

The self-reported symptoms and illnesses from the most recent health survey showed 17.3% with sinusitis; 12.2% with bronchitis; 9.3% with asthma; and 4.1% with COPD/emphysema. The rates were greatest among the retirees, but there was very little difference between EMS workers and firefighters. Those arriving early at Ground Zero reported an MD-diagnosed asthma of 14%, while those arriving later had an asthma rate of 5.9%. This yielded an OR of 3.3 (95% CI: 2.4, 4.8). This pattern was the same for all respiratory diagnoses. After adjusting for smoking, age, arrival group, and duration of exposure to dust, retirees were 10.2 times more likely to have asthma (95% CI: 8.3, 12.4) than active men; and they were 7.4 times more likely to have COPD/emphysema (95% CI: 5.3, 10.5). The authors also reported a link between the quintile of FEV_1% and self-reported OAD. Thus, the lowest FEV_1% predicted 41.1% of men with asthma and 50.6% with COPD/emphysema, while those firefighters in the highest FEV_1% had only 10.5% with asthma and 6.8% with COPD/emphysema. By contrast, of those firefighters not reporting any respiratory diagnosis (i.e., those without any respiratory conditions), 23.5% were in the highest quintile and 14.6% were in the lowest FEV_1%. EMS workers showed the same pattern. Sinusitis (9.7%) and asthma (8.8%) were the most common physician diagnoses, and those with the longest exposures, that is, 4–11 months at WTC site, had the most reported cases of sinusitis (11.4%) and bronchitis (10.3%). Comparing fire-fighters arriving in exposure Group 1 with those arriving in Group 4, there was 11.4% with asthma contrasted with 5.3%. This produces an OR of 1.4 (95% CI: 1.0, 2.1). After adjusting for smoking, age on 9/11, and arrival group, the retirees had an OR of 10.0 (95% CI: 7.8, 11.9) compared with active duty firefighters. Cough, shortness of breath, and wheeze were clearly correlated with lowest

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quintiles of FEV_1%, whereas those without respiratory symptoms showed the opposite pattern.

Antao et al. (2011) reviewed reports of serious respiratory illness among RRWs in the WTC Health Registry following the WTC attacks to assess the effects of different respiratory protection equipment (RPE) types on respiratory outcomes, that is, recurrent respiratory symptoms and diseases possibly associated with 9/11 exposures. They performed descriptive and multivariate analyses adjusting for demographics and exposure variables. The strongest predictors of using adequate RPE were being affiliated with construction, utilities, or environmental remediation organizations and having received RPE training. Workers who used respirators were less likely to report adverse respiratory outcomes compared with those who reported no/lower levels of respiratory protection.

Kazeros et al. (2013) hypothesized that persistent asthma-like symptoms in WTC Dust-exposed individuals would be associated with systemic inflammation characterized by peripheral eosinophils. Their WTC Environmental Health Center (WTCEHC) patients underwent a standardized evaluation including questionnaires and complete blood count. Between September 2005 and March 2009, 2462 individuals enrolled in the program and were available for analysis. Individuals with preexisting respiratory symptoms or lung disease diagnoses prior to September 2001 and current or significant tobacco use were excluded, and 1,517 individuals met the inclusion criteria. Patients had a mean age of 47 years, with 51% being female and with a diverse race/ethnicity. Respiratory symptoms that developed after WTC Dust/fume exposure and remained persistent included dyspnea on exertion (DOE) (68%), cough (57%), chest tightness (47%), and wheeze (33%). A larger percentage of patients with wheeze had elevated peripheral eosinophils compared with those without wheeze (21% vs. 13%, $p < 0.0001$). Individuals with elevated peripheral eosinophils were more likely to have airflow obstruction on spirometry (16% vs. 7%, $p < 0.0003$). These data suggest that eosinophils may participate in lung inflammation in this population with symptoms consistent with WTC-related asthma.

World Trade Center Day Laborer Medical Monitoring Project at Queens College

Malievskaya et al. (2002) described a free medical screening program provided by Queens College (the WTC Day Laborer Medical Monitoring Project) for building cleanup workers who did not work at Ground Zero, but were responsible to clean contaminated office and residential buildings in the vicinity. Many of the building workers were day laborers, who were hired from street corners on a daily or weekly basis, were of Hispanic ethnicity, did not speak English, lacked health insurance, and did not have training working with hazardous materials. From 1/15/02 to 2/28/02, 418 building cleanup workers who worked in indoor cleaning operations for at least 1 week were examined in a mobile clinic. Workers were also fitted and provided with respirators and provided instructions about potential work hazards and safety practices. Most of the participants worked in the cleanup for 6–12 weeks, and had stopped such work 4–8 weeks prior to examination. “Nearly all” of the examined workers reported current health symptoms that first appeared or worsened after 9/11, including irritation of the airways (cough, sore throat, nasal congestion, and chest tightness) and

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systemic symptoms (headaches, fatigue, dizziness, and sleep disturbances). Most of those who reported symptoms experienced little or no improvement despite cessation of work 4–8 weeks prior to examination. Unfortunately, no quantitative data were reported.

Residential and working community members with WTC Dust exposure

Several studies have documented adverse health effects in the local community. New-onset symptoms in the residential community were described in a field study of community members. A dose–response relationship was described that was related to home conditions (Lin et al. 2005, Reibman et al. 2005).

Analysis of the WTC registry population demonstrated an increase in upper and lower respiratory symptoms (many papers demonstrate this) and an analysis of a subgroup showed a dose–response relationship between the persistence of lower respiratory symptoms, lung function, and exposure (Maslow et al. 2012)

According to Reibman et al. (2009), over 360,000 local workers and over 57,000 residents south of Canal Street in Lower Manhattan alone have been estimated to have had potential for WTC Dust and fume exposure following 9/11/01 (Farfel et al. 2008). Most local workers returned to the surrounding offices 1 week after the event when Lower Manhattan was officially reopened for business. Some residents closest to the site were evacuated and returned over the ensuing 3 months. Many residents remained in their apartments and were never evacuated. Although most individuals cleaned their own residence or worksite, formal cleanup of indoor and outdoor commercial sites, and of some residential sites was performed by workers hired specifically for the activity.

Reibman et al. (2009) described physical symptoms in local residents, local workers, and cleanup workers who were enrolled in the WTCEHC treatment program, had been examined at Bellevue Hospital by NYU physicians, and had reported symptoms and exposure to the dust, gas, and fumes released with the destruction of the WTC on 9/11/01. Of the 1,898 individuals who participated between September 2005 and May 2008, upper and lower respiratory symptoms that began after 9/11/01 and had persisted at the time of examination were common in each exposed population. The most common abnormality was “low FVC,” a finding similar to that for individuals involved in rescue and recovery activities. This was observed in each exposure category. Since they could not identify a clear relationship between exposure to the dust cloud and the presence of abnormal spirometry pattern, and to further clarify the mechanism for respiratory symptoms in the patients with normal lung function, they sampled the population to evaluate whether the symptoms were associated with airway hyperresponsiveness. Between October 2007 and March 2008, individuals with normal spirometry and any lower respiratory symptom, defined as cough, shortness of breath, or wheeze, were referred for Mch challenge studies. Sixty-eight individuals completed the examination; 51% of them had a $PC_{20} < 4$ mg/ml, consistent with airway hyperreactivity. They examined whether patients with any of the abnormal spirometry patterns had improved lung function after bronchodilator administration. There was a significant improvement in FEV_1in patients with the “obstructed” pattern ($p < 0.0001$) and a significant, but small improvement in FEV_1 in patients with a “low FVC” pattern ($p <$

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0.0003). Both the $FEV_1$and FVC improved in response to bronchodilator in the "obstructed and low FVC" group ($p < 0.0001$). As DOE was the most common symptom identified, they examined whether there was an association between a severity level of "3" or more in the MRC dyspnea scale and abnormal spirometry. A dyspnea score of "3" or more was associated with a "low FVC," or an "obstructed and low FVC" pattern in the total population ($p < 0.0001$ and $p < 0.0004$, respectively) and in the population with a 5 pack/year tobacco smoking history ($p < 0.005$ and $p < 0.05$, respectively).

In summary, spirometry measurements below the lower limit of normal were found in 31% of those studied. Thus, residents and local workers, who were believed to have had less exposure to WTC Dust compared with those with work-associated exposure to WTC Dust, also had new and persistent respiratory symptoms with lung function abnormalities 5 or more years after the WTC Towers' destruction.

Populations with work-related or residential exposures to WTC Dust based on questionnaire responses

Rescue, recovery, and cleanup workers were usually regarded as the ones most heavily exposed to WTC Dust, as they engaged in activities that routinely brought them into dust-contaminated areas. However, other groups could be heavily exposed simply by being submerged in the heavy dust cloud in Lower Manhattan on 9/11/01 or soon thereafter if they moved about as they returned to work, homes, and schools before the dust was removed, for example, residents, students, or workers in downtown office buildings or schools. Overall, while the exposures of these latter groups were never measured, they were generally considered to be less intense and/or shorter in duration than those of the rescue, recovery, and cleanup workers. In any case, the short-term and cumulative exposures of these other populations were to the same WTC Dust constituents and NIEHS supported population-based studies to determine if they would be at risk for the same kinds of adverse health responses as the on-site Ground Zero workers.

Trout et al. (2002) examined data on the health status of Federal employees working in an office building close to the WTC on 9/11. A cross-sectional assessment of their health symptoms was conducted 3 months post-9/11 on a total of 191 NYC employees and 155 employees in an office building in Dallas that served as a comparison population. Limited industrial hygiene sampling in the NYC building revealed low levels of WTC contaminants of concern. Only 4 of the NYC employees (2%) resided in Lower Manhattan post-9/11. The NYC and Dallas cohorts were similar with respect to age, gender, race, history of asthma, history of bronchitis, current smoking status, and degree of social support, and only differed significantly with respect to education ($p < 0.01$, higher educational attainment in Dallas) and history of allergy, hay fever, or eczema ($p < 0.01$, higher rates in Dallas). Employees in NYC reported multiple constitutional symptoms at a higher frequency than Dallas workers, including a 6-fold higher prevalence of shortness of breath (prevalence ratio [PR] = 6.1, 95% CI: 2.9–13.1) and chest tightness (PR = 6.0, 95% CI: 2.8–12.9), a 3.5-fold higher prevalence of wheezing (PR = 3.5, 95% CI: 1.8–7.1), and a 2-fold higher prevalence of cough (PR = 2.1, 95% CI: 1.6–2.8), among others. Adjustment for covariates such as gender, race, education, age, and cigaret smoking did not account for the differences in symptom

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prevalence between NYC and Dallas Federal workers. For most symptoms, the majority of NYC workers reported worsening of the symptom with exposure to the worksite after 9/11.

Bernard et al. (2002) reported the results from a Centers for Disease Control and Prevention (CDC) survey of physical and mental health symptoms among workers at four NYC schools. Two schools near the WTC site (High School A, reopened to staff on 10/20/11; college A, reopened to staff on 9/26/11) were compared with a high school (High School B) and college (College B) that were located 5 or more miles from the WTC site. High School A and College A were both within two blocks of the still-burning WTC site and adjacent to a barge operation carrying the debris to the landfill site outside Manhattan, but no information was provided on the degree of contamination present in the schools at the time of reopening. Surveys were administered in January and March 2002 to teaching, administrative, support, and non-contract staff. Questions about symptoms were based on presumed types of exposures and employee concerns. Persistent symptoms were defined as either symptoms that existed before 9/11 but worsened after 9/11, or new symptoms that developed after 9/11 and had not improved. Participation rates were high in both high schools and moderate in both colleges, and staff at all four workplaces were comparable on age, sex, race, education, and smoking status. The prevalence of self-reported irritative and respiratory symptoms was significantly higher for the exposed schools compared with the comparison schools ($p \leq 0.05$), and strengthened further when considering persistent symptoms 4–6 months after 9/11.

Fagan et al. (2002) summarized the results of a telephone survey conducted 5–9 weeks after 9/11 among 988 Manhattan residents, aged ≥ 18 years, living south of 110th Street, identified by random digit dialing. Of 134 respondents who self-reported having been told by a doctor that they had asthma prior to 9/11, 34 (27%) reported worsening of asthma symptoms after 9/11. Respondents with asthma who lived or were present south of Canal Street on 9/11 were more likely than others to report increased asthma symptoms (OR = 1.7, 95% CI: 0.5–5.7), although the association failed to attain statistical significance, most likely because of the small number of individuals reporting this exposure ($n = 17$) in the sample. Exposure to smoke/debris causing difficulty breathing was significantly associated with worsening asthma (OR = 4.6, 95% CI: 1.7–12.1), which strengthened after multivariate adjustment for significant pre- and post-9/11 psychological predictors and potential confounders (OR = 7.0, 95% CI: 2.3–21.3).

Wagner et al. (2005) conducted a cross-sectional study conducted between July 2001 and September 2002 examining asthma status following the WTC collapse in NYC Medicaid managed care enrollees aged 5–56 years. In order to be eligible for the study, enrollees had to meet one or more of the following criteria between September 1, 2000 and August 31, 2001: 1) ≥ 4 asthma medication dispensing events, 2) ≥ 1 emergency department visits related to asthma, 3) ≥ 1 acute inpatient hospitalization related to asthma, and 4) ≥ 4 outpatient visits related to asthma and ≥ 2 asthma medication dispensing events. A questionnaire regarding asthma indicators and general health status was sent to all eligible enrollees, and respondents' demographic characteristics, medical service utilization, and pharmacy data were extracted from the Medicaid Encounter Data System through December 31, 2001. Complete data were available on 3,557 participants. A total of 44.7% of

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participants reported that their asthma became worse after 9/11. The prevalence of worsened asthma post-9/11 differed significantly by neighborhood on 9/11 ($p < 0.001$), with the highest proportion reporting worsened asthma in Lower Manhattan (70.2%), followed by Western Brooklyn (61.3%) and the rest of NYC (43.1%). Time spent in Lower Manhattan was also significantly associated ($p < 0.0001$) with prevalence of worsened asthma post-9/11, with the highest proportion in individuals with worsened asthma spending 4 or more days (63.2%), followed by 1–3 days (56.5%) and 0 days (37.5%). Increasing prevalence of worsened asthma post-9/11 was also significantly associated with poorer health status ($p < 0.0001$), increased asthma severity ($p < 0.0001$), and increased use of inhaled steroids ($p < 0.0001$). The most frequently reported self-described reason why asthma worsened post-9/11 was more dust in the air (63%). In a multivariate model controlling for numerous demographic, usage, location, and disease status variables, the following ORs were calculated for worsened asthma post-9/11: neighborhood on 9/11 in Lower Manhattan (OR = 2.28, 95% CI: 1.76–2.95), neighborhood on 9/11 in Western Brooklyn (OR = 2.40, 95% CI: 1.87–3.07), 4 + days spent in Lower Manhattan (OR = 2.43, 95% CI: 2.04–2.89), 1–3 days spent in Lower Manhattan (OR = 1.95, 95% CI: 1.78–2.14), and poor health status (OR = 3.37, 95% CI: 2.69–4.22). Despite a low response rate (25%) and cross-sectional design used to collect the questionnaire data, the use of Medicaid usage data allowed for the identification of persistent physician-diagnosed asthma prior to 9/11. Therefore, this prospective data series on asthma status supports the proposition that exacerbation of asthma symptoms post-9/11 can be directly linked to exposures related to the WTC Tower's collapsing.

Green et al. (2006) examined changes in health care use among residents of NYC using health care claims data from a large insurance provider. Compared with average usage rates in the New York Consolidated Metropolitan Statistical Area or MSA between January and August 2001 (i.e., prior to 9/11), average rates of healthcare visits among individuals residing within 10 miles of the WTC site increased significantly in the post-9/11 period from October to December 2001 for respiratory diseases and conditions including cough (14.6% increase, $p < 0.01$), asthma (4.1% increase, $p < 0.01$), acute upper respiratory infection (6.2% increase, $p < 0.01$), and bronchitis (1.5% increase, $p < 0.01$). In contrast, during the same time period, for individuals residing 10–50 miles from the WTC site, decreases in usage were seen for the same respiratory diseases and conditions, indicating that the observed increases of these conditions among residents within 10 miles of the WTC were not an artifact of generalized trends, such as seasonal differences. The increases in respiratory diseases and conditions observed within 10 miles of the WTC site are of further significance given that health care services use in the region declined significantly during the 3-week period post-9/11. These data reflect health care usage among insured individuals; they do not represent the entire population of individuals exposed to WTC Dust. However, the availability of pre-9/11 data supports a finding that significant increases in respiratory disease morbidity occurred post-9/11 among individuals residing in geographical proximity to the WTC site.

Lin and Reibman reported a series of results from a study aimed at determining whether there was an increase in the incidence of new-onset and persistent upper and lower

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respiratory symptoms in residents living near Ground Zero compared with residents of a control area (Reibmanet al. 2005, Lin et al. 2005, 2007, 2010b). The affected area was located within 1.5 km of Ground Zero, and included 49 buildings with ≈ 9,200 households. Since the health histories prior to 9/11 of residents living near the WTC were not available, and respiratory diseases usually have a strong seasonal component, a control area was selected by identifying control buildings in census blocks with similar characteristics as the affected area that were considered not impacted by WTC Dust. A total of ≈ 1,000 households from five Upper Manhattan apartment buildings more than 9 km from the WTC were selected. The affected area was sampled at an approximately 9:1 ratio compared with the control area. Individuals were excluded if they were born after 9/11, temporarily moved out of the residence after 9/11 and returned on or after 1/1/02, did not reside at the address on 9/11, or lived in the control area but worked in the affected area. In households with more than four persons, two adult residents and the two oldest residents under age 18 years were asked to complete the individual questionnaire. Questionnaires were distributed 1 year (± 4 months) after 9/11. Responses were obtained from 2,520 residents in the exposed area and 295 in the control area.

Approximately 1 year after 9/11, the cumulative incidence of upper respiratory symptoms was significantly higher in the WTC-affected area compared with the control area, both for new-onset symptoms and new-onset persistent symptoms (defined as a new-onset symptom that had bothered the subject “some” or “a lot” in the 4 weeks prior to completing the survey). Significantly higher rates were also seen in the WTC-affected area for unplanned medical visits for respiratory problems in the prior month, initiation of respiratory medication post-9/11, and use of respiratory medications and/or asthma medications in the past 4 weeks. Physician diagnoses of asthma after 9/11 were slightly higher in the affected area, but did not attain statistical significance. Self-reported prevalence of shortness of breath with varying levels of exertion was found to be increased in both the affected and control areas when comparing pre-9/11 to post-9/11 periods. In the post-9/11 period, shortness of breath was significantly worse in the affected area compared with that in the control area, even after adjustment for potential confounders (Lin et al. 2005). Analyses restricted to 2,103 exposed and 254 control residents who did not have a pre-9/11 diagnosis of respiratory disease observed similar statistically significant increased risks of new-onset and persistent new-onset respiratory symptoms. No significant differences in baseline spirometry were observed between control asymptomatic subjects, exposed asymptomatic subjects, and exposed subjects with persistent symptoms (Reibman et al. 2005).

A total of 30.7% of affected area residents reported some physical damage to their home after 9/11, resulting in significantly higher rates of indoor dust and odors in the affected area compared with those in the control area. Residential damage, the presence of dust, and cleaning activities were associated with elevated risks of any new-onset upper and lower respiratory symptoms, which remained after control for potential confounders. The presence of dust in the residence showed the strongest association with any upper respiratory symptom (CIR = 1.35, 95% CI: 1.18–1.54). Risks were further elevated for persistent upper and lower respiratory symptoms. A significant dose–response relationship was observed with duration of dust or odors in the home for new-onset upper respiratory ($p < 0.05$ for

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trend), new-onset lower respiratory ($p < 0.05$ for trend), new persistent upper respiratory ($p < 0.05$ for trend), and new persistent lower respiratory symptoms ($p < 0.05$ for trend). In a model that combined residential exposure, work exposure, and the presence below Canal Street on 9/11, residential exposure was a significant predictor of upper and lower respiratory symptoms, which strengthened further with the addition of workplace and/or 9/11 exposures (Lin 2007).

Lin et al. (2010b) reported on lower respiratory symptoms after an additional ~3 years of follow-up. The proportion of WTC-affected residents reporting any lower respiratory symptom had declined from 55.5% to 47.8% at 2- and 4-year post-9/11, but remained considerably higher than the post-9/11 rates reported among controls (20.0%). Individual symptoms followed similar trends, and objective indicators (e.g., use of medicines for asthma and new diagnoses of lower respiratory disease) showed improvement over time. In WTC-affected residents who did not have a diagnosis of asthma, COPD, chronic bronchitis, or other lung disease prior to 9/11 ("previously healthy"), exposure to WTC Dust in the home was associated with elevated and often statistically significant risks of lower respiratory symptoms, at both the 2- and 4-year time points. Similar to the previous study (Lin 2007), both living and working in the affected area were associated with a higher prevalence of reported lower respiratory symptoms at 2 years compared with only living in the affected area. Comparable analyses examining upper respiratory symptoms at 2 and 4 years did not observe any major differences between the control and affected areas, nor did they find an association with home conditions. However, this was not unexpected, as most upper respiratory symptoms evaluated represent more short-term acute effects rather than long-term chronic effects of environmental exposure.

Laumbach et al. (2009) used data from a representative population sample of 1,810 respondents surveyed ≈ 6 months after 9/11 by telephone, and modeled estimates of WTC plume intensity to assess the relationship between estimated plume intensity and respiratory symptoms. Estimated plume data came from an existing WTC model, and survey participants were assigned a cumulative residential plume intensity estimate based on their address on 9/11. Respondents living outside of NYC on 9/11 were assigned a plume intensity estimate corresponding to the center of the town in which they lived. The 5-day cumulative relative plume intensity at the location of residence was used as a proxy for WTC exposure. After excluding residents living in Lower Manhattan, subjects were classified as exposed if their plume intensity was ≥ 75th percentile of the distribution among all study subjects. Exposed participants were more likely to report difficulty breathing because of smoke or debris during the WTC collapse, which was statistically significant among individuals without asthma prior to 9/11 ($p < 0.01$) and of borderline significance among prior asthmatics ($p = 0.08$). After adjustment for potential confounders, there was no association observed between WTC exposure among non-Lower Manhattan residents and new-onset wheeze/cough in non-asthmatics (adjusted OR range = 1.0–1.1), or for worsening asthma among pre-9/11 asthmatics (adjusted OR range = 0.5–1.0). When comparing Lower Manhattan residents to Upper Manhattan (above 14th Street) residents, however, a significant association was observed among non-asthmatics for new-onset wheeze/cough (adjusted OR = 1.9, 95% CI: 1.1–3.5) and persistent new-onset wheeze/cough (adjusted OR

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= 2.5, 95% CI: 1.1–5.9). However, no association was observed for worsening asthma among asthmatics (adjusted OR range = 0.4–0.9). Results from additional sensitivity analyses were mixed. The general findings of this study stand in contrast to most other studies of WTC-exposed populations. While the use of plume modeling to assign exposure was a strength of the study, no information on work location was captured, which could result in exposure misclassification. Furthermore, a large numbers of residents in the vicinity of WTC were displaced after the collapse, and would not have been captured by the survey.

Lin et al. (2010a) used hospital admission records from 1999 to 2001 with a diagnosis of respiratory, cardiovascular, or cerebrovascular illness and a residential address in Lower Manhattan (the “hot zone” and “near zone”) or Queens to compare changes in admission rates in Queens (control area) to rates in Lower Manhattan before and after 9/11. The control area in Queens was selected because it was at least 5 miles from the affected area, less likely to have been affected by the plume, and was similar (± 5%) to the affected area with respect to population density, race, ethnicity, median household income, and poverty status. Hospital records were identified from the NYS Department of Health or NYSDOH Statewide Planning and Research Cooperative System or SPARCS, which contains hospital discharge data for at least 95% of all acute care hospital admissions in the State (not including psychiatric and federal hospital admissions). Respiratory diseases included the following principal diagnoses: chronic bronchitis, emphysema, asthma, COPD, acute bronchiolitis (in children aged 0–4 years only), and acute bronchitis (in children aged 0–4 years only). Average rates in the 4-week pre- and post-9/11 were used for a more stable estimate that would be less prone to weekly and seasonal fluctuations. The 8-week period pre- and post-9/11 was also used to further explore temporal patterns of admissions. Pre- versus post-9/11 comparisons were conducted within the affected area only. Additionally, weekly hospital admission rates pre- and post-9/11 were compared with the average rate during the same week in the preceding 10 years, and a weekly rate in 2001 was considered statistically significant if it was above the upper 95% confidence limit of the 1991–2000 average weekly rate. Compared with the control area, hospital admissions for respiratory diseases in the affected area were lower prior to 9/11 (8/14–9/10) (PR = 0.74, 95% CI = 0.14–3.87), and then increased significantly in the week of 9/11–9/17 (PR = 5.24, 95% CI: 1.44–19.00). Rates in the affected area dropped again in the subsequent weeks, with an additional peak observed during the week of 10/16–10/22. For asthma, hospital admissions in the affected area were higher than the control area prior to 9/11 (8/14–9/10) (PR = 1.31, 95% CI = 0.12–14.06). Rates peaked during the week of 9/11–9/17, although no prevalence rate was calculated because there were 0 admissions in the control area for asthma during that week. A similar drop-off was observed in the subsequent weeks, but admissions returned to higher levels in the affected area in October. Using the period pre-9/11 as reference, hospital admissions in the affected area were higher for both respiratory diseases and asthma from 9/11 through early-to-mid October. Compared with the average rates in the affected area from 1991 to 2000, hospitalization rates in 2001 for respiratory diseases and asthma were observed to peak significantly immediately after 9/11, drop off in the subsequent weeks, and then reemerge later at a lower frequency. These trends were remarkably consistent over several different analytical designs, supporting the validity of the

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observed temporal cluster of respiratory-related hospital admissions occurring immediately after 9/11/01.

Mauer et al. (2010 a,b, and c) described long-term respiratory symptoms in NYS employees who were WTC responders on or after 9/11/2001. They were initially mailed self-administered questionnaires (initial, Year 1, and Year 2) and then they completed a telephone interview in Year 3. WTC exposure was associated with lower respiratory symptoms (LRS), including cough symptoms suggestive of chronic bronchitis, 5 years post-9/11. When exposure was characterized using an exposure assessment method, the magnitude of effect was greater in those with exposure scores above the mean. WTC exposure was associated with persistence of LRS over the 3-year study period. Participants with the highest exposures were more likely to experience increased severity of their asthma condition and/or LRS. Even in a moderately exposed responder population, lower respiratory effects were a persistent problem 5 years post-9/11.

Udasin et al. (2011) sought to determine if WTC disaster responders had lower lung function and higher bronchodilator responsiveness than those with respiratory symptoms and conditions. They evaluated cardinal respiratory symptoms (dyspnea, wheezing, dry cough, and productive cough) and determined the difference in FEV_1, FVC, and bronchodilator responsiveness. All respiratory symptoms were associated with a lower FEV_1 and FVC, and a larger bronchodilator response. Responders reporting chronic productive cough, starting during WTC work and persisting, had a mean FEV_1 109 ml lower than those without chronic persistent cough; their odds of having abnormally low FEV_1 was 1.40 times higher; and they were 1.65 times as likely to demonstrate bronchodilator responsiveness. The conclusions reached from these data were that responders reporting chronic persistent cough, wheezing, or dyspnea at first medical examination were more likely to have lower lung function and bronchodilator responsiveness.

Li et al. (2011) examined new-onset GERS after 9/11/2011 and persisting up to 5–6 years in relation to WTC-related exposures among 37,118 adult (i.e., RRWs, local residents, area workers, and passersby in Lower Manhattan) WTC Health Registry enrollees, and potential associations with comorbid asthma and PTSD. Cumulative incidence was 20% for post-9/11 GERS and 13% for persistent GERS. Among enrollees with neither asthma nor PTSD, the aRR for persistent GERS was elevated among workers arriving at the WTC pile on 9/11 (aRR = 1.6; 95% CI = 1.3–2.1) or working at the WTC site > 90 d (aRR = 1.6; 1.4–2.0), residents exposed to the intense dust cloud on 9/11 (aRR = 1.5; CI = 1.0–2.3) or who did not evacuate their homes (aRR = 1.7; CI = 1.2–2.3), and area workers exposed to the intense dust cloud (aRR = 1.5; CI = 1.2–1.8).

Summary and conclusions for population-based studies that compared health status of groups with relatively high WTC Dust exposure groups with that of groups with little/no WTC Dust exposure

Guidotti et al. (2011) summarized available peer-reviewed clinical and epidemiology literature in order to account for the complex nature of WTC Dust and pulmonary health

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effects, including persistent chronic airway disorders found among both smokers and non-smokers. These disorders present as acute asthma, non-specific bronchitis, early cough, and includes aggravation of existing COPD, asthma, or other respiratory conditions. These ailments can include air trapping and small airways disease, even though a very large proportion of the WTC Dust was present in relatively large particles. They concluded that the very high alkalinity (pH = 9–12) appeared to play a powerful role in the pulmonary conditions now being detected years after the disaster. Another characteristic of exposure to WTC Dust that they noted was the loss of pulmonary function and the taking of early disability or retirement, especially in view of how healthy First Responders (FRs) and cleanup workers were in contrast to the general population. Loss of pulmonary function was dose dependent, as shown by Weiden et al. (2010). Bronchial hyperreactivity and persistent asthma were shown to be hallmarks of the risks related to the levels of dust seen among firefighters (Prezant et al. 2002, Banauch et al. 2003). Guidotti et al. (2011) summed up their assessment by noting that "findings of air trapping and increased small airways resistance support the conclusion that airways obstruction has developed, expressing itself early on as small airways disease possibly at the level of the terminal bronchiole." There is evidence for relative risks for respiratory disease for WTC Dust exposure that exceed 2.0, as seen in Herbert et al. (2006), Webber et al. (2011), and Kim et al. (2012). Workers arriving early, or near 9/11, or those working the most time had greater risks than workers arriving later or working for shorter times.

The initial focus of the occupational health aspects of inhalation exposures to WTC Dust was appropriate and, as summarized by Guidotti et al. (2011) and others, demonstrated that such exposures were potent inducers of a variety of respiratory and GI tract disorders. More surprising, to many interested parties, was the demonstration of coherent responses, albeit generally less severe, in populations of Lower Manhattan office workers, school workers, and residents, who were presumed to have lower and even minimal levels of WTC Dust exposure.

Table 6 provides a summary of health-related responses reported in the peer-reviewed literature for cohorts studied in clinical settings at MSSM, NYU, and Queens College, as well as responses gathered through analyses of data on questionnaire responses among groups with incidental exposures in residences and office work locations. Table 6A shows statistically significant responses for groups engaged in rescue and recovery activities out-of-doors, while Table 6B provides a summary of health-related responses reported in the peer-reviewed literature for other population groups based on responses to exposures that took place mostly in indoor environments. The plausibility of causal relationships between exposure to WTC Dust and an increased risk of the specific respiratory effects for the data collected in clinical settings is strengthened by the evidence of overall respiratory toxicity associated with exposure to WTC Dust for other population groups whose data were collected via questionnaires. Some of the differences in the response patterns in Table 6 may be due primarily to the differences in the year of publication. The ones published prior to 2007 tended to report more of the shorter-term responses such as cough and respiratory symptoms, while those published in later years more frequently cited declines in pulmonary function and diagnoses for sarcoid that became more clearly evident with increasing time since the substantial initial exposures. Lastly, it is important to indicate to the readers that

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for each study shown in Table 6, what might appear to be selective positive findings is really reflective of outcomes in some categories not being positive simply because these were not studied at the time or reported in that particular paper.

The similarities and differences in the responses in Table 6 between those with occupational exposures and those with incidental exposures in residences and offices are notable. Furthermore, the various studies had somewhat different objectives and different strengths in terms of population size and the sensitivities of its assays, as well as the homogeneity of the WTC Dust exposures within the groupings. What is remarkable, in our view, is that the responses to incidental exposures appear to be so similar to those of the groups engaged in rescue and recovery activities that were believed, initially, to have been more heavily exposed. This suggests that duration of exposure to undisturbed dust residues may be as or more important than the shorter-term exposure to higher concentrations.

Many other WTC studies that we have not discussed in the text, or summarized in Table 6, have examined broader groupings of adverse respiratory effects, and found WTC exposures to be associated with increased risks and/or an elevated prevalence of the following general categories of symptoms as evidence for new or worsening

1) Upper respiratory symptoms (Feldman et al. 2004, Levin et al. 2004, Mauer et al. 2007, Tapp et al. 2005);

2) Lower respiratory symptoms, including cough, phlegm, dyspnea, and wheezing (Brackbill et al. 2006, Debchoudhury et al. 2011, Levin et al. 2002, Mauer et al. 2007, Niles et al. 2011, Salzman et al. 2004, Tao et al. 2007, Tapp et al. 2005); and

3) Respiratory symptoms (Brackbill et al. 2006 2014, Farfel et al. 2008, Feldman et al. 2004, Levin et al. 2002, Salzman et al. 2004, Spadafora 2002, Webber et al. 2011).

Temporal sequence is a critical criterion for attributing causation to WTC Dust exposure, since disease cannot precede exposure or be coincidental with it. In all cases discussed above, the asthma and other respiratory disease excesses occurred after 9/11/2001, and this was especially true among workers studied without respiratory ailments prior to 9/11 as seen in Herbstman et al. (2005). Almost all study authors were aware that smoking and age are potential confounding factors and investigators adjusted for them in their analysis. Every investigative team was aware that the WTC Dust was the specific risk factor they were testing for pulmonary effects, and there were multiple health effects found for this exposure including small airways impacts, impaired PFT, the presence of GERD, and the risk for asthma, COPD, and other chronic lung diseases. Overall, the cumulative evidence fits together and has been confirmed authoritatively by the WTC Health Program (Howard 2014).

The epidemiological studies are consistent and supportive of a causal association between WTC Dust exposure and adverse respiratory, upper digestive, and cardiac effects. Even short-term exposures were associated with increased risks of adverse conditions, and the risks often increased in a dose-related fashion, with more prolonged or more intensive

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exposures being associated with greater health risks. The evidence of a temporal association between exposures sustained on and following 9/11, and adverse health effects has been strengthened by the availability of pre-9/11 information and longitudinal data within the epidemiological database.

The plausibility of a causal link between WTC Dust and the health outcomes has been strengthened by the consistency of the findings outlined in this critical review. Overall, there is sufficient evidence that, to a reasonable degree of scientific certainty, exposure to WTC Dust is causally associated with increased risk of

- **a.** COPD;
- **b.** RADS;
- **c.** interstitial lung disease;
- **d.** restrictive lung disease;
- **e.** chronic laryngitis/pharyngitis;
- **f.** chronic rhinosinusitis; and/or
- **g.** specific upper digestive disorders, including GERD.

Insights gained from *in vivo* and *in vitro* studies of biologic responses to WTC Dusts

In vivo studies

While the evidence that the inhalation of WTC Dust produced adverse health effects in people is substantial, as discussed earlier in this review, there has, to date, been little supporting evidence from inhalation exposure studies in laboratory animals. Overall, conventional rodent studies have proven impractical, since particles with diameters > 2.5 μm would not penetrate the nasal passages of these obligatory nose-breathing species. To overcome this, Vaughan et al. (2014) developed a novel system to deliver the WTC Dusts, which are all in the coarse/supercoarse particle size ranges, into the lungs of rats. Using that system, some studies of acute and some chronic effects of WTC Dusts delivered by intratracheal (IT) instillation have been performed, and the outcomes described below are now appearing in the literature.

In one study, Cohen et al. (2014) used the Vaughan et al. (2014) IT inhalation exposure system to expose rats to samples (primarily supercoarse fraction) of settled WTC Dust that had been collected on-site in the period from 9/12 to 13/01. They administered two daily 2-h exposures at concentrations extrapolated to simulate that of mouth-breathing FRs present at Ground Zero in the first 72 h after the WTC collapsed. The study sought to examine, for the first time, potential toxicities in the lungs directly relevant to those likely faced by those FRs. To gain a general understanding of changes induced by the exposures, lungs of the exposed rats were harvested 2 h post-exposure, and total RNA was extracted for subsequent global gene expression analysis. Among the > 1,000 genes affected by WTC Dust (under isoflurane anesthesia) or isoflurane alone, 166 were unique to the dust exposure. In many instances, genes maximally induced by the WTC Dust exposure (relative to in naïve rats)

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were unchanged/inhibited by isoflurane only; similarly, several genes maximally inhibited in WTC Dust rats were largely induced/unchanged in rats that received isoflurane only. Overall, the data showed that lungs of rats exposed to WTC Dust—after accounting for any impact from isoflurane alone—displayed increased expression of genes related to lung inflammation, oxidative stress, and cell-cycle control, while several genes involved in antioxidant functions were inhibited. These changes suggested acute inflammogenic effects and oxidative stress in the lungs of WTC Dust-exposed rats. From this, the authors concluded that a single *very high* exposure to WTC Dusts could potentially have adversely affected the respiratory system—in terms of early inflammatory and oxidative stress processes. The authors also noted that these changes differed from those potentially induced by other types of dusts. At that time, the uniqueness of these WTC-mediated effects remained to be confirmed. Subsequent studies by the same investigators sought to determine if the noted effects might have any relevance to chronic lung pathologies that had become evident among FRs who encountered the highest dust levels on September 11–13, 2001 as well as if the effects on genes were acute, reversible, or persistent, and associated with the corresponding histopathologic and/or biochemical changes *in situ*.

More recently, Cohen et al. 2015, in press investigated the potential for changes in particle clearance induced by the alkaline nature of the WTC Dusts. Specifically, the study sought to ascertain if the inhaled WTC Dust caused damage *in situ* that modulated the retention, and thus impact of the WTC Dust itself and potentially two other major rescuerelated co-pollutants present in Ground Zero air, metal-cutting fume particles (CFP) and diesel exhaust particles (DEP). In examining rats exposed to WTC Dust, as in the earlier study, and then isolating their lungs over a 1-year period post-exposure, they found that the WTC Dust induced a significant decrease in the presence of ciliated cells in the airways and an increase in the levels of hyperplastic goblet cells in the lungs. They also showed that these changes were associated with significant prolonged retention of the dusts (≈90–95%) over the 1-year period. These findings were in line with observations by McMahon et al. (2011), who noted ultrastructural ciliary abnormalities in some Ground Zero workers that corresponded to respiratory and ciliary functional abnormalities, including impaired ciliary motility. Among the ultrastructural abnormalities was a disarray of axonemal microtubules and/or axonemes that were replaced by homogeneously dense cores.

The findings in these newer studies contrast to those of the earliest rodent exposure studies that were performed in the immediate aftermath of the disaster (Gavett et al. 2003). That series of studies sought to evaluate potential respiratory health effects from exposure to WTC Dust, and to gain information about potential short- and long-term toxicity of the different samples after a very high-dose, short-term exposure. The selected samples of settled WTC Dust were separated based on size, extracted, and then used for analyses of *in vivo* and *in vitro* toxicity. To investigate the toxicities of WTC Dust in comparison to previously tested PM materials, exposures of mice were done using particles in the respirable size range that were derived by aerodynamic size fractionation of bulk WTC samples. The tested samples included a sample of pooled $WTC_{2.5}$ from 7 individual collection sites (WTCX), and a sieved sample from an eighth site that was separated based on size for nose-only aerosol exposure (WTC*b*). Reference $PM_{2.5}$ samples of Mount St.

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Helens dust [MSH] and residual oil fly ash [ROFA] were also tested. Pooled WTCX was administered by oropharyngeal aspiration at 10, 31.6, or 100 μg/dose. Respiratory responses 24 h after the exposure were compared with those induced by the similarly aspirated low (MSH) and high (ROFA) toxicity reference $PM_{2.5}$; vehicle controls received saline only.

The Gavett et al. (2003) studies showed that aspirated WTCX induced significant neutrophilic inflammation (without a concurrent macrophage influx) at a relatively high dose (100 μg); the effect was not to a level as great as that induced by 100 μg of ROFA, and only slightly more than that from 100 μg of MSH (Figure 8). However, this same dose of WTCX caused airway hyperresponsiveness to Mch aerosol to a greater degree than did ROFA (Figure 9). Mice exposed to lower doses of WTCX (10 μg and 31.6 μg) and mice exposed by nose-only inhalation (WTC*b*, average level of 10.64 ± 3.10 mg/m^3, MMAD = 1.05 μm) did not display any biologically significant changes in Mch responsiveness or neutrophilic inflammation 24 h after their respective exposures (data not shown). In a parallel study, mice were also exposed to $WTC_{2.5}$ from 7 sites around Ground Zero; all groups of mice exposed to the individual site samples developed hyperresponsiveness to Mch aerosol challenge in the manner seen with the mice exposed to $WTCX_{2.5}$. No particular pattern of responses was found to correspond to geographical location where samples were taken (data not shown). Overall, these *in vivo* studies showed that high doses of $WTC_{2.5}$ could promote mechanisms of airflow obstruction in mice.

It must be noted that Gavett et al. (2003) indicated that airborne levels of $WTC_{2.5}$—when extrapolated to humans based on the doses used in mice—would have to have been quite high in the period after the WTC Towers' collapse when rescue and recovery efforts were in effect. This was a clear understatement; given that $WTC_{2.5}$ only represented ≈1% of the total WTC Dust mass and did not include the alkalinity that was present only in particles larger than 2.5 μm. Furthermore, the effective 100 μg of $WTC_{2.5}$ dose used would have had to reflect an ***instantaneous total dust*** deposition of ≈ 10 mg of WTC Dust to each mouse. Based on the established deposition efficiencies for fine particles in the mouse lung (10–20%), murine minute volume (0.035 LPM), and assuming an exposure equivalent to the period established for a reference FR (i.e., 4 h; Mayor's WTC Medical Working Group; personal communication), the 100 μg of $WTC_{2.5}$ dose would have then reflected an atmosphere of ≈ 6,000 mg *total dust*/m^3. Such an atmosphere would be far above the surmised upper range of Ground Zero (non-immediate cloud) air levels of ≈ 1000 mg of *total dust*/m^3. Had that upper level been used as the basis for dosing the mice, this would have meant the maximal amount of material that may have been deposited in a 4-h representative exposure would have been only ≈16.8 μg of $WTC_{2.5}$.

Despite their severe limitations in conception and relevant dose delivery, the early studies nonetheless provided some of the earliest clues as to potential health effects that could be induced by short-term exposures to the WTC Dusts.

In vitro studies of potential biological mechanisms

As with the *in vivo* studies, there has been little information to date in the literature on potential mechanisms of effects of the WTC Dusts based on *in vitro* studies. In one of the

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earliest studies, Payne et al. (2004) sought to identify potential mechanisms by which the WTC Dusts might affect the function of cells in the lungs with multiple vital roles, that is, AM and Type II (TII) epithelial cells. For this, they assessed induced changes in cell production/release of select cytokines. Various sized samples (e.g., $WTC_{2.5}$ and larger $WTC_{10–53}$) of dust collected during 9/11–9/13 were tested for effects on AM and on TII cells isolated from healthy human tissue [Royal Brompton Hospital, London]. WTC Dust samples were suspended in serum-free, low-protein media at 10 mg/ml, sonicated, and then diluted to 10, 1, or 0.1 mg/ml. Cultured cells then received the particle suspension (5, 50, or 500 μg particles/well and were incubated for 6 or 24 h in a humidified incubator (37°C, 5% CO_2). The conditioned media were then collected and analyzed for tumor necrosis factor-α (TNFα), interleukin (IL)-6, and IL-8 by ELISA.

$WTC_{2.5}$ caused significant increases in AM IL-8 release after just 6 h; smaller increases were seen only with the lower dose after 24 h. TII cell responses after 24 h were mostly analogous to that of the 6 h-treated AM. The $WTC_{10–53}$ particles caused small increases in AM IL-8 release (significant only after 6 h with 5 μg of dose) and failed to induce TII cell IL-8 release. Levels of AM IL-8 release at 24 h were always significantly greater than those at 6 h, but there were no significant particle effects. The results also showed that, unlike with IL-8, 50 μg of $WTC_{2.5}$ consistently induced maximal AM release of IL-6 and TNFα, and that these levels were always significantly greater than those induced with a 5-μg dose. It was also clear that increasing the length of incubation led to significant time-dependent differences in levels of each cytokine; this seemed to amplify the toxic impact of the particles, as the maximum levels of AM IL-6 and TNFα release achieved after 24 h with 50 μg of $WTC_{2.5}$ increased ≈7- and 5-folds above those seen after just 6 h. For TII cells incubated 24 h with $WTC_{2.5}$, IL-6 release responses fell between those of the 6- and 24-h-treated AM and there were no TNFα release responses at all. When $WTC_{10–53}$ Dusts were tested, the only effect noted was a non-dose-related increase in AM IL-6 release after a 24-h incubation; TII cells only had a nominal IL-6 release after 24 h. With regard to TNFα, TII cells again failed to respond; AM only showed a response after 24 h, with the maximum once again at a 50-μg dose. Lastly, in both cells types and at either exposure duration, use of the highest (500 μg) dose of either dust fraction uniformly caused significant declines (from 50-μg levels) in cytokine release (except, clearly, for TII cell TNFα case). These results showed that the exposure of lung epithelium or resident macrophages to WTC Dusts could cause a release of several factors that could contribute to inflammation and airway remodeling processes when released in an intact lung. These data also showed that prolonging the period in which WTC Dust could interact with cells and lead to concurrent increases in these effects (and so, *in situ*, a likely worsening of these situations in the lung of an exposed host).

A later study by Xu et al. (2011) examined whether the WTC Dusts demonstrate direct cytotoxicity to two airway cell types that were most directly exposed to inhaled dust, and airway epithelial and smooth muscle cells. They also sought to determine if the presence of the WTC Dusts could modulate effects of cigaret smoke on these cell types, since many of the individuals who responded to the WTC Dust exposure were smokers. Here, human cultured airway epithelial (BEAS-2B) cells were exposed to 10% cigaret smoke extract

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(CSE), $WTC_{10–53}$ (at 0.01–0.5 μg/μl), or a combination of the two for 2–24 hr. Cell viability was measured by determining mitochondrial integrity (MTT assays) and apoptosis (poly-ADP-ribose polymerase or PARP immunoblotting). Conditioned cell culture media recovered from the CSE- and/or WTC Dust-exposed BEAS-2B cells were then applied to cultured human airway smooth muscle cells that were subsequently assayed for mitochondrial integrity and ability to synthesize cyclic AMP (a regulator of airway smooth muscle constriction). BEAS-2B cells underwent necrotic cell death following exposure to WTC Dust or CSE for 2–24 h without evidence of apoptosis. Smooth muscle cells demonstrated cellular toxicity and enhanced cyclic AMP synthesis following exposure to conditioned media from WTC Dust- or CSE-exposed epithelial cells. These studies clearly showed that WTC Dust (at least the supercoarse fraction) or CSE alone exerted direct adverse effects on airway epithelial and smooth muscle cells, and altered signaling properties of airway smooth muscle cells. In addition, the combination of CSE and WTC Dust exerted an interactive effect on cell toxicity. Xu et al. (2011) posited whether these initial cell death events might account, in part, for the chronic lung effects associated with WTC Dust exposure in FRs.

Building on the original Payne et al. (2004) studies, Wang et al. (2010) hoped to identify some of the potential mechanisms for the increases in cytokine release that were induced by the fine WTC Dust. They surmised that because activation of mitogen-activated protein kinase (MAPK) signaling pathways is known to cause cytokine induction, these pathways were likely impacted on by the WTC Dust. The study used lung epithelial cells (BEAS-2B cells) exposed to $WTC_{2.5}$ for a period of 5 h. Exposures to various doses of $WTC_{2.5}$ caused significant increases in *IL-6* mRNA expression in the BEAS-2B cells, as well as in the corresponding protein levels in the culture media, in a dose-related manner. Apart from IL-6, cytokine multiplex analyses revealed that formation of IL-8 and IL-10 was also elevated by the exposure. Both extracellular signal-regulated kinase (ERK) and p38, but not c-Jun N-terminal protein kinase signaling pathways, were activated in the WTC Dust-exposed cells. Inactivation of ERK signaling pathways by PD98059 effectively blocked IL-6, -8, and -10 induction by the $WTC_{2.5}$; p38 kinase inhibitor SB203580 significantly decreased induction of IL-8 and -10. Taken together, these data demonstrated that activation of MAPK signaling pathway(s) likely played an important role in $WTC_{2.5}$-induced formation of several inflammatory (and, subsequently, anti-inflammatory) cytokines. Wang et al. (2010) indicated that the results were important in that they helped define one mechanism via which WTC Dusts may have acted to cause the documented increases in asthma and other inflammation-associated respiratory dysfunctions in FRs.

Most recently, Weiden et al. (2012), in one of a series of studies (see also Naveed et al. 2011a,b), compared the effects of WTC Dust size on macrophage inflammatory and/or cytokine/chemokine release *in vitro*. Here, normal adherent AM from 15 subjects without WTC Dust exposure were incubated in media alone, media with 40 ng of LPS/ml, or media containing suspensions of $WTC_{10–53}$ or $WTC_{2.5}$ at 10, 50, or 100 μg/ml for 24 hr. The culture supernatants were then assayed for 39 chemokines/cytokines. To assess potential translatability of the *in vitro* findings, sera from WTC Dust-exposed subjects who developed lung injury were also assayed for the same cytokines. In the *in vitro* studies, cytokines

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formed two clusters, with granulocyte/macrophage colony-stimulating factor (GM-CSF) and macrophage-derived cytokine (MDC, CCL22) as a result of $WTC_{10–53}$ and $WTC_{2.5}$. GM-CSF clustered with IL-6 and IL-12(p70) at baseline, after exposure to $WTC_{10–53}$ and in sera of WTC Dust-exposed subjects (n = 70) with WTC lung injury. Similarly, MDC clustered with the chemokines growth-regulated oncogene (GRO; CXCL1) and monocyte chemotactic protein-1 (MCP-1). $WTC_{10–53}$ consistently induced more cytokine release than $WTC_{2.5}$. $WTC_{10–53}$ induced a stronger inflammatory response by the human AM than did $WTC_{2.5}$. This large particle exposure may have contributed to the high incidence of lung injury in those exposed to particles at the WTC site. The authors concluded that as GM-CSF and MDC consistently clustered separately—these chemokines likely had a key role in the ultimate differential cytokine release seen during WTC Dust-induced lung injuries.

Key insights from toxicology studies

From these early and more recent *in vivo* and *in vitro* studies it is clear that the WTC Dusts can cause toxic responses in various cell types found in the lungs. Whether these changes themselves ultimately give rise to many of the observed pulmonary/cardiovascular health effects that have been noted with still-increasing frequency among FRs and others exposed to WTC Dusts remains to be determined. Ongoing studies in rodent hosts may provide critical proof that the WTC Dusts were actual causative agents for the noted pathologies. It is also possible, as noted by Cohen et al. 2015, in press in the studies of dust effects on ciliated lung cells, that the WTC Dusts were ultimately *contributive* to rather than directly *causative* of many of the reported health effects. This too is the subject of a series of ongoing studies using co-exposure of rodent models to WTC Dusts and major co-pollutants that were also heavily present in the air at Ground Zero, i.e., combustion-related $PM_{2.5}$(CFP) and DEP.

While definitive mechanisms of effect for the WTC Dusts are still not yet fully defined, recent studies have nevertheless built on the above-noted findings and have begun to identify biomarkers of *potential* health alterations due to exposure to the WTC Dusts. Using serum collected from—and non-invasive measures to examine—FRs and others who were exposed at Ground Zero, novel biomarkers of *potential* lung injury, altered cardiovascular status, and dysregulated inflammatory status have been identified. These have included significant changes in expression of matrix metalloproteinases (MMPs) (i.e., MMP-2, -3, and -12) (Kwon et al. 2013, Nolan et al. 2014), serum immunoglobulin (IgA and IgG) (Ferrier et al. 2011), select cytokines and/or chemokines (IL-6, IL-8, GRO, GM-CSF, granulocyte CSF [G-CSF], and interferon-inducible protein-10 or IP-10) (Nolan et al. 2012, Cho et al. 2014), cardiovascular disease (CVD) markers (apolipoprotein-AII, C-reactive protein, and macrophage inflammatory protein-4) (Weiden et al. 2013, Schenck et al. 2014) that could be correlated with increased risks for CVD or lung injury.

In conclusion, while there has been significant progress in the identification of potential mechanisms of toxicity for the WTC Dusts as well as in biomarkers of pulmonary/CVDs associated with exposure to these dusts, it is clear that much more toxicological research with regard to the effects of *in vivo* and *in vitro* exposures to the WTC Dusts needs to be done. As noted, exposures to the WTC Dusts did not occur in a vacuum and so the

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interactive toxicities/effects from co-exposures to other major co-pollutants at Ground Zero remain to be described. Similarly, while many immune-system-related endpoints have been examined of late, it remains unclear if the WTC Dusts were active immunomodulants that allowed nascent diseases (i.e., cancers, autoimmune diseases, and asthma) in hosts to flourish when they might not have otherwise. Lastly, there is an unmet need for development, identification, and validation of non-invasive methods to quantitate the remaining dust burdens in the lungs of WTC Dust-exposed workers and residents.

Possible roles of minor mass components as potential causal factors for observed health effects from WTC Dusts

The initial concerns about possible adverse health effects that might occur, especially in relation to chronic health effects and in relation to cancer in particular were focused on known toxicants and carcinogens that were present at relatively low concentration levels, that is, asbestos fibers, transition metals (e.g., Cd, Cr, and Fe), heavy metals (e.g., Pb, Hg, and As), combustion products (e.g., PAHs and PCBs), and ambient air $PM_{2.5}$. Due to these initial concerns, most of the subsequent air quality analyses both indoors and outdoors involved monitoring of these components based on $PM_{2.5}$ samples. However, there were, at least in retrospect, at least two good reasons why these initial concerns were misplaced. First, the concentrations of these components within the $PM_{2.5}$ fraction were initially quite low, and then had declined markedly over time. Second, most of the excess disease incidences found in the epidemiological studies were not those most closely associated with these components of the $PM_{2.5}$ samples that were collected in Lower Manhattan after the collapses of the WTC Towers.

By contrast, the three major mass components of the settled WTC Dust that were present in particles > 2.5 μm are all known irritants, with the highly alkaline cement and gypsum components being chemical irritants, and the SVFs being physical irritants. In any case, their concentrations in PM_{10} and larger particle size fractions were seldom measured. Furthermore, there is good reason to expect a biological response to these components that were inhaled, based on their interaction following airway deposition. The physical irritation induced by the crushed SVFs is viewed as providing greater access of the alkaline components to the epithelial cells. The chronic diseases in the exposed populations are quite plausibly caused by either the initially high-level exposures of the rescue and recovery workers during the first week, or by the prolonged periods of indoor exposures to resuspended residual dusts of high alkalinity for cleanup workers and of residents and commercial workers who were exposed to WTC Dusts that had not been neutralized by rainwater.

The misplaced initial focus on trace-level components within the $PM_{2.5}$ particle size fraction of the WTC Dusts was never reconsidered by the governmental agencies or by those responsible for controlling the exposures to WTC Dust in Lower Manhattan. Many thousands of $PM_{2.5}$ air measurements were made at Ground Zero and inside buildings contaminated with WTC Dust during the periods that extended for many months before they were declared clean enough for reoccupancy. None of the routine/special purpose $PM_{2.5}$ sampling filters were ever assayed for their alkalinity or SVF content. Some settled dust

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samples collected in Lower Manhattan were analyzed for their percentage of SVFs, and generally showed that 20–25% of the settled dust was SVF.

SVF and asbestos fibers are very different in terms of the toxic effects that they are likely to produce when inhaled at concentration normally encountered (Lippmann 2014a). First, they differ in terms of fiber diameter, which determines aerodynamic diameter. Asbestos are almost always present in the air in fibers having respirable aerodynamic diameters, while conventional SVF have aerodynamic diameters > 10 μm, and such fibers are both less likely to be dispersed into the air, and less likely to penetrate into thoracic airways following inhalation. Second, SVF dissolve more rapidly in the fluid linings of the epithelia and to break up into shorter length segments than asbestos fibers. Third, asbestos fibers, and especially chrysotile fibers, are less rigid than SVF, and therefore less likely to lacerate the surface epithelia.

When one of the authors of the current review (ML) served on an EPA Panel whose charge was to advise the Agency on the development of a signature component of WTC Dust for the detection of residual dust from collapse of the WTC buildings as described by Lowers et al. (2009), the Panel came up with a unanimous recommendation that the ideal component for a signature marker for WTC Dust was SVF. The basis for the recommendation was that SVF was a non-reactive component that could readily be measured in samples of residual surface dust. At that time, SVF was deemed an unlikely causal factor for adverse health effects based on the then available information in the scientific literature. The panel was surprised to learn that EPA suddenly disbanded the panel before it could state its case, and shelved its recommendation to use SVF level as a guide to future residential cleanup, on the basis of concerns expressed by some of its in-house statistical staff. Some of the panel members (Meeker et al. 2010) felt compelled to object publicly, in a Letter to the Editor.

We know now, from an examination of the recent literature on the associations between WTC Dust exposure and adverse respiratory and gastroesophageal effects, as discussed in this review, that inhalation exposures to resuspended SVF, in the presence of highly alkaline co-contaminants, has caused adverse pulmonary and gastroesophageal effects in humans. It is also now recognized that there is some supporting evidence, as discussed in this critical review, in which the same kinds of effects can be caused by inhalation exposures of laboratory animals. Thus, it appears that SVF may be a causal factor as well as a signature component of the mixture of concrete, gypsum, and SVF in WTC Dusts. The expression of disease following inhalation of airborne fibers may require disruption of the clearance capacity of the lung, as for workers having chronic exposures to amphibole asbestos fibers at very high concentrations (Lippmann and Timbrell 1990) or to people exposed to a mixture of SVF and alkaline co-contaminants, as discussed herein.

Roles of major mass components as potential causal factors for observed health effects from WTC Dusts

It is clear that the settled WTC Dust, which was largely in particles ≥ 2.5 μm in aerodynamic diameter, was highly alkaline for the outdoor dust prior to the first rain, and remained highly alkaline for the indoor dust until nearly all of it was removed. There is evidence in the

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literature that highly alkaline coarse particles can cause responses similar to those that we have associated with exposures to WTC Dusts, as discussed below.

Zeleke et al. (2010) conducted a combined cross-sectional and cross-shift study at a cement factory in Ethiopia. Personal "total" dust was measured in the workers' breathing zones and peak expiratory flow (PEF) before and after the shift. When the dayshift ended, the acute respiratory symptoms were recorded on a 5-point scale using a respiratory symptom score questionnaire. The highest geometric mean dust exposure was found in the crusher section (38.6 mg/m^3) followed by the packing section (18.5 mg/m^3) and the guards (0.4 mg/m^3). The highest prevalence of respiratory symptoms for the highly exposed workers was stuffy nose (85%) followed by shortness of breath (47%) and "sneezing" (45%); PEF decreased significantly across the shift in the highly exposed group. Multiple linear regressions showed a significant negative association between the percentage cross-shift change in PEF and total dust exposure. The number of years of work in high-exposure sections and current smoking were also associated with cross-shift decrease in PEF.

Meo (2004), in a review of the literature on cement dust and its health effects, described cement particles as ranging in aerodynamic diameter from 0.05 to 5.0 μm. He concluded that a high concentration of or prolonged inhalation to, or both, cement dust in industry workers could provoke clinical symptoms and inflammatory responses that may result in functional and structural abnormalities. The most frequently reported clinical features in cement mill workers were chronic cough and phlegm production, impaired lung function, chest tightness, obstructive and restrictive lung diseases, conjunctivitis, stomachache, headache, fatigue, and carcinoma of the lung, stomach, and colon. In terms of the GI system, Meo (2004) also listed diffuse swelling and proliferation of sinusoidal (hepatic) lining cells, and hepatic lesions. The particle size of the cement mill dust was not as large as the WTC Dust, but just as alkaline as indoor WTC Dust (see Figure 4).

We could not identify any literature on the combined effects of highly alkaline dust and SVF exposure to test our hypothesis that laceration of epithelia by crushed SVF is likely to exacerbate the effects of the WTC Dust alkalinity. Thus, this remains a hypothesis, albeit one suitable for toxicological investigation. Nevertheless, there is literature on human, animal, and cellular responses to very high mass concentrations of other coarse and supercoarse dusts, primarily to volcanic dusts, as reviewed by Baxter et al. (2014) in relation to emissions from Mt. St. Helens (MSH) in Oregon in May 1980, and the island of Montserrat for a series of eruptions extending from 1995 to 2010. Volcanic dusts contain PM over a large particle size range, but such dusts are not alkaline or readily soluble in the lung, and sometimes are acidic. Buist and Bernstein (1986) summed up the outcomes of the health research sparked off by MSH as "The effects of both short- and long-term exposures to the relatively low levels of airborne ash that are typical following such a volcanic eruption were minor, and related more to the irritant effects of the ash on the airways than to the potential of the ash to initiate a fibrotic response." Baxter et al. (2014) summarized the risk assessment performed for the ~13,000 residents of Montserrat and concluded that, in the absence of clinically manifest disease, the disease endpoint commonly used in occupational epidemiological studies of silicosis is a radiological one—in this case the International Labour Organization or ILO International Classification of radiographs for pneumoconiosis

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—and its category was 1/0–1/1 small opacities. The risks in the north of the island, where most of the population lives, as computed by the model, were so small and uncertain that they could be ignored. In terms of the estimated exposures and risks in the inhabited areas in the central part of the island, which receives the most ashfall and where the minority of the population lives, the "best estimate" probability of developing early radiological evidence of silicosis in the general population is less than 1 per 1000 after 5 years of volcanic activity. Thus, these studies of the health effects of volcanic ash, and the results of the comparative toxicological studies (see Figures 8 and 9) indicate that the alkalinity of the WTC Dusts is a major determinant of its health effects.

Limitations of air quality and settled dust measurements made in Lower Manhattan following WTC tower collapses on 9/11/2001

Most of the airborne dust samples, being limited to $PM_{2.5}$, provided no useful information on the health risk potential of inhaled WTC Dust, since almost all of the WTC Dust was in particles > 2.5 μm in aerodynamic diameter. There were too few PM_{10} samples to permit even a first crude estimate of WTC Dust exposure to the lower end of its particle size distribution range, and there were no total suspended PM (TSP) samples that could have, at least crudely, suggested the extent of the WTC Dust inhalation for all of the readily resuspendable WTC Dust (Lee 2014, Personal Communication). The ease with which WTC Dust could be resuspended varied with venue and time, that is, being easy for 1) outdoor settled WTC Dust, before the first rain; and 2) indoors within commercial buildings for much longer times, extending until the first successful thorough dust removal over succeeding months.

Early and prolonged failures in exposure assessment, risk assessment, and risk management for WTC Dusts

It is relatively easy, in hindsight, to fault the governmental agencies that launched investigations into WTC Dust exposures and their potential health effects in terms of the early lack of their 1) recognition of likely extent and magnitude of inhalation exposures; 2) evaluation of exposures to major mass components of settled dust that were readily resuspended; 3) recognition of very high frequency of cough and other acute responses in relation to likelihood of chronic health effects; 4) application of more appropriate work practice guidelines for prevention of dust resuspension (a major source of inhalation exposures to WTC Dust); and 5) reliance on inappropriate respirators to protect against prolonged exposures to unusually high dust levels. The governmental agencies were faced with an unprecedented disaster with unknown hazards to FRs, recovery workers, and volunteers, as well as a huge number of Lower Manhattan residents and commercial workers with obvious exposures to WTC Dusts and combustion effluents and their reaction products. The agencies, including their staff scientists, had no prior experience or literature to guide them in their well-intentioned efforts to both minimize adverse exposures and their health effects, and at the same time encourage members of the public to not panic and create chaos as efforts were made to get started in a resumption of normal work and lifestyle patterns.

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While the deficiencies of the initial agency responses were readily understandable, the obvious lack of recognition that changes in guidance to the public and building owners and managers in Lower Manhattan would be needed, based on early experience, is less so. The best example of a need for more targeted guidance was the widespread and prolonged prevalence of WTC cough among members of the public and the more heavily exposed Ground Zero rescue and recovery workers. The need to determine what components of the WTC Dust were responsible for the cough, and what the prevalence of the cough implied for more chronic health effects, should have been obvious. We should not have had to await the publication of peer-reviewed epidemiology describing excessive pulmonary responses and GERD among WTC Dust-exposed populations to document the need for research or to revise exposure prevention guidelines. In addition, there was no action taken to deal with evidence that the filter canisters of the recommended negative-pressure respirators were, in many cases, overloaded during a work shift, preventing them from providing the protection against dust inhalation that they were intended to provide. To our knowledge, no attempt was made to switch to positive-pressure respirators.

Discussion of lessons learned in relation to risk assessment, risk management, and risk communication

Whenever an unprecedented disaster with public health implications occurs in the US, such as Hurricane Katrina in 2005, the Exxon Valdez and BP oil spills, and massive forest fires in our western states, or in foreign crises that threaten the health of people in the US, such as the 2014 outbreak of Ebola in West Africa, we usually find the abilities of our Public Agencies to respond to the challenges in effective and timely manners fall at least somewhat short of optimal. Aside from a lack of experience in how best to define the nature and scope of new and different challenge, and how to mobilize existing resources and personnel to limit exposures to people and natural environments on appropriate scales, there is a need to document the effectiveness, or lack thereof, of the actions taken. One consistent lesson we have learned from the past disasters is that there is usually the generic problem of too limited histories of effective coordination of Public Agency responses.

In terms of dealing with the unprecedented nature and magnitude of WTC Dust exposures of very large numbers of people in Lower Manhattan, there was prompt mobilization of teams of experts from many different public agencies, including Federal, State, and Local governmental units. Their on-site activities included the determination of the geographic extent of the WTC Dust dispersion, the physical and chemical characteristics of the WTC Dust, and determinations of the airborne concentrations of WTC Dust components deemed to be risk factors in relation to disease causation, and providing timely information on possible health risks and appropriate precautions for limiting future WTC Dust exposures to members of the public and the owners and managers of WTC Dust contaminated buildings. This included provision of guidance on air quality measurement strategies; what to measure; work practices to limit exposures from resuspended dusts; and respiratory protective devices for limiting inhalation exposures.

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Unfortunately, the timely responses and guidance that were provided did not prove to be effective at either providing adequate public health protection or of documenting the exposure factors that were causal of the adverse health effects. There is a need to resurrect the original tool kit of the hygiene profession and community, whose watchwords are Recognition, Evaluation, and Control, and to institutionalize it within the federal and local governmental agencies.

Need for a standing interdisciplinary interagency and external advisory panel to deal with unanticipated toxicant exposures

There is a need to anticipate that we are likely to be faced with natural as well as terrorist-sponsored disruptions of infrastructure resources that lead to exposures of the public to chemical, biological, radioactive contaminants and/or mixtures. We could be better prepared for such contingencies by having sets of standing guidelines on contingency plans along the lines of the EPA Science Advisory Board (SAB) Reports on Future Risk (SAB 1988a), Reducing Risk (SAB 1988b), and Beyond the Horizon (SAB 1995). Such a newly constituted Expert Panel Report could provide timely guidance on dealing with occupational and environmental exposures to complex mixtures not previously encountered, with respect to 1) component concentrations of toxicants that should be monitored; 2) ambient air and personal exposure guidelines; 3) work practices and local exhaust ventilation to minimize exposures; and 4) personal protective devices to be worn when conventional work practices/ local exhaust ventilation for minimizing exposure are inadequate.

Implications to risk assessment, risk management, and risk communication

There were clearly failures to 1) anticipate the importance of the atypical particle size distribution and chemical composition of the WTC Dust; and 2) recognize the importance of the early reports of high pH of the coarse dust, and/or of widespread cough and other symptoms. These led to misleading communications emanating from Public Agencies, which minimized the potential health risks from exposures to WTC Dust in the period shortly after the collapse of the WTC Towers. As a consequence, both the public and the building owners and managers were never informed about the limitations of the early risk management decisions. We now know that

1) There was a premature focus on asbestos fibers, trace metals, and organics, such as PAHs, PCBs, and dioxins, as likely causal factors for excessive inhalation exposures and subsequent excesses of preventable diseases;

2) There were premature assurances that airborne exposures were not excessive;

3) Airborne concentrations of the most irritating components, the alkaline coarse particles and SVFs, were not monitored.

4) Adverse respiratory and gastroesophageal health effects observed in people exposed to WTC Dusts were not likely due to $PM_{2.5,}$ which was ≈ pH 7 and contained most of the asbestos, trace metals, and organics that were present at low concentrations. While these agents have been associated with some other

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adverse health effects, these other effects have occurred in other organs and have only been associated with much higher levels of exposure.

5) Adverse respiratory and gastroesophageal health effects observed in people exposed to WTC Dusts were most likely due to combined effects of a high alkalinity of the concrete and gypsum components and physical irritation attributable to crushed SVF.

The failure of the public agencies to inform the building managers and the public of the consequences of these early risk management decisions, and their inaction in terms of providing revised guidance, which could have minimized later exposures associated with cleanup of WTC Dust in residential and commercial buildings, contributed to at least some of the adverse health effects that did occur.

The Public Agencies' failure to adequately identify the health risks to populations exposed to WTC Dusts originated in their failure to consult with an appropriate panel of scientific experts having a broad range of expertise in industrial hygiene, dosimetry, toxicology, and risk assessment that were needed to address the possible health consequences of human exposures to the unique chemical and physical characteristics of WTC Dusts, and to develop adequate guidance on

1) Appropriate exposure monitoring;

2) Appropriate personal protection for exposure reduction for those living and/or working in Lower Manhattan; and

3) Research needed to identify likely causal factors within the WTC Dusts, and the biological mechanisms that could account for their adverse effects.

To be able to provide better risk assessment, risk management, and guidance to the public in the future, there is a need to establish a standing Scientific Committee or Panel that can advise national, statewide, and local governments on the management of public health emergencies, including

1) Monitoring risk factors that can be anticipated to lead to excessive exposures to toxicants;

2) Guidance on recommendations for effective procedures for minimizing toxicant exposures;

3) Maintaining oversight on emerging extent/trends of exposure data and disease incidence; and

4) Issuing timely recommendations for supplemental exposure protection methods and monitoring, and for toxicological research needed to determine factors affecting disease causation.

Conclusions

The spectacular collapses of the WTC Twin Towers on the morning of 9/11/2001 posed a unique challenge to the nation, and especially in terms of the public health risks of hundreds

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of thousands of people who worked and/or lived in Lower Manhattan. The conversion of the WTC Towers into an enormous cloud of dust that spread throughout Lower Manhattan, and a massive pile of debris at Ground Zero, led to inhalation exposures of an unprecedented nature and amount due initially to the dust levels remaining suspended in the air, as well as to the subsequent resuspension of the dust that had settled onto the streets and within the buildings. Within the first few days, the public agencies involved in occupational and environmental risk assessment and risk management sought to help, but were unprepared to provide adequate public health protection in terms of their too limited abilities to 1) assess the nature and magnitudes of the risks; 2) prescribe suitable methods for monitoring the subsequent exposures; and 3) prescribe effective means of minimizing the exposures. Further, the inadequate guidance that the public agencies did provide shortly after 9/11 was never adequately reconsidered and revised in light of emerging evidence that there were substantial unanticipated adverse health effects among workers and residents that were attributable to inhalation of components of the WTC Dusts that were not being monitored. The evidence assembled to support these overall conclusions has been presented in this critical review; the key elements are summarized as follows:

1) The collapses of the WTC Towers on 9/11/2001 created a dense dust cloud that radiated out at very high velocity, creating settled dust deposits, ranging from clearly visible to inches thick on the streets, building exteriors, interior building surfaces, and in building air ducts throughout Lower Manhattan. Dust deposition was much lower in other parts of NYC and the adjacent areas;

2) The settled WTC Dusts differed in important ways from conventional settled dusts in regard to a) particle size distributions; b) chemical composition; and c) ease of redispersion into the ambient air (i.e., by air movement/physical disturbance caused by peoples' activities);

3) In terms of particle size distribution of WTC settled dusts, ~1% had < 2.5-μmin aerodynamic diameter, 0.3–0.4% ranged from 2.5 to 10 μm,~40% ranged from 10 to 53 μm, and 52–63% that did not pass through a screen with 53-μm pores. As compared with outdoor settled WTC Dust, the deposits within buildings were depleted of particles in the upper end of the particle size range;

4) In terms of sources of WTC Dusts, 80–90% was attributable to a mixture of SVFs from glass and slag wool insulation, gypsum from wallboards, and cement from the concrete originally within the Towers. Cellulose accounted for 9–20% and chrysotile asbestos fibers for 0.8–3.0%, with other components having much smaller amounts;

5) In terms of particle chemistry, the aqueous solubility of calcium oxide from the cement and calcium sulfate from the gypsum resulted in a very high pH (9–11) for the outdoor settled dust samples collected within the first few days, and even higher pH levels in indoor dust (pH > 12). By contrast, the pH in particles in the fine dust fraction (< 2.5 μm) was nearly neutral (pH = 7–8). Thus, the particle size range of the alkaline dust created by the collapses did not extend down to 2.5 μm. On the other hand, the initially somewhat elevated $PM_{2.5}$ fraction in the ambient air near Ground Zero included combustion products, complex organics

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synthesized in the flames at Ground Zero, and metals that were volatilized and condensed as ultrafine particles;

6) Almost all the air monitoring for PM in Lower Manhattan after 9/11/2001 were based on determinations of total gravimetric mass of $PM_{2.5}$, or of specific components of the $PM_{2.5}$ air samples. Thus, there were very few determinations of levels of the major mass components generated by the buildings' collapse, which were in particle sizes > 2.5 μm (SVFs, cement, and gypsum);

7) Coarse (> 2.5 μm) alkaline particles that were inhaled were deposited in conductive airways in the head and LRT tracheobronchial airways, including most that were between 2.5 and 10 μm, as well as smaller percentages of particles of~10–30 μm that had not been deposited in the URT airways;

8) The high pH of these coarse particles could have over-whelmed the capacity of the conductive airways to maintain the homeostasis that removes debris from airways to the esophagus by mucociliary clearance due to alkalinity of the surface fluids, thereby inducing acute responses such as cough, chest pain, and other respiratory symptoms, as well as inducing gastroesophageal reflux. The epidemiological literature now shows significant excesses of these responses in residents and workers exposed to WTC Dusts;

9) There is overwhelming epidemiologic evidence that individuals working/living in Lower Manhattan on and after 9/11/2001 have also exhibited more chronic disease, such as incident cases/greater prevalence of respiratory and gastroesophageal illness than comparison populations that lived and worked at further distances from Ground Zero;

10) The rise of manifestations of adverse acute and chronic respiratory tract and gastroesophageal effects in people working/residing in Lower Manhattan after 9/11/2001, which was not seen in other populations in the region, provides convincing evidence of a causal association attributable to WTC Dust exposures that began on 9/11. Since the types of responses known to have occurred in these populations have not been associated with exposures to the toxicants that were monitored after 9/11, that is, asbestos fibers, trace metals, PAHs, PCBs, and dioxins, they had to be due to components spread throughout the area post-9/11 that were not monitored;

11) The most plausible causal candidates for inhalation exposures that were not monitored, and were present at extraordinarily high concentrations post-9/11, were coarse particles composed of cement, gypsum, and SVFs. All the three components are known irritants to large airways, and the deposition sites for these coarse particles are consistent with locations of the adverse responses. Further, the WTC Dusts, a mixture of all these components, were shown to be unusually easy to resuspend into the air, and the dust that remained inside buildings was not washed away or neutralized by rainwater, unlike the dusts outside of the buildings.

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12) The fact that the concentrations of fine particle toxicants that were monitored were within recognized exposure limits led some people to conclude that exposure to WTC Dust could not have caused the excess disease among workers and residents in Lower Manhattan since 9/11/2001. This conclusion is demonstrably false since exposure limits cited were specified for concentrations of insoluble/poorly soluble dust overall mass, or the mass concentrations of some specific components, while the concentrations measured were limited to those within the fine particle fraction ($PM_{2.5}$). In fact, having a $PM_{2.5}$ inlet prior to the filter that collected the sample to be analyzed precluded measurements of the larger particles in the ambient air that were most likely to be causal;

13) Since the monitored airborne $PM_{2.5}$ concentrations were too low to have caused clogging of the filters in respirator cartridges during one day, the fact the respirators often became overloaded provided evidence that the respirator filters were being clogged by coarse particles at much higher concentrations, that is, by particles that could be deposited in upper respiratory tract and tracheobronchial airways; and

14) It is clear that, even almost 14 years on from the WTC disaster, much remains to be done to not only identify how exposures to WTC Dusts may have contributed to diseases/adverse health effects in those who were at/near Ground Zero, but to also devise methodologies to ascertain who is still healthy but at risk for developing exposure-related lung, cardiovascular, and other pathologies.

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Declaration of interest

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Abbreviations

ACGIH American Conference of Governmental Industrial Hygienists

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AM	alveolar macrophage
AQI	US Air Quality Index
ATSDR	US Agency for Toxic Substances and Disease Registry
CDC	US Centers for Disease Control and Prevention
CEN	European Economic Community
CI	confidence interval, generally 95% interval
COPD	chronic obstructive pulmonary disease
CSE	cigaret smoke extract
CT	computerized tomography
DOE	dyspnea on exertion
EMS	emergency medical service
EPA	US Environmental Protection Agency
FDNY	NYC Fire Department
FEV_1	forced expiratory volume in 1 s
FRs	first responders
FVC	forced vital capacity
ISO	International Standards Organization
IT	intratracheal (instillation)
GAO	US Government Accountability Office
GERS	gastroesophageal reflux disease symptoms
GERD	gastroesopageal disease
LRS	lower respiratory symptoms
LRT	lower respiratory tract
Mch	methacholine
MMAD	mass median aerodynamic diameter
MSA	Metropolitan Statistical Area
MSSM	Mount Sinai School of Medicine
NAAQS	US National Ambient Air Quality Standard
NHANES	National Health & Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences
NIOSH	US National Institute of Occupational Safety and Health
NYC	New York City

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NYPD	New York City Police Department
NYS	New York State
NYSDOH	New York State Department of Health
NYU	New York University
OAD	obstructive airways disease
OR	odds ratio
ORD	EPA Office of Research and Development
OSHA	US Occupational Safety and Health Administration
PAHs	polyaromatic hydrocarbons
PCBs	polychlorinated biphenyls
PEL	OSHA Permissible Exposure Limit
PFT	pulmonary function test
PM	Particulate matter
$PM_{2.5}$	PM with MMAD < 2.5 μm
PPE	personal protective equipment
PTSD	post-traumatic stress disorder
RADs	reactive airways dysfunction syndrome
REL	NIOSH Recommended Exposure Limits
RPE	respiratory protection equipment
RR	relative risk
RRW	rescue/recovery workers
RUDS	reactive upper airways dysfunction syndrome
SAB	EPA Science Advisory Board
SMR	standardized mortality ratio
SVF	Synthetic vitreous fiber
TII	Type II epithelial cells
US	United States
USGS	US Geological Survey
VOCs	volatile organic compounds
WTC	World Trade Center
WTC Dust	dust created during the WTC collapse
WTCEHC	WTC Environmental Health Center

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WTCHP	WTC Health Program
WVMS	WTC Worker and Volunteer Medical Screening Program

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Figure 1.
(A) View along plaza heading toward Chase Building on 9/13/11. (B) Scene from an indoor residence near Ground Zero. (photographs property of C. Prophete, M. Cohen, and L. Chen).

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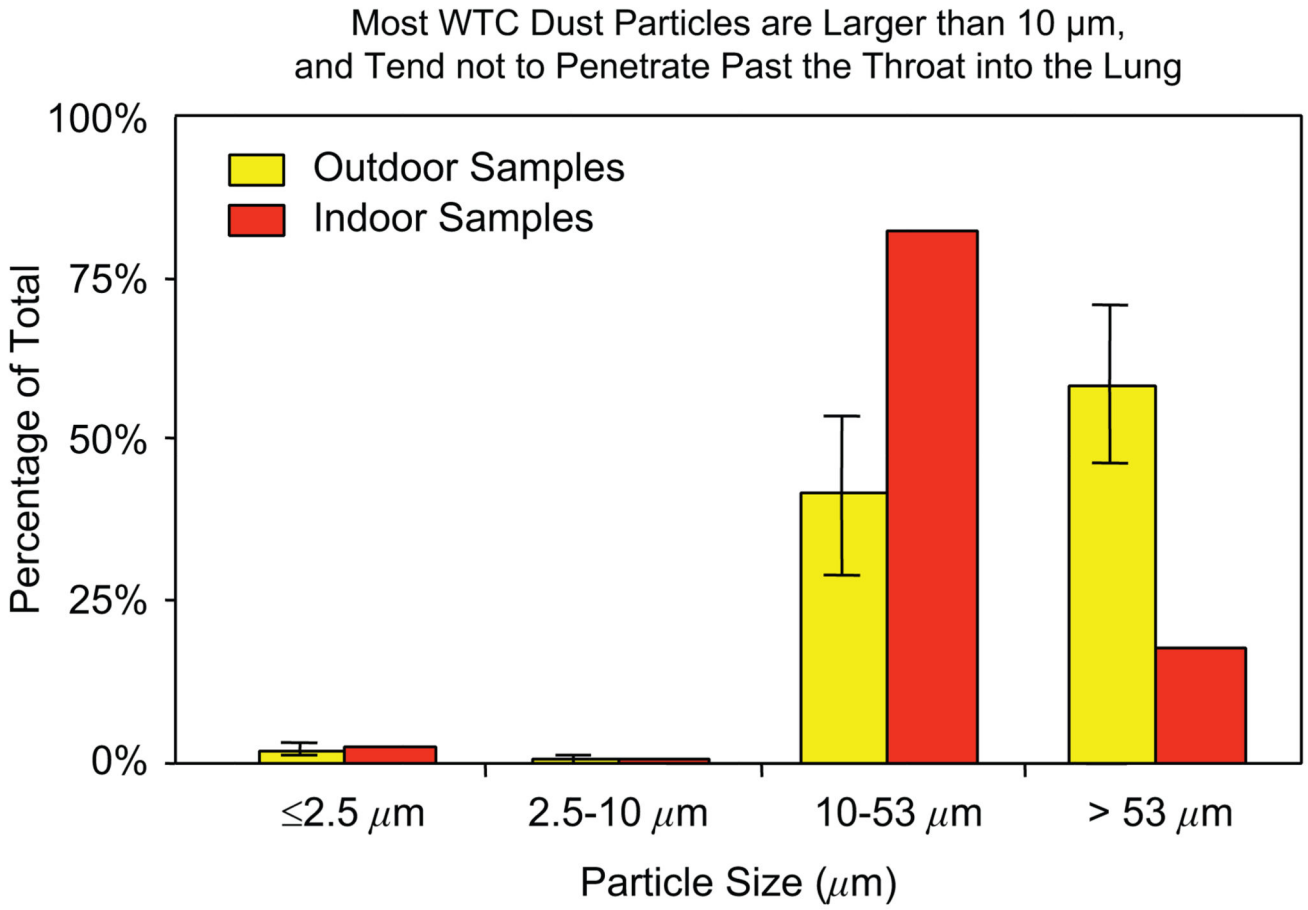

Figure 2.

Particle size distribution from indoor and outdoor dust samples collected in the period of 9/12-13/11 (modification of the original figure from Maciejczyk et al.2004).

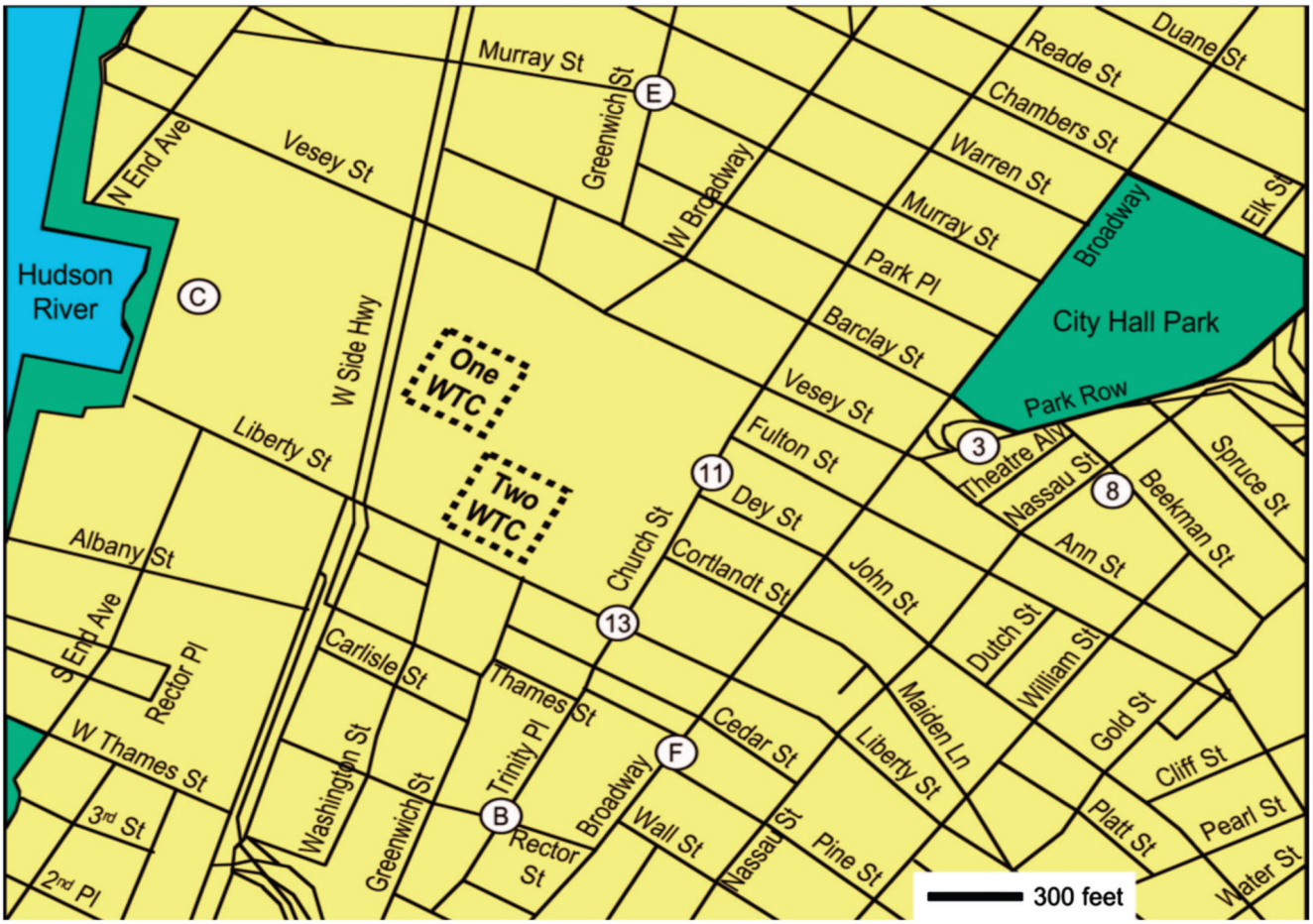

Figure 3.
Sampling sites for Chen et al. analyses (from McGee et al. 2003).

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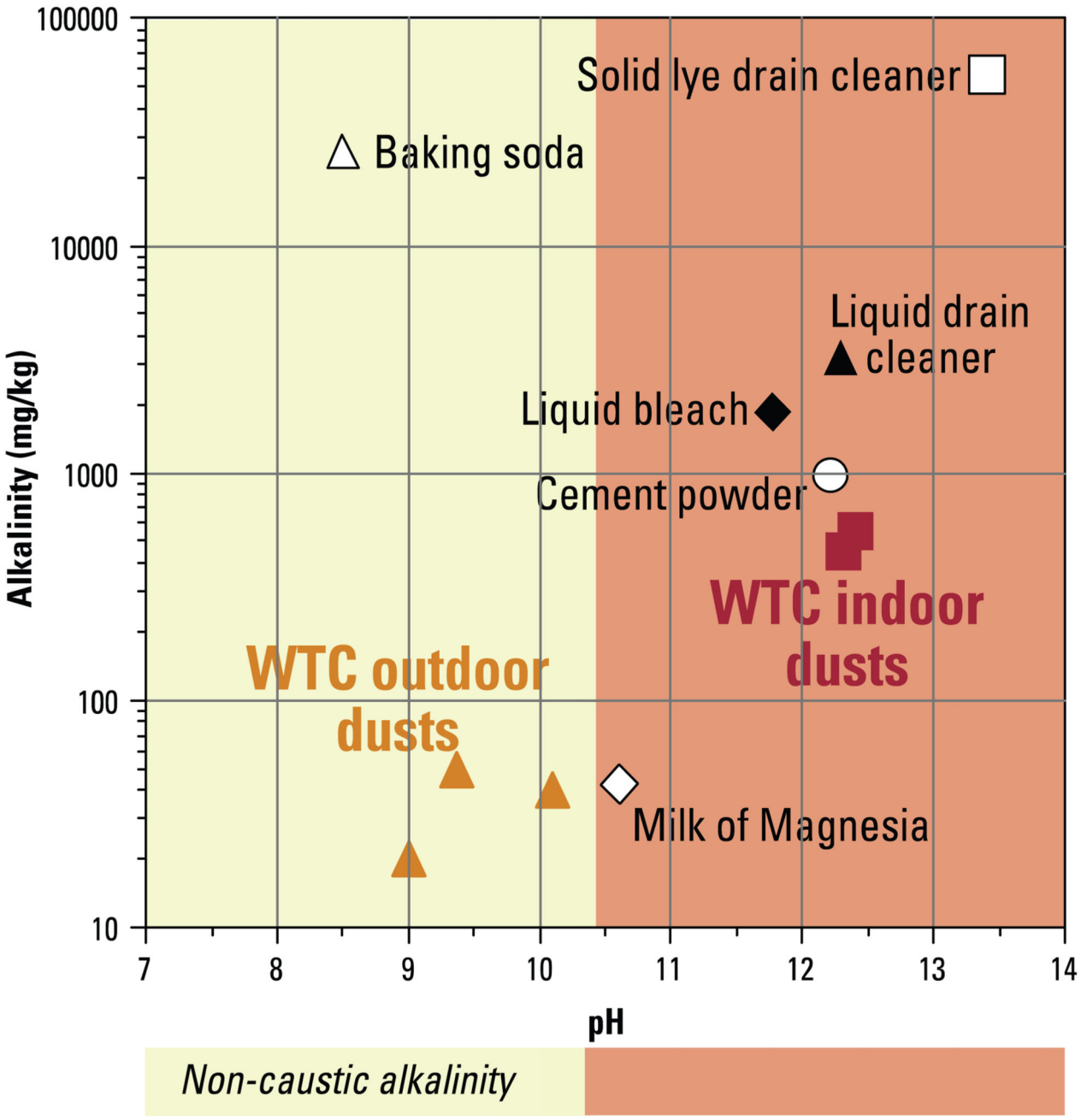

Figure 4.
Alkalinity and pH of WTC Dusts in relation to other alkaline materials (from USGS internet posting [2002]).

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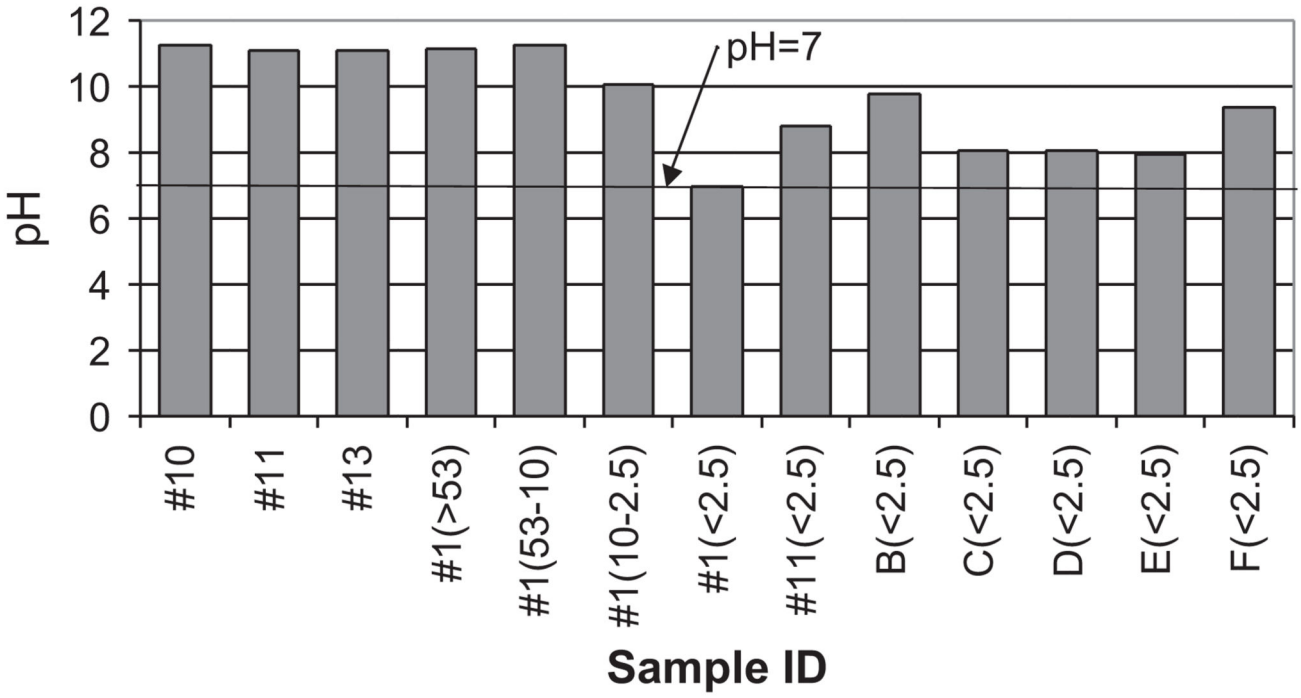

Figure 5.

pH of the suspensions of the selected dust samples. Sample size fraction is indicated in parenthesis unless bulk dust (from Maciejczyk et al. 2004).

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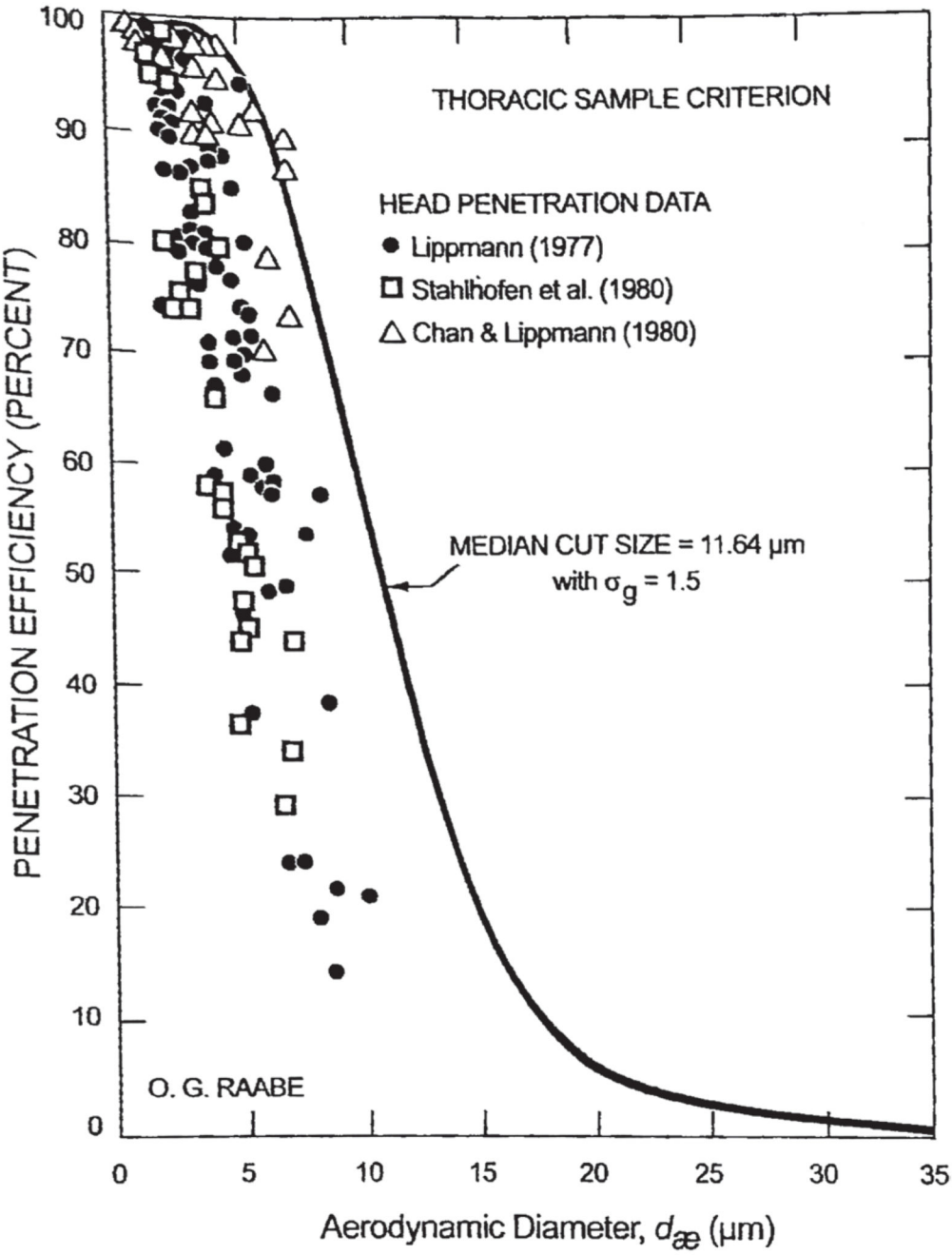

Figure 6.

Thoracic PM or TPM sample criterion for particles entering the mouth during oral inhalation given as sample collection efficiency for those particles that penetrate a separator whose size collection efficiency is described by a cumulative lognormal function with median cut size of 11.64-μm aerodynamic diameter and with geometric standard deviation of 1.5. Also, the selected data for the observed human head penetration during inhalation by mouth corrected to the appropriate aerodynamic diameter for reference worker for an inspiratory flow rate of 43.5 L/min are shown.

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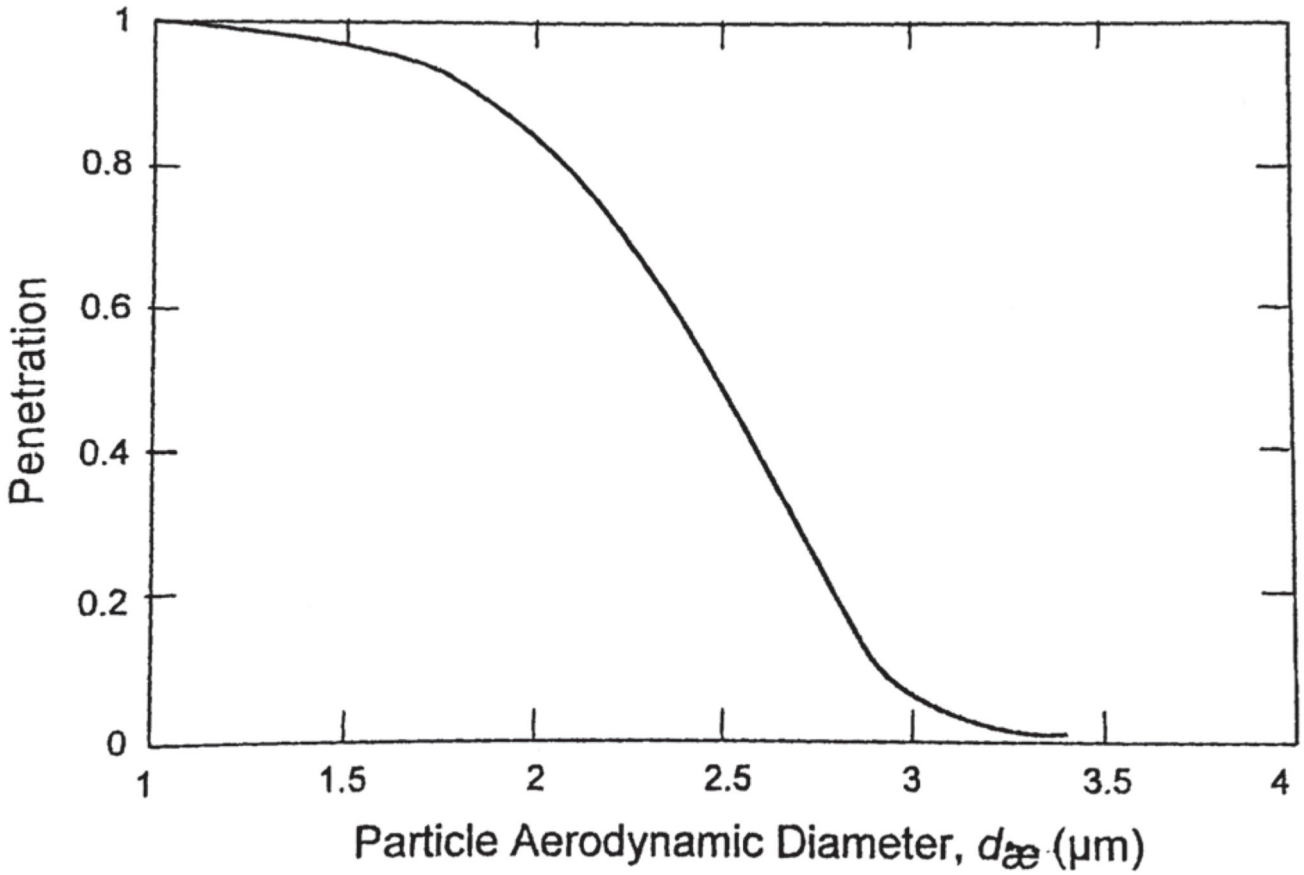

Figure 7.
Sampling efficiency versus particle aerodynamic diameter for the $PM_{2.5}$ Federal Reference Method sampler (EPA, 1997a).

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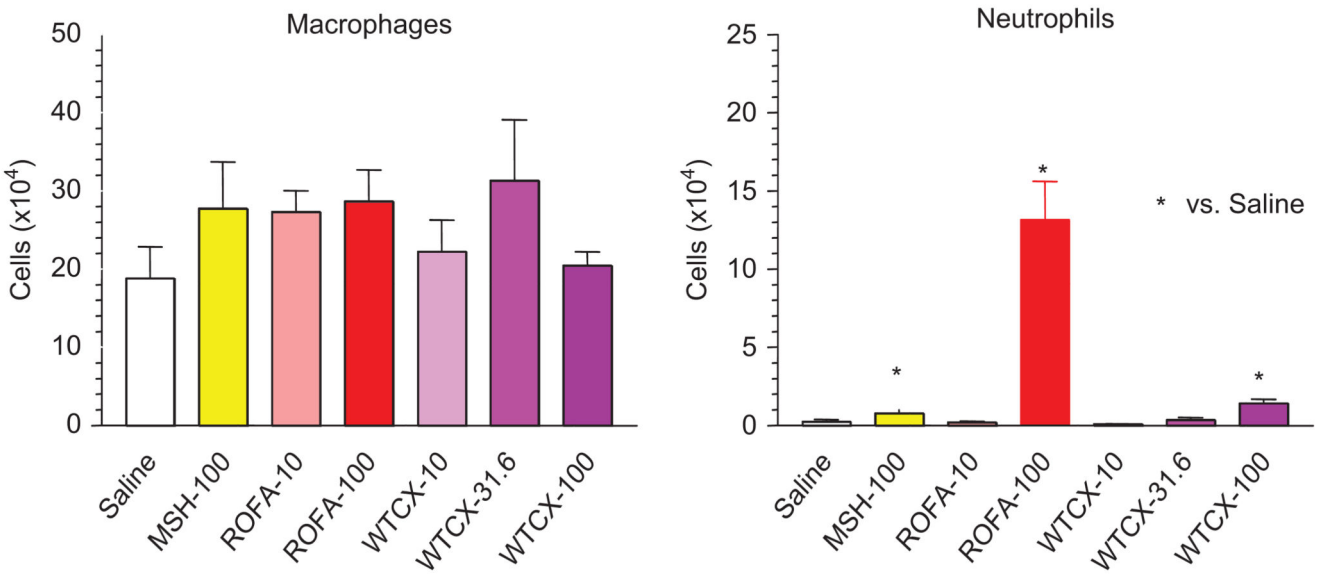

Figure 8.

Bronchoalveolar lavage cell numbers recovered from mice 1 day after aspiration of WTC or standard PM samples in saline or saline vehicle alone. WTCX represents pooled WTC Dust samples. Number following particle type reflects dose (μg). Bars are mean (± SE) from n = 12 mice per treatment. *Significant at $p < 0.05$ (adapted from Gavett et al. 2003).

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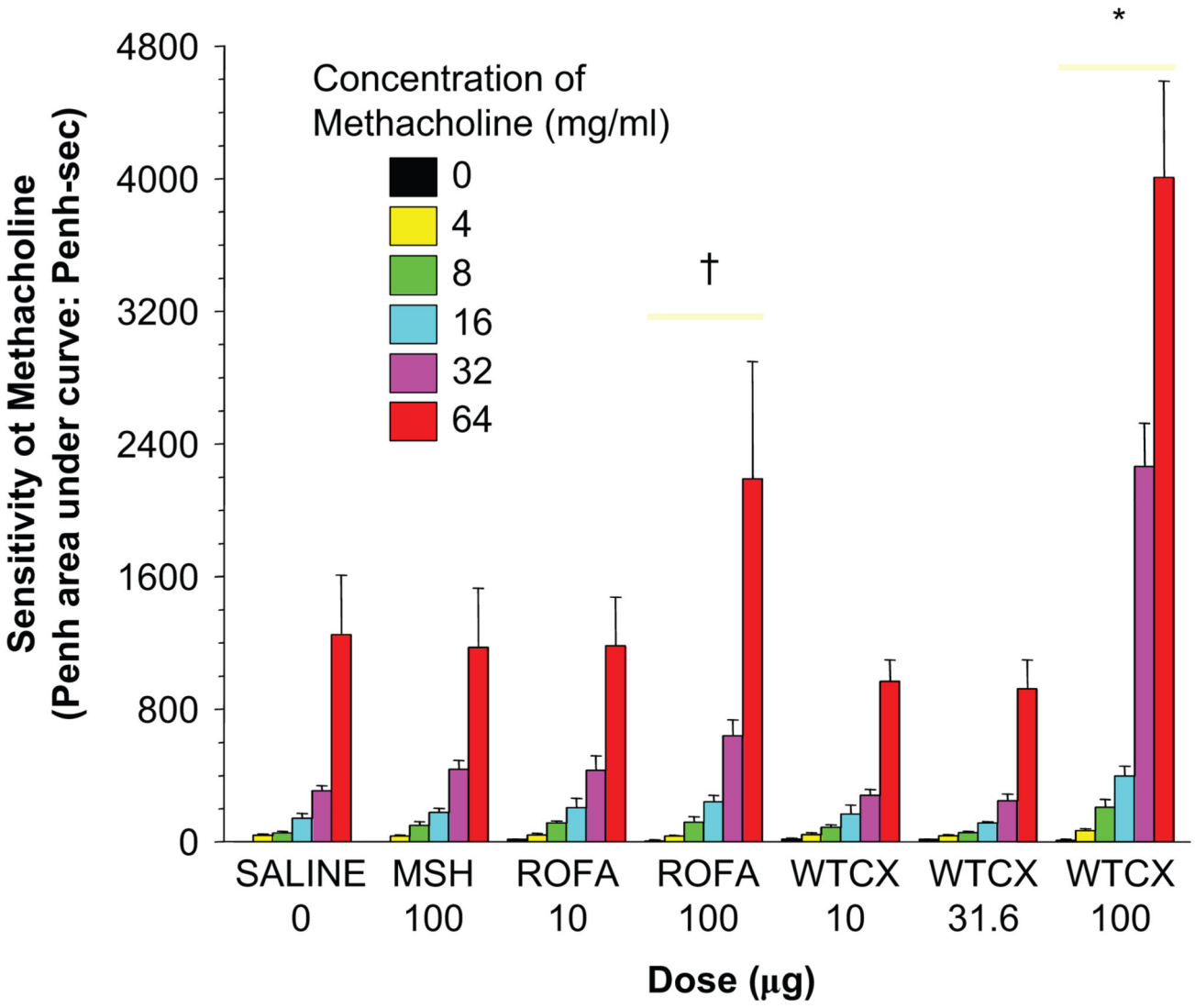

Figure 9.

Airway hyperresponsiveness of mice exposed intratracheally to test WTC, PM standards, or saline and tested one day later (n = 8/group; data are mean ± SEM). When power function equations were fitted to each respective treatment set: ‡significantly ($p < 0.001$) different exponent versus that seen with saline-treated mice or *significantly ($p < 0.03$) different coefficient versus saline coefficient.

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Table 1

Comparison of ambient air fine and coarse mode particles.

	Fine mode	Coarse mode
Formed from	Gases	Large solids/droplets
Formed by	Chemical reaction; nucleation; condensation; coagulation; evaporation of fog and cloud droplets in which gases have dissolved and reacted	Mechanical disruption (e.g., crushing, grinding, abrasion of surfaces); evaporation of sprays; suspension of dusts
Composed of	Sulfate, SO_4^{2-}; nitrate, NO_3^-; ammonium, NH_4^+; hydrogen ion, H^+; elemental carbon; organic compounds (e.g., PAHs, PNAs); metals (e.g., Pb, Cd, V, Ni, Cu. Zn, Mn, Fe); particle-bound water	Resuspended dusts (e.g., soil dust, street dust); coal and oil fly ash; metal oxides of crustal elements (Si, Al, Ti, Fe); $CaCO_3$, NaCI, sea salt, pollen, mold spores; plant/animal fragments; tire wear debris
Solubility	Largely soluble, hygroscopic and deliquescent	Largely insoluble and non-hygroscopic
Sources	Combustion of coal, oil, gasoline, diesel, wood; atmospheric transformation products of NO_2, SO_2, and organic compounds including biogenic species (e.g., terpenes); high temperature processes, smelters, steel mills, etc.	Resuspension of industrial dust and soil tracked onto roads; suspension from disturbed soil (e.g., farming, mining, unpaved roads); biological sources; construction and demolition; coal and oil combustion; ocean spray
Lifetimes	Days to weeks	Minutes to hours
Travel distance	100s to 1000s of kilometers	< 1–10s of kilometers

Source: EPA (1996).

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Table 2

Governmental support for studies of health effects of exposures to WTC Dust (from GAO Report).

	Administrator	Eligible populations	Participation	Monitoring methods	Treatment referral	Intended duration and federal funding
WTC Health Registry	NYC Department of Health and Mental Hygiene	Between 250,000 and 400,000 responders and people living or attending school in the area of the WTC or working or being present in the vicinity on September 11	As of 9/2004, 60,483 people were enrolled	Telephone-based health interview; plan to reinterview subset of population in 2005	Provides information on where treatment can be sought; Refers participants to LIFENET for mental health services	Agency for Toxi Substances and Disease Registry intends to fund through fiscal year 2008—$20 million total Environmental Protection Agency allocated in fiscal year 2004—$1.5 million total
FDNY WTC Medical Monitoring Program (FDNY program)	FDNY Bureau of Health Services (FDNY-BHS)	About 11,000 firefighters and 3,500 emergency medical service (EMS) technicians	As of 4/2004, 11.770 firefighters and EMS technicians were enrolled	Medical examination and questionnaire; three follow-up examinations planned	Refers to FDNY-BHS	National Institute for Occupational Safety and Health (NIOSH) intends to fund through 672009—$25 million total National Center for Environmental Health funded initial monitoring—$4,8 million total
WTC Worker and Volunteer Medical Monitoring Program (Mount Sinai program)	Mount Sinai's Irving J. Selikoff Clinical Center for Occupational And Environmental Medicine	About 12,000 responders	As of 8/2004, about 11,793 people were enrolled	Medical examination and questionnaire; three follow-up examinations planned	Refers to Privately funded program available for responders	NIOSH intends to fund through 7/2009—$56 million total NIOSH funded initial Monitoring—S15.8 million total
The medical monitoring program for New York State Workers (NYS program)	New York State Department of Health	About 9,800 New York State employees and National Guard personnel	As of 10/2003, 1,677 employees received medical evaluations	Medical examination and questionnaire; follow-up on subset of 300 employees planned	Instructs participants to see their primary care physician or the state's occupational health unit	National Center for Environmental Health funded through fiscal year 2003—$2.4 million total
WTC cleanup and recovery worker registry (Johns Hopkins registry)	Johns Hopkins Bloomberg School of Public Health	About 12,000 members from three unions and the NYC Department of Sanitation	As of 6/2003, 1,337 workers responded to the mailed questionnaire	Mail-in health survey	Provides participants with brochures about health services; refers uninsured to Columbia University for mental health services	National Institute of Environmental Health Sciences (NIEHS) funded through fiscal year 2003—$1.2 million total
WTC responder Screening program for	Department of Health	About 10,000 federal workers responding to	As of 3/2004, 412 examinations were	Medical examination and questionnaire	Instructs participants to see their primary care	HHS intends to fund through 12/2005—$3.7 million total

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	Administrator	Eligible populations	Participation	Monitoring methods	Treatment referral	Intended duration and federal funding
federal workers (FOH program)	and Human Services (HHS) Federal Occupational Health services	WTC	completed and reviewed		physician	

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Table 3

NIEHS center's collaborators.

NIEHS center	Research projects	
New York University	**1**	Assessment of heat and lung effects on NYC firefighters
	2	Checking of Lower Manhattan residents' respiratory (lung) health
	3	Collection and analysis of indoor and outdoor settled dust samples
	4	Analyses of the characteristics of particle air pollution in Lower Manhattan during September thru December 2001
	5	Toxicity tests of WTC Dust
	6	Conducting community forums to inform the public of the latest scientific progress and plans
Johns Hopkins University	•	Health assessment and monitoring of truckers, heavy equipment operators and laborers
	•	Long-term effects of cleanup at the WTC site
Columbia University	•	Chemical assessment of WTC emissions—air and sediments
	•	Pollution database development
	•	Prospective study of pregnant women and infants exposed in utero to WTC air pollution
	•	Public dissemination of information
Mount Sinai School of Medicine	•	Studies of WTC ironworkers for respiratory abnormalities
	•	Study of pregnant women and children near WTC
	•	Remote sensing imagery of the dust plume combined with ground measurements
	•	Outreach to children and families
	•	Analysis of organochlorines in NY and Hudson River
University of Medicine & Dentistry of New Jersey (Rutgers)	•	Comparison of perceived (expected) vs. actual risks
	•	Study of possible psychological effects (e.g., stress) of WTC disaster
	•	Analysis of indoor settled dust/smoke samples
	•	Develop mathematical tools for assessing contaminant release on air quality
	•	Study time trends for adverse reproductive outcomes
	•	Assessment of NJ, NY, and CT department of health personnel's environmental public health capacity
	•	Implementation of community forums for New Jersey commuters
	•	Development of case study for students to study WTC Dust and possibly related "WTC cough"
	•	Development of website featuring WTC environmental health research and information
University of North Carolina, Chapel Hill	•	Community air quality exposures
	•	Modeling using geographical information systems (GIS)
University of Rochester (Collaborating with NYU)	•	Assessment of very small (ultrafine) WTC Dust
	•	Community Outreach

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Table 4

Research papers published by 5 NIEHS centers (only lists those supported by NIEHS supplemental funds. Because of collaborative nature of these efforts, there were overlapping publications).

NYU	**1**	Rom WN, Reibman J, Rogers L, Weiden MD, Oppenheimer B, Berger K, et al. (2010). Emerging exposures and respiratory health—World Trade Center dust. Proc Am ThoracSoc,7, 142–5. PubMed PMID: 12231487.
	2	Lioy PJ, Weisel CP, Millette JR, Eisenreich S, Vallero D, Offenberg J, et al.(2002). Characterization of the dust/smoke aerosol that settled east of the World Trade Center (WTC) in Lower Manhattan after the collapse of the WTC 11 September 2001. Env Health Perspect,110, 703–14. PubMed PMID: 12117648; PubMed Central PMCID:PMC1240917.
	3	Offenberg JH, Eisenreich SJ, Gigliotti CL, Chen LC, Xiong JQ, Quan C, et al. (2004).Persistent organic pollutants in dusts that settled indoors in lower Manhattan after September 11, 2001. J Expo Anal Environ Epidemiol,14, 164–72. PubMed PMID:15014547.
	4	Offenberg JH, Eisenreich SJ, Chen LC, Cohen MD, Chee G, Prophete C, et al. (2003). Persistent organic pollutants in the dusts that settled across lower Manhattan after September 11, 2001. Environ SciTechnol, 37, 502–8. PubMed PMID: 12630465.
	5	Yiin L-M, Millette JR, Vette A, Ilacqua V, Quan C, Gorczynski J, et al.(2006). Comparisons of the dust/smoke particulate that settled inside the surrounding buildings and outside on the streets of southern New York City after the collapse of the World Trade center, September 11, 2001. J Air Waste Manage Assoc,54, 515–28. PubMed PMID: 15149040.
	6	Reibman J, Lin S, Hwang SA, Gulati M, Bowers JA, Rogers I, et al. (2005). The World Trade Center residents' respiratory health study: new-onset respiratory symptoms and pulmonary function. Environ Health Perspect,113, 406–11. PubMed PMID: 15811830; PubMed Central PMCID:PMC1278479.
	7	Oppenheimer BW, Goldring RM, Herberg ME, Hofer IS, Reyfman PA, Liautaud S, et al. (2007). Distal airway function in symptomatic subjects with normal spirometry following World Trade Center dust exposure. Chest, 132, 1275–82. Epub 2007 Sep 21. PubMed PMID: 17890470.
Columbia	**1**	Geyh AS, Chillrud S, Williams DI, Herbstman J, Symons JM, Rees K, et al. (2005). Assessing truck driver exposure at the World Trade Center disaster site: personal and area monitoring for particulate matter and volatile organic compounds during October 2001 and April 2002. J Occup Environ Hyg,2, 179–93.PubMed PMID: 15764541.
	2	Landrigan PJ, Lioy PJ, Thurston G, Berkowitz G, Chen LC, Chillrud SN, et al. (2004). The NIEHS World Trade Center Working Group. Health and environmental consequences of the World Trade Center disaster. Environ Health Perspect, 112, 731–9. PubMed PMID: 15121517; PubMed Central PMCID: PMC1241968.
	3	Lederman SA, Rauh V, Weiss L, Stein JL, Hoepner LA, Becker M, Perera FP. (2004). The effects of the World Trade Center event on birth outcomes among term deliveries at three lower Manhattan hospitals. Environ Health Perspect,112, 1772–8. PubMed PMID: 15579426; PubMed Central PMCID: PMC1253672.
	4	Perera F, Tang D, Whyatt R, Lederman SA, Jedrychowski W. (2005). DNA damage from polycyclic aromatic hydrocarbons measured by benzo[a]pyrene-DNA adducts in mothers and newborns from Northern Manhattan, the World Trade Center Area, Poland, and China. Cancer Epidemiol Biomarkers Prev, 14, 709–14. PubMed PMID: 15767354.
	5	Perera FP, Tang D, Rauh V, Lester K, Tsai WY, Tu YH, et al. (2005). Relationships among polycyclic aromatic hydrocarbon-DNA adducts, proximity to the World Trade Center, and effects on fetal growth. Environ Health Perspect,113, 1062–7. PubMed PMID:16079080; PubMed Central PMCID: PMC1280350.
	6	Gross R, Neria Y, Tao XG, Massa J, Ashwell L, Davis K, Geyh A. (2006). Posttraumatic stress disorder and other psychological sequelae among World Trade Center cleanup and recovery workers. Ann N Y AcadSci, 1071, 495–9. PubMed PMID: 16891606; PubMed Central PMCID: PMC3622541.
	7	Perera FP, Tang D, Rauh V, Tu YH, Tsai WY, Becker M, et al. (2007). Relationship between polycyclic aromatic hydrocarbon-DNA adducts, environmental tobacco smoke, and child development in the World Trade Center cohort. Environ Health Perspect,115, 1497–502. PubMed PMID:17938742; PubMed Central PMCID: PMC2022637.
	8	Lederman SA, Becker M, Sheets S, Stein J, Tang D, Weiss L, Perera FP. (2008). Modeling exposure to air pollution from the WTC disaster based on reports of perceived air pollution. Risk Anal,28,287–301.doi: 10.1111/j.1539- 6924.2008.01019.x. PubMed PMID: 18419649.
	9	Lederman SA, Jones RL, Caldwell KL, Rauh V, Sheets SE, Tang D, et al. (2008). Relation between cord blood mercury levels and early child development in a World Trade Center cohort. Environ Health Perspect,116, 1085–91. doi:10.1289/ehp.10831. PubMed PMID: 18709170; PubMed Central PMCID: PMC2516590.
Mt. Sinai School of Medicine	**1**	Landrigan PJ, Lioy, PJ, Thurston G, Berkowitz G, Chen LC, Chillrud SN, et al. (2004). The NIEHS World Trade Center Working Group. Health and environmental consequences of the World Trade Center disaster. Environ Health Perspect, 112, 731–9. PubMed PMID: 15121517; PubMed Central PMCID: PMC1241968.

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Table 5

Element concentrations (in μg/g) in the selected dust samples (from Maciejczyk et al.[2004]).

	10–53 μm		2.5–10 μm		< 2.5 μm	
	mean	**st. dev.**	**mean**	**st. dev.**	**mean**	**st. dev.**
Na	5,300	1,500	1,300	420	1,500	460
Mg	28,000	3,000	7,100	1,400	4,400	1,800
Al	27,000	2,600	8,800	1,400	7,200	2,200
Si					28,000	6,000
S					130,000	23,000
Cl	19	3.2	24	7.4	1,400	1,600
K	300	780	< DL		1,300	610
Ca	220,000	5,900	230,000	3,200	97,000	16,000
Ti	2,200	210	930	140	540	400
V	31	2.3	17	2.4	8.3	5.7
Cr	85	22	75	21	30	15
Mn	1,200	180	180	49	41	14
Fe	10,000	2,400	5,700	1,200	2,300	950
Co	4.4	1.0	3.1	0.60	6.0	4.6
Cu	230	120	160	140	64	35
Zn	1,400	370	1,100	230	550	290
As	2.7	0.8	2.0	0.4	< DL	
Se					20	7.3
Br					68	24
Rb	16	3.3	12	1.8	32	10
Sr					210	37
Sb	40	14	54	18	3,800	630
Ba					27	37
Pb					65	27
La	38.0	12.0	9.3	3.6		
Sm	9.1	2.5	1.5	0.3		
Ag	1.6	0.7	< DL			
Ce	80	22	17	7.1		
Hf	3.0	0.7	0.6	0.1		
Sc	6.2	1.6	1.5	0.3		
Th	7.2	1.9	1.4	0.3		

Note: $n = 7$ (10–53 μm), $n = 7$ (2.5–10 μm), and $n = 28$ (< 2.5 μm). Potassium in size fraction 10–53 μm was detected only in one sample. No values reported if element was not measured by the method; < DL is reported if value was below the detection limit of the method.

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Table 6

Summary of reports of excess respiratory and gastroesophageal responses to WTC Dust exposures.

1st author	Year	Population	Clinic location	Respiratory symptoms	Pulmonary function	Asthma	Wheeze	SOB	Sarcoid	GERD	Other responses
A. Occupational exposures											
Landriqan	2004	Resc.-Recov.	MSSM	*			*				
Skloot	2004	Ironworkers	MSSM	*							
Herbstman	2005	Clean-Recov.	MSSM	*			*				
Herbert	2006	Construction	MSSM	*	*						
Buyantseva	2007	Police	MSSM	*							
Wheeler	2007	Resc.-Recov.	MSSM			*					
de la Hoz	2008	Med. Monitor	MSSM	*				*			
Skloot	2009	Med. Monitor	MSSM		*						
Bowers	2010	Rescue Work	MSSM						*		
Brackbill	2009	Med. Monitor	MSSM			*					
Crowley	2011a,b	Med. Monitor	MSSM						*		
Jordan	2011	Med. Monitor	MSSM						*		
Wisnivesky	2011	Rescue, Recov	MSSM	*	*	*				*	
Li	2011	Work &Resid.	MSSM							*	
Kim	2012	Med. Monitor	MSSM	*		*					
Prezant	2002	Firefighters	NYU	*				*		*	
Banauch	2002	FDNY	NYU	*	*	*	*	*			*
Banauch	2005	FDNY	NYU	*	*	*				*	RADS,RUDS
Banauch	2006	FDNY	NYU	*							
Izbicki	2007	Firefiqhters	NYU		*						
Webber	2009	FDNY	NYU	*							
Weiden	2010	FDNY	NYU		*						
Aldrich	2010	FDNY	NYU		*						
Banauch	2010	Firefiqhters	NYU		*				*		
Weakley	2011	Firefiqhters	NYU	*							
Aldrich	2013	Firefighters	NYU		*						
Malievskaya	2002	Cleanup Work	Queens Coll.	*							

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1st author	Year	Population	Clinic location	Respiratory symptoms	Pulmonary function	Asthma	Wheeze	SOB	Sarcoid	GERD	Other responses
Kleinman	2011	Police	NYPD	*	*						
B. Incidental exposures											
Lin	2007	Residents	NYU	*							
Reibman	2009	Residents	NYU	*	*						
Rom	2010	FDNY &Resid.	NYU	*	*			*		*	
Friedman	2011	Residents	NYU		*						
Maslow	2012	Residents	NYU	*							
Ka zeros	2013	Residents	NYU	*	*	*	*				
Bernard	2002	School Employ	None	*							
Trout	2002	Fed. Employ.	None	*							
Faqan	2002	Residents	None	*							
Waqner	2005	Residents	None			*					
Green	2006	Residents	None	*		*					*
Lin & Reibman	2005,2007	Residents	None	*		*		*			*
La um bach	2009	Residents	None	*			*				
Lin	2010a	Residents	None			*					