April 17, 2019

John Howard, MD
National Institute for Occupational Safety and Health
395 E. Street SW, Suite 9200
Patriots Plaza Building
Washington, DC 20201

Dear Dr. Howard,

I write to file a petition pursuant to Sec. 3312(a)(6) of the Zadroga Act requesting that endometrial cancer be added to the current list of rare cancers under the Zadroga Act.

The Mount Sinai World Trade Center Health Program previously published a study in the *Environmental Health Perspectives* which confirmed that those exposed to the toxins released from Ground Zero are at a higher risk of developing cancer than the greater population. It has been that the toxins released at Ground Zero included, but were not limited to, calcium sulfate, silicon, and cadmium. (https://doi.org/10.1289/ehp.1205894) (*See Exhibit 1*). Fifteen of the toxins present at Ground Zero, including cadmium, are classified by the International Agency for Research on Cancer ("IARC") as being carcinogenic in humans. The IARC confirms that exposure to cadmium is generally though the form of airborne dust and fume. (*See Exhibit 2*))

In 2017, PLOS One published a study that confirms that those exposed to the toxic metal cadmium have an increased risk of developing endometrial cancer. (*See Exhibit 3*). Cadmium has similar effects to that of estrogen which explains its link to hormone dependent cancers. The study found that "the rate of endometrial cancer incidence increased by 22 percent in individuals with increased cadmium levels" (McElroy, J. A., Kruse, R. L., Guthrie, J., Gangnon, R. E., & Robertson, J. D. (2017). Cadmium exposure and endometrial cancer risk: A large midwestern U.S. population-based case-control study. PloS one, 12(7), e0179360. doi:10.1371/journal.pone.0179360).

Considering the findings of the presence of cadmium in the 9/11 released toxins and the studies of cadmium exposure increasing the risk of endometrial cancer, I believe that endometrial cancer should be added to the list of certifiable cancers.

Thank you for your considering in reviewing this petition.
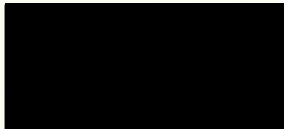
Exhibit 1

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

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The explosion and collapse of the World Trade Center (WTC) was a catastrophic event that produced an aerosol plume impacting many workers, residents, and commuters during the first few days after 11 September 2001. Three bulk samples of the total settled dust and smoke were collected at weather-protected locations east of the WTC on 16 and 17 September 2001; these samples are representative of the generated material that settled immediately after the explosion and fire and the concurrent collapse of the two structures. We analyzed each sample, not differentiated by particle size, for inorganic and organic composition. In the inorganic analyses, we identified metals, radionuclides, ionic species, asbestos, and inorganic species. In the organic analyses, we identified polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls, polychlorinated dibenzodioxins, polychlorinated dibenzofurans, pesticides, phthalate esters, brominated diphenyl ethers, and other hydrocarbons. Each sample had a basic pH. Asbestos levels ranged from 0.8% to 3.0% of the mass, the PAHs were > 0.1% of the mass, and lead ranged from 101 to 625 µg/g. The content and distribution of material was indicative of a complex mixture of building debris and combustion products in the resulting plume. These three samples were composed primarily of construction materials, soot, paint (leaded and unleaded), and glass fibers (mineral wool and fiberglass). Levels of hydrocarbons indicated unburned or partially burned jet fuel, plastic, cellulose, and other materials that were ignited by the fire. In morphologic analyses we found that a majority of the mass was fibrous and composed of many types of fibers (e.g., mineral wool, fiberglass, asbestos, wood, paper, and cotton). The particles were separated into size classifications by gravimetric and aerodynamic methods. Material < 2.5 µm in aerodynamic diameter was 0.88–1.98% of the total mass. The largest mass concentrations were > 53 µm in diameter. The results obtained from these samples can be used to understand the contact and types of exposures to this unprecedented complex mixture experienced by the surviving residents, commuters, and rescue workers directly affected by the plume from 11 to 12 September and the evaluations of any acute or long-term health effects from resuspendable dust and smoke to the residents, commuters, and local workers, as well as from the materials released after 11 September until the fires were extinguished. Further, these results support the need to have the interior of residences, buildings, and their respective HVAC systems professionally cleaned to reduce long-term residential risks before rehabitation. *Key words:* aerosol, inorganic components, morphologic characterization, organic components, World Trade Center. *Environ Health Perspect* 110:703–714 (2002). [Online 4 June 2002]
http://ehpnet1.niehs.nih.gov/docs/2002/110p703-714lioy/abstract.html

The 11 September 2001 attack on the World Trade Center (WTC) in New York City (NYC) resulted in an intense fire and the subsequent complete collapse of the two main structures and adjacent buildings. It also led to significant damage to many surrounding buildings within and around the WTC complex. The 16-acre area has become known as Ground Zero. A consequence of the pulverization of buildings and the fires was the development of a large plume of dust and smoke that released both particles and gases into the atmosphere. The initial plume impacted all directions immediately adjacent to the WTC site, and the dust and smoke settled at many outdoor and indoor locations. From the first hours to 18 hr after the collapse, the winds transported the plume to the east (Figure 1) and then to the southeast across and beyond Brooklyn, New York.

To begin assessing the exposure to dust and smoke among the residential and commuter population during the first few days, samples of particles that initially settled in downtown NYC were taken from three undisturbed protected locations to the east of the WTC site. Two samples were taken on day 5 (16 September 2001) and the third sample was taken on day 6 (17 September 2001) after the terrorist attack. The purposes for collecting the samples were *a*) to determine the chemical and physical characteristics of the material that was present in the dust and smoke that settled from the initial plume, and *b*) to determine the absence or presence of contaminants that could affect acute or long-term human health by inhalation or ingestion. It was anticipated that the actual compounds and materials present in the plume would be similar to those found in building fires or implosion of collapsed buildings. The primary differences would be the simultaneous occurrence of each type of event, the intense fire (> 1,000°C), the extremely large mass of material (> 10 × 10⁶

tons) reduced to dust and smoke, and the previously unseen degree of pulverization of the building materials. A summary of the potentially present types of carcinogenic and noncarcinogenic materials was reported in *EHP* in November 2001 (*1*).

The dust and smoke would be inhaled by individuals either directly or after the settled aerosol was resuspended by turbulence. Deposition and retention of the dust and smoke on surfaces inside homes, as well as the residuals of dust and smoke remaining if residences and building ventilation systems were not properly cleaned before rehabitation, would be available for uptake by children and adults via nondietary ingestion. Indoor inhalation exposures would also be possible because of resuspension from the ventilation system. Any large-particle inhalation could also lead to ingestion exposure after particles are cleared from the upper airways of the lung by mucocilliary clearance processes.

A number of initial measurements made by various organizations focused on the general composition of the dust and smoke, with a primary concern being asbestos (*1*). The approach we used for analyzing the three dust and smoke samples included detailed measurement of the inorganic and organic components of the mass and a general characterization of the percent distribution by mass or volume of various materials present in each sample.

Samples of the total settled dust and smoke were collected at three different locations. The first sample was collected from protected external ledges around the entrance of a building on Cortlandt Street, which is one block east of the WTC building complex. The initial direction of the plume was from west to east (Figure 1); thus, the other two samples were collected at locations to the east of Cortlandt Street. These two samples were collected from 10–15 cm-thick deposits that were on the top of two automobiles about 0.7 km from the WTC site. The automobiles were in locations protected from rain that occurred on Friday, 15 September 2001. One automobile was located on Cherry Street,
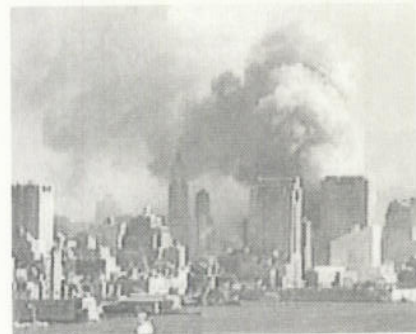
Figure 1. The WTC dust and smoke plume moving east on 11 September 2001.

and the other was on Market Street, one and two city blocks, respectively, west of the East River between the Manhattan and Brooklyn Bridges. These cars appeared to have been in their respective locations since 11 September, but it is possible that each could have been moved from an adjacent thoroughfare on the east side of NYC (FDR Drive).

One of the reasons for collecting samples from these locations was to determine whether chemical composition and physical morphology of the particles changed with distance from the WTC site. The samples were collected using the protocols established for surface soil collection in our studies of the dispersal of chromium-laden hazardous waste in Jersey City, New Jersey (*2*), and the National Human Exposure Assessment Survey (*3*). After collection, all samples were stored in a 4°C room prior to sending the subfractions to individual laboratories for analysis. We maintained chain of custody throughout sample transferal and analyses.

Methods

Approach

The analyses conducted on each sample were based on the nature of the sources of the particles that were aerosolized on 11 September 2001. The force of the collapse pulverized the two main WTC structures and several adjacent low-rise buildings (e.g., WTC3, WTC7); therefore, our analytic plan included qualitative and quantitative analyses to detect construction and furnishing debris, and combustible materials and products of incomplete combustion associated with the fires in each building. We accomplished the tasks by completing analyses to identify inorganic and organic constituents.

We designed the first sets of analyses to provide a general characterization of the content of the samples using a combination of microscopic techniques. This provided an opportunity to classify the general morphology and to focus the chemical analyses subsequently performed on each sample based on the types of materials detected by the microscopic analyses. The second type of analyses included the inorganic analyses (including trace and toxic elements, ionic species, and functional groups) and the organic analyses [including polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls (PCBs), pesticides, dioxins, furans, phthalate esters, and general hydrocarbons]. All of these analyses were performed exclusively on the total of bulk samples.

The third set of analyses included the particle size fractionation experiments on each sample. We used two different approaches: *a*) a gravimetric sieving analysis that separated the mass of lint and nonfibrous material into

fractions > 300 μm, 75–300 μm, and < 75 μm in diameter; and *b*) an aerodynamic separation for the particle size fractions of < 2.5 μm, 2.5–10 μm, and 10–53 μm in diameter, with a gravimetric sieving that separated the particles > 53 μm in diameter before the aerodynamic sizing of the samples. The separations were based on the design or availability of specific size separation techniques in the laboratories.

We selected all of the analyses described above for the three bulk samples based on the nature of the events and the materials that could be associated with the buildings and the burning jet fuel. The collapse resulted in a pulverization of the buildings. Thus, it was important to complete morphologic analyses to obtain a general idea about the composition and the structure of the particles that were produced from the building materials. We conducted the organic analyses to determine the chemical nature of the products of incomplete combustion produced by the fires and to identify any other organic materials. The inorganic analyses were completed to obtain quantitative information on the levels of various heavy metals and other inorganic materials present in the pulverized building materials and in the fire. Finally, we conducted the particle size analyses to provide a general description of the types and levels of material available that could be inhaled and deposited in various locations within the lung. These size-separated samples were stored for analyses of the same compounds in the individual size fractions. These results are the subject of future manuscripts.

Analytic Methods

Because each of the total mass dust and smoke samples was determined to contain a complex mixture of materials, the analytic plan required the inclusion of a number of different techniques for examining chemical and physical characteristics. Our approach included microscopic analysis to identify major components and the morphology of particles in each sample. Using stereomicroscopy, we estimated relative percentages of larger particles and identified large dust components. We used polarized light microscopy with microchemical testing to identify most particles including minerals, building products, and hair and fibers > 1 μm in diameter. We used scanning electron microscopy with X-ray elemental analysis to identify metal fragments, building product pieces, and other particles < 1 μm. Transmission electron microscopy, with electron diffraction and X-ray elemental analysis was used to identify the smallest fraction of particles including single asbestos fibrils and carbon soot.

We extracted the portions of each total mass sample (not differentiated by particles

size) for determination of trace and toxic elements by inductively coupled plasma spectroscopy; ion chromatography was used to determine the ionic and cationic components of the mass. Other portions of each total mass sample were then extracted and analyzed for organic constituents. We included materials that are typically measured in air or dust samples by gas chromatographic and mass spectrometric techniques; we then scanned for unknown extracts using other mass spectroscopic analyses. Other analyses completed on these total mass samples included the measurement of pH, corrosion, aerodynamic particle size for fine and coarse particle fractions, percentage of mass by particle sieving, general radiation levels, and asbestos. Details on each analysis conducted on the three dust and smoke samples are provided below.

Morphologic and gravimetric analyses. The dust samples were characterized by both gravimetric measurement of sieved size fractions and by polarized light microscopy analyses. The samples were sieved using standard 4-inch diameter brass sieves (U.S. Standard Sieve Mesh 50 and 200) as reported previously (*4*). The gravimetric determinations were made in triplicate with a SETRA EZ2-500 electronic 3-place balance (Setra Systems, Inc., Boxborough, MA). All sample-handling activities were performed inside a hood with a HEPA exhaust filter. Samples were separated into fibrous (lint) and nonfibrous fractions using tweezers under the stereomicroscope. Indoor dust has been shown to be composed of both fibrous and nonfibrous fractions (*5*). The fibrous and nonfibrous parts are expected to respond differently to dust disruptions, which include cleaning procedures.

We determined the weight of the lint (plus attached fine nonfibrous particulate). The remaining particulate was then dry sieved at the following size fractions: > 300 μm (collected on Mesh 50), 75–300 μm (collected on Mesh 200), < 75 μm (through Mesh 200). The weight of each fraction was determined and the relative weight percentages were then calculated. The lint fraction is found in the large (> 300 μm) fraction. The fractions were combined and examined by stereomicroscopy using a Zeiss Stemi 2000 stereomicroscope (Carl Zeiss, Inc., Thornwood, NY) with a magnification range of 6.5× to 47×. The physical characteristics of the samples were then analyzed using an Olympus BH-2 polarized light microscope (Olympus America, Inc., Melville, NY) with a magnification range of 40× to 1,000×. A visual estimate was made of the relative percentage by volume of loosely aggregated separable fibrous lint (hair + natural fibers + manmade fibers).

Each sample was characterized morphologically for major constituents using a form

developed by MVA (*4,6*). Identified constituents were then rated as to whether it was "common" (consistently found throughout the sample) or "present" (detected but infrequently) (*7–11*). This designation does not necessarily indicate the relative abundance of a constituent by weight or volume within a sample; it is an indictor of numerical abundance of a constituent. The < 75 μm size fraction portion was analyzed by scanning electron microscopy (SEM), which was performed using a JEOL 6400 (JEOL Inc., Peabody, MA) equipped with a Noran Voyager energy dispersive X-ray analysis unit (Noran Instruments, Inc., Middleton, WI) and both the secondary and backscattered modes. For SEM analysis, portions of the particles from the sample were transferred to conductive carbon tape and coated with a thin layer of carbon to provide a conductive surface in the electron microscope. Using the backscattered electron mode, the sample was examined for particles that contained heavy elements. This procedure is useful in locating particles containing toxic metals such as lead and cadmium. Using the secondary electron mode, the sample was examined for particles that were consistent with asbestos fibers. We performed X-ray elemental analysis (energy dispersive spectrometry) on each particle located for further study by either the backscattered electron or secondary electron scans. We prepared the < 75 μm size fraction of the samples following the ASTM D6602 procedure (*6*) and analyzed them with analytic electron microscopy using a JEOL 1200, 100 kV scanning transmission electron microscope equipped with a Noran energy dispersive spectrometry X-ray analysis system. Each sample was subjected to morphologic and gravimetric analyses.

Aerodynamic particle separation. The samples were first mechanically separated using a sieve with a mesh size of 53 μm. The fraction of particles < 53 μm was further separated aerodynamically into three size fractions: 10–53 μm, 2.5–10 μm, and < 2.5 μm. Particles were resuspended by a jet of filtered air passing through an inlet (Wedding Inlet, 10 μm cut size; Anderson Instrument Co., Fultonville, NY) before entering a cyclone with a cut size of 2.5 μm (BGI, Inc., Waltham, MA). Particles between 10 and 2.5 μm were collected by the cyclone, whereas particles < 2.5 μm, which penetrated through the cyclone, were collected on Teflon filters.

Corrosion. We evaluated the corrosive properties of the dust samples using copper mirrors. For each dust sample, a small amount was sprinkled onto a copper mirror and a second copper mirror was set aside as a control; hence, there were a total of three exposed mirrors and three controls. These six mirrors were placed in a sealed container

together with a beaker of water to maintain the relative humidity near 100%. After a 14-day exposure, the samples were examined for pinholes and discoloration.

Radionuclides. We analyzed the gamma spectrum of the samples using an EG&G/Ortec high-purity Ge detector (50% relative efficiency) gamma counter (EG&G/Ortec Instruments, Inc., Oak Ridge, TN). We analyzed approximately 50 peaks based on statistical significance (counting/lack of interferences). These included thorium, uranium, actinium series, and primordial radionuclides. Liquid scintillation analyses were conducted for emissions on the total dust and smoke samples using a Packard Tri-Carb Model 2770 TR/SL (Packard Instrument, Meriden, CT). The MDA for alpha radioactivity was 0.30 DPM (0.14 pCi) based on a NIST-traceable ^{226}Ra standard (National Institute of Standards and Technology, Gaithersburg, MD). When placed in the liquid scintillation fluid, the WTC samples are somewhat darker than the backgrounds and calibration standard, which may cause slight underreporting of the beta activity due to quenching and standard-to-sample efficiency bias.

Inductively coupled plasma mass spectrometry (ICP-MS) analysis for trace and toxic elements. All samples were analyzed in duplicate for trace or toxic elements. Approximately 0.1 g of sample was accurately weighed and placed in a CEM HP500 microwave vessel (CEM Corporation, Matthews, NC). Fisher optima concentrated nitric acid (10 mL) was then added to the vessels. The six sample vessels plus those of two method blanks were sealed and placed in the CEM MARS microwave unit at 1,200 watts for 5 min. The samples were allowed to cool for approximately 15 min inside the MARS unit and were then removed and placed in the cold room for 1 hr at 4°C. After cooling, the samples were then diluted to 50 mL. A 2-mL aliquot was then diluted to 8 mL for a final acid concentration of 5%.

We scanned the samples for metals on a Fissons PQ3 ICP/MS (Fissons Instruments, Inc., Merrimac, MA) over a mass range of 9–238 at 1,350 watts, with a dwell time of 1,000 μsec with 40 sweeps for a total acquisition time of 70 sec. We used high purity multielement standard and NIST A&B calibrant for quality control. Acceptable quality assurance checks were deemed to be 100 ± 20% of the certified values.

Ion chromatography for ionic species and pH analyses. We weighed the samples (Fisher Scientific XT Balance; Fisher Scientific, Pittsburgh, PA) and placed them in test tubes; aliquots of distilled, deionized water were added to make a concentration of approximately 30 mg/mL. The tubes were

inverted several times and were then sonicated. The samples were left at room temperature for several days before centrifugation. The extract from each filter sample was removed to a new test tube before centrifugation. All samples were centrifuged and the supernatant was removed to new tubes and stored in the refrigerator.

A 1-mL aliquot of extract was used for pH measurement. This was performed using an Orion Research Digital pH Meter 611 (Dionex Corporation, Sunnyvale, CA). The ion analysis was performed using a Dionex DX500 system. The anion analyses column-IonPac AS14 (Dionex) was used in Suppressor-ASRS Ultra-AutoSuppressor Recycle Mode. The eluent was 3.5 mM Na_2CO_3/1.0mM $NaHCO_3$. We used cation analyses column IonPac CS12A in the Suppressor-CSRS II Ultra-AutoSuppressor Recycle Mode. The eluent was 20 mM methanesulfonic acid.

We constructed calibration curves using seven standards prepared by diluting a NIST-traceable standard (Fisher) using Milli-Q water. Each standard was subsequently run as a sample to verify the calibration curve. Samples were run once the calibration curve was verified. After all samples were analyzed, these seven standards were analyzed again, followed by two additional NIST traceable stock standards (Dionex). Samples that were originally off scale were diluted with Milli-Q water and tested again.

Fourier transform infrared (FTIR) spectrometry. Each sample was analyzed for functional groups by FTIR after a portion of the sample was converted to a standard infrared pellet. The pellet was made by combining a small quantity of sample dust material (~ 30 mg) and approximately 200 mg of spectrograde potassium bromide powder (ICL Laboratories, Garfield, NJ). This mixture was preliminarily ground together using an agate motor and pestle, then transferred to a metal vial and placed in a mixing mill (SPEX Model 5300; SPEX Industries, Edison, NJ) and agitated for 30 sec at approximately 50 cycles/sec. The resultant homogeneous mixture was then transferred to a die (13 mm Macro-Micro KBr pellet die; ICL Laboratories) connected to a vacuum pump, which was placed in a lab press. Approximately 8,500 psi was applied to the mixture for 30 secs. The resulting infrared pellet consisted of a mid-infrared transparent solid matrix of potassium bromide containing a uniform distribution of the dust sample to be analyzed.

We obtained all infrared spectra using an FTIR Spectrometer (Mattson Instruments, Madison, WI) (12). The spectrometer was configured to obtain standard transmission FTIR spectra using a deuterated triglycine

sulfate detector. Each spectrum collected was an average of 200 scans at 4/cm resolution. The resulting profile was illustrated as a plot of percent transmittance of infrared radiation as a function of wave number from 4,000 to 450/cm. The transmission spectra of the three samples were then examined for functional group content.

Volatile organic compounds. We used thermal desorption (Perkin-Elmer ATD400; Perkin-Elmer, Norwalk, CT) with a gas chromatograph (GC)/MS detector (Hewlett Packard 5890/5971; Hewlett Packard, Wilmington, DE) to analyze samples of dust from the destruction of the World Trade Center complex for volatile organic compounds. Approximately 200 mg of each of the three samples were heated at 180°C for 1 min in a stainless steel tube with the emitted compounds transferred in a helium stream to a Tenax absorbent trap (Supelco, Bellefonte, PA) held at –28°C. The absorbent trap was heated to 250°C within a few seconds, with the compounds transferred to a capillary GC/MS. Full scan mass spectra were collected above 30 atomic mass units (amu) to identify the volatile compounds.

The chromatographic peaks were identified based on comparisons to standards run under the same conditions as the samples, evaluation of the mass spectral pattern, and library matches within the Wiley Mass Spectra Library (The Wiley/NBS Registry of Mass Spectral Data). Due to the unresolved background present in the chromatograph after a retention time of 20 min, we performed a background subtraction of an area near each peak of interest before the library search.

Semivolatile organic chemical analysis. Many of the compounds or compound classes measured for semivolatile organics were analyzed by well-established techniques for PAHs, PCBs, dioxins, and furans. However, because the fire at the WTC was very complex and included the burning of fuel, plastics, furniture, and other materials, we conducted additional analyses to detect and quantify unknown organics in the total mass samples. These are described below.

Standard PAH, chlordane, and PCB analyses. Each sample was analyzed by GC/MS on a Hewlett Packard 6890/5973 for 40 individual PAHs and six chlordane species (*oxy*-chlordane, *trans*-chlordane, *cis*-chlordane, *trans*-nonachlor, *cis*-nonachlor, and MC5), and by GC/electron capture detection with a Hewlett Packard 6890 equipped with a [63]Ni electron capture detector for quantification of 68 PCB congeners, hexachlorobenzene, DDTs (4,4'-DDE, 2,4'-DDT, and 4,4'-DDT), and mirex (13,14). By weighing triplicate aliquots of approximately 0.7 g of each dust sample,

ultrasonically extracting each in 30 mL dichloromethane, and reducing the volume before analysis, we identified and quantified all compounds against known concentrations of authentic standards and NIST Standard Reference Material 1649a (Urban Dust, Organics) (15), which was processed in parallel with each sample for comparison and verification of the results.

Unknown semivolatile hydrocarbon identification. The analysis for semivolatile organic compounds included microwave-assisted solvent extraction (MASE) followed by GC/ion trap mass spectrometer (ITMS) (16,17). MASE was carried out using an MDS-2000 microwave extraction system (CEM) equipped with an inboard pressure control system. The MDS-2000 is able to extract 12 samples simultaneously in Teflon PFA-lined extraction vessels under approximately the same conditions of temperature and pressure. A 2.5-g portion of each sample was accurately weighed and quantitatively transferred into Teflon PFA-lined extraction vessels of the MDS-2000. We added extraction solvents (7.5 mL methylene chloride-acetone; 1:1 v/v) to each vessel and fitted new rupture membranes into each cap, which screwed onto the vessel. We then placed the vessels symmetrically on the microwave turntable. After the extraction was completed, the vessels were allowed to cool before the caps were opened. After cooling, we transferred 1.5 mL extract from the supernatant of the vessels into GC vials without a preconcentration step before GC/ITMS analysis.

We performed GC/MS on a Varian 3400 CX GC coupled to a Saturn 2000 GC/MS ITMS (Varian Instruments, Palo Alto, CA). A septum programmable split/splitless injector was used in the splitless mode. The GC was equipped with a 30-m 5% phenyl/95% dimethylsilicone fused silica DB-XLB capillary column with 0.32 mm i.d. and 0.25 μm film thickness (J&W Scientific, Folsom, CA).

The ITMS was operated in electron ionization-positive mode and optimized with perfluorotributylamine (FC-34) using automatic gain control. The electron multiplier, emission current, and modulation amplitude were set at 1,800 V, 10 μA, and 7.5 V, respectively. The transfer line and the ion trap manifold were set to 270°C and 225°C, respectively. The mass range scanned was from 45 to 450 *m/z* at 0.3–0.6 sec/scan. We used Saturn GC/MS workstation version 5.3 software for data acquisition.

We identified the analytes by comparing the mass spectrum (after background subtraction) to the vendor's library and NIST 98 library spectrum. As with the identification of other unknowns, we defined a positive identification as one with a correlation to the library spectrum of > 85% fit. We

added EPA 525 internal standards (Supelco) to the sample run as quality control checks for rough quantitation and retention time quality control. A secondary identification was performed using retention time confirmation with quality control standards, when available. We analyzed a 1-µL aliquot of standard with the GC/ITMS system under the same conditions used for samples and quality control samples. Approximately 300 semivolatile organic compound standards including EPA 525, 625, and 8270 standards (Supelco) were injected to build the GC retention time library. We defined a retention time match as an analyte compound eluting within ± 5 sec of the standard sample retention time. All reported compounds met these criteria.

Polychlorinated dioxins (PCDDs) and furans (PCDFs). We used U.S. Environmental Protection Agency (EPA) Methods 1613 and RCRA SW846 Method 8290 for dioxin analyses (*18,19*). In these methods, a clean extraction thimble was charged with 5.0 g of 100/200-mesh silica topped with 100 g of quartz sand. The silica layer was left undisturbed throughout the extraction process. The thimble was placed in a clean extractor with 30–40 mL of toluene in the receiver and 200–250 mL of toluene in the flask. The wet sample, filter, and/or disk were loaded and any nonaqueous liquid removed. The remaining sample was placed in the thimble and manually mixed into the sand layer with a clean metal spatula, carefully breaking up any large lumps of sample.

The dust and smoke extracts, which were blown to dryness in conical vials and refrigerated, were analyzed via GC/high-resolution mass spectrometry (GC/HRMS) after the addition of an internal standard and nonane. We programmed the column temperature to separate the 2,3,7,8-TCDD congener from other TCDD analytes. The tetra congeners had to be eluted from the column after 20 min for this to occur. The seventeen congeners of interest were then detected with the HRMS. We identified compounds eluting from the GC column by the retention time reference obtained from the corresponding labeled isotope and the ion ratio of the measured ions during selective ion response. We calculated the concentration of each congener by using the relative response factors of each native congener to its respective 13C12-labeled congener.

Standards used in the analyses were concentration of stock and spiking solutions containing PCDDs/PCDFs and labeled compounds. We included a cleanup standard (Cl_4, 2,3,7,8-TCDD, 0.8 ng/mL) and internal standards (Cl_2, 1,2,3,4-TCDD, 200 ng/mL; and Cl_2, 1,2,3,7,8,9-hexaCDD, 200 ng/mL).
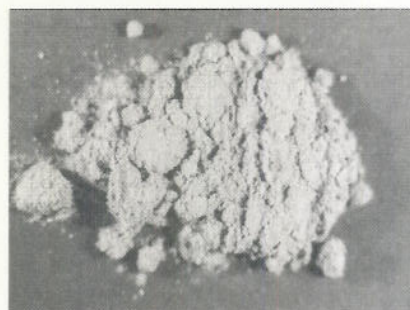
Brominated diphenyl ethers. The analytic methodology for detecting brominated diphenyls and diphenyl ethers have been described previously (*20*). Briefly, we subjected total dust samples to enhanced solvent extraction using methylene chloride. Extracts were purified by size exclusion and silica gel liquid chromatography. Compound quantification

was performed by GC with halogen-selective electrolytic conductivity detection with multipoint calibration. Decachlorodiphenyl ether was used as an internal standard. 2,2′,4,4′,5,6′,6′-Octachlorobiphenyl was added before extraction as a surrogate standard, and results were corrected for its recovery (mean ± SD, 68.1 ± 2.02). We confirmed compound identities by GC/MS in the full scan electron ionization mode. None of the target compounds were detected in the blank.

Results

The general characteristics of each total settled dust and smoke sample are shown in Table 1; these characteristics indicate that the composition of major components in each sample were similar, with slight differences in total composition for the Market Street sample. Generally, the samples were very light and fluffy, and were white to pinkish-gray. The general physical appearance of the Market Street sample is shown in Figure 2 as an example. The mass of each sample was dominated by nonfibrous material and construction debris, and the Cortlandt and Cherry Street samples contained approximately 0.8% asbestos. In contrast, of the mass collected, the Market Street sample contained 3.0% asbestos. We found only background levels of alpha radionuclide activity by liquid scintillation counter analysis of all three samples. Beta activity was slightly elevated, but not more than twice the background level. There were no levels of gamma activity > 1 Bq/g except for naturally occurring potassium-40.

The pH of an aqueous suspension of each sample was > 7; the Cortlandt Street sample had a pH of 11.5. Both the Cherry and Market Street samples had a pH of ≈9 (Table 1). Significant amounts (≈10% of the mass) of cellulose were found in all three samples. This observation is consistent with the release of large amounts of disintegrated paper and other products that were originally part of the indoor work environments.

Table 1. General characteristics of settled dust and smoke samples (percent by mass) from the first days after the collapse and fires of the WTC.

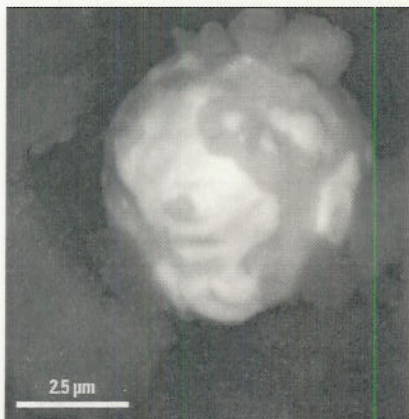|	Street		
Sample	Cortlandt	Cherry	Market
Color	Pinkish gray	Pinkish gray	Pinkish gray
pH	11.5	9.2	9.3
Nonfiber (cement/carbon; %)[a]	50.0	49.2	37.0
Glass fiber (%)[a]	40.0	40.0	40.0
Cellulose (%)[a]	9.2	10.0	20.0
Chrysotile asbestos (%)[a]	0.8	0.8	3.0
Aerodynamically separated sample (% mass)			
< 2.5 µm diameter	1.12	0.88	1.30
2.5–10 µm diameter	0.35	0.30	0.40
10–53 µm diameter	37.03	46.61	34.69
> 53 µm diameter	61.50	52.21	63.60
Sieved sample (% mass)			
< 75 µm diameter	38.00	30.00	37.00
75–300 µm diameter	46.00	49.00	42.00
> 300 µm diameter	16.00	23.00	21.00
Anions/cations (ng/g)			
Fluoride	220	70	ND
Chloride	800	270	220
Nitrate	330	ND	ND
Sulfate	41,400	35,200	42,100
Calcium	18,200	14,000	17,700
Sodium	400	200	130
Potassium	60	170	270

ND, not detectable.
[a]Values reported to L.C. Chen by the Ambient Group, TNC (New York, NY), measured by polarized light microscopy (400–450×).

Figure 2. The general appearance of the bulk dust collected at the Market Street location east of the WTC site. Dust samples from the other two sites were similar in appearance. Magnification = 4×.

We detected no differences between the exposed copper mirrors and the controls, indicating that these dust samples were not corrosive toward base metals. This finding is consistent with the pH measurements.

Morphologic analyses. Detailed morphologic analyses of each sample supported the general characterizations presented in Table 1.

Cortlandt Street sample. The Cortlandt Street sample was mainly composed of construction debris [including vermiculite, plaster, synthetic foam, glass fragments, paint particles, glass fibers, lead (Figure 3), calcite grains, and paper fragments], quartz grains, low-temperature combustion material (including charred woody fragments), and glass shards. Chrysotile asbestos fibers were estimated to comprise < 1% of the sample by volume, and much of the chrysotile adhered to carbonate binder. Some skin cells and dyed cotton fibers were present (5,21–23).

Figure 3. Appearance of lead from the Cortlandt Street sample.
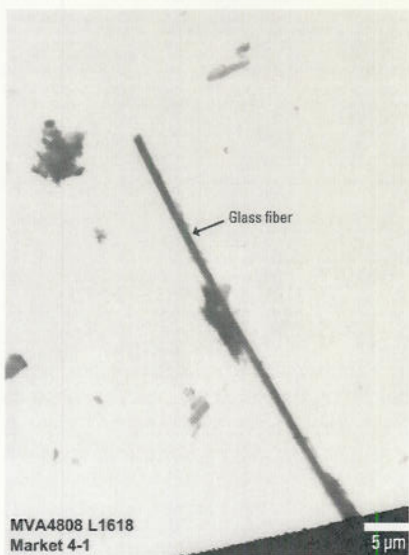
Figure 4. Glass fiber detected in the Market Street sample.

The findings of skin cells was consistent with the types of particles usually found in dust in the indoor environment.

Approximately 35% of the volume of the sample was in the form of loosely consolidated clumps of fibrous lint, of which the greatest portion was glass fibers. An example of the typical form of the glass fibers is shown in Figure 4. In many cases the width was ≅ 1 μm (to > 10 μm), and the length ranged from 5 to 100 μm. The fiber shown in Figure 4 is not a "clean" glass fiber; other materials are agglomerated along the rod. This is typical of features noted for many different types of particles in each sample. The SEM analysis of the fraction < 75 μm in diameter revealed many glass fibers and cement particles, some in a fibrous form containing calcium, silicon, and sulfur, and some particles were composed of calcium carbonate (Figure 5).

Chrysotile asbestos fibers, identified by transmission electron microscopy (TEM), were found in the < 75-μm fraction. None of the analyzed particles contained lead, chromium, cadmium, or mercury, although chromium and cadmium were quantified in this sample by ICP/MS analyses.

Cherry Avenue sample. The Cherry Avenue sample is mainly composed of

Figure 5. Coarse calcium carbonate particle detected in the Cortlandt Street sample.
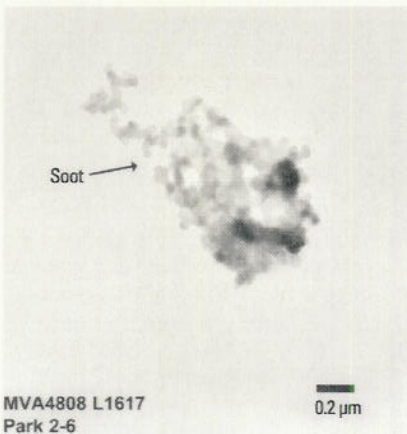
Figure 6. A soot particle containing coagulated ultra-fine particles detected in the Cherry Street sample.

construction debris (including cement, vermiculite, plaster, synthetic foam, glass fragments, mineral wool fibers, paint particles, glass fibers, metals, calcite grains, and paper fragments), quartz grains, low-temperature combustion material (including charred woody fragments), and metal flakes. We estimated that chrysotile asbestos fibers comprised < 1% of the sample by volume. Much of the chrysotile asbestos had carbonate binder adhered to it. We observed some hair fibers and tarry fragments in the sample. Approximately 10% of the volume of the sample was in the form of loosely consolidated clumps of fibrous lint, of which the greatest portion was glass fibers. The SEM analysis of the fraction < 75 μm in diameter revealed many glass fibers and cement particles, some in a fibrous form, containing calcium, silicon, and sulfur.

We used SEM and TEM to examine chrysotile asbestos fibers, lead paint fragments, iron–chromium particles, and soot particles found in the < 75-μm fraction. The soot particles were in the submicron size range (Figure 6). No particles containing cadmium (detected by ICP/MS) or mercury were found at less than minimum detection limits in the 1,000 particles analyzed from this sample.

Market Street sample. The Market Street sample was also composed of construction debris (including vermiculite, plaster, synthetic foam, glass fragments, paint particles, mineral wool fibers, glass fibers, calcite grains, and paper fragments), quartz grains, low-temperature combustion material (including charred woody fragments), and metal flakes. Chrysotile asbestos fibers made up < 1% of the sample by volume, and much of the chrysotile adhered to carbonate binder. This result is different from the bulk mass results, which indicated 3.0% asbestos; this indicates that the sample was not homogeneous. Some dyed cotton fibers, tarry fragments, pollen grains, and metal flakes were also present. Approximately 10% of the volume of the sample was in the form of loosely consolidated clumps of fibrous lint, of which the greatest portion was glass fibers. The SEM analysis of the fraction < 75 μm in diameter revealed many glass fibers and cement particles, some in a fibrous form containing calcium, silicon, and sulfur.

Chrysotile asbestos fibers, identified by TEM, were found in the fine fraction. We found no particles containing lead, chromium, cadmium, or mercury in the single particles analyzed from the Market Street sample, although all but mercury were detected by the ICP/MS analyses.

The morphologic differences between each of the collected samples were minor and could be attributed to the fact that we

analyzed only 1,000 particles per sample. This limitation in particle number would preclude consistent detection of all materials that comprise < 0.1% of each sample.

A minor difference between the Cortlandt Street and the Market and Cherry Street samples was that the Cortlandt Street sample had 0.88% fine particles (particles < 2.5 μm in diameter), while the other two samples had > 1.1% fine particle mass. Using microscopic analysis to generally describe the distribution of materials among the mass fractions, we found that large particles were primarily made up of building materials including gypsum, glass fiber, mineral wool fibers, wood fibers, and paper fragments. Chrysotile adhered to building material, chrysotile bundles, and plaster were also components of large particles. This is consistent with the fact that the lint with fibrous particle bundles was in the > 300-μm particle size range.

The smaller particles (< 75 μm in diameter) included asbestos, soot, lead, and other trace elements. This is consistent with the dual nature of the event—the collapse of two buildings overlaying intensely burning structures—which would result primarily in individual and population exposures to large particles and in much lower exposures to fine particles. However, the large amounts of material in the air during the first 2 days could lead to high exposures within unprotected individuals.

Inorganic and metals. The concentrations of elements found in the samples are shown in Table 2, which provides values for

an array of elements detectable by ICP/MS. The levels of many of the elements are consistent with their presence in building materials, including chromium, magnesium, manganese, aluminum, and barium. The very high levels of titanium (> 0.1%) were due to their presence in paint, especially white paint. The lead levels are elevated due to the use of lead-based paint on metallic surfaces during construction of the building. The detected lead dust concentrations were lower than would be found outdoors in older cities affected by tailpipe emissions from leaded gasoline (*24*). The lead levels, however, could not be discounted in concerns about exposure. Because of the large mass of material deposited within rehabitable buildings throughout lower Manhattan, surface loading could enhance potential nondietary exposures (*25*). In contrast, mercury was not at quantifiable levels, and the concentrations of arsenic and cadmium were relatively low, but in the micrograms/gram (parts per million) concentration range.

In addition to the elements quantified by ICP/MS analyses, the SEM dispersive X-ray analyses showed large signals for iron and calcium, which are major components of construction materials. Similar observations were found for silicon, which is consistent with the glass fragments and fiberglass found in each sample. FTIR functional group analysis detected a signal that is indicative of calcium sulfate dihydrate, a component of gypsum board, and calcium carbonate, which is extensively used as filler for many materials. Other SEM analyses found signals of trace elements, which are indicative of fiberglass and other nonorganic fibers, especially asbestos fiber.

We found detectable levels of typical anionic and cationic species that are usually measured in aerosol samples (ion chromatography results shown in Table 1). We found chloride and sulfate in all samples. The Cortlandt, Cherry, and Market Street samples had sulfate levels of 41,400, 35,200, and 42,100 ng/g, respectively, which probably were formed in the fires. We also detected calcium in the nanograms per gram concentration range; this is probably a result of the pulverization of building materials, with Cortlandt, Cherry, and Market Streets having values of 18,200, 14,000, and 17,000 ng/g, respectively. The high calcium levels are consistent with the FTIR and morphologic analyses. A major difference between these samples was that Cortlandt Street had approximately three times the levels of both fluoride and chloride as the other streets.

PAHs. In the morphologic analyses, we found that the particles < 75 μm in diameter were gray. Thus, we focused the analyses on products of incomplete combustion as well as other organic species. The results for PAHs are shown in Tables 3 and 4. For the three dust and smoke samples, which were undifferentiated by particle size, the total concentrations of 40 typical PAHs with higher molecular weights were in excess of 200–300 μg/g. The distribution of the 40 PAH compounds are shown in Figure 7, with levels of individual PAHs ranging from hundreds of nanograms per gram to > 40 μg/g. Benzo[a]pyrene ranged from 12 to 24 μg/g, with the highest values detected at Cortlandt Street. The values for phenanthrene ranged from 22 to 44 μg/g, with the highest value also detected at the Cortlandt Street.

Table 2. Concentrations of elements (ng/g dry weight) found in the three settled dust and smoke samples.

Element	Cortlandt	Cherry	Market
Li	26,800	22,650	29,520
Be	3,292	2,638	3,754
Mg	110,300	118,300	179,000
Al	814,700	558,800	908,700
Ti	1,717,000	1,485,000	1,797,000
V	40,370	33,890	42,610
Cr	182,000	142,600	171,500
Mn	781,400	565,100	828,100
Co	8,316	7,230	10,460
Ni	41,140	42,040	47,290
Cu	133,500	336,300	325,600
Zn	1,718,000	2,555,000	2,992,000
Ga	30,300	26,990	34,060
As	2,464	2,792	2,613
Rb	21,390	18,630	21,710
Sr	691,000	478,900	720,800
Ag	2,565	1,945	2,247
Cd	5,695	8,454	7,459
Cs	1,165	1,085	1,327
Ba	365,300	370,000	406,500
Hg	ND	ND	ND
Tl	905	1,954	1,290
Pb	142,400	483,500	289,200
Bi	1,087	1,405	1,466
U	4,117	3,920	4,213

Table 3. Concentrations of pesticides, PCBs, and selected PAHs (ng/g) found in the three settled dust and smoke samples.

Compound	Cortlandt	Cherry	Market
Pesticides			
Hexachlorobenzene	1.9	0.9	1.2
Heptachlor	ND	ND	ND
4,4 DDE	1.3	2.1	3.0
2,4 DDT	ND	ND	ND
4,4 DDT	ND	ND	ND
Mirex	ND	0.8	ND
Total chlordanes	3.1	5.6	3.7
PCBs[a]			
Total PCBs (without 8 and 5)	631	562	723
Total PCBs (with 8 and 5)	659	589	753
Selected PAHs			
Fluorene	6,800	2,620	32,200
Phenanthrene	44,100	22,300	32,100
Fluoranthrene	40,300	13,700	32,600
Benzo[a]pyrene	23,000	12,100	19,300
Benzo[b+k]fluoranthane	36,600	15,600	29,500
Total PAHs (40 compounds)[b]	383,300	218,100	376,100

ND, not detected.
[a]PCB concentrations are the sum of 68 congeners (66 congeners in the case of sum PCB without IUPAC congeners 5 and 8).
[b]Other compounds shown in Figure 7.

We found other PAHs in each sample (Table 4); for example, 7H-benzo[*c*]fluorene and 11H-benzo[*b*]fluorene were found in the Market Street sample, with values of 39 ppm and 33 µg/g, respectively. Additional PAHs were detected in the Cortlandt and Cherry Street samples, although these samples had a much less diverse mix of additional PAHs and neither had detectable levels of the two compounds mentioned above. For example, the Cortlandt Street sample had two methylated phenanthrene compounds at concentrations < 10 µg/g. If we add the quantifiable PAHs in each sample, the total PAHs in the settled dust and smoke was > 0.1% of the mass.

The highest concentrations of the 40 specific PAHs reported in Table 4 and Figure 7 were found in the Cortlandt Street sample. This is logical because it was the site closest to the fire after the collapse; however, a larger variety of other PAHs at concentrations > 10 µg/g were found in the Market

samples. The intense and uncontrolled fire(s) would be expected to burn at different temperatures, and the homogeneity of the material that burned would lead to a variety of unburned or partially burned hydrocarbons. These were derived from burning plastics, metals, woods, synthetic products, and other materials; using morphologic analyses, we found charred wood particles in all three samples.

Other organic compounds. A significant product of incomplete combustion found in all three samples was the class of contaminants called phthalate esters; as shown in Table 4, the levels were > 10 µg/g for specific compounds. The total level of detectable phthalate esters in the Market Street sample was > 100 µg/g. Hydrocarbons identified and shown in Figure 8 indicated the presence of a fuel, which in this case was associated with the approximately 91,000 L of unburned or burning jet fuel that cascaded down each building after the explosions and during the

collapse of each tower. Results of all three samples showed an unresolved envelope of high boiling hydrocarbons of 10 carbons or greater and had individual compound peaks superimposed on the envelope (Figure 8). The mass spectrum of the unresolved envelope was consistent with saturated hydrocarbon chains (masses separated by 14 amu starting at 43 amu) and naphthalene ring structure (128 amu). All samples also showed major peaks of the lightest PAHs (naphthalene, substituted naphthalene, acenaphthalene, and fluorene), which were consistent with the presence of products of combustion and the quantitative results reported in Tables 3 and 4. The alkane peaks were much more pronounced and distinct in the sample collected farthest to the east of Ground Zero (0.7 km; Market Street) (Figure 8). The alkanes detected were the same as those found in uncombusted fuel. Jet fuel is composed of a mixture of saturated hydrocarbons (representing > 50% of the total fuel)

Table 4. Concentrations of semivolatile hydrocarbons (µg/g) found in the three dust and smoke samples (includes only compounds > 5 µg/g in concentration).

Compound name	CAS No.	Market	Cherry	Cortlandt
2-Hexyl-1-decanol	2425-77-6	ND	37.2	37.4
1-Dodecanol, 2-methyl-, (*S*)-	57289-26-6	ND	ND	6.8
1H-1,2,4-Triazole, 1-ethyl	16778-70-4	ND	12.1	ND
1H-Indene, 1-(phenylmethylene)-	NA	ND	ND	10.0
1H-Pyrrole-3-propanoic acid, 2,5-dihydro-4-methyl-2, 5-dioxo	487-65-0	9.0	ND	ND
1-Hexadecanol, 2-methyl	2490-48-4	ND	19.7	ND
1-Hexyl-2-nitrocyclohexane	NA	27.0	ND	ND
1-Hydroxypyrene	5315-79-7	14.4	ND	ND
2,3-Dimethyl-1-pentanol,	10143-23-4	20.4	ND	ND
1-Pentacontanol	NA	ND	ND	27.7
4-Methyl-2-propyl-1-pentanol	54004-41-0	ND	ND	27.5
1,2,3-Triphenyl-3-vinyl-cyclopropene	NA	ND	ND	24.5
2-Benzylquinoline	1745-77-3	ND	ND	18.8
2-Methylnaphthalene	91-57-6	ND	ND	5.1
2,3-Dihydrofluoranthene	30339-87-8	13.4	ND	ND
2-(3'-Hydroxyphenylamino)-5-methyl-4-oxo-3,4-dihydrophyrimidine	57456-60-8	ND	ND	41.4
3-Methoxycarbonyl-2-methyl-5-(2,3,5-tri-*O*-acetyl-beta-*d*-ribofuranosyl)	N/A	32.1	ND	ND
3,3'-Dichlorobenzidine	91-94-1	10.0	ND	ND
3,4-Dihydrocyclopenta(*cd*)pyrene (acepyrene)	25732-74-5	35.5	ND	ND
4-Hydroxymandelic acid-TRITMS	N/A	26.8	ND	ND
7-Methyl-3,4,5(2H)-tetrahydroazepine	N/A	ND	ND	18.5
Benzo[*c*]fluorene	205-12-9	39.4	ND	ND
9H-Fluorene, 9-(phenylmethylene)	4425-82-5	13.8	ND	ND
9,10-Anthraquinone	84-65-1	21.4	ND	11.5
11H-Benzo[*a*]fluorene	NA	19.6	ND	ND
11H-Benzo[*b*]fluorene	NA	33.3	ND	ND
12-Acetoxydaphnetoxin	NA	ND	ND	8.0
1-Methylanthracene	610-48-0	8.9	ND	ND
Auraptenol	61235-25-4	ND	ND	13.5
Benz[*a*]acridine, 10-methyl-	3781-67-7	ND	ND	7.2
Benz[*a*]acridine	225-11-6	ND	12.4	ND
Benzamide, *N*-acetyl-	1575-95-7	ND	ND	22.9
Benzene, 1,1'-(1,3-butadiyne-1,4-diyl)bis-	886-66-8	79.8	ND	ND
Benzimidazo [2,1-*a*] isoquinoline	239-44-1	ND	17.3	ND
Benzo[*a*]acridine	225-11-6	9.3	ND	ND
Benzo[*a*]anthracene	56-55-3	61.0	ND	ND
Benzo[*b*]fluoranthene (benz[*e*]acephenanthrylene)	205-99-2	49.9	ND	ND
Benzo[*b*]naphtho[2,3-*d*]furan	243-42-5	ND	ND	28.2
Benzo[*c*]phenanthrene	195-19-7	ND	ND	43.7
Benzo[*h*]quinoline	230-27-3	ND	ND	5.9
Benzyl butyl phthalate	85-68-7	ND	ND	94.1

Continued, next page

and aromatic hydrocarbons (26). Paraffins and cycloparaffins in the C9–C16 range dominate the composition. Gas chromatograms of the vapor phase of jet fuel show both the unresolved envelope and individual hydrocarbon peaks of the straight chain pariffins observed in the thermal desorption profile from the collected dust sample (27). The additional peaks identified within the dust samples represent PAHs that resulted from the incomplete combustion of the building material, the jet fuel from the planes after the explosion and fire, and the collapse of both of the World Trade Center towers. The results suggest that particles transported away from the site during the initial conflagration contained a mixture of combustion products and jet fuel. Thus, residents downwind during the initial hours would have been exposed to particles from construction debris, products of incomplete combustion, and some coated with jet fuel. Other materials could have shown similar
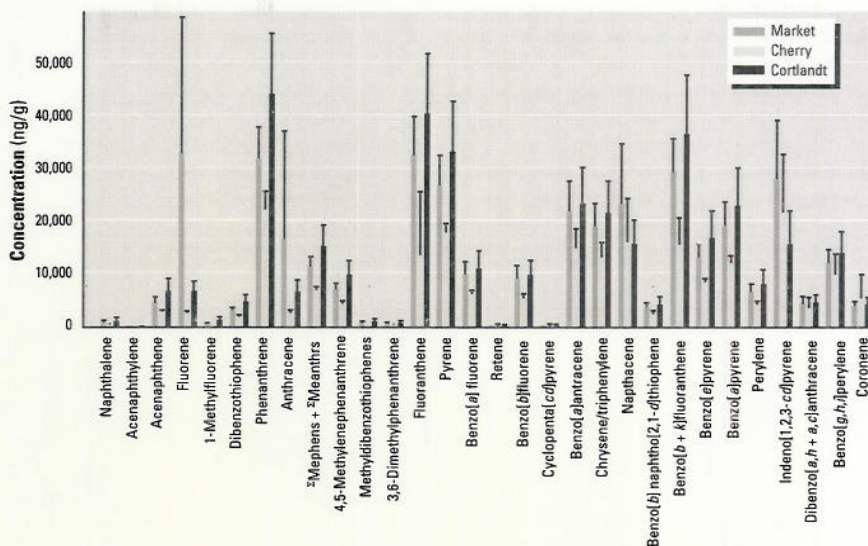

Figure 7. PAH concentrations measured in the Cortlandt, Market, and Cherry Street samples [average PAH concentrations ± 1 SD (n = 3)]. ΣMephens + ΣMeanthrs, Σmethylphenanthrenes + Σmethylanthracenes.

Table 4. Continued

Compound name	CAS no.	Market	Cherry	Cortlandt
Biphenyl	92-52-4	6.5	ND	ND
Carbazole	86-74-8	28.6	8.1	22.1
Dimethylcyanamide	1467-79-4	ND	ND	14.4
Cyclohexanemethanol	100-49-2	ND	ND	16.8
Cycloate	1134-23-2	ND	32.4	46.0
Diisobutyl phthalate	84-69-5	27.5	ND	ND
Di-n-butyl phthalate	84-74-2	12.6	ND	ND
Dibenzofuran	132-64-9	14.5	ND	9.2
Dibenzothiophene	132-65-0	ND	ND	12.7
Dibutyl phthalate	84-74-2	16.5	14.6	19.7
Dicyclohexyl phthalate	84-61-7	ND	77.8	ND
Didodecyl phthalate	2432-90-8	80.0	ND	ND
Diethyl phthalate	84-66-2	31.7	ND	ND
Dihydrogeraniol	NA	51.4	ND	ND
Droserone (2,8-dihydroxy-3-methyl-1, 4-naphthoquinone)	NA	9.8	ND	ND
(E)-2-(6-Nonexnoxy)-tetrahydropyran	55305-36-7	14.5	ND	ND
Ether, hexyl pentyl	32357-83-8	31.6	31.3	ND
2,4-Dimethylheptane	2213-23-2	ND	28.5	ND
2,3,4-Trimethylhexane	921-47-1	12.2	15.6	12.7
2,4-Dimethylhexane	589-43-5	ND	ND	13-3
3,3-Dimethylhexane	563-16-6	ND	14.1	30.8
Hexyl N-butyrate	2639-63-6	ND	ND	8.0
Methyl alpha-ketopalmitate	NA	ND	ND	37.3
Metribuzin	21087-64-9	22.1	ND	ND
Monobutyl phthalate	131-70-4	ND	ND	62.4
n-Octane	111-65-9	43.3	ND	ND
Naphthalene, 1-(methylthio)-	10075-72-6	ND	ND	7.5
Naphthalene, 1,3-dimethylene	575-417	5.3	ND	ND
Nefopam	13669-70-0	10.2	ND	ND
Octane	111-65-9	ND	6.9	ND
Pentanoic acid, 4, 4-dimethyl-3methylene-, ethyl ester	36976-64-4	ND	19.5	ND
1-Methylphenanthrene	832-69-9	ND	ND	10.5
4-Methylphenanthrene	832-64-4	ND	ND	12.9
Phthalate	NA	ND	6.9	ND
Phthalic acid, 2-hexyl ester	NA	ND	47.9	ND
Prometryn (caparol)	7287-19-6	10.7	ND	ND
4,4'-Biphenyldicarbonitrile	1591-30-6	ND	ND	19.6
Chrysene	218-01-9	ND	18.2	ND
1-Azabicyclo[2.2.2]octan-3-one	3731-38-2	ND	12.3	ND
Vernolate (vernam)	1929-77-7	ND	ND	14.9
Xanthene	92-83-1	9.5	ND	ND

Abbreviations: NA, not available; ND, not detected. The 40 PAHs shown in Figure 7 are not included.

patterns, but the large amount of jet fuel released during the crashes would have overwhelmed contributions from other materials such as fuel oil and other petroleum-based products.

The levels of PCBs and polychlorinated dibenzo-*p*-diozins (PCDDs) and dibenzofurans (PCDFs) were in the nanograms per gram and picograms per gram range as shown in Tables 3 and 5, respectively. Thus, the situation yielded detectable, but not excessive, levels of these categories of environmental contaminants. The toxic equivalent values for PCDDs and PCDFs in dust (approximately 100 ng/kg) in this study were consistent with those of dust sampled directly from the pile (maximum total equivalents of about 300 ng/kg) (*28*). Neither our study nor the U.S. EPA found PCDD levels in dust above background (*29*). The levels of polybrominated biphenyls and brominated diphenyl ethers (BDEs) were also determined (Table 6) and were similar to levels found in sewage sludge (*30*). The penta-mixture (BDE-47, BDE-99, and BDE-100) is used in flame retardants for polyurethane foam, which is common as padding in office furniture. The highest concentration was for BDE-209, which is present in thermoplastics (e.g., computers). However, the large volume of material present would lead to significant ambient levels of polybrominated biphenyls, BDEs, and other materials during the first day after the attack on the WTC. We found no concentrations above background for the pesticide chlordane.

Discussion

The composition of each sample collected from the three locations east of the WTC site were complex because of the dual nature of the released aerosol and the magnitude of the event. The aerosol that was released and deposited on surfaces downwind of the complex included pulverized building debris and products of incomplete combustion produced by the explosion that ignited the thousands of liters of jet fuel. The mass of material deposited was extremely high and, in many indoor locations, the deposited particle loadings were 1–3 cm thick (Figure 9). In outdoor situations, the dust and smoke loadings sometimes reached a thickness of > 10 cm. Thus, on the first and second days after the attack on the WTC, > 70% of the mass was associated with construction materials, including pulverized cement, wallboard, and office furnishings, which included a large percentage by weight of glass fiber. A small percentage of the carcinogen asbestos was found in these samples (≈0.8% by volume), although some individual samples yielded higher levels. The products of incomplete combustion were produced by the intense fire that consumed

many materials in the buildings (e.g., furnishings, equipment, debris, wiring, metal, wood, etc.). PAHs, products of incomplete combustion, were present in the samples at levels of 5 µg/g to hundreds of micrograms per gram. Concentrations of the individual compounds (e.g., benzo[*a*]pyrene) were > 20

µg/g, and the total mass of PAHs present were in excess of 0.1% of the mass. When placed in the context of the vast amounts of other materials present in the air during the first day after the collapse and fires, these levels were high and could lead to significant short-term inhalation exposure. In fact,
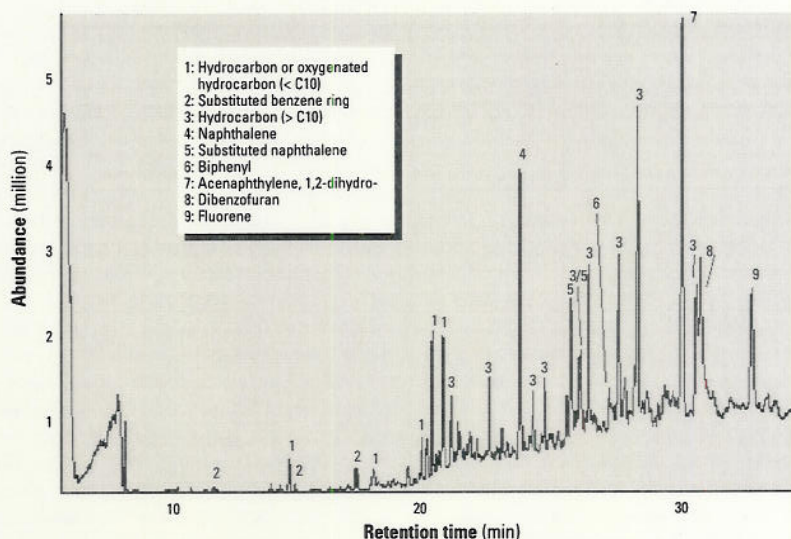
Figure 8. GC/MS analysis of the Market Street sample and the compounds detected that are components of jet fuel.

Table 5. Concentrations (ng/kg) of PCDDs and PCDFs in the three settled dust samples.

	Street		
Compound	Cortlandt	Market	Cherry
PCDDs			
2,3,7,8-TCDD	7.00	5.81	6.53
1,2,3,7,8-PentaCDD	29.4	6.01	7.05
1,2,3,4,7,8-HexaCDD	32.2	4.93	4.95
1,2,3,6,7,8-HexaCDD	35.0	16.6	18.0
1,2,3,7,8,9-HexaCDD	38.5	19.0	18.8
1,2,3,4,6,7,8-HeptaCDD	158	304	325
1,2,3,4,6,7,8,9-OctaCDD	1,450	3,630	3,410
PCDFs			
2,3,7,8-TetraCDF	78.2	194	221
1,2,3,7,8-PentaCDF	40.3	39.4	42.7
2,3,4,7,8-PentaCDF	54.5	77.3	85.0
1,2,3,4,7,8-HexaCDF	57.4	46.0	46.4
1,2,3,6,7,8-HexaCDF	46.1	46.0	48.0
1,2,3,7,8,9-HexaCDF	28.7	24.4	4.95
2,3,4,6,7,8-HexaCDF	39.5	37.0	37.9
1,2,3,4,6,7,8-HeptaCDF	91.6	171	177
1,2,3,4,7,8,9-HeptaCDF	40.1	32	31.1
1,2,3,4,6,7,8,9-OctaCDF	118	171	182
2,3,7,8-Dioxin total equivalents	104	96.1	103

Table 6. Concentrations of some brominated flame retardants detected in the dust and smoke released by the collapse of the WTC (µg/kg, dry weight basis).

Street	BDE47	BDE100	BDE99	BDE153	BDE154 + PBB153	BDE209
Cherry	146	74.1	243	45.9	219	1,330
Cortlandt	107	64.2	155	42.0	305	2,660
Market	174	51.1	293	53.4	243	2,330

Abbreviations: BDE47, 2,2′,4,4′-tetrabromodiphenyl ether; BDE99, 2,2′,4,4′,5-pentabromodiphenyl ether; BDE100, 2′,4,4′,6-pentabromodiphenyl ether; BDE153, 2,2′,4,4′,5,5′-hexabromodiphenyl ether; BDE154, 2,2′,4,4′,5,6-hexabromodiphenyl ether; BDE209, 2,2′,3,3′,4,4′,5,5′,6,6′-hexabromodiphenyl ether; PBB153, 2,2′,4,4′,5,5′-hexabromobiphenyl.

based on the PAH results obtained from air samples after 25 September, the types of PAHs released into the atmosphere at that time were similar to the PAHs detected in the settled dust and smoke samples collected during the first week after the collapse and fires (*29*). The levels of PCDDs and PCDFs were similar to those found in other studies (*29*), but the levels of 2,2´,4,4´,5,5´-hexabromobiphenyl were higher than those found in sludge, which is likely due to its use during the construction of the WTC in the 1970s (*30*). The concentrations of lead ranged from 100 to > 600 ppm; these concentrations are not very high compared to the levels found in typical urban soils. However, the actual levels of dust and smoke deposited in individual buildings and businesses need to be assessed for cleanup based on the actual surface loading of lead and asbestos. A systematic effort will be required to properly clean indoor locations in order to eliminate persistent levels of lead, asbestos, and other hazardous materials on surfaces and in the air ducts that service each residence or building (air ducts can be a reservoir of material that could be released into the indoor air if not properly cleaned).

The high pH of the samples was probably caused by cement and other basic materials associated with construction debris in the deposited particles. This factor, along with the presence of long and thin glass fibers (nonasbestos) and attached agglomerated fine particles, must be considered when evaluating the initial lung irritations reported by residents and workers in the initial days and weeks after the collapse of the WTC buildings. The rain on 15 September and

Figure 9. Indoor deposition of dust and smoke released by the collapse of the WTC on 11 September 2001.

especially the heavy rains that fell on 24 September washed away much of the material from outdoor surfaces. However, because of the extremely dry weather pattern in the Northeast during fall 2001, dust still remained on some outdoor surfaces and rooftops through November. The WTC site itself was continually sprayed with water to keep the resuspendable dust levels down during recovery operations. The persistence of significant levels of the initial dust and smoke into the late fall were also associated with indoor locations, including buildings that had open ventilation systems or open windows at the time of the collapse, or had windows blown out during the collapse. The quantities of settled and resuspendable dust and smoke are of concern indoors. WTC dust and smoke could lead to health impacts if the toxic constituents present on the indoor surfaces are not cleaned properly and if the HVAC system of each structure is not concurrently cleaned, or cleaned before the cleanup of the indoor surfaces and reentry into the residence or office. The U.S. EPA and other organizations have repeatedly recommended using methods for removal of hazardous materials in residences and offices before rehabilitation. This approach to cleanup is necessary to ensure that rehabitation clearance values are achieved for contaminants such as lead (i.e., 40 µg/ft² on floors) (*31*).

Some types of material that were released are similar to materials that we are exposed to during our daily lives. At a minimum, however, extraordinarily high quantities of coarse and fine particles were released and dispersed after the WTC collapse; future analysis is needed on the health consequences of the exposure among commuters, workers, and residents. The differences in the three samples that we analyzed suggest that there were inhomogenities among aerosol materials released on 11 September and during the subsequent weeks. This is expected because of the large amounts of different materials present in each of the collapsed and burning structures.

The outdoor cleanup of the initially deposited material began days after the attack and continued for several months. The indoor cleanup activities have proceeded more slowly. Eventually, estimates of human exposure to the materials characterized in these three bulk samples will be made. In addition, the results for composition and particle size, with and without agglomerates on glass fiber and other fibrous particles, will be used in assessments of short-term and long-term effects among various populations including sensitive subgroups. The people potentially exposed to the initially suspended dust and smoke, or subsequently settled dust

and smoke, would include unprotected rescue workers, residents, and workers in downtown Manhattan immediately after and in the first few weeks after the collapse. The settled dust and smoke could be resuspended and expose unprotected residential cleanup workers and workers and residents in poorly or inefficiently cleaned buildings for weeks to months after 11 September. Finally, the levels of exposure encountered will have to be placed into context with the materials that have been released from the diminishing smoldering fires that continued to burn until 14 December 2001.

Conclusions

The analyses of the three settled dust samples collected from areas downwind of the collapsed WTC have provided information that is valuable in assessing exposures of workers and residents to related dusts. These exposures have occurred during resuspension of such dusts, both outdoors and indoors, in the course of rescue, cleanup, and routine day-to-day activities. The vast majority of the mass was pulverized building and construction materials including cement, cellulose, and glass fibers. However, the fires produced aerosol particles that contained products of incomplete combustion. Toxicants with significant concentrations or potential surface loadings included asbestos, glass fibers, lead, and PAHs. Further, many of these particles had much smaller particles agglomerated on the surface. The identification of these major components is important for assessing acute inhalation of resuspendable dust and smoke, or direct inhalation during the first week after the attack. Because the material also settled indoors, if indoor locations are not cleaned properly, there is a potential for long-term inhalation contact or ingestion contact.

The types of PAHs detected in these initial samples are similar to the PAHs detected in air samples 3 weeks after the attack. The fires continued at Ground Zero until 14 December 2001, resulting in the need for longer exposure characterization for products of incomplete combustion. The levels of dioxin and PCBs are similar to those found in the general environment.

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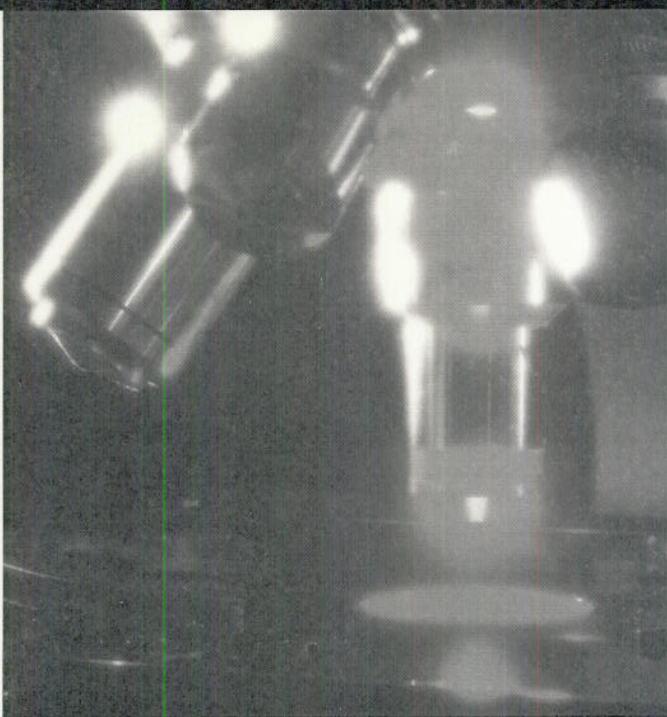
Exhibit 2

5. Summary of Data Reported and Evaluation

5.1 Exposure data

Cadmium is found at low concentrations in the Earth's crust, mainly as the sulfide in zinc-containing mineral deposits. Since the early twentieth century, it has been produced and used in a variety of applications in alloys and in compounds. Among the important compounds of cadmium are cadmium oxide (used in batteries, as an intermediate and catalyst and in electroplating), cadmium sulfide (used as a pigment), cadmium sulfate (used as an intermediate and in electroplating) and cadmium stearate (used as a plastics stabilizer).

Occupational exposure to cadmium and cadmium compounds occurs mainly in the form of airborne dust and fume. Occupations in which the highest potential exposures occur include cadmium production and refining, nickel–cadmium battery manufacture, cadmium pigment manufacture and formulation, cadmium alloy production, mechanical plating, zinc smelting, soldering and polyvinylchloride compounding. Although levels vary widely among the different industries, occupational exposures generally have decreased in the last two decades.

Urinary and blood cadmium concentrations are generally much lower in non-occupationally exposed people, for whom the most important sources of exposure are cigarette smoking and, especially in polluted areas, eating certain foods (e.g. rice). Acidification of cadmium-containing soils and sediments may increase the concentrations of cadmium in surface waters and crops.

5.2 Human carcinogenicity data

Following a report of the occurrence of prostatic cancers in a small group of workers employed before 1965 in a plant manufacturing nickel–cadmium batteries in the United

Kingdom, a series of cohort analyses were undertaken, which did not confirm the excess among the remaining workers; however, an increase in mortality rates from lung cancer was detected. A small cohort working in the same industry was studied in Sweden: no excess of prostatic cancer was detected, but a nonsignificant increase in mortality from lung cancer was found among workers who had the longest duration of employment and latency.

Two small copper–cadmium alloy plants were studied in the United Kingdom. The rate of mortality from lung cancer was increased in one of them but decreased in the other. A case–control analysis of lung cancer did not show any association with exposure to cadmium. No increase in mortality from prostatic cancer was found in these two plants, while in a similar plant in Sweden a nonsignificant excess was detected.

Excess mortality from lung cancer was reported among workers employed in a US cadmium recovery plant, and a dose–response relationship was demonstrated between estimated cumulative exposure to cadmium and lung cancer risk. The latter was unlikely to be due to confounding by cigarette smoking and persisted among workers employed after 1940, when little arsenic was present in feedstock. Excess mortality from prostatic cancer was found initially, but the relative risk diminished and became nonsignificant with further follow-up.

In a large cohort of workers from 17 cadmium processing plants in the United Kingdom, decreased mortality from prostatic cancer was observed, while that from lung cancer was increased in the overall cohort and there were suggested trends with duration of employment and with intensity of exposure. The increase in lung cancer risk was stronger in the small proportion of workers with high cadmium exposure. Confounding by concomitant exposure to other cancer determinants, including arsenic, was not controlled for. Excess mortality from stomach cancer, which was not related to intensity of cadmium exposure, was also reported among these workers.

A number of early studies reported an increased risk for prostatic cancer among cadmium workers, but the results of later studies were not consistent. Early and recent studies provide consistent evidence that the risk for lung cancer is increased among workers exposed to cadmium.

Constraints that influence the assessment of both lung and prostatic cancer risk are that the number of long-term, highly exposed workers is small, the historical data on exposure to cadmium are limited, particularly for the non-US plants, and the ability to define and examine a gradient of cumulative exposure varies across studies. Additionally, for cohort studies, prostatic cancer poses special difficulties in that it is subject to the possibility of detection bias. Confounding by cigarette smoking in relation to lung cancer was addressed directly only in the study from the USA, but some other studies provided analyses based on internal comparisons, which are not likely to be affected by this problem. Control of the confounding effect of co-exposure to other metals, particularly arsenic and nickel, was limited; however, the analyses in which an attempt was made to distinguish US cadmium-exposed workers with different levels of exposure to arsenic indicated that the increase in lung cancer risk was unlikely to be explained by exposure to arsenic.

5.3 Animal carcinogenicity data

Cadmium chloride, cadmium sulfate and cadmium acetate have been tested by oral administration in several studies in mice and rats. Most of the studies were inadequate for an evaluation of carcinogenicity. Two adequate studies on cadmium chloride in rats are available. In one study with controlled dietary zinc levels in male rats, cadmium chloride produced dose-related increases in the incidences of leukaemia, interstitial-cell tumours of the testis and proliferative lesions of the prostate. In another study on cadmium chloride in rats, in which zinc levels in diet were not controlled, no increase in tumour incidence was seen.

In two inhalation studies in rats, malignant lung tumours were produced by cadmium chloride, cadmium sulfide/sulfate, cadmium sulfate and cadmium oxide fume and dust at low levels of exposure for short durations. In one study in rats by intratracheal instillation, malignant pulmonary tumours were produced by cadmium sulfide and cadmium chloride, but not by cadmium oxide. In one inhalation study in mice of cadmium chloride, cadmium sulfide/sulfate, cadmium sulfate and cadmium oxide fume and dust, some groups exposed to cadmium oxide fume or dust had increased incidences of lung tumours. In one inhalation study in hamsters of cadmium chloride, cadmium sulfide/sulfate, cadmium sulfate and cadmium oxide fume and dust, no increase in the incidence of lung tumours was found.

In several studies, single or multiple subcutaneous injections of cadmium chloride, cadmium sulfide, cadmium sulfate and cadmium oxide and of cadmium-containing rat liver ferritin caused local sarcomas in rats. Mice appear to be generally less susceptible than rats to induction of local tumours by cadmium compounds. Cadmium powder, cadmium chloride and cadmium sulfide produced local sarcomas in rats following intramuscular administration. In a single study by intraperitoneal injection in rats, cadmium sulfide induced malignant tumours within the peritoneal cavity. Cadmium chloride in mice and rats and cadmium sulfate and cadmium-precipitated rat liver ferritin in rats produced testicular interstitial tumours after subcutaneous administration. Dietary zinc deficiency enhanced the multiplicity of cadmium-induced interstitial-cell tumours of the testis and increased the incidence of local tumours at the site of subcutaneous cadmium injections. Subcutaneous injection of cadmium chloride to rats produced tumours of the prostate but only at doses below the level that induced cadmium-induced testicular degeneration or when such degeneration was prevented by concurrent exposure to zinc. Intramuscular administration of cadmium chloride also induced prostatic tumours in rats. Subcutaneous administration of cadmium chloride increased the incidence of pancreatic tumours in rats in one study and decreased the incidence in another.

In limited studies in rats, injection of cadmium chloride into the prostate produced malignant prostatic tumours.

Administration of excess zinc by inhalation, parenteral and oral routes has been shown to reduce the carcinogenic potential of cadmium after exposure systemically or by inhalation. When combined with known carcinogens, cadmium enhanced, suppressed or had no effect on tumour incidence, depending on a complex set of circumstances including, at least in part, the dose, time sequence of administration, site of tumour and route of administration.

5.4 Other relevant data

Cadmium enters the body mainly by inhalation and by ingestion. Fractional intestinal absorption is influenced by dietary factors and increases with dietary cadmium concentration. Pulmonary fractional absorption depends partly on the solubility *in vivo* of the compound. Cadmium induces synthesis of metallothionein, a low-molecular-weight protein that binds cadmium primarily in the liver and kidney. Metallothionein production can also be induced by e.g. zinc. When metallothionein-bound cadmium is released into the blood, it is filtered through the glomeruli and then reabsorbed in the proximal tubules. In certain mammalian tissues, such as rat ventral prostate, hamster ovary and rat, mouse and monkey testis, the concentrations of metallothionein are low and its synthesis is not induced by exposure to cadmium. Most of the body burden of cadmium is retained in the kidneys and the liver. The half-life of cadmium in human kidneys is probably 10–20 years. Cadmium concentrations in whole blood are affected by both recent exposure and body burden. Excretion occurs mainly *via* the urine. Urinary excretion of cadmium by individuals without renal dysfunction primarily reflects the amount of cadmium retained in the kidneys.

The target organs for cadmium toxicity depend on the type of exposure. Inhalation of cadmium can lead to chronic obstructive airway disease. Following long-term exposure, renal tubular and glomerular dysfunction can develop. Renal function can deteriorate further, even after cessation of exposure to cadmium. Cadmium can suppress cell-mediated immune responses *in vitro*.

Parenteral administration of cadmium salts produces adverse effects on the testes, ovaries, placenta and embryo in experimental animals; many of these effects have been shown to be preventable by administration of zinc compounds. Administration of cadmium at doses that affect placental morphology or function induces fetal anaemia, growth retardation, teratogenicity and embryonic and fetal death in experimental animals. Reproductive and developmental toxicity have been reported following exposure to cadmium compounds by oral and inhalation routes, but the effects are generally much less severe than after parenteral administration.

In three of five studies, the frequencies of chromosomal aberration were increased in peripheral blood lymphocytes of workers exposed to cadmium in the metal industry, where they were usually also exposed to other metals. No effect of cadmium was observed in a limited study of workers from a Swedish alkaline battery factory. In two studies of cadmium pigment plant workers, no increase in the frequency of chromosomal aberrations was observed. No increase in the frequency of sister chromatid exchange was seen in one study of workers exposed to cadmium.

In one of two limited studies of *itai-itai* patients, increased frequency and severity of chromosomal aberrations were observed. In one study, no increase in sister chromatid exchange frequency was observed in people living in a cadmium-polluted region of Japan. In a study of subjects living in a cadmium-polluted region of China, there were small but significant increases in chromosomal aberration frequency. A significant dose–effect relationship between urinary levels of cadmium and chromosomal aberration frequency was also observed, and more severe aberration types were observed in individuals with high urinary levels of cadmium.

In those studies in which significant responses were observed, the chromosomal aberrations tended to occur in the more heavily exposed groups and were of more complex types.

Chromosomal aberrations and aneuploidy were observed in animals exposed to cadmium chloride *in vivo*. Dominant lethal mutations were generally not induced in mice.

Cadmium chloride damages DNA of human cells *in vitro*. In the few studies available, chromosomal aberrations were observed in human cells treated with cadmium sulfide but not in those treated with cadmium chloride. Indications of aneuploidy were observed in human fibroblasts after treatment with cadmium chloride.

Studies using cultured animal cells show that exposure to cadmium compounds damages genetic material. DNA strand breaks, mutations, chromosomal damage and cell transformation have been observed *in vitro*. Cadmium compounds inhibit the repair of DNA damaged by other agents, thereby enhancing their genotoxicity.

Mutations have generally not been observed in *Drosophila* or bacteria; however, a weak response was observed in some studies in bacteria and there is evidence for cadmium-induced DNA damage in bacteria.

5.5 Evaluation[1]

There is *sufficient evidence* in humans for the carcinogenicity of cadmium and cadmium compounds.

There is *sufficient evidence* in experimental animals for the carcinogenicity of cadmium compounds.

There is *limited evidence* in experimental animals for the carcinogenicity of cadmium metal.

In making the overall evaluation, the Working Group took into consideration the evidence that ionic cadmium causes genotoxic effects in a variety of types of eukaryotic cells, including human cells.

Overall evaluation

Cadmium and cadmium compounds *are carcinogenic to humans (Group 1)*.

Exhibit 3

Cadmium exposure and endometrial cancer risk: A large midwestern U.S. population-based case-control study

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Abstract

Estrogen-mimicking chemicals, such as cadmium, may be associated with increased susceptibility to hormone-dependent cancers, though supporting data are sparse, particularly for endometrial cancer. The Health and Environmental Exposure Research (HEER) study worked with the Arkansas Central Cancer Registry, Iowa Cancer Registry and Missouri Cancer Registry to obtain names of women diagnosed with endometrial cancer who were willing to be contacted for participation in our case control study. Voter registration lists from Iowa and Missouri were used to randomly select similarly aged women as represented in the case population. Participants were interviewed by telephone to obtain information on known or suspected endometrial risk factors. Urine kits were sent to participants for home collection and returned for analysis. Our case-control study consisted of 631 incident cases of endometrial cancer diagnosed from January 2010 to October 2012 and 879 age-matched population-based controls, ages 18–81 years (mean age 65 years). We quantified cadmium amounts in urine and standardized these values through creatinine adjustment. Using data from all survey completers, we developed a multivariable model for endometrial cancer. Creatinine-adjusted cadmium concentration was added to this model. Odds ratio (OR) and 95% confidence intervals (CIs) for endometrial cancer were calculated. After multivariable adjustment, higher creatinine-adjusted cadmium exposure was associated with a statistically significant increase of endometrial cancer risk (OR: 1.22; 95% CI: 1.03–1.44). Our results provide evidence that cadmium may increase the risk of endometrial cancer, possibly through estrogenic effects.

Introduction

Cadmium is a toxic, bioaccumulating, non-essential, and highly persistent metal with a variety of adverse health effects. These include renal dysfunction; breast, lung, pancreatic, and

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endometrial cancer risk; and disturbances in calcium homeostasis [1–5]. Ingesting food containing cadmium (e.g., kidney, liver, crustaceans, cereals) is the primary non-occupational source [6,7]. Smoking is the second major source of cadmium exposure in the general population [7]. Tobacco plants readily take up agricultural sources of cadmium [8]. A doubling of urinary cadmium levels may be found in heavy smokers (>300 pack years (number of smoking years times usual number of cigarettes per day)) compared to non-smokers [9].

Because the estimated biological half-life of cadmium is from 10 to 30 years [10], only a small fraction of inhaled or ingested cadmium is excreted, and the body burden increases over time. Women generally have higher cadmium levels than men [11], and parous women are more likely to have depleted iron stores and therefore absorb more cadmium when compared to nulliparous women [12].

Endometrial cancer, the fourth most common cancer for women, occurs primarily in post-menopausal women. In 2016, approximately 60,050 women are expected to be diagnosed with cancer of the body of the uterus (endometrial cancers and uterine sarcomas), with 10,470 projected deaths [13]. Endometrial cancer is associated with both endogenous and exogenous estrogen exposure [14]. Cadmium mimics estrogen and may increase estrogen-receptor-mediated proliferation—the classical estrogen signaling, thereby potentially contributing to endometrial cancer risk [15,16]. Two nuclear estrogen receptors, (estrogen receptor alpha (ERα) and estrogen receptor beta (ERβ)) are involved in the classical estrogen signaling. The ERα and ERβ directly interact with specific DNA binding sites that regulate gene expression [17,18]. Alternatively, Ali and colleagues demonstrated that cadmium exposure in mice affected the height of the uterine luminal epithelium in a dose-dependent manner. They suggested that the effects of cadmium exposure was through non-classical estrogen receptor signaling [19]. In 2008, Akesson et al reported a significant association between endometrial cancer and cadmium intake based on assignment of cadmium exposure levels from a food frequency questionnaire [1]. However, more recent studies using food frequency questionnaires to estimate cadmium levels have not reported an association [20–22]. Vacchi-Suzzi [23] reported minimal correlation between urinary cadmium levels and estimates of dietary cadmium intake. This finding and inconsistent observational studies using estimated cadmium exposure from self-reported dietary intake has brought the validity of food frequency questionnaires for cadmium estimation into question [24–26].

The Health and Environmental Exposure Research (HEER) study aimed to investigate the association between endometrial cancer risk from cadmium exposure after adjusting for confounders in a population-based case-control study using cases from the Arkansas, Iowa and Missouri state cancer registries and age-matched controls from voter registration lists.

Materials and methods

Study population

Incident cases of endometrial carcinoma diagnosed from January 2010 to October 2012 were obtained from three cancer registries: Arkansas Central Cancer Registry, Iowa Cancer Registry and Missouri Cancer Registry. In situ and non-carcinomas, such as Müllerian and mesodermal malignant tumors, were excluded. Case ascertainment also included local or regional stages, excluding metastatic endometrial cancer cases. Cases were contacted by each registry to obtain written permission to pass their names to our study. Of those that agreed, contact information was sent to HEER study staff.

Age-matched controls were randomly selected from the Iowa and Missouri voter registration lists only as the Arkansas voter registration list was not available. The Iowa voter registration list provided date of birth, whereas the Missouri voter registration list provided age. For Missouri controls, the age of the participant was at the last voter registration period and was

thus approximately one to three years younger than the current year. We therefore used the listed age plus 2 years for matching. For each case, four to five controls were randomly selected from the voter registration lists with replacements on names for which the telephone number or residential address in Missouri or Iowa was missing. Imperfect age matching occurred due to variable responses by potential controls. The age or year of cancer diagnosis for cases was used as the reference age or year for the matched controls, respectively. Most questions asked for information during the year before diagnosis, i.e. reference age/year minus one.

Introductory letters with a study brochure and consent information were sent to all potential participants. For participants who did not contact the study to decline participation and for whom a valid address was obtained, contact information was sent to the University of South Carolina Call Center for telephone interviews.

Assessment of cadmium and covariates

All participants were interviewed by telephone by trained interviewers. The 35-minute interview asked about physical activity, reproductive history, alcohol consumption, height and weight, use of oral contraceptives and hormone replacement therapy, personal and family medical history, demographic factors, a limited set of dietary components, and smoking history.

Upon completion of the telephone interview a kit to collect saliva and urine at home and return to the study center was sent to participants. Urine sample containers and urine hats used to collect the sample were exhaustively cleaned using multistep acid leachings before sending to participants [27]. Analyses of acid leaching solutions from kit materials revealed no detectable cadmium. Urine collection containers were used to prepare method blanks. Detailed photo-essay instructions were carefully designed for the urine collection kits to minimize trace element contamination during specimen collection and handling.

Urine samples were immediately refrigerated (4° Celsius) upon receipt. The University of Missouri Research Reactor (MURR) has a laboratory that is specially designed for trace element analysis and is subject to high-efficiency particulate air filtration. The trace-analysis laboratory at MURR has been has been conducting elemental analyses of biological monitors for 35 years [28]. Cadmium was quantified by using inductively coupled plasma-dynamic reaction cell-mass spectrometry (ICP-DRC-MS) following an established protocol from the National Health and Nutritional Examination Study (NHANES) [29], with an additional correction for the effect of strontium on the tin interference. Trace metal analyses were performed from November 2012 to July 2014. A comprehensive quality-control program incorporating numerous methods including method blanks, monitoring multiple cadmium isotopes, internal and external controls, stability samples, replicates, spikes, and routine inclusion of National Institute of Standards and Technology (NIST) standard reference materials (SRM) ensured high-quality data. The instrument detection limit (DL) for cadmium was 0.0017 µg/L, the method detection limit (MDL) was 0.0082 µg/L, and the limit of quantification (3.3 x MDL) was 0.027 µg/L. Cadmium levels in every sample exceeded the MDL, and in no case did the method blank (prepared using urine vials from empty specimen collection kits) exhibit [Cd] > DL. Measurements of NIST SRM 2670a "low" yielded (average ± standard. deviation, % relative standard deviation [RSD]) 0.045 ± 0.006 µg/L, 13%RSD (n = 19); 2670a "high" yielded 4.90 ± 0.16 µg/L, 3.3%RSD (n = 18). Three participant samples were aliquoted and measured repeatedly throughout the study, yielding 0.223 ± 0.016 µg/L, 7.2%RSD (n = 17); 0.184 ± 0.013 µg/L, 7.0%RSD (n = 17); 0.650 ± 0.030 µg/L, 4.7%RSD (n = 17). Urine creatinine level was also measured using a colorimetric assay based on the Jaffé reaction to control for kidney function [30].

This study and all HEER consent documents and procedures were approved by the University of Missouri Health Sciences Institutional Review Board as well as the review boards of the

respective state cancer registries. Participants provided written consent to have their names passed to the HEER study. Each cancer registry kept these written consents. Invitation letters were sent to registry-consented participants with an explanation of the study as well as information about the next step—to telephone the participant to conduct the survey. Contact information was also included in the invitation letter for those who did not wish to be called to opt out of being telephoned. Upon telephoning the participants, the study was explained with an opportunity to ask questions to clarify any concerns. Those who agreed to be interviewed were considered to have provided verbally informed consent.

Statistical analysis

We initially compared creatinine-adjusted cadmium concentration between cases and controls using a t-test. We performed cross-tabulations of survey variables with case-control status to screen for inclusion in a multivariable model. Missing data were relatively rare however we imputed missing values with multiple imputation using the Markov chain Monte Carlo method to impute 20 datasets to be used in the multivariable conditional logistic models. Prior to multiple imputation, we imputed menopausal status based on participant report, smoking status, and use of hormone replacement therapy. A woman was classified as premenopausal if she reported still having periods and was not using hormone replacement therapy. A participant was classified as postmenopausal if she reported an oophorectomy or natural menopause (no menstrual periods for at least 6 months) before the reference date. Women who were taking postmenopausal hormones and still having periods, and women who reported hysterectomy alone were classified as premenopausal if their reference ages were in the first decile of age at natural menopause among the controls (32 years old for current smokers and 36 years old for nonsmokers), and postmenopausal if their reference ages were in the highest decile for age at natural menopause in the control group (56 years old for both current smokers and nonsmokers). For six women in the intermediate age category (second to ninth deciles), menopausal status was considered unknown. Thus, we defined three categories of menopausal status: premenopausal, postmenopausal, and unknown [31].

We developed a multivariable conditional logistic model, stratifying on age at diagnosis. Variables that were selected a priori (race, marital status, body mass index (BMI)), menopause at age 56 or older, menopausal status at diagnosis, smoking history, second hand smoke exposure, age at menarche, number of live births, weight gain, history of weight loss attempt, family history of endometrial cancer in a first degree relative, exposure to unopposed estrogen, oral contraceptive use, history of breast or ovarian cancer, history of uterine fibroids, history of diabetes, sleep habits, irregular work schedule, alcohol use, protein shake and whole milk consumption) were tested for association with case-control status in a multivariable conditional logistic regression. Those with p<0.1 were retained for further analysis. BMI, weight in kilograms divided by squared height in meters, was capped at a maximum value of 70 kg/m^2 to avoid undue influence of extreme outliers. Variables were selected by both forward stepwise inclusion and backwards elimination, using p = 0.1 for both entry and exit. Both stepwise models retained the same set of variables. Interactions between variables in the model were tested; none were retained.

After the "best" case-control model had been achieved, the base-2 logarithm of creatinine-adjusted cadmium was added to the model to test for its association with case-control status after controlling for other risk factors, using data from women who returned a urine sample. Because the women who opted to provide urine samples differed from those who did not, we developed a multivariable logistic model to adjust for a potential non-response bias in the case-control model [32]. The inverse of the predicted probability of returning a sample was used as a weight in the conditional logistic regression model. The final set of independent

variables were race; marital status; BMI; history of weight loss attempt; smoking status; pack-years of cigarette smoking for former and current smokers; history of endometriosis, breast cancer, ovarian cancer or uterine fibroids; family history of endometrial cancer; years of oral contraceptive use; years of unopposed estrogen use; menopause at age 56 years or older; menopausal status at diagnosis; protein shake and whole milk consumption; and non-response bias. We also ran the model with only post-menopausal women and a model that excluded smoking status. SAS for Windows v9.4 (SAS Institute Inc., Cary, NC, USA) was used.

Results

Of those approached by the cancer registries (n = 2597) for permission to send their names to our study for potential enrollment, 29% of the names (m = 749) were sent to the call center for interviewing (approximately 25% of MO and AR and 44% of IA). Of 711 eligible cases 89% (n = 631) completed an interview. In comparison to those who declined to pass their names to our study from the cancer registries, those who passed their names were more likely to be White (94% versus 90%) or married or living with partner (66% versus 55%) and less likely to be diagnosed with endometrioid carcinoma (International Classification of Diseases for Oncology: 8380) (74% versus 78%). The proportion with tumor grade I or II and age at diagnosis were similar between the two groups.

For the controls, 4280 age-matched names were randomly selected from the voter registration lists. Of the 4280 controls, 3120 were eligible and 888 completed the survey (28% participation proportion). Of the 2597 cases, 749 women with endometrial cancer were passed to the HEER study and 631 completed the survey (24% participation proportion for cases). Among these 1519 participants, 498 cases (79%) and 545 controls (61%) also returned urine specimens. For the current study, we excluded 9 controls with a history of endometrial cancer, leaving 1510 participants (631 cases and 879 controls). See Fig 1 for a summary of participant enrollment.

Controls were slightly older than cases (mean age 63 years versus 60 years, respectively), with less education (high school graduate or less: 43% versus 37%). Both marital status and racial compositions differed between the two groups (Table 1). The cases and controls were similar in income and employment status. Among the cases, 86% had Type I, mostly endometrioid adenocarcinomas, which is driven by hormonal mechanisms, and 14% were Type II, endometrial carcinomas, which often display as serous or clear cell histology [33].

Characteristics of refusal at enrollment

Of those who actively declined to participate, 17% (9 cases and 194 controls) agreed to answer a few demographic questions. Compared to participants who completed the interview, these helpful refusals were more likely to be high school graduate or less (40% versus 54%) and be married or living with partner (71% versus 82%). The educational attainment of spouse or partner, percent of Hispanic ethnicity, race, income and sexual orientation were similar between these two groups.

Reliability substudy

Of the 165 respondents contacted for a second interview, 2 individuals refused to be interviewed, 29 could not be reached, and 134 were re-interviewed (81%; 69 cases and 65 controls). Mean time between interviews was 13.9 months (range 3.1–20.8 months). Time between interviews was not different between cases and controls.

Participation in moderate and vigorous physical activity showed good concordance between interviews (93% and 82% respectively); the kappa for moderate physical activity was 0.54 (lower confidence limit (LCL) 0.27) and vigorous physical activity was 0.64 (LCL 0.51).

History of ever using mineral supplements showed good concordance (84.2%) with a low kappa (0.27, LCL 0.05). The kappa for BMI category was .84 (LCL .75) with 89.6% concordance. There was high concordance for ever being diagnosed with polycystic ovarian syndrome (97%); the kappa was 0.48 (LCL 0.05). Ever being diagnosed with diabetes showed high concordance (95.5%); the kappa was 0.85 (LCL .74). Having a biological family member that was ever diagnosed with endometrial cancer had high concordance between interviews (88.1). Correlation between the repeated measures of weight, height, BMI, and age of diabetes diagnosis was high (0.98, 0.97, 0.95, and 0.92, respectively).

Cadmium analysis

Creatinine-adjusted cadmium levels ranged from to 0.005 to 0.417 (mean 0.037) µg/g in case participants and from 0.006 to 0.649 (mean 0.041) µg/g in control subjects. A t-test of the
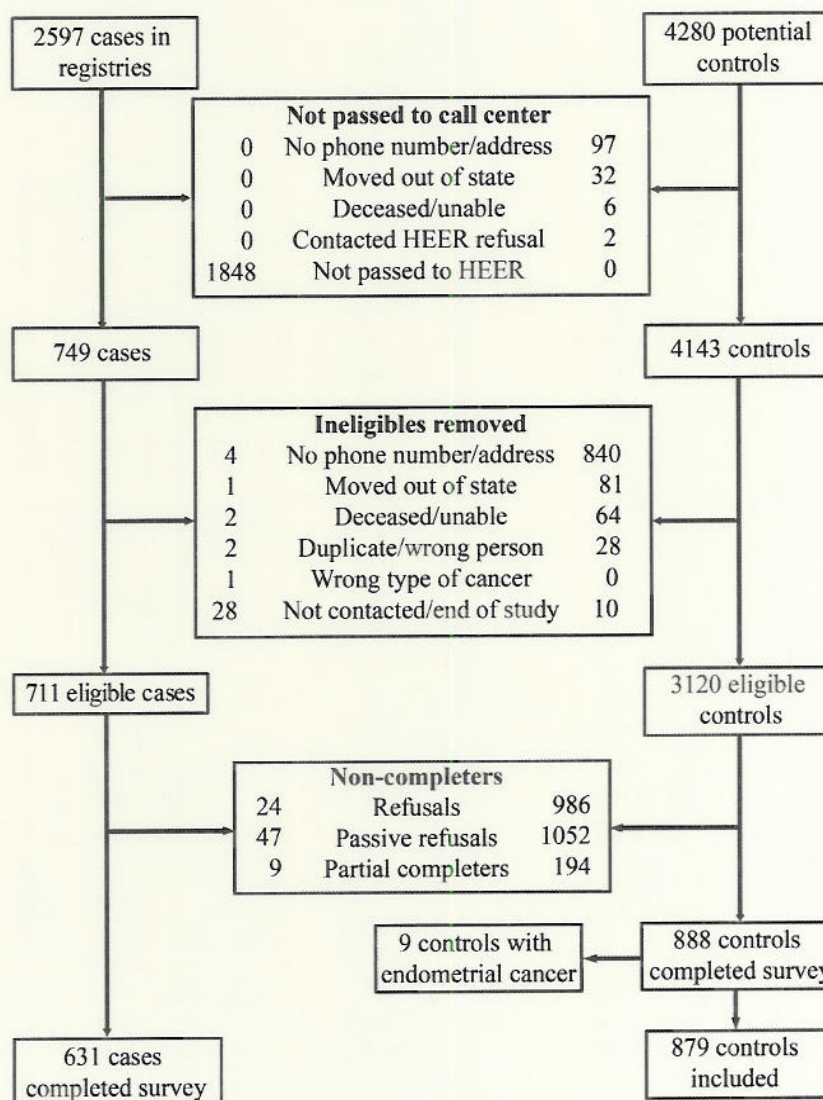
Fig 1. Exclusion and enrollment of participants in the Health and Environmental Exposure Research study.

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Table 1. Characteristics of endometrial cancer cases and population-based controls*.

Characteristic (N missing)	Number (Percent)	Cases (N = 631)	Controls (N = 879)	p-value**
Demographics				
Age at diagnosis				< .0001
<40	32 (2.1)	20 (3.2)	12 (1.4)	
40–44	38 (2.5)	24 (3.8)	14 (1.6)	
45–49	54 (3.6)	30 (4.8)	24 (2.7)	
50–54	144 (9.5)	82 (13.0)	62 (7.0)	
55+	1242 (82.2)	475 (75.3)	767 (87.3)	
Mean (SD)	61.7 (9.1)	60.1 (9.5)	62.9 (8.6)	< .0001
Education				
High school or less	607 (40.2)	231 (36.6)	376 (42.8)	.046
1–3 years of college	414 (27.4)	179 (28.4)	235 (26.7)	
College or more	489 (32.4)	221 (35.0)	268 (30.5)	
Employment				.22
Not in labor force	722 (47.8)	290 (46.0)	432 (49.2)	
Working	788 (52.2)	341 (54.0)	447 (50.8)	
Family income, annual (101)				.09
≤ $30,000	417 (29.6)	188 (31.3)	229 (28.3)	
$30,001–$50,000	389 (27.6)	177 (29.4)	212 (26.2)	
$50,001–$100,000	424 (30.1)	160 (26.6)	264 (32.7)	
>$100,000	179 (12.7)	76 (12.6)	103 (12.8)	
Marital status				< .0001
Married/living with partner	1078 (71.4)	417 (66.1)	661 (75.2)	
Divorced, separated, widowed	342 (22.6)	153 (24.2)	189 (21.5)	
Never married	90 (6.0)	61 (9.7)	29 (3.3)	
Race/ethnicity (6)				
Hispanic	11 (0.7)	5 (0.8)	6 (0.7)	.79
Non-Hispanic Black	37 (2.5)	26 (4.1)	11 (1.3)	.0004
Non-Hispanic White	1437 (95.6)	595 (94.6)	842 (96.2)	
Other Non-Hispanic	19 (1.3)	3 (0.5)	16 (1.8)	.024
Work schedule (723)				.32
Regular daytime shift	650 (82.6)	286 (84.1)	364 (81.4)	
Other shift	137 (17.4)	54 (15.9)	83 (18.6)	
Dietary habits				
Drink alcoholic beverages, days/week (18)				
0	706 (47.3)	290 (46.5)	416 (47.9)	.07
<1	405 (27.1)	190 (30.4)	215 (24.8)	
1–2.9	183 (12.3)	70 (11.2)	113 (13.0)	
3 or more	198 (13.3)	74 (11.9)	124 (14.3)	
Protein shake consumption (5)				.02
None	1328 (88.2)	542 (86.0)	786 (89.8)	
Less than 2 per week	73 (4.8)	31 (4.9)	42 (4.8)	
2 per week or more	104 (6.9)	57 (9.0)	47 (5.4)	
Whole milk consumption				.038
5 or more times per week	75 (5.0)	40 (6.3)	35 (4.0)	
Less than 5 times per week	1435 (95.0)	591 (94.7)	844 (96.0)	
Physical activity and weight				
Body mass index, year before diagnosis (20)				
Mean (SD)	32.0 (8.9)	35.7 (9.9)	29.3 (7.0)	< .0001

(Continued)

Table 1. (Continued)

Characteristic (N missing)	Number (Percent)	Cases (N = 631)	Controls (N = 879)	p-value**
MET-hours/week, total (8)				
Mean (SD)	38.2 (58.9)	32.5 (51.5)	42.3 (63.4)	.001
Weight gain since age 25 (23)				
Mean (SD)	20.5 (18.3)	25.0 (20.4)	17.2 (15.9)	< .0001
Smoking history				
Smoke cigarettes (3)				.003
Never	946 (62.8)	413 (65.7)	533 (60.7)	
Former	418 (27.7)	175 (27.8)	243 (27.7)	
Current	143 (9.5)	41 (6.5)	102 (11.6)	
Smoking, total pack-years (6)				
Mean for ever-smokers (SD)	9.0 (18.8)	7.6 (13.5)	10.9 (16.7)	.0002
Medical history				
Breast cancer (3)				.0002
Yes	75 (5.0)	16 (2.5)	59 (6.7)	
No	1432 (95.0)	614 (97.5)	818 (93.3)	
Diabetes (4)				< .0001
Yes	291 (19.3)	155 (24.7)	136 (15.5)	
No	1215 (80.7)	476 (75.3)	742 (84.5)	
Endometrial cancer in first degree relative (67)				.0001
Yes	48 (3.3)	33 (5.5)	15 (1.8)	
No	1395 (96.7)	570 (94.5)	825 (98.2)	
Endometriosis (31)				.07
Yes	250 (16.9)	116 (19.0)	134 (15.4)	
No	1229 (83.1)	494 (81.0)	735 (84.6)	
Hypertension (8)				.008
Yes	799 (53.2)	359 (57.3)	440 (50.3)	
No	703 (46.8)	268 (42.7)	435 (49.7)	
Ovarian cancer (10)				< .0001
Yes	46 (3.1)	35 (5.6)	11 (1.3)	
No	1454 (96.9)	590 (94.4)	864 (98.7)	
Medications and treatments				
Birth control, years used (7)***				
Mean (SD)	5.8 (7.2)	4.8 (6.0)	6.5 (7.9)	< .0001
Hormone replacement therapy, years used (22)				
Mean (SD)	3.2 (7.1)	2.0 (5.6)	4.1 (7.9)	< .0001
Reproductive history				
Age of menarche 11 or earlier				.004
Yes	330 (21.8)	161 (25.5)	169 (19.2)	
No	1180 (78.2)	470 (74.5)	710 (80.8)	
Menopause status, year before diagnosis (6)				< .0001
Premenopausal	220 (14.6)	149 (23.6)	71 (8.1)	
Postmenopausal	1284 (85.0)	481 (76.2)	803 (91.4)	

*9 controls who reported a diagnosis of endometrial cancer were excluded. Variables refer to the year prior to diagnosis of endometrial cancer unless otherwise specified.

**P-value for chi-square analysis except for means, which were compared with a t-test. Fisher's Exact test was used for race/ethnicity where there were low numbers of participants in one category.

***Birth control refers to methods that release hormones, such as birth control pills, injections, patches, progestogen implants (Norplant), progestin-releasing intrauterine devices, or vaginal rings.

creatinine-adjusted cadmium concentration between cases and controls was not statistically significant (p = .101).

After multivariable adjustment, a doubling of urine cadmium increased the endometrial cancer risk by 22% (Table 2; odds ratio (OR) = 1.22, 95% confidence interval (CI): 1.03–1.44; p-value = .02) No substantive changes were observed in any parameter estimates when only post-menopausal women were included (S1 Table). A similarly elevated endometrial risk for cadmium exposure was also observed among those diagnosed with Type I endometrial carcinoma (n = 550) compared to controls (OR: 1.21 95% CI 1.03–1.47). Women diagnosed with endometrial carcinoma who were also 50 pounds over ideal weight had an increased endometrial cancer risk for cadmium exposure (S2 Table). When we re-ran the model and did not include current smoking, cadmium concentration remained statistically significant (OR: 1.19, 95% CI: 1.01–1.41) (S3 Table). A similarly elevated endometrial risk for cadmium exposure was also observed when we re-ran the model and include two additional established risk factors, age of menarche and number of live births, (S4 Table). We also re-ran the model and included creatinine concentration as a separate covariant and base-2 logarithm of unadjusted cadmium concentration. Cadmium concentration remained statistically significant (S5 Table).

Discussion

In this population-based case-control study of Midwestern U.S. women, we found a statistically significant positive association between urine cadmium levels and endometrial cancer

Table 2. Multivariable conditional logistic regression of risk factors for endometrial cancer.

Characteristic	Base model with all participants		Model with adjusted Cd* and inverse probability weights	
	Odds ratio (95% CI)	P-value	Odds ratio (95% CI)	P-value
Non-Hispanic African-American race	3.07 (1.33, 7.10)	.0085	4.91 (1.88, 12.82)	.0012
Marital status (reference never married)				
Married, living with partner	0.47 (0.27, 0.82)	.0077	0.36 (0.17, 0.77)	.0088
Divorced, separated, widowed	0.58 (0.32, 1.06)	.0791	0.44 (0.20, 1.00)	.0497
Body Mass Index at diagnosis[†]	1.08 (1.06, 1.10)	< .0001	1.09 (1.06, 1.11)	< .0001
History of trying to lose weight	1.75 (1.18, 2.60)	.0058	1.59 (0.99, 2.57)	.0573
Current smoker	0.52 (0.32, 0.85)	.0086	0.52 (0.28, 0.96)	.0381
Cigarette smoking (10 pack-years)	0.94 (0.87, 1.01)	.0864	0.88 (0.80, 0.97)	.0086
History of endometriosis	1.64 (1.17, 2.29)	.0037	1.66 (1.10, 2.50)	.0151
History of breast cancer	0.47 (0.25, 0.88)	.0182	0.39 (0.16, 0.93)	.0337
History of ovarian cancer	4.27 (1.89, 9.69)	.0005	9.99 (2.67, 37.38)	.0006
History of uterine fibroids	0.77 (0.57, 1.03)	.0797	0.71 (0.50, 1.00)	.0508
Endometrial cancer in first degree relative	2.70 (1.32, 5.52)	.0065	3.31 (1.37, 8.01)	.0079
Oral contraceptive use (5 years)	0.86 (0.79, 0.95)	.0014	0.88 (0.79, 0.97)	.0138
Unopposed estrogen use (5 years)	0.64 (0.53, 0.77)	< .0001	0.67 (0.53, 0.84)	.0006
Menopause at age 56 or later	1.90 (1.33, 2.70)	.0004	1.70 (1.13, 2.56)	.0113
Post-menopausal at diagnosis	0.43 (0.26, 0.70)	.0009	0.33 (0.21, 0.52)	< .0001
Protein shake consumption, days/week	1.12 (1.01, 1.24)	.0276	1.20 (1.04, 1.39)	.0133
Whole milk consumption, ≥ 5 days/week	1.96 (1.13, 3.42)	.0173	2.57 (1.28, 5.15)	.0078
Base-2 logarithm of adjusted cadmium concentration			1.22 (1.03, 1.44)	.0212

CI = confidence interval

*Cadmium concentration adjusted by urine concentration of creatinine

[†]Body mass index is weight in kilograms divided by (height in meters)^2

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risk. Specifically, a 22% increased risk of endometrial cancer was associated with doubling cadmium exposure. Our confidence in the findings is strengthened by our large number of cases, evaluation of those who declined to participate at various points in our study, use of population-based controls that were age-matched to cases, inclusion of a reliability study, the use of urine as the biomarker to ascertain lifetime cadmium exposure, additional analyses to account for potential bias, and using an established protocol for urine analysis with an additional correction factor.

To our knowledge, this is the first published report on cadmium exposure and endometrial cancer risk using urine as a biomarker for cadmium measurement. Four other cohort studies conducted in Japan, Denmark, Sweden, and the United States have reported on this association; all have estimated cadmium exposure using food frequency questionnaires with mixed results. Eriksen et al reported a null finding for cadmium exposure and risk of endometrial cancer (192 endometrial cancer cases over 13 year period) using a Danish population-based prospective study as did Sawada in the Japan Public Health Center-based Prospective Study (75 endometrial cancer cases over 9 year period) [20,34]. The Women's Health Initiative has also reported a null finding on cadmium exposure and endometrial cancer (1198 endometrial cancer cases over 10 year period) [21]. In contrast, Akesson et al reported an increased endometrial cancer risk (relative risk [RR]: 1.39; 95% CI, 1.04–1.86) among the Swedish Mammography Cohort comprised of postmenopausal women (378 endometrial cancer cases over 16 year period) [1]. In a meta-analysis of dietary cadmium intake and cancer risk, Cho reported an increase cancer risk among studies with Western populations (RR: 1.15; 95% CI 1.08–1.23) particularly for hormone-related cancers (prostate, breast and endometrial) though only two of the aforementioned four cohort studies were included in Cho's meta-analysis [22]. One recent cancer mortality study using NHANES III data (1988–1994) and creatinine adjusted urinary cadmium found a suggestion of an increased risk for uterine cancer among those with highest level of urinary Cd (n = 7 deaths, mean follow-up 14 years; adjusted hazard ratio (aHR): 1.03; 95% CI 0.23–4.62 and aHR per 2-fold urinary Cd: 1.63; 95% CI 1.06–2.51) [35].

After humans ingest or inhale cadmium, the body excretes only a very small fraction and efficiently retains the rest [7]. Among the potential matrices used to measure cadmium (blood, nail, hair, urine), urine specimens more closely reflect lifetime cadmium exposure than the other matrices [11]. Although not without criticism [36], using creatinine-adjusted values in the field of toxicology for spot urine samples, such as in this study, is common and several papers support this analytic technique [37]. For example, the Jaffé reaction may cause overestimation of creatinine, as mentioned in National Health and Nutrition Examination material [38]. Barr et al suggest using urinary creatinine as an independent variable which allows for urinary dilution and demographic difference adjustment [39]. When we included the base-2 logarithm of unadjusted cadmium concentration and creatinine concentration in our model, results were essentially unchanged from those reported in Table 2. Our unadjusted geometric mean of cadmium was slightly higher (0.32, 95% CI: 0.31–0.34 μg/l) than those reported from 1999–2010 NHANES for women age 20–85 years (0.25, 95% CI: 0.24–0.26 μg/l), though this may reflect a different age structure between these two samples. As noted by Adams and Newcomb, urinary cadmium values for those aged 60–69 years was 2.7 fold greater compared to those 20–29 years old [40].

Cadmium levels are related to level of smoking. Heavy smokers may have twice as much cadmium, and moderate smokers' cadmium burden may increase by approximately sixty percent compared to non-smokers [9]. Former smokers have a cadmium body burden that is intermediate [24,41]. Smoking has been shown to decrease the risk of endometrial cancer, likely through endometrial atrophy [42]. However, Brinton and others suggest that smoking in conjunction with use of exogenous estrogens significantly multiplies the risk of developing

endometrial cancer, especially in thin women [43]. Unfortunately we did not have a sufficient number of thin smokers to confirm this finding and only 6.5% of cases were smokers.

With our extensive survey we were able to consider numerous variables that are known or suspected to increase the risk of endometrial cancer in the logistic regression models. Well documented endometrial cancer risk factors include late menopause, early menarche, nulliparity, and obesity [14]. Among these risk factors, obesity is strongly associated with an increased endometrial cancer risk [43]. Davies et al suggests this is especially true for those who are 50 pounds or heavier than their ideal weight [44]. Additional risk factors that may be associated with endometrial cancer risk include hypertension [45], family history of cancers (breast, endometrial, ovarian, and/or Lynch's syndrome) [46], history of endometriosis [47], sleep [48], irregular work schedule [49], uterine fibroids [50], alcohol consumption [51], and dietary choices [52], such as milk consumption [53]. We explored the risk of endometrial cancer and consumption of protein shakes. Besides the typical consumption of milk as part of the protein shake, undeclared anabolic androgenic steroids are found in up to 15% of commercially available non-hormonal supplements (i.e., protein drinks) [54]. Though no data are available on this consumption and endometrial cancer, one risk factor of PCOS relates to dysfunction of androgen receptors leading to hyperandrogenism and an increased risk of endometrial cancer [55,56]. Protective factors may be physical activity [57] and oral contraceptive use [58]. Among these risk factors, we found obesity, late age of menopause, selected dietary choices (milk and protein shakes), history of ovarian cancer or endometriosis, and family history of endometrial cancer as characteristics that increased the risk of endometrial cancer. In our analysis, years of oral contraceptive use, years of unopposed estrogen use, history of breast cancer, smoking and being married were protective factors.

Several limitations should be considered in evaluating our results. One limitation was the low participation proportion of women diagnosed with endometrial cancer. Obtaining consent was a two-stage process. Each cancer registry approached eligible cancer cases and required written consent to pass their names to the HEER study. The second stage involved verbal consent upon contact by telephone by the HEER study team. Only 25%-44% of the women agreed to let their respective cancer registry pass their names onto HEER for enrollment. The second stage participation proportion was 89% of the eligible cases; another 1% who declined to participate answered a few questions to obtain a few details. Those not consenting at stage one were more likely to be married or living with partner while those opting to not enroll at stage two were less likely to be married or living with partner. Differences were also observed in racial composition. Those not consenting to pass their names were more likely to be Black, but no difference was observed in declining to enrollment by race. Proportion of tumor grade I and II and age of diagnoses was similar at both stage one and two among the two groups—those consenting and those declining to participate. Among the controls, our participation proportion was 28%. Although we assessed some characteristics between the two groups at the time of interview (n = 203) in our refusal sub-study, we cannot rule out the possibility of selection bias.

As with any case-control study, the risk of recall bias is also a limitation. All data except information about urinary cadmium measurement and tumor characteristics for cases ere self-reported. However, of the few questions we re-asked of participants, the concordance between the two time periods was quite good. Nevertheless, we cannot eliminate the possibility of recall bias.

In conclusion, our results provide evidence that cadmium may increase the risk of endometrial cancer, possibly through estrogenic effects. Further studies that employ urinary cadmium as the biomarker are necessary given the weak association with estimated cadmium from dietary sources. A comprehensive list of suspected and known risk factors should also be collected to fully adjust the regression models.

Supporting information

S1 Table. Multivariable conditional logistic regression of risk factors for endometrial cancer, excluding premenopausal women from the analysis.
(DOCX)

S2 Table. Multivariable conditional logistic regression of risk factors for endometrial cancer, including weight at least 50 pounds above ideal weight in the model.
(DOCX)

S3 Table. Multivariable conditional logistic regression of risk factors for endometrial cancer, excluding current smoking status from model.
(DOCX)

S4 Table. Multivariable conditional logistic regression of risk factors for endometrial cancer, including age at menarche and number of live births.
(DOCX)

S5 Table. Multivariable conditional logistic regression of risk factors for endometrial cancer, including unadjusted cadmium concentration and creatinine concentration.
(DOCX)

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Author Contributions

Conceptualization: JM JDR.

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