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WORLD TRADE CENTER (WTC) DUST

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26.1 INTRODUCTION

On the morning of September 11, 2001, two passenger jet planes separately impacted on the 100-story WTC North and South Towers in New York City (NYC), and both towers collapsed within just 2 h. As a result, dense clouds of dust were generated by successive collisions of collapsing concrete floor slabs, with a resultant crushing of concrete, wallboard, and glass/slag-wool insulation into dense clouds of airborne particles that were deposited over wide areas of southern Manhattan Island (south of Canal Street), as well as portions of westernmost Brooklyn and northernmost Staten Island. In the vicinity of the towers, dust layers on the streets/sidewalks and within buildings with shattered/open windows reached, in some cases, inches in thickness. Ultimately, due to dust resuspension by air currents or mechanical disturbance during on-site/local activities, there were additional exposures of rescue/recovery workers, clean-up workers, office/various other types of workers in affected buildings and of local residents. These dusts generated by the collapse of the WTC Towers, and subsequently resuspended, designated herein as "WTC Dust," were unique in terms of particle size distribution and composition. Of the total mass in the settled WTC Dust, <1% was deemed fine (<2.5 μm in aerodynamic diameter), and >90% was coarse/supercoarse (2.5–100 μm) (Lioy et al., 2002, 2006; McGee et al., 2003; Yiin et al., 2006).

Compositionally, WTC Dusts differed from normally encountered (in Eastern United States) ambient particulate matter (PM) in that they did not originate from organic/inorganic vapor-phase pollutants, were not primarily carbonaceous, and were neither strongly acidic nor hydroscopic. Interestingly, WTC Dusts also differed from typical building construction and demolition site dusts; the latter are generally composed of much larger particles and are not as readily resuspended into the air or as rapidly dissoluble in aqueous surface fluids (e.g., in the respiratory and/or gastrointestinal [GI] tracts). The WTC Dusts were of a more uniform chemical composition, with 80–90% being composed of a

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well-blended mixture of concrete, gypsum, and synthetic vitreous fibers (SVFs). Furthermore, it is important to note that the WTC Dusts deposited out of doors in the initial period after the disaster differed from those encountered indoors after September 14 when a heavy rain washed away some of it and changed the chemical composition of the remainder (i.e., by removal of soluble components). Similarly, dusts found in outside locations—while not likely compositionally different—did differ from indoor WTC Dust in terms of physicochemical characteristics (i.e., primarily with respect to median particle sizes and pH).

In addition, the composition of the outdoor WTC Dusts was changing with time due to site-related activities, such as the generation of fumes generated by metal-cutting torches and by the disturbances caused by the continuing movement into and out of the Ground Zero area of diesel-powered trucks and other heavy equipment, as well as of the ever-shifting composition of the effluents of the ongoing fires on and within the debris pile at Ground Zero, which were not completely extinguished until December of 2011. Thus, when one speaks of WTC Dusts, one must consider various temporal and spatial aspects affecting their distributions of particle size and composition.

26.2 POST-COLLAPSE HUMAN INHALATION EXPOSURES TO WTC DUSTS

26.2.1 Temporal Sequence

In the aftermath of the disaster, many inhalation exposures scenarios confronted the residents of Lower Manhattan, Ground Zero rescue and recovery workers, and cleanup workers:

1. On 9/11, most people living/working in Lower Manhattan were required to undergo mandatory evacuation from the vicinity of the WTC site. Many evacuees ended up being caught in both the aftermath of the building collapse and resuspended dust clouds and as a result became both covered with dust and underwent significant WTC Dust inhalation exposures. Even greater acute inhalation exposures befell firefighters, police personnel, and volunteers who had arrived at the WTC to help rescue survivors of the original airplane impacts. Many of these individuals did so without access to/proper use of personal protective equipment (PPE), that is, respirators.
2. On 9/12 and 9/13, while acute inhalation exposures of evacuees were much lower than on 9/11, increasing numbers of newly arrived rescue and recovery workers were highly exposed as their activities on and around Ground Zero resulted in resuspension of settled dusts. Even at this point, only a small fraction of the workers had respirators, and, of these, only some used them. The reasons were multiple, that is, apart from the high ambient temperatures on those days/nights in combination with heat generated from fires at Ground Zero and from constantly working engines of trucks/moving equipment, PPE respirator filters quickly became clogged with dust, making the work of breathing through them too great.
3. During succeeding days, weeks, and then months, inhalation exposures of outdoor workers were lowered due to rains that removal of residual settled dusts and debris was also continuing. However, increasing numbers of workers (and later, residents)

became engaged in indoor dust removal, and their potentials for exposures increased. While many of the workers that were engaged to clean contaminated commercial buildings were asbestos remediation workers trained in use of negative pressure respirators for which they had been fit-tested, their filters often became clogged within the first few hours of a standard workday, and as a result, their inhalation exposures later in a given workday could become high.

4. Exposures of residential and commercial office evacuees remained low, as long as they stayed away from areas abutting Ground Zero. In fact, most residents were not permitted to return to their buildings until the site was certified as clean. For most residents, reoccupation took place over many weeks. In the cases of workers who had left offices that had become contaminated with WTC Dusts, many were back at work within several weeks. However, the adequacy of initial cleanings was often disputed, leading to many second-stage cleanings because building owners and managers lack experience with this type of unprecedented disaster. While government agency mandates and guidelines for minimizing inhalation exposures to WTC Dust were generally followed, these guidelines were in many cases inadequate with respect to health protection.

Many government agencies were sufficiently concerned about potential health effects from exposures to WTC Dusts to undertake collection and analyses of samples of both settled and airborne dusts in the days and weeks after the disaster to clarify the nature and extent of ongoing toxicant exposures. However, these efforts relied primarily on analyses of ambient air samples of $PM_{2.5}$ collected by fixed-site monitors located at the perimeter of the WTC Ground Zero and at various other sites in Lower Manhattan and surrounding areas. Beyond characterizing the mass concentrations of $PM_{2.5}$ (and, in some cases, their physicochemical characteristics), these analyses were relied upon to help estimate potential inhalation exposures and human health risk incurred by those working at/in the vicinity of the WTC. The data were also utilized to help evaluate similar parameters for individuals (local residents/office workers) who were exposed to the WTC Dust generated by the initial collapse and who faced dust-filled apartments when the quarantine was lifted.

26.2.2 What Was Measured

The ambient air ($PM_{2.5}$) monitoring activities primarily focused on overall mass concentrations and specifically the concentrations of individual constituents such as lead (Pb), chromium (Cr), and nickel (Ni), polychlorinated biphenyls (PCBs), dioxin-like compounds, asbestos fibers, and volatile organic compounds (VOCs). Some of these choices were based upon factors associated with the buildings themselves and their contents, that is, Pb and asbestos were part of the original materials used when WTC construction began in the 1960s and PCBs were used as dielectric fluid in transformers and capacitors. Others were selected as they were related to the disaster itself, that is, dioxin and VOCs produced as a result of fuel combustion/volatilization. As noteworthy as the agents whose levels were monitored were those that were not, especially the dust components that contributed to 80–90% of the mass of settled WTC Dusts, that is, crushed concrete, gypsum, and SVF.

Significant elevations of the concentrations of these evaluated contaminants were found in/near Ground Zero for a short period immediately after September 11, with

elevations denoting concentrations higher by a factor of 10 or more and often by factors of 100 or 1000, compared with other measures of contaminants taken post-September 14. Many of the elevated values occurred in "restricted zones," that is, access limited to emergency management and rescue personnel and to other credentialed people. Though ambient air $PM_{2.5}$ levels for all these substances decreased to background concentrations (characteristic of pre-September 11 levels in NYC metro-area by February 2002), regulators still concluded that (1) persons exposed to extremely high levels of ambient $PM_{2.5}$ (i.e., including small fractions of WTC Dusts) and its components during the collapse and over several hours afterwards were at risk for immediate acute (possibly chronic) respiratory and other types of symptoms [e.g., cardiovascular (CV)]; (2) because the first measures were taken on September 14 and those of other contaminants not until September 23, and as levels in/near Ground Zero were highest in the first few days after the disaster, 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 judged, by the public agencies, to be unlikely to suffer short- or long-term adverse health effects caused by exposure to elevations in ambient air concentrations of the contaminants that were evaluated.

Despite their limited scope, the analyses did prove revelatory. The EPA provided summaries of findings for each contaminant/class of contaminants that it selected as a likely, or at least a possible, risk factor.

26.2.3 Particulate Matter (PM) in Terms of Mass Concentration

People caught in the initial dust/smoke cloud were briefly exposed (4–8 h) airborne $PM_{2.5}$ in the mg/m^3 range (thousands of $\mu g/m^3$). During the first several days post-disaster, levels at the WTC perimeter exceeded the EPA National Ambient Air Quality Standards (NAAQS) for PM2.5 (65 $\mu g/m^3$, 24-h); levels at other nearby Lower Manhattan sites exceeded the 40 $\mu g/m^3$ 24-h air quality index (AQI) level of concern for susceptible subgroups in the general population. By mid-late October, $PM_{2.5}$ levels in the region had largely returned to levels typical of NYC and other urban areas; only a few WTC/nearby sites occasionally approached or exceeding the AQI level of concern.

26.2.4 Lead (Pb), Chromium (Cr), Nickel (Ni), and Other Metals

Persons caught in the initial WTC-related dust cloud experienced brief exposures to high Pb levels based on analyses of settled dust samples. In late September 2001, airborne Pb concentrations at the WTC perimeter sites reached >1.5 $\mu g/m^3$ 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 typical of NYC and other Northeast U.S. urban areas. Samples evaluated for total airborne Cr at Ground Zero/surrounding sites never exceeded the OSHA permissible exposure limit (PEL) (1 mg/m^3) or ATSDR's intermediate minimum risk level (MRL) for Cr(VI) particles (1 $\mu g/m^3$). Airborne nickel in Ground Zero/surrounding site samples never exceeded the OSHA PEL (1 mg/m^3). Levels of other elements [e.g., calcium (Ca), sulfur (S), silicon (Si), etc.] in WTC PM2.5 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/November 2001.

26.2.5 Polychlorinated Biphenyls (PCBs) and Dioxins

Of several hundred PCB air measurements, only one was >100 ng/m^3 (at 153 ng/m^3) and three at >50 ng/m^3. This is compared to typical urban background PCB concentrations in the 1–8 ng PCB/m^3 range. After 1 month, nearly all readings were in the range of typical urban PCB levels or not detected. There were no exceedences of any short-term occupational health benchmark. Dioxin toxic equivalent (TEQ) levels in air near Ground Zero were up to three orders of magnitude higher than typical for urban areas (0.1–0.2 pg TEQ/m^3). Levels in/near Ground Zero, starting September 23 (date of first sample) and through late November, ranged from 10 to >150 pg TEQ/m^3. Levels measured several blocks from Ground Zero were elevated above typical urban background but considerably less than in or near Ground Zero. Even these elevations soon dropped, that is, background by December.

26.2.6 Volatile Organic Compounds (VOCs)

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

26.2.7 Asbestos Fibers

The large majority of outside measures of airborne asbestos fiber 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 systematic study in late 2001 suggested indoor levels of asbestos fibers in WTC Dusts were slightly higher near Ground Zero as compared with indoor levels in buildings further away. Analyses performed for several residential apartments (NYCDOHMH/ATSDR) between November 4 and December 11, which included 57 apartments in Lower Manhattan as well as 5 comparison apartments in areas outside the exclusion zone, showed that airborne fibers were not detected above background levels. However, bulk settled dust samples showed that there was asbestos in 16% of the apartments (but none in more distant comparison sites). Further, SVFs (i.e., slag wool or fibrous glass) were found in both indoor and outdoor settled dust samples. Another study sampling indoor air and dust on September 18, in two locations very near Ground Zero, found asbestos in both airborne and settled dust. However, those same analyses also found there were low background concentrations of dioxins, PCBs, and metals. That levels of asbestos fibers in the WTC Dust samples were not high was not unexpected. There was chrysotile asbestos insulation within the first 20 floors of the WTC

North Tower, but none in the other 80 floors or in the adjacent South Tower. There was no amphibole asbestos insulation installed in either tower. Ultimately, very few of the airborne asbestos measures in the EPA WTC database exceeded conservative fiber count limits, even in the first few days when the fiber concentrations were "highest."

26.2.8 Other PM Properties and Their Interpretations

Other analyses, primarily dealing with physicochemical characteristics of the WTC Dust samples, also yielded important information about the potential for entrainment, retention, and subsequent health risks from exposures to the WTC Dusts in the earliest days after the disaster. Among these was pH. The issue of alkalinity of the WTC Dust, and its potential as a possible health concern for exposed individuals, was that there was a consistent particle size-related difference in pH values for the dusts. Specifically, very high pH (≥10.0) values were measured for aqueous solutions of the initial samples of settled supercoarse WTC Dusts (i.e., not leached by 9/14 rainfall).

26.2.9 Relevance of Established Concentration Standards and Guidelines

There were, and remain, problems in interpreting the WTC-related air quality monitoring. These include issues concerning the protocols that were selected for characterizing exposures related to indoor cleanup and documentation of exposure and health risks to people in Lower Manhattan buildings. One was the failure to first adequately consider (1) the unique particle size distribution/chemical composition of the WTC Dust, (2) the likelihood of excessive inhalation exposures, and (3) optimal means for preventing/controlling excessive exposures. Most importantly, there was too much focus on toxicants that were present as small mass fractions that, collectively, made up only a small percentage of the WTC Dust in air samples analyzed, that is, recall nearly all the WTC Dust was made up of >2.5 μm diameter particles, with most of that within particles >10 μm. Little consideration was given to potential toxic effects of inhaling the three major mass components in these coarse and supercoarse particles, for example, crushed concrete, gypsum, and SVF, each a known irritant. These problems were compounded by the intense initial EPA focus on asbestos fibers as the index toxicant for WTC Dust. There was a secondary focus on other trace components that were generally considered to pose health risks, that is, metals, molds, PAHs, PCBs, and dioxins. The measured airborne concentrations of these agents were also almost all below current occupational exposure limits.

Since many rescue and recovery workers did develop respiratory illnesses after exposure to WTC Dusts, and it is known that established occupational/ambient air exposure limits had seldom (and only briefly) been exceeded, it is likely that exposure components that were not measured (such as the coarse alkaline particles and SVF) were potentially the most likely to be responsible for these observed increases in incidence of adverse health effects.

26.3 POTENTIAL DOSIMETRY OF WTC DUSTS

The WTC Dust, as summarized above, differed greatly from conventional airborne dusts encountered in occupational and community settings in terms of both particle size distribution and chemical composition. Many thick deposits of WTC Dust were deposited on a

variety of outdoor surfaces in Lower Manhattan during the first day after the disaster. These settled WTC Dust deposits persisted until either the major rain of 9/14 or their removal by responders at Ground Zero. In contrast, WTC Dusts that covered indoor surfaces often remained for much longer periods of time (due to quarantines of contaminated buildings, which limited the startup of indoor cleanup).

26.3.1 Use of Particle Size-Selective Dust Samples

Teams from New York University (NYU) and Rutgers University collected and analyzed WTC Dust samples in order to characterize the chemical composition, particle size distribution, and potential for resuspension of the settled dust particles into human breathing zones, settled WTC Dust samples were collected on September 12 and 13, 2001, and aliquots were separated into size fractions through mesh. The PM_{53} fraction passing through the screens was aerosolized into an elutriation chamber and passed in a size-selective air sampler inlet with a 10-μm aerodynamic cut size (to remove/isolate $PM_{10–53}$ as well as a distinct PM_{10} fraction). The PM_{10} fraction, in turn, was aspirated through a 2.5-μm cut cyclone to remove the coarse fraction ($PM_{2.5–10}$). Any remaining airborne $PM_{2.5}$ was collected on Teflon membrane filters. Each size fraction was then subjected to physical and chemical/compositional analyses. Similar work was done on settled indoor WTC Dust samples collected on September 13 and in June 2002. For the latter, there were substantial commonalities in the findings.

Because of the shift toward coarse/supercoarse sizes among the WTC Dust particles, it would be expected that how these are handling upon entrainment would impact on how each exposed individual ultimately responded to their exposure on 9/11 or the days thereafter. Specifically, penetration of inhaled particles into the thorax is limited by deposition in the upper respiratory tract (URT) during inspiration, and this varies with particle size distribution, flow rate and tidal volume, the fraction passing through oral pathway, and *in vivo* airway dimensions. All of these can vary considerably from person to person, depending on age, transient illness, history of cigarette 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.

26.3.2 Impact of Oral Versus Nasal Inhalation on Dosimetry

One must also consider that the vast majority of the inhalation exposures were by mouth breathing and less so via the nose. For particles that penetrate the lower respiratory tract (LRT) (airways within thorax), deposition patterns and efficiencies within thoracic conductive airways (trachea, bronchi, bronchioles) are mainly by impaction and sedimentation, and those of particles that deposit in smaller gas exchange airways by diffusion. In addition, some entrained particles remain airborne during tidal breath inhalation/exhalation and are not deposited. Even so, ≈15% of inhaled air remains in the deep lung over multiple breaths, and a corresponding volume of residual lung air is exhaled. Particles (or aggregates) >1 μm in diameter deposit in 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 a day, swallowed, and pass through to the GI tract. Particles that deposit in oral and ciliated nasal passages of the URT are also swallowed and pass to the GI tract. Lastly, most insoluble particles and their components >0.1 μm that reach the non-ciliated deep lung airways are phagocytosed by alveolar macrophages (AM) within weeks; these

cells and the particles within them are drawn into terminal bronchioles due to the high surface tension of the lining fluid and then cleared by mucociliary clearance and passage to the GI tract. In each scenario, it is believed that with WTC Dusts this might have contributed to increases in the incidence of both gastroesophageal reflux disease (GERD) and symptoms (GERS).

While these patterns could explain effects of conventional particle exposure, WTC Dust contained a lot of its total PM in the coarse thoracic range ($PM_{10–2.5}$), and even greater mass fractions were present in the $PM_{10–53}$ and $PM_{>53}$ size ranges. Further, alkalinity of the PM in the larger size ranges was greater than in dust $PM_{2.5}$ particles. As a result, as deposition of highly alkaline particles in the URT and in tracheobronchial airways in lower tract represent a unique challenge to the ability to clear the airways without eliciting adverse effects (such as erosion or death of airway surface epithelial cells), normal defense mechanisms in larger airways could have been overloaded in the WTC Dust-exposed individuals.

26.3.3 Disruption of Mucociliary Particle Clearance in the Airways

The disruption of mucociliary particle clearance in the airways by highly alkaline irritants could explain the excess incidences of cough and of respiratory (and GI) region pathologies seen in populations exposed to high levels of the large-diameter WTC Dust particles. Very high acute exposures/lower levels of chronic exposure to irritants can not only disrupt clearance but also destroy ciliated and mucus-secreting epithelial cells in the airways, leading to increased retention of all kinds of PM in the lungs and not just the irritant particles themselves. There is evidence that exposure to WTC Dust caused disruption of mucociliary clearance, that is, unusual ultrastructural ciliary abnormalities were noted in WTC response workers that corresponded to their respiratory and ciliary functional abnormalities. More recent studies in rat models showed extensive persistent damage to local ciliated cells and ultimately prolonged retention (i.e., ≈90%) of original WTC Dust burdens being retained for up to 1-year post-exposure [by intratracheal (IT) inhalation of WTC Dusts from 9/12 or 9/13 at levels modeling first responder (FR) exposure paradigms].

In view of the unique particle size distributions/high alkalinity of WTC Dust, standard dosimetry models and data tabulations were of little value in describing either acute or cumulative dust dosages received by individuals or distributions of doses in exposed population groups. Such estimations were further complicated by airborne WTC Dust levels that were highly variable temporally and spatially, with localized hot spots of exposure being related to human activities causing resuspension. Dose variations were also caused by use/nonuse of respiratory protection (even some used gauze masks and handkerchiefs to block inhalable particles) in the first few hours and days.

26.4 ASSOCIATIONS BETWEEN WTC DUST INHALATION AND HEALTH EFFECTS

26.4.1 Introduction

Several studies documented excesses in both acute and chronic health effects in rescue and recovery workers and volunteers heavily exposed to WTC Dust during the first few days post-9/11. Others noted effects in residents and local workers heavily exposed by the initial

dust clouds and then from more chronic exposures from resuspended dusts over longer periods. Despite differences in exposure pattern and intensity, the literature has shown associations of clinical disease with exposure to WTC Dust that demonstrate similarities in effects experienced and causality. Populations with the highest disease incidence and most severe responses included those likely exposed to quite high WTC Dust levels, that is, those at Ground Zero and FDNY employees. Less is known about local residents/workers; however, dose–response relationships for adverse effects have been shown in these populations. Clinical examinations have also been done on individuals exposed to lesser WTC Dust levels initially but had exposures extending over subsequent months, including local residents and office workers. Other population groups not given clinical exams, and whose exposures were less well defined, have been evaluated by questionnaires.

Despite different temporal patterns of WTC Dust exposure, most groups exhibited very similar clusters of specific disease categories within three specific anatomic regions, that is, upper respiratory, lower respiratory, and GI tract. One early clinical manifestation reported among those working in areas where dust contamination was substantial was "WTC cough." This "cough" was accompanied by bronchial hyperreactivity and respiratory distress. Of 332 firefighters having "WTC cough," 95% had symptoms of shortness of breath; 87% had GERD; and 54% had nasal symptoms. Beyond this "cough," many of the population groups had elevated incidences of chronic diseases that developed in the same three anatomic regions. Among the pathologies that the World Trade Center Health Program (WTCHP) was mandated to identify as related to occupational exposures to WTC Dusts were 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).

26.4.2 Occupational Groups Exposed to WTC Dust with Clinical Examinations

Levin et al. (2004) reported that from a subset of 1138 of the 11,768 non-FDNY workers and volunteers during July to December 2002, a substantial proportion experienced new-onset or worsened preexisting lower and upper respiratory symptoms, with persistence for months after their specific WTC work stopped [46% worked September 11 and 84% over September 11–14 when exposures were greatest, with a median length of time worked of 966 h (range 24—4080 h)]. In that period, 21% reported using respiratory protection (i.e., full- or half-face respirators). Of 610 examinees present in Lower Manhattan on September 11, 51% reported being directly in the main dust clouds, and an additional 31% reported exposure to substantial amounts of dust. Lower and upper respiratory symptoms were reported by 60 and 74%, respectively: 40% had WTC-incident lower respiratory symptoms that persisted to the month before screening, and 50% had persistent upper respiratory symptoms. Among 851 participants with persistent symptoms, an average of 32 weeks (range: 7–63 weeks) had elapsed since they stopped working at the site. Of all participants, 46% had nasal mucosal inflammation, with other respiratory abnormalities (e.g., abnormal nasal turbinates or sinuses, rhonchi, wheezing) being less common.

Skloot et al. (2004) studied 96 male ironworkers using physical exams, spirometry, and chest radiographs. Cough was the most common symptom, upper/lower pulmonary complaints were common among almost half, and 19 had abnormal radiographs. Cough was more common among those who began work on 9/11 compared with those who arrived later (78 vs. 54%). Spirometry did not differ between smokers and nonsmokers, and those

who wore protection seemed to have less respiratory symptoms than those who did not. The analyses revealed a significant odds ratio (OR) between cough and exposure during 9/11 (OR = 3.64, 95% CI = 1.35–9.83); however, changes in lung function (tests) were not associated with exposure duration or onset.

Herbstman et al. (2005) studied 183 WTC cleanup/recovery workers, among whom 91% wore a respirator some of the time. The subjects were divided according to whether they had respiratory symptoms (64 subjects, 35%) or not (119 subjects, 65%) when they began working at the WTC site. The data showed that of the groups with existing illnesses and symptom-free, 31 and 34% developed new cough, 23 and 24% developed new phlegm, and 16 and 19% developed *de novo* wheeze. New-onset cough in subjects with no lung problems was the only symptom that followed a (length of) exposure–response pattern. 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.

Herbert et al. (2006) gathered background information for studies of chronic respiratory diseases resulting from exposures to WTC Dust. Eligible workers/volunteers who worked 4 h on September 11, 24 h during September 2001, or 80 h any time within September to December were examined clinically, completed a standardized medical questionnaire, had a pulmonary function assessment, and provided responses about personal health before and after 9/11. Of the 9442 study participants, all had fewer lower or upper respiratory symptoms before than after 9/11. Symptoms tended to clearly show a greater risk for those whose exposures to WTC Dust happened in the first few weeks. Still, 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 (≈2 times the percentage prior to 9/11). When pulmonary function was assessed, the subjects had low forced vital capacities (FVC). Among 4641 never smokers in the cohort, there was a >2× increased prevalence of lowered pulmonary function as compared against all U.S. Caucasian males (27 vs. 13%). Ultimately, time of arrival at Ground Zero was correlated with reduced FVC, with those arriving on 9/11 having much poorer FVC than those arriving October 1 or later.

Buyantseva et al. (2007) studied 1588 NYC police officers—categorized as having heavy, moderate, or light exposure to WTC Dust—and compared adverse pulmonary effects pre- vs. post-9/11. Among the officers, prior to 9/11 there was a 4.8% prevalence of cough compared with 43.5% after 9/11. The OR, and race/sex-adjusted OR, rose 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 in tandem with level of WTC Dust exposure. Bowers et al. (2010) examined exposure-related sarcoidosis (multisystem inflammatory disorder, unknown etiology, characterized pathologically by non-caseating granulomas). The study described two cases of sarcoidosis in rescue workers with significant exposure to the dusts and who presented with extrapulmonary rheumatologic manifestations. The first was a 33-year-old white police detective found to have sarcoidosis after evaluation of diffuse joint pain. The second was a 40-year-old African-American officer who presented with uveitis and was then diagnosed with sarcoidosis.

Kleinman et al. (2011b) compared pulmonary function within an NYPD emergency responder cohort, without history of repetitive respiratory exposures. Of 206 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 (vs. baseline) in FVC of 190 mL (3.7%) in 2002 and 330 mL (6.4%) in 2007. FEV_1 was not significantly affected in 2002 but declined 160 mL (3.9%) after a further 5 years. Abnormal spirometry was observed in (5.3%) of subjects, particularly those who experienced higher exposure intensity/duration. The smokers in the group, and subjects who failed to wear protective respiratory masks, tended to display the greater declines. In 2002, 11 subjects (5.3%) exhibited mild pulmonary dysfunction (60–80% of predicted). Upon reevaluation in 2007, abnormalities had resolved in 4 of the 11, but 6 (54.5%) continued to exhibit mild pulmonary dysfunction.

Wisnivesky et al. (2011), along these longitudinal lines of analyses, evaluated a cohort of >50,000 police officers, firefighters, construction workers, and municipal workers who had participated in the rescue and recovery work phases and reported on the incidence/prevalence rates of disorders in a span of 9-year post-9/11 period. Incidence rates were also assessed by level of exposure (days worked at WTC site/exposure to dust cloud). The 9-year cumulative incidence of asthma was found to be 27.6% (number at risk: 7027), sinusitis was 42.3% (5870), and spirometric abnormalities was 41.8% (5769)—with three-quarters of these being low FVC. Incidence of disorders was highest in workers who had had greater levels of dust exposure.

Kim et al. (2012) studied risk of asthma among 20,834 participants in a cohort evaluated between July 2002 and December 2007. All subjects underwent a baseline clinical exam, with follow-up every 12–18 months from 2002 to 2007. If a respondent said they had an asthma attack in the past 12 months, they were chosen to serve as a control group for annual asthma risk. The results indicated there were exposure-related increases in lifetime asthma prevalence; pre-9/11 it was 2.9%, rose to 12.8% in 2002, and reached 19.4% in 2007. WTC FR had an age-standardized lifetime asthma SMR prevalence of 1.6 (95% CI = 1.6, 1.7) after 9/11 for all years of follow-up. Age-adjusted 12-month SMR were increased in the 2002–2005 timeframe; it was 1.7 (95% CI = 1.6, 1.8) compared with 0.3 (95% CI = 0.3, 0.4) in 2000. The increasing trend from 2002 on was the same for both women and men, and it increased for all ages (highest being for 40–49-year-olds). SMR were elevated for all occupational groups, with protective services having an SMR of 1.5 (95% CI = 1.5, 1.6) and installation, maintenance, and repair workers having an SMR of 2.0 (95% CI = 1.8, 2.2). Acute asthma SMR were elevated for all professions.

26.4.3 Firefighters/Emergency Medical Technicians

Studies on FDNY workers who had pre-9/11 health baselines that, in turn, provided ideal benchmarks by which to judge the impact of exposures to WTC Dust. Banauch et al. (2002) reported injuries and illnesses among FDNY rescue workers who had responded to the disaster. In the 48 h after the collapses, ≈90% of 10,116 FDNY rescue workers evaluated at the WTC site reported an acute cough, often accompanied by nasal congestion, chest tightness, or chest burning, but only 3 of them required hospitalization. Compared with numbers of service-connected respiratory medical leave incidents during the 11 months pre-9/11, the number increased fivefold during the 11 months post-9/11. Banauch et al. (2002) also reported that during the 6 months after the disaster, 332 firefighters and 1 EMS worker had WTC-related cough severe enough to require >4 consecutive weeks of medical leave. Despite treatment of upper and lower aero-digestive tract irritation (i.e., sinusitis,

GERS, and/or asthma), 173 (52%) showed only partial improvements. As of August 2002, a total of 358 firefighters and 5 EMS workers remained on medical leave or light-duty assignment because of respiratory illness. The high incidence of respiratory problems and related medical leave among FDNY rescue workers demonstrated a need for adequate respiratory protection.

Banauch et al. (2003) then conducted a prospective study of a representative sample of 179 FDNY fire/rescue workers to examine links between dust exposures and pulmonary hyperreactivity and WTC cough. At 1, 3, or 6 months post-9/11, subjects in both highly and moderately exposed groups showed significant declines in FVC, FEV_1, and FEV_1/FVC, compared with control workers. Bronchial hyperreactivity also showed an exposure dose–response trend at each follow-up time point. After adjusting for smoking and airflow obstruction, highly exposed workers at 1 month were 7.3 times more likely to have hyperreactive airways than controls. For moderately exposed workers, the risk was 6.3 times (at 6 months, it was 6.8 times). Among subjects who had hyperreactive airways at 6 months, respiratory symptoms were more frequent, and leave for respiratory illnesses was significantly longer (i.e., 45 vs. 12 days in nonreactive workers). Banauch et al. (2005) then reviewed aero-digestive inhalation lung injuries resulting from the WTC Dust exposures and the persistence of nonspecific bronchial hyperreactivity. Aero-digestive inflammatory injuries, like declines in pulmonary function, RADS, asthma, reactive upper airways dysfunction syndrome (RUDS), GERD, and (rare) inflammatory pulmonary parenchymal diseases, were documented. In the FDNY 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 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 workers employed on or before September 11, 2001. Between January 1, 1997, and September 11, 2002, a total of 31,994 spirometries were obtained, and 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 then compared with that in the 5-year period before the disaster. Median time between September 11, 2001, and a worker's first spirometry afterward was 3 months; 90% were assessed within 5 months. WTC-exposed FDNY workers experienced substantial reductions in adjusted average FEV_1 during the year post-9/11 (mean, 372 mL). The exposure-related FEV_1 decrements 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 ($p = 0.048$). Symptoms also predicted further FEV_1 decreases. Similar findings were noted for adjusted average FVC.

Weiden et al. (2010) studied the FDNY cohort and 1720 subjects sent for pulmonary medicine evaluations, that is, including 919 PFT, 122 methacholine challenge tests, and 982 CT (computerized tomography) scans. For subjects who had a PFT pre-9/11, there were significant declines in median FEV_1 and FEV_1/FVC ratios; 59% had obstructive airways diseases (OAD) based on a variety of factors. When adjusted for age, race, gender, height, weight, and smoking, declines in FEV_1 were significantly correlated with predicted residual volume % (RV) and responses to bronchodilators. These findings were consistent with injury to the airways, including bronchial wall thickening of the large airways and air trapping, which was seen in CT scans. The Weiden et al. (2010) findings helped to explain, in part, those of Rom et al. (2010) who reported that FDNY workers had significant

respiratory symptoms characterized by cough, dyspnea, gastroesophageal reflux, and nasal stuffiness with a significant group 1-year decline in FVC and FEV_1. In these workers, bronchial hyperreactivity (methacholine challenge) correlated with bronchial wall thickening on CT scans.

Webber et al. (2011) examined physician-diagnosed asthma and other respiratory ailments in a cohort of FDNY workers [14,314 firefighters and emergency medical service (EMS) providers]. After exclusions, there were 9715 male firefighters and 1228 male EMS workers studied; there were also 863 retired firefighters (7.9% of total) who returned to work to assist in rescue efforts. Subjects with a history of OAD were excluded from employment by the FDNY. Thus, in this group, there were only 85 asthma cases diagnosed pre-9/11 and no cases of emphysema. Exposure category was determined according to time of arrival at WTC site: group 1 = morning of 9/11; group 2 = afternoon of 9/11; group 3 = after 9/12; and group 4 = days 3 and 14 after 9/11. Duration of exposure to dust was also categorized into 1–3 months and 4–11 months. Self-reported symptoms/illnesses from the most recent health survey showed 17.3% of the subjects now with sinusitis, 12.2% bronchitis, 9.3% asthma, and 4.1% COPD/emphysema. Rates were greatest among the retirees, but little difference between EMS workers and firefighters.

Those arriving early at Ground Zero reported diagnosed asthma at a rate of 14%, while those arriving later had a rate of 5.9% (OR = 3.3; 95% CI = 2.4, 4.8). This pattern was the same for all respiratory diagnoses. After adjusting for smoking, age, arrival time, and duration of exposure, retirees were 10.2 times more likely to have asthma than active men and 7.4 times more likely to have COPD/emphysema. The authors also reported a link between quintile of FEV_1% and 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% asthma and 6.8% COPD/emphysema. Among firefighters not reporting any respiratory diagnosis (i.e., those without any respiratory conditions), 23.5% were in the highest quintile, and 14.6% the lowest FEV_1%. EMS workers showed the same pattern. Sinusitis (9.7%) and asthma (8.8%) were the most common physician diagnosis, and those with the longest exposures had the most reported cases of sinusitis (11.4%) and bronchitis (10.3%). Comparing firefighters in group 1 with those in group 4, there was 11.4% asthma contrasted with 5.3%. Cough, shortness of breath, and wheeze was correlated with lowest quintile FEV_1%; in those without respiratory symptoms, an opposite pattern emerged.

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. For this study, an initial population of 2462 subjects in the WTC Environmental Health Center (WTCEHC) who had undergone standardized evaluations including answering questionnaires and complete blood count in the period of September 2005–March 2009 was identified. From this pool, individuals with preexisting respiratory symptoms/lung disease diagnoses prior to 9/11 and current tobacco use were excluded. Among the final analyzed 1517 subjects, the data showed respiratory symptoms that developed after WTC Dust exposure, including persistent included dyspnea on exertion (68%), cough (57%), chest tightness (47%), and wheeze (33%). A larger percentage of those with wheeze had elevated peripheral eosinophil levels compared with those without wheeze (21 vs. 13%). Individuals with elevated peripheral eosinophils were also found to be more likely to have airflow obstruction on spirometry (16 vs. 7%). Thus, the data was suggestive of a role for eosinophils in the lung inflammation in this population, the latter which would be consistent with the development of a WTC-related asthma.

26.4.4 Residential/Working Community Members

Several studies documented adverse health effects in the local community. According to Reibman et al. (2009), >360,000 local workers and >57,000 residents (south of Canal St.) were estimated to have had potential WTC Dust exposures after 9/11. Analysis of WTCHC registry populations demonstrated an increase in upper and lower respiratory symptoms and analysis of subgroups showed a dose–response relationship between exposure to WTC Dusts and persistence of lower respiratory symptoms/impacted lung function (Maslow et al. 2012).

Reibman et al. (2009) described how among 1898 individuals evaluated between September 2005 and May 2008 upper and lower respiratory symptoms developed post-9/11 and persisted. The most common abnormality was low FVC, a finding similar to that in rescue and recovery individuals. To clarify the mechanism for respiratory symptom with normal lung function, the population was evaluated to see symptoms in subjects that were associated with airway hyper-responsiveness (i.e., using methacholine challenge). Of those with normal lung function ($n = 68$), 51% had a $PC_{20} < 4$ mg/mL, consistent with airway hyperreactivity. The study also examined whether patients with any abnormal spirometry had improved lung function after using a bronchodilator. In these individuals, there was significant improvement in FEV_1 in patients with an "obstructed" pattern and significant but small improvements in FEV_1 in patients with a "low FVC" pattern. Both FEV_1 and FVC improved in response to bronchodilator in the "obstructed and low FVC" group. In the end, spirometry measurements below the lower limit of normal in 31% of the subjects evaluated. Thus, residents and local workers, believed to have had less exposure to WTC Dusts compared with those with work-associated exposures, also had persistent respiratory symptoms with lung function abnormalities at 5 or more years after the disaster.

As noted above, there were several populations with work-related or residential exposures to WTC Dust who were solely evaluated based upon their responses to questionnaires. For details of those studies and their findings, the Reader is directed to Lippmann et al. (2015).

26.5 STUDIES OF BIOLOGIC RESPONSES TO WTC DUSTS

26.5.1 Summary of Responses to WTC Dust Exposures in Monitored Populations

Similarities/differences in responses between individuals who underwent occupational exposures to WTC Dusts and those who had incidental exposures in residences and office environs are notable. Even with variations in terms of population size and sensitivities of assays, as well as homogeneity of dust exposures within evaluated populations, it is noteworthy that response patterns to incidental exposures have appeared to be so similar to those among individuals who had been engaged in rescue and recovery activities (and thus believed, initially, to have been more heavily exposed). This suggested that duration of exposure to undisturbed dust residues might have been as or more important than shorter-term exposures to higher dust levels. Nevertheless, temporal sequence was a critical criterion for the attribution of causation to the WTC Dust exposure. In the studies reviewed here, after adjusting analyses for smoking and age as potential confounders, asthma and other respiratory disease excesses were found to have occurred *post*-9/11; this was especially true among workers studied without respiratory ailments prior to 9/11. The upshot

from the epidemiology studies to date has been that there was a consistent 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, with risks often increased in a dose-related fashion, with more prolonged or more intensive exposures being associated with greater risk. The plausibility of a causal link between WTC Dust and adverse health outcomes has been strengthened by the consistency of the findings over time. Overall, there is sufficient evidence that, to a reasonable degree of scientific certainty, exposure to WTC Dust is causally associated with increased risk of COPD, RADS, interstitial lung disease, restrictive lung disease, and chronic laryngitis, pharyngitis, and rhinosinusitis.

26.5.2 *In Vivo* Studies

To date, there has been little research from potential health effects from WTC Dusts following controlled inhalation exposure studies in laboratory animals. Conventional exposure studies with rodents have proven impractical, as particles with diameters >2.5 μm for the most part do not penetrate nasal passages in these obligatory nose-breathing species. For the most part, some of the earliest studies used WTC Dusts, but only in the fine mode fraction, and others used exposures by IT instillation. The earliest rodent exposure studies performed in the immediate aftermath of the disaster (Gavett et al., 2003) sought to evaluate potential respiratory health effects from inhalation exposure to a fine-sized fraction of WTC Dust. These studies hoped (at time when no information at all was available) to gain information about potential short/long-term toxicities of the dusts after a very high-dose, short-term exposure and in *in vitro* evaluations.To compare WTC Dust toxicities to previously tested PM materials, mice were exposed using respirable size particles derived by size-fractionated samples. The samples included a sample of pooled $WTC_{2.5}$ from seven individual collection sites (WTCX) and a sieved sample from another site that was size-separated for nose-only aerosol exposure (WTCb). Reference $PM_{2.5}$ samples of Mount St. 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 post-exposure were compared with those by similarly aspirated low (MSH) and high (ROFA) toxicity reference $PM_{2.5}$; vehicles received saline only. The study showed the aspirated WTCX induced significant neutrophilic inflammation (without concurrent macrophage influx) at a relatively high dose (100 μg); the effect was not as great as that from 100 μg ROFA and only slightly more than that of 100 μg MSH. However, this same dose of WTCX caused airway hyperresponsiveness to methacholine (Mch) aerosol to a greater degree than did ROFA. Mice exposed to lower (10 and 31.6 μg) WTCX doses and mice exposed nose only to WTC*b* ($10.64 \pm 3.10\,mg/m^3$, MMAD 1.05 μm) had no significant changes in Mch responsiveness or inflammation 24 h after their exposures. In a parallel study, mice were also exposed to $WTC_{2.5}$ from seven sites around Ground Zero; all mice exposed to the individual dust developed hyperresponsiveness to Mch as seen with $WTCX_{2.5}$-exposed mice. No particular response patterns were found that related to geographical location of the samples. Thus, these initial *in vivo* studies showed that high doses of $WTC_{2.5}$ could promote mechanisms of airflow obstruction in mice. No analyses on the coarse/supercoarse materials were done at the time.

The major caveat with these early studies was that airborne $WTC_{2.5}$ levels—if extrapolated to humans based on mouse doses—would have to have been quite high in the period after the building collapses when rescue and recovery efforts were in effect. Given that

$WTC_{2.5}$ only represented ≈1% of the total WTC Dust mass (and did not even take into account alkalinity of the particles >2.5 μm), the effective 100 μg $WTC_{2.5}$ dose used would have had to reflect an instantaneous total dust deposition of ≈10 mg WTC Dust to each mouse.

Based on 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 $WTC_{2.5}$ dose would have then reflected an atmosphere of ≈6000 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 *total dust*/m^3. Had that upper level been used as the basis to dose mice, this would have meant that a maximal amount of material that may have been deposited in a 4-h representative exposure would have been only ≈16.8 μg $WTC_{2.5}$. Nonetheless, at the early time post-exposure, these data were considered to be critical in terms of providing some context of potential human health effects from exposure to the WTC Dusts.

With time, modeling of exposures at/around Ground Zero using rodent hosts became refined. In a "realistic exposure" study, Cohen et al. (2014) used a novel system developed by Vaughan et al. (2014) to expose rats to WTC Dust using paradigms that mimicked mouth breathing exposures faced by rescue workers/other personnel (i.e., FR) at Ground Zero over the course of the first week post-disaster. Here, coarse/supercoarse WTC Dust particles (collected on-site on September 12, 2001, and September 13, 2001) were delivered directly into the lungs of rats via IT instillation. Responses in the lungs were evaluated after rat exposures to two daily 2-h regimens at dust levels extrapolated to simulate those of the FR. To understand potential changes induced by the dusts, lungs of the rats were harvested 2 h post-exposure, and total RNA was extracted for global gene expression analysis. Among the >1000 genes affected by WTC Dust [under isofluorane (ISO) anesthesia] or ISO alone, 166 were unique to the dust. In many instances, genes maximally induced by the dust exposure (relative to in naïve rats) were unchanged/inhibited by ISO only; similarly, several genes maximally inhibited in dust-exposed rats were largely induced/unchanged in rats that received ISO only.

Overall, these data showed that lungs of rats exposed to WTC Dust—after accounting for any impact from ISO—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, it was concluded 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. Subsequent studies have sought to determine if the effects might have any relevance to chronic lung pathologies that had become evident among FR 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 corresponding histopathologic and/or biochemical changes *in situ*.

In a follow-on study, Cohen et al. (2015) investigated potential changes in particle clearance induced by the alkaline nature of the WTC Dusts. That study ascertained if entrained WTC Dust caused damage *in situ* that modulated the retention, and thus potential impacts, of the WTC Dust itself, and possibly of other major Ground Zero airborne co-pollutants, for example, metal-cutting fume particle (CFP) and diesel exhaust particle (DEP). In examining rats exposed to WTC Dust (as earlier), and then isolating their lungs

over a 1-year period post-exposure, it was found that WTC Dust induced significant decreases in levels of airway ciliated cells and increases in hyperplastic goblet cells. These changes were associated with significant prolonged dust retention (≈90–95%) over the 1-year period. These findings were in line with those of McMahon et al. (2011), who noted ultrastructural ciliary abnormalities in some Ground Zero workers that corresponded to ciliary and respiratory function abnormalities. Among the ultrastructural abnormalities was a disarray of axonemal microtubules/axonemes that were replaced by homogeneously dense cores.

26.5.3 *In Vitro* Studies of Potential Biological Mechanisms

As for *in vivo* studies, there is little information in the literature on potential mechanisms of effects of WTC Dusts based on *in vitro* studies. In an early study, Payne et al. (2004) examined potential mechanisms for how WTC Dusts might affect functions of lung cells with multiple vital roles, that is, AM and type II (TII) epithelial cells, including changes in their ability to produce/release select cytokines. $WTC_{2.5}$ and $WTC_{10–53}$ from samples collected over 9/12–9/13 by the NYU research team were tested for effects using cells isolated from healthy humans (Royal Brompton Hospital, London). Dust samples were suspended at 10 mg/mL in serum-free low protein media; sonicated; diluted to 10, 1, or 0.1 mg/mL; and applied to the cells at particle suspensions of 5, 50, or 500 μg particles/well.

Conditioned media were collected after 6 or 24 h of culture at 37°C (5% CO_2) and analyzed for TNFα, IL-6, and IL-8 (ELISA). The data showed that $WTC_{2.5}$ caused significant AM IL-8 release after just 6 h; small increases were seen only with the lower dose after 24 h. TII responses at 24 h were mostly analogous to 6-h-treated AM. $WTC_{10–53}$ particles caused small increases in AM IL-8 release (significant only after 6 h with 5 μg dose) and failed to induce TII IL-8 release. Levels of AM IL-8 release at 24 h were always greater than those at 6 h, but there were no significant particle effects. Unlike with IL-8, 50 μg $WTC_{2.5}$ consistently induced maximal AM release of IL-6 and TNFα, and these levels were always significantly greater than that induced by 5 μg dust. Increasing length of incubation also led to significant time-dependent differences in cytokine levels; this seemed to amplify the particle toxic impact, that is, maximum AM IL-6 and TNFα release achieved after 24 h with 50 μg dose increased seven- and fivefold above that at 6 h. For TII cells incubated 24 h with $WTC_{2.5}$, IL-6 release responses fell between those of 6- and 24-h-treated AM; there were no TNFα release responses at all.

When $WTC_{10–53}$ was tested, the only effect noted was a non-dose-related increase in AM IL-6 release after 24 h; TII cells only had nominal IL-6 release after 24 h. With TNFα, TII cells again *failed to respond*; AM only showed a response after 24 h, with a maximum once again at a 50 μg. In both cell types and at either exposure duration, the use of the highest (500 μg) dose of either dust fraction uniformly caused significant declines (from 50 μg levels) in cytokine release (except for TII TNFα). These results showed that lung epithelium/resident macrophage exposure to WTC Dusts could cause release of several factors that could contribute to inflammation/airway remodeling processes if they were also released in an intact lung. The data also showed that a prolonging of the period in which WTC Dust could interact with cells led to concurrent increases in these effects (and so, *in situ*, a likely worsening of situations in lung of exposed host). In the context of the Cohen et al. (2015) retention data, the latter is more likely an ongoing issue in exposed FR.

Another study by Xu et al. (2011) examined if WTC Dusts caused direct cytotoxicity to two airway cell types most directly exposed to inhaled dust, that is, airway epithelial and

smooth muscle cells. The study also evaluated if the presence of the dusts could modulate effects of cigarette smoke on these cell types as a good number of individuals who responded to the disaster were smokers. Human cultured airway epithelial (BEAS-2B) cells were exposed to 10% cigarette smoke extract (CSE), $WTC_{10–53}$ (at 0.01–0.5 μg/μL), or a combination of the two for 2–24 h. Cell viability was measured via changes in mitochondrial integrity (MTT assays) and apoptosis [poly-ADP-ribose polymerase (PARP) immunoblotting]. Conditioned cell culture media from the CSE ± WTC Dust-exposed cells were then applied to cultured human airway smooth muscle cells that, in turn, were assayed for mitochondrial integrity and ability to synthesize cyclic AMP (a regulator of airway smooth muscle constriction). The data indicated that the BEAS-2B cells underwent necrotic cell death after 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 after their exposures to conditioned media from the exposed epithelia. These studies clearly showed that WTC Dust (at least its 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. Further, the combination of CSE + WTC Dust exerted an interactive effect on cell toxicity. Xu et al. (2011) posited if these initial cell death events might have contributed to some of the chronic lung effects associated with WTC Dust exposure among FR.

Building on the original Payne et al. (2004) studies, Wang et al. (2010) hoped to identify some potential mechanisms for the increases in cytokine release induced by fine WTC Dust. It was surmised that because activation of mitogen-activated protein kinase (MAPK) signaling pathways causes cytokine induction, these pathways were likely impacted by WTC Dust. The study used BEAS-2B cells exposed to $WTC_{2.5}$ for 5 h. Exposures to various doses of $WTC_{2.5}$ caused significant dose-related increases in *IL-6* mRNA expression, as well as in corresponding protein levels in the media. Apart from IL-6, cytokine multiplex analyses revealed that IL-8 and IL-10 formation was also elevated. Both extracellular signal-regulated kinase (ERK) and p38, but not c-Jun N-terminal protein kinase signaling pathways, were activated in the dust-exposed cells. Inactivation of ERK signaling pathways by PD98059 effectively blocked the IL-6, IL-8, and IL-10 induction; p38 kinase inhibitor SB203580 significantly decreased induction of IL-8 and IL-10. 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) noted the results were important in that they helped define one mechanism by which WTC Dusts may have acted to cause the documented increases in asthma/other inflammation-associated respiratory dysfunctions in Ground Zero-exposed FR.

Weiden et al. (2012), in a series of studies (see also Naveed et al., 2011a, 2011b), compared the effects of WTC Dust size on AM inflammatory cytokine/chemokine release *in vitro*. Normal adherent AM from 15 subjects without dust exposure were incubated in media alone, media with 40 ng LPS/mL, or media containing suspensions of $WTC_{10–53}$ or $WTC_{2.5}$ at 10, 50, or 100 μg/mL for 24 h. Culture supernatants were then collected and assayed for 39 chemokines/cytokines. To assess potential translatability of the findings, sera from WTC Dust-exposed subjects who developed lung injury (n = 70) were also assayed for the cytokines. In the *in vitro* studies, cytokines 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 dust-exposed subjects with lung injury. Similarly, MDC clustered with chemokines GRO (CXCL1) and MCP-1.

$WTC_{10–53}$ consistently induced greater cytokine release than $WTC_{2.5}$ and a stronger inflammatory response than $WTC_{2.5}$. 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.

26.5.4 Overview of Biologic Responses

From these early and more recent *in vivo* and *in vitro* studies, it is clear that WTC Dusts could cause toxic responses in various cell types found in the lungs. Whether such changes alone gave rise to many of the observed pulmonary/CV health effects noted with still increasing frequency among FR and others exposed to WTC Dusts remains to be determined. Ongoing studies in rodents may provide critical proof that the dusts were actual causative agents for the noted pathologies. It is also possible WTC Dusts were *contributive* to rather than directly *causative* of many health effects. This too is a subject of ongoing studies using co-exposure of rodent models to WTC Dusts and key co-pollutants that were present in Ground Zero air, that is, 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 noninvasive measures to examine—FR and others exposed at Ground Zero, novel biomarkers of *potential* lung injury, altered CV status, and dysregulated inflammation have been identified. These included significant changes in expression of matrix metalloproteinases (i.e., MMP-2, -3, -12) (Kwon et al., 2013; Nolan et al., 2014), serum immunoglobulin (IgA, IgG) (Ferrier et al., 2011), select cytokines/chemokines [IL-6, IL-8, GRO, GM-CSF, granulocyte colony-stimulating factor (G-CSF), and IFN-inducible protein-10 (IP-10)] (Nolan et al., 2012; Cho et al., 2014), and select cardiovascular disease (CVD) markers (apolipoprotein-AII, C-reactive protein, macrophage inflammatory protein-4) (Weiden et al., 2013, 2015; Schenck et al., 2014) that could be correlated with increased risks for CVD or lung injury.

In conclusion, there has been significant progress in identifying potential mechanisms of toxicity for WTC Dusts as well as of biomarkers of pulmonary/CV diseases associated with exposure to the dusts. Still, much more research into effects from *in vivo* and *in vitro* exposures to WTC Dusts is needed. Among the areas needing additional analyses, as noted, exposures to WTC Dusts did not occur in a vacuum, and so interactive toxicities/effects from co-exposures to other major co-pollutants at Ground Zero remain to be described. Also, while some immune system-related endpoints have been examined, it remains unclear if WTC Dusts were immunomodulants that allowed nascent diseases (i.e., cancers, autoimmune diseases, asthma) to flourish when they may not otherwise. Lastly, there is an unmet need to develop, identify, and validate noninvasive methods to quantitate remaining dust burdens in the lungs of WTC Dust-exposed workers and residents.

26.6 POSSIBLE ROLES OF MINOR MASS COMPONENTS AS CAUSAL FACTORS FOR OBSERVED HEALTH EFFECTS

Initial concerns about possible adverse health effects that might occur, especially in relation to chronic health effects, focused on known toxicants/carcinogens that were present at relatively low concentration levels, that is, asbestos, metals (Cd, Cr, Fe, Pb, Hg, As), combustion products (PAHs, PCBs), and ambient air $PM_{2.5}$. There were, in retrospect, two

good reasons why these initial concerns were misplaced. First, levels of these components in the WTC Dust $PM_{2.5}$ fraction were initially quite low and then declined markedly. Second, most of the excess disease incidences found in epidemiological studies were not those most closely associated with these components. In contrast, the three major mass components of settled WTC Dusts that were present in particles >2.5 μm were all known irritants, that is, highly alkaline cement and gypsum components as chemical irritants and SVF as physical irritants.

There is good reason to expect biological responses to these components based on interactions post-airway deposition. No routine/special-purpose $PM_{2.5}$ sampling filters were ever assayed for alkalinity or SVF content. Some settled dust samples collected were analyzed for their percentage of SVF and generally showed that 20–25% of the dust was SVF. From an examination of literature on associations between WTC Dust exposure and adverse respiratory/GI effects, inhalation exposures to resuspended SVF, in the presence of highly alkaline co-contaminants, cause adverse pulmonary/gastroesophageal effects in humans. There is also supporting evidence that the same kinds of effects can be seen following inhalation exposures of laboratory animal models. Thus, it appears SVF may be one causal factor as well as a signature component in WTC Dusts.

26.7 ROLES OF MAJOR MASS COMPONENTS AS POTENTIAL CAUSAL FACTORS FOR OBSERVED HEALTH EFFECTS

Zeleke et al. (2010) conducted a cross-sectional/cross-shift study at a cement factory in Ethiopia where personal "total" dust was measured in worker breathing zones and PEF before and after the shift. When a dayshift ended, acute respiratory symptoms were recorded on a 5-point scale via questionnaire. The highest (geometric) mean dust exposure was 38.6 mg/m^3 (crusher section), then 18.5 mg/m^3 (packing section), and then 0.4 mg/m^3 (guards). Prevalence of respiratory symptoms among the highly exposed workers was stuffy nose (85%), shortness of breath (47%), and "sneezing" (45%); PEF decreased significantly across the shift in the highly exposed group. Multiple linear regression showed a significant negative association between the percentage cross-shift change in PEF and total dust exposure. Number of years of work in high-exposure sections and current smoking were also associated with cross-shift decreases in PEF. Meo (2004) noted that cement particles ranged in aerodynamic diameter from 0.05 to 5.0 μm and concluded that a high level of/prolonged inhalation to cement dust could provoke clinical symptoms and inflammatory responses that may result in functional and structural abnormalities. The commonest clinical complaints among the cement mill workers in that study were chronic cough and phlegm production, impaired lung function, chest tightness, obstructive and restrictive lung diseases, conjunctivitis, headache, fatigue, and carcinoma of the lung, stomach, and colon. The particle size of the cement mill dust was not as large as the WTC Dust, but just as alkaline.

Similarly, there is data on human, animal, and cellular responses to high mass doses of other (super)coarse dusts, primarily volcanic dusts. The latter contain PM over a large particle size range, but are not alkaline or readily soluble in the lung; sometimes these dusts are acidic. Buist and Bernstein reviewed health effects by Mount St. Helen dusts and concluded "Effects of both short- and long-term exposures to the relatively low levels of airborne ash typical following such a volcanic eruption were minor, and related more to irritant effects of the ash on airways than to potential of the ash to initiate fibrotic responses."

Baxter et al. (2014) evaluated risk assessment performed for 13,000 Montserrat residents and concluded, in an absence of clinically manifest diseases, the endpoint commonly used in occupational epidemiological studies of silicosis was a radiologic one, that is, for pneumoconiosis and small opacities. Risks in the island north, where most lived, were computed by a model so small and uncertain that it could be ignored. In terms of lesser inhabited areas (central island) that received the most ashfall, the "best estimate" probability of developing early radiological evidence of silicosis was <1/1000 after 5 years of volcanic activity. This cluster of studies of the health effects of volcanic ashes, when taken in conjunction with data from comparative toxicological studies, indicates that the alkalinity of the WTC Dusts was likely to be a major determinate of its ultimate health effects.

26.8 CONCLUSIONS

The spectacular collapses of the WTC Twin Towers on the morning of September 11, 2001 posed a unique challenge to New York City (NYC) and the nation and especially in terms of the public health risks of hundreds of thousands of people who worked and/or lived in Lower Manhattan. This disaster resulted in the conversion of major fractions of the WTC Towers into an enormous cloud of dust that spread throughout Lower Manhattan, as well as a massive pile of debris at Ground Zero. Ultimately, each of these type of dust dispersion gave rise to inhalation exposures of an unprecedented nature and amount, due initially to the dust levels that were suspended in the air and then to the subsequent resuspension of dusts that had settled onto the streets and within buildings. Within the first few days, public agencies involved in occupational and environmental risk assessment and management sought to help, but they were unprepared to provide adequate public health protection in terms of abilities to (1) adequately assess the nature and magnitudes of the risks, (2) prescribe suitable methods to monitor subsequent exposures, and (3) prescribe effective means to minimize exposures. Further, this guidance was never adequately revised in light of emerging evidence of substantial unanticipated adverse health effects among workers/residents attributable to inhalation of components of the WTC Dusts.

In summary, it is our view that the key elements associated with WTC Dust exposures by various populations of workers and local residents are as follows:

1. The collapses of the WTC Towers on September 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 within air ducts throughout Lower Manhattan. WTC Dust deposition was much lower in other parts of NYC and adjacent areas. These settled 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).
2. In terms of particle size distribution of WTC settled dusts, ~1% was <2.5 μm in aerodynamic diameter, 0.3–0.4% ranged from 2.5 to 10 μm, ~ 40% ranged from 10 to 53 μm; the remainder did not pass through a screen with a 53 μm cut-off pore size. As compared to outdoor settled WTC Dust, the deposits within buildings were depleted of particles in the upper end of the particle size range. In terms of the major components, 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, attributable to paper, accounted for 9–20%, and chrysotile asbestos fibers for 0.8–3.0%, with other components having much smaller amounts. With regard to particle chemistry, the aqueous solubility of calcium oxide from the cement and the calcium sulfate from the gypsum resulted in a very high pH (9–11) for the outdoor settled dust samples collected over the first few days and even higher pH levels in indoor dusts (pH > 12) that had a smaller percentage of supercoarse dust. 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 dusts created by the collapses did not extend to ≤2.5 μm.

3. Almost all the air monitoring for PM mass concentration in Lower Manhattan after September 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. There were very few measures of levels of major mass components generated by the buildings' collapse, that is, in particles >2.5 μm (SVF, cement, gypsum).
4. Coarse (>2.5 μm) alkaline particles that were *inhaled* via the nose were likely deposited in conductive airways in the head and LRT tracheobronchial airways, including most that were between 2.5–10 μm as well as smaller percentages of particles of ~10–30 μm that had not been deposited in the URT airways. On the other hand, for cleanup workers having higher tidal volumes and switching to mouth breathing, there was more penetration of coarse and supercoarse dust into their LRT.
5. The high pH of these coarse particles could have overwhelmed the capacity of the conductive airways to maintain the homeostasis that removes debris from airways, thereby inducing acute responses such as cough, chest pain, and other respiratory symptoms and, after clearance to the GI tract, gastroesophageal reflux. This also could have subsequently permitted prolonged retention of the WTC Dust particles themselves and, possibly, other major co-pollutants that were present in the air at Ground Zero [metal-cutting fume particle and diesel exhaust particle].
6. The epidemiological literature now shows significant excesses of adverse health effects among FR and other worker and local residents exposed to the WTC Dusts. These include several chronic diseases/pathologies, such as respiratory and gastroesophageal illness, as well as CV abnormalities, at levels greater than seen in comparison populations that lived and worked at further distances from Ground Zero. That many of these adverse outcomes began to manifest post-9/11 provides evidence of a causal association attributable to WTC Dust exposures. Because the types of responses known to have occurred in these populations have not been associated with exposures to toxicants that were monitored after 9/11, that is, asbestos fibers, trace metals, PAHs, PCBs, and dioxins, they thus had to be due to the unmonitored components spread throughout the area post-9/11, including the coarse and supercoarse particles composed of cement, gypsum and SVFs, all known irritants to large airways.

It is clear that, more than 16 years since the 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 also devise methodologies to ascertain who is still healthy but at risk for developing exposure-related lung, CV, and other pathologies.

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