March 31, 2012

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Dear Dr. Howard:

We are writing in response to your letter of October 5, 2011 requesting advice from the World Trade Center (WTC) Health Program Scientific/Technical Advisory Committee (STAC) on whether to add cancer, or a certain type of cancer, to the List of World Trade Center (WTC)-Related Health Conditions in the James Zadroga Act ("List").

The STAC has reviewed available information on cancer outcomes that may be associated with the exposures resulting from the September 11, 2001 terrorist attacks, and believes that exposures resulting from the collapse of the buildings and high-temperature fires are likely to increase the probability of developing some cancers. This conclusion is based primarily on the presence of approximately 70 known and potential carcinogens in the smoke, dust, volatile and semi-volatile contaminants identified at the World Trade Center site (Table 1). Fifteen of these substances are classified by the International Agency for Research on Cancer (IARC) as known to cause cancer in humans, and 37 are classified by the National Toxicology Program (NTP) as reasonably anticipated to cause cancer in humans; others are classified by IARC as probable and possible carcinogens. Many of these carcinogens are genotoxic and it is therefore assumed that any level of exposure carries some risk.

Exposure data are extremely limited. No data were collected in the first 4 days after the attacks, when the highest levels of air contaminants occured, and the variety of samples taken on or after September 16, 2001 are insufficient to provide quantitative estimates of exposure on an individual or area level. However, the committee considers that the high prevalence of acute symptoms and chronic conditions observed in large numbers of rescue, recovery, clean up and restoration workers and survivors, as well as qualitative descriptions of exposure conditions in downtown Manhattan, represent highly credible evidence that significant toxic exposures occurred. Furthermore, the salient biological reaction that underlies many currently recognized WTC health conditions—persistent inflammation—is now believed to be an important mechanism underlying cancer through generating DNA-reactive substances, increasing cell turnover, and releasing biologically active substances that promote tumor

growth, invasion and metastasis. Given that cancer latencies for solid tumors average 20 years or more, it is noteworthy that the published FDNY study of fire fighters showed a statistically significant excess in all-site cancer with only 7 years of follow-up.

The committee deliberated on whether to designate all cancers as WTC-related conditions or to list only cancers with the strongest evidence. Some members proposed to include all cancers based on the incomplete and limited epidemiological data available to identify specific cancers, and others argued for the alternative of listing specific cancers based on best available evidence. The committee agreed to proceed by generating a list of cancers potentially related to WTC exposures based on evidence from three sources described below:

(1) cancers with *limited* or *sufficient* evidence in humans based on the International Agency for Research (IARC) Monographs reviews for carcinogens present at the WTC site (Table 2);

(2) cancers arising in regions of the respiratory and digestive tracts where WTC-related inflammatory conditions have been documented (Table 3); and

(3) cancers for which epidemiologic studies have found some evidence of increased risk in WTC responder and survivor populations (Table 4).

The organ sites identified from any of the three sources are listed in Table 4. The committee reviewed the evidence summarized for each organ site or site grouping in Table 4 to develop its recommendation on which sites should be listed as WTC-related conditions. In addition, the committee considered the evidence for inclusion of several sites that were not identified from Table 4.

The committee recommends listing the following site groupings and sites as WTC-related conditions based on the strength of the evidence summarized in Table 4 and/or additional information provided below.

- The committee recommends that malignant neoplasms of the respiratory system (including nose, nasal cavity and middle ear (ICD-O-3 site codes C300-C301, C310-319), larynx C320-C329), lung and bronchus (CC340-C349), pleura (C384), trachea, mediastinum and other respiratory organs (C339, C381-C383, C388, C390, C398, C399)) be listed as WTC-related conditions. These cancers are associated with exposure to many carcinogenic agents of concern at the WTC, including arsenic, asbestos, beryllium, cadmium, chromium, nickel, silica dust and soot. The respiratory tract is also the major site for acute and chronic toxicity resulting from WTC-exposures, including chronic nasopharyngitis, upper airway hyperreactivity, chronic laryngitis, interstitial lung disease, “chronic respiratory disorder – fumes/vapors”, reactive airways disease syndrome (RADS) and chronic cough syndrome. Although the Zeig-Owens study[1] did not find evidence for an increased risk of lung or

other respiratory cancers among FDNY firefighters, both internal and external comparisons may have been affected by greater declines in smoking among WTC-exposed firefighters (due in part to their respiratory symptoms) than unexposed firefighters or the general public. Commendably, in 2002 a joint labor-management initiative offered a comprehensive voluntary smoking cessation program free of charge to FDNY smokers and family members[2]. Smoking cessation reduces lung cancer rates within 5–10 years after quitting. Thus, any increased risk of lung cancer associated with WTC exposures may have been obscured by lower rates of smoking-related lung cancer.

- The committee recommends that certain cancers of the digestive system, including esophagus (C150-C159), stomach (CC160-C169), colon and rectum (C180-189, C260, C199, C209), liver and intrahepatic bile duct (C220-CC221), retroperitoneum, peritoneum, omentum and mesentery (C480-C482, C488) be listed as WTC-related conditions. Esophageal cancer is associated with tetrachloroethylene, stomach cancer is associated with asbestos and inorganic lead compounds, and colorectal cancer is associated with asbestos (Table 4). Cancer of the liver has been associated with vinyl chloride, arsenic and inorganic arsenic compounds, polychlorinated biphenyls, and trichloroethylene (Table 4). Gastrointestinal reflux disease (GERD) is associated with cancer of the esophagus, especially if it progresses to Barrett esophagus. Since cancer of the distal esophagus, gastroesophageal junction and gastric cardia share common risk factors, Table 4 shows GERD as a WTC-related condition for stomach as well as esophageal cancer. The Zeig-Owens study[1] found evidence of an increased risk of stomach (including gastro-esophageal junction) and colorectal cancer among FDNY firefighters.
- The committee recommends that cancers of the oral cavity and pharynx, including lip (C000-C009), tongue (C019-C029), salivary gland (C079-C089), floor of mouth (C040-C049), gum and other mouth (C030-C039, C050-C059, C060-C069), nasopharynx (C110-C119), tonsil (C090-C099), oropharynx (C100-C109), hypopharynx (C129, C130-C139) and other oral cavity and pharynx (C140-C148) be listed as WTC-related conditions. IARC has found *limited* evidence that asbestos causes pharyngeal cancer in humans and *sufficient* evidence that formaldehyde causes cancer of the nasopharynx. The lip, oral cavity and pharynx are areas with high potential for direct exposure to toxic materials through hand-to-mouth contact.
- The committee recommends that soft tissue sarcomas (C380, C470-C479, C490-C499) be listed as WTC-related conditions. IARC has found *limited* evidence for increased risk of soft tissue sarcoma associated with exposure to polychorophenols and their sodium salts and 2,3,7,8-TCDD. Soft tissue

sarcoma rates are very low in the general population (age-adjusted incidence rate approximately 3 per 100,000) and therefore excesses are difficult to detect in epidemiologic studies.

- The committee recommends that melanoma (C440-449) and non-melanoma skin cancers (C440-C449), including scrotal cancer (C632), be listed as WTC-related conditions. According to IARC, skin cancer is associated with exposure to arsenic and inorganic arsenic compounds and soot (Table 4). The Zeig-Owens study[1] found a statistically significant increase in melanoma among exposed firefighters compared to the general population; the Standardized Incidence Ratio (SIR) was slightly larger but not significant when compared to non-exposed firefighters. No adjustment for surveillance bias was reported for malignant melanoma, although early detection through medical surveillance is likely.
- The committee recommends that mesothelioma (ICD-O-3 histology 9050-9055) be listed as WTC-related conditions. Asbestos exposure is the only known cause of mesothelioma, and mesotheliomas have been documented in association with very low levels of community or household contact with asbestos. Mesothelioma rates are very low in the general population (age-adjusted incidence rate approximately 1 per 100,000), and may have exceptionally long latency—perhaps as much as 40 years—making excesses difficult to detect in epidemiologic studies.
- The committee recommends that cancer of the ovary (C569) be listed as a WTC-related condition. IARC has found *sufficient* evidence that asbestos exposure causes ovarian cancer. The incidence of ovarian cancer is relatively low (age-adjusted incidence rate approximately 6 per 100,000 women) and therefore difficult to detect in epidemiologic studies.
- The committee recommends that cancers of the urinary tract, including urinary bladder (C670-679), kidney and renal pelvis (C649, C659), ureter (C669), and other urinary organs (C680-C689), be listed as WTC-related conditions. IARC found *limited* evidence that exposure to "arsenic and inorganic arsenic compounds" and "cadmium and cadmium compounds" causes kidney cancer, *sufficient* evidence that arsenic and inorganic arsenic compounds" cause cancer of the urinary bladder, and *limited* evidence that diesel engine exhaust and soot cause cancer of the urinary bladder. Transitional cell cancers of the renal pelvis, ureter and urinary bladder have been associated with a number of occupational and environmental exposures.
- The committee recommends that cancer of the eye and orbit (C690-C699) be listed as a WTC-related condition. Eye injuries were among the top three conditions treated formally in the first few days after 9/11[3] and, including informal, ad hoc eye irrigations on-site, eye irritation by foreign bodies were by far the most common acute treatments. Including cancer of the eye and orbit is

consistent with including lip, skin and respiratory and digestive tract sites with direct dust and fume contact and irritation/inflammation related to WTC exposures.

- The committee recommends that thyroid cancer (C739) be listed as a WTC-related condition. Thyroid cancer has not been associated with any of the agents known to be present at the WTC, and the primary evidence for an excess in risk comes from the Zeig-Owens study[1]. In that study, 17 thyroid cancers were observed and 6 expected based on national rates, yielding a statistically significant SIR of 3.07. The SIR was 5.21 and statistically significant compared with unexposed firefighters, and was 2.17 and significant after a two-year lag was applied. The magnitude of the SIR for thyroid cancer was relatively large, although the significance of this finding is tempered by the possibility that a 2-year lag may not fully account for medical surveillance bias.
- The committee recommends that lymphoma, leukemia and myeloma (see following link for ICDO-3 site and histology codes: http://seer.cancer.gov/siterecode/icdo3_d01272003/) be listed as WTC-related conditions. All lymphatic and hematopoietic cancers (LHC's) are combined in this document because of variation in how these cancers have been classified and grouped in epidemiologic studies, inaccuracy of death certificate diagnosis for these cancers, and changes in clinical nomenclature over time. Various LHC's have been associated in humans with exposure to benzene, 1,3-butadiene, formaldehyde, polychlorophenols or their sodium salts (combined exposures), styrene and 2,3,7,8-tetrachlorodibenzo-para-dioxin (Table 4). In addition, the Zeig-Owens study found a statistically significant increase in non-Hodgkin lymphoma which was only modestly attenuated when adjusted for surveillance bias. Case–series reports have noted that a potential excess of multiple myeloma among WTC responders[4]. LHC's are associated with a variety of carcinogenic exposures; elevated rates of some LHC's have been observed in atomic bomb survivors as well as cancer patients treated with radiation and some forms of chemotherapy. The average latency for LHC's after radiation or chemical exposure is generally shorter (< 10 years) than for solid tumors (≥ 20 years). Many leukemogens, including benzene, radiation and chemotherapy agents are associated with bone marrow toxicity at high doses. Some LHC's are associated with immunosuppression (such as AIDS-related lymphomas) while others appear to be related to immune stimulation, including inflammation[5]. It is increasingly recognized that many LHC's have pre-clinical phases, and the STAC recommends that the pre-malignant and myelodysplastic diseases be included as WTC-related conditions as well.
- The committee recommends that childhood cancers (all cancers diagnosed in persons less than 20 years old) be listed as WTC-related conditions. The unique vulnerability of children to synthetic

chemicals commonly found in the environment has been documented in the landmark 1993 US National Academy of Sciences report[6]. Children drink more water, breathe more air and eat more food per pound, and have higher exposures than adults[7,8]. In addition, childhood cancers are rare (total incidence of 15 per 100,000 children age 0-19) and excess risks are not likely to be detectable in the small number of children being followed in epidemiologic studies.

- The committee recommends that rare cancers be listed as WTC-related conditions. There is no uniform definition of a rare cancer, and the committee recommends that definitions be based on age-specific incidence rates by gender, decade of age, site and histology. Site/histology combinations to be considered as unique cancers should be determined *a priori* in consultation with appropriate experts.
- The committee recommends that breast cancer (C500-509) be added to the list of covered conditions. There is evidence of PCB exposures to WTC responders and survivors based on air samples[9], window film samples[10] and one biomonitoring study[11]. Studies have linked total and congener-specific PCB levels in serum and adipose tissue with breast cancer, although evidence has been conflicting[12-17]. PCBs and some other substances at the WTC site are endocrine disruptors. Breast cancer risks are highly related to hormonal factors, including endogenous and exogenous estrogens, and could plausibly be affected by endocrine disruptors. A recent study found that PCBS enhanced the metastatic properties of breast cancer cells by activating rho-associated kinase[18]. Shiftwork involving circadian rhythm disruption has been classified by IARC as probably carcinogenic to humans, based in part on epidemiologic studies associating shiftwork with increased risks of breast cancer[19]. Both shiftwork and long shifts were common for workers involved in rescue, recovery, clean up, restoration and other activities at the WTC site. Finally, the Committee recognizes that the main source of data used to identify sites of cancer that might be associated with WTC exposures is studies of industrial workers, which have often been limited to men because so few women worked in these occupations. Thus, the opportunity to find evidence for associations between occupational and environmental exposures and female breast cancer has been very limited.

The Committee recognizes that additional epidemiologic studies will soon become available, and recommends that as they do become available, their findings be reviewed and modifications made to the list as appropriate.

The Committee also recommends that, in addition to treatment for the listed cancer sites, the WTC Health Program provides funding and guidelines for medical screening and early detection based

on a review of evidence regarding the risks and benefits of the relevant screening and early detection modalities and appropriate counseling for individuals offered such screening.

With respect to the use of the IARC data to identify potential cancer sites in humans, the committee wishes to emphasize that the body of evidence regarding carcinogenicity of substances present in WTC dusts and smoke is not limited to those considered by IARC to have *sufficient* or *limited* evidence of carcinogenicity in humans. Many substances present in WTC dusts and smoke have been classified by IARC as known, probable or possible carcinogens based on animal studies and mechanistic data, and the committee believes that such evidence is highly predictive for human carcinogenicity. However, because there is limited concordance between specific cancer sites affected in humans and in animals, only those substances classified based on human data are informative regarding organ sites of carcinogenicity in humans.

In addition to the evidence considered by the committee to identify potential WTC-related cancers, arguments in favor of listing cancer as a WTC-related condition include the presence of multiple exposures and mixtures with the potential to act synergistically and to produce unexpected health effects, the major gaps in the data with respect to the range and levels of carcinogens, the potential for heterogeneous exposures and hot spots representing exceptionally high or unique exposures both on the WTC site and in surrounding communities, the potential for bioaccumulation of some of the compounds, limitations of testing for carcinogenicity of many of the 287 agents and chemical groups cited in the first NIOSH Periodic Review, and the large volume of toxic materials present in the WTC towers. Although acknowledging some lack of certainty in the evidence for targeting specific organs or organ site groupings as WTC-related, the majority of the committee agreed that recommending the specified cancer sites and site groupings was based on a sound scientific rationale and the best evidence available to date.

We appreciate the opportunity to consider this important issue and would be happy to provide clarification or respond to any questions you may have.

Sincerely,

Elizabeth M. Ward, PhD
Chair, World Trade Center Scientific Advisory Committee

Supporting documentation for the Committee's recommendation

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1. Evidence regarding carcinogenic exposures

The collapse of the World Trade Center produced a dense dust and smoke cloud containing gypsum from wallboard, plastics, cement, fibrous glass, asbestos insulation, metals, and volatile and semi-volatile organic compounds and other products of high-temperature combustion from burning jet fuel, heating oil, transformer oil and gasoline [20,21]. Individuals caught in the dust cloud on 9/11 and working on or near the site in the days immediately following the attack experienced intense acute exposures to a mixture of substances whose concentration and composition was not measured and will never be fully known. However, it is known that the dust was highly alkaline, due to pulverized cement and other construction materials, and contained numerous particles, fibers and glass shards, resulting in acute eye, nose and throat irritation, leading rapidly to what came to be known as WTC cough. Smoke from fires that persisted into December 2011 contained polycyclic aromatic hydrocarbons, metals, organic chemicals and many other known or potential carcinogens. Heavy equipment and trucks contributed diesel emissions, and there was repeated resuspension of sediment and dust during the subsequent 10-month demolition and cleanup process. Although levels of airborne contaminants were not measured in the first four days, the high prevalence of acute and chronic respiratory conditions in rescue, recovery, clean-up and restoration workers provides evidence for significant exposure levels and toxicity[22]. Although some of the dust and smoke was carried away into higher levels of the atmosphere, significant amounts settled in surrounding streets, residences and office buildings. Dusts entered buildings through broken windows, open windows, and air intakes, and highly respirable particles entered through closed windows. Many residents returned to homes that were highly contaminated and/or not adequately remediated. Area residents and workers exposed to WTC dust have also been affected by chronic respiratory diseases, including newly diagnosed asthma and asthma exacerbation[23].

Members of the STAC and individuals providing public comments have noted that exposures resulting from collapse of the World Trade Center were unlike any other exposures in intensity and variety in history. We believe that to be the case, both because of the enormous forces that pulverized the buildings and their contents and the combustion products generated by the high-temperature fires. Compounding the uniqueness of the exposures is the absence of any data on air contaminant levels or the composition of the dust and fumes in the first four days after the attack, and the presence of multiple and complex exposures. However, while acknowledging these unknown and unknowable factors, we believe that it is possible to make some judgments about the potential increased risks of developing some cancers based on the substances known to have been present. This information can be

gleaned from a variety of sources, including peer-reviewed literature, government reports and unpublished reports from private laboratories and contractors.

Based on these reports, the committee believes that both responder populations and area residents and workers had potential for significant exposures to toxic and carcinogenic components of WTC dust and smoke. Factors that influence the intensity of exposures among individuals engaged in rescue, recovery, demolition, debris cleanup and/or other related services include the time and date of arrival at the WTC site and other areas where WTC materials were transported or stored, total days and hours worked, specific jobs performed, breathing rates, work locations, particularly work in areas of smoldering fires, and availability and use of personal protective equipment and other controls. Especially in the early period of rescue and recovery, many individuals worked long shifts without adequate respiratory protection and in clothing saturated with dust from the debris, likely experiencing significant exposures through inhalation, ingestion, and skin absorption. Although these exposures may be considered relatively brief compared to longer exposures typically associated with occupational cancer, many individuals had high-intensity exposures, especially in the early weeks, and many continued to work in the area for weeks and months. Numerous animal studies provide evidence that brief exposures to carcinogens can cause cancer. Evaluation of the Single-Exposure Carcinogen Database containing 5576 studies involving 800 chemicals from 2000 articles showed that in 4271 of the studies, a single dose of an agent administered by multiple routes of exposure caused tumors to develop in many different animal models. In addition to PAHs, many of the tested chemicals are environmentally relevant and are on various pollutant lists, including the IARC and NTP lists. In support of the relevance of the single-exposure carcinogen concept to human cancer, Calabrese and Blain[24] identified published occupational studies on benzene, beryllium, aromatic amines including benzidine, and arsenic in which exposures for less than a year were implicated as the causal factor in the development of cancer. In addition, studies of second or higher order tumors among cancer survivors have shown that both radiation therapy and some forms of chemotherapy increase risk for subsequent cancers, often with shorter latency periods than observed for lower-dose, longer-duration occupational and environmental exposures [25]. Recent *in vivo* and *in vitro* studies using biomarkers of gene expression are consistent with potential increased cancer risks following relatively brief exposures to carcinogenic agents. The results of these studies indicate that the multistep process of chemical carcinogenesis can begin following exposures that range in duration from 1 to 90 days. In addition, some of the chemicals, dusts, fibers, metals and other materials with long half-lives may be retained in the lung and other body compartments for long periods after an environmental exposure.

Exposures among community residents and those working and attending school in the area also have the potential to be significant, although in many ways they may be even more difficult to categorize than those of responders. Some residents were not evacuated; some individuals returned within days of the disaster to grossly dust-contaminated homes that they cleaned themselves; others returned to homes with less visible contamination that were later found to contain high levels of asbestos and other toxic substances[26]. Many government offices are housed in buildings below Canal Street, and many workers were required to return before any decontamination or cleaning took place and without personal protective equipment. Others worked, attended school or lived near sites where debris was transported or transferred in processes that continued to generate dusts. Still others volunteered in support activities near the site as well as residing in the community. Residential, office and school building exposures have the potential to be of longer duration than those among workers at the site if the buildings and occupied spaces were not properly remediated. Longer, lower-level exposures may be a particular issue for individuals with preexisting asthma and allergies and those who are already sensitized to dust contaminants such as nickel and hexavalent chromium. Children in contaminated homes, daycare settings and schools have greater exposure potential than adults due to crawling on floors, hand-to-mouth activities and higher respiratory rates, and may also be more susceptible to mutagens and carcinogens due to growth and rapid cell turnover.

In discussing the potential that exposures to WTC dust and smoke may cause cancer, the committee focused on classes of exposure known to be present in substantial quantities in WTC dust and smoke which also have substantial evidence regarding cancer in animals and humans. These include asbestos, polycyclic aromatic hydrocarbons (PAH's), polychlorinated biphenyls, dioxins and furans, metals and volatile and semi volatile organic compounds (VOC's). In addition, we considered some contaminants present in lower quantities due to potential toxicity and/or biological persistence (polychlorinated biphenyls, dioxins and furans).

a. Asbestos

As presented by committee member Dr. John Dement, asbestos is designated as a known human carcinogen by IARC, with sufficient evidence for cancer of the larynx, lung, mesothelioma and ovary and limited evidence for cancer of the colorectum, pharynx and stomach. Bulk samples of outdoor dusts collected on September 16, 2001 on Cortland Street, Cherry Avenue, and Market Street, outside the perimeter of the WTC site, had 0.8 to 3% asbestos by weight [27]. Air concentrations of dust were estimated to be in excess of 100,000 $\mu g/m^3$ [21], and persons exposed to the dust cloud may have

experienced the equivalent of a lifetime of urban air particulate exposures [28]. The main source of asbestos was the chrysotile used to insulate the lower half of the first tower. Chrysotile fibers in the WTC dust were predominantly shorter than 5 µm and/or less than 0.3 µm in diameter, and therefore not measured in the Phase Contrast Microscopy (PCM) method used by NIOSH and OSHA for determining compliance with OSHA Permissible Exposure Limits (PELS). Dr. Dement noted that fibers < 5 µm in length also predominate in occupational settings [29] and represent the predominant exposures to workers used for cancer risk assessments. Fibers < 5 µm in length represent 90% or more of the total airborne fiber exposures in South Carolina and North Carolina asbestos textile plants, where excess risks of lung cancer and mesothelioma have been well-documented [30,31]. Selection of the PCM sampling method that did not count fibers < 5 *u*m in length was historically based on sampling reproducibility and feasibility, and not strong data demonstrating lack of toxicity of shorter fibers. Animal studies have suggested that longer fibers are more effective in producing lung cancer and mesothelioma than shorter ones, but this has not been addressed extensively in human studies which always involve mixed length fibers. Recent studies of asbestos textile workers in which size-specific exposures to chrysotile were estimated by transmission electron microscopy found all that exposures to all fiber lengths were strongly predictive of lung cancer risk with a higher risk for longer and thinner fibers [29,32].

All forms of asbestos are carcinogenic, although it appears that amphibole asbestos has the highest potency for inducing mesothelioma. Amphibole asbestos does not appear to have been present in significant quantities at the WTC site. Numerous risk assessments have been done for asbestos based on data from occupational cohorts, and there has been no documented threshold below which cancer does not occur. Additionally, the exposure metric used for occupational risk assessments is cumulative exposure, expressed as the product of exposure level by PCM and exposure duration (fiber-years), and short-term exposures to high airborne concentrations have been associated with increased cancer risk. Inhaled asbestos fibers are retained in the lung for periods of months to years and are able to migrate into the pleural and peritoneal cavity, where they induce pleural plaques and mesothelioma. The relative risk of lung cancer from exposure to asbestos and other lung carcinogens, such as tobacco smoke, is between additive and multiplicative. Case-control studies of mesothelioma have documented odds ratios in the range of 4–8 for asbestos exposures below 1 fiber years [33,34]. The risk assessment that OSHA used to set the PEL of 0.1 fibers > 5 μm in length per cm^3 as an 8-hour time-weighted average exposure found that exposures to 0.1 f/cc over a working lifetime is associated with an excess risk of 3.4 cancers per 1,000 workers.

b. Polycyclic Aromatic Hydrocarbons

As presented by committee member Dr. Glenn Talaska, carcinogenic polycyclic aromatic hydrocarbons (PAHs) are among the earliest recognized human and animal carcinogens. Carcinogenic PAHs were largely responsible for the excess of scrotal cancer observed by Dr. Percival Pott among chimney sweeps, and were subsequently documented to cause cancer when painted on the skin or lavaged into the lungs of experimental animals. PAHs are produced by combustion of wood, coal and any other carbonaceous material. PAH are important causes of occupational lung cancer among tobacco smokers, coke oven workers, aluminum workers and other occupational groups. Because PAHs are formed from combustion, they always occur in occupational and environmental settings in combination as complex mixtures and it is therefore not possible to isolate the effect of a single compound in epidemiologic studies. The carcinogenicity of specific PAHs has been evaluated by IARC based on evidence in animals and mechanistic considerations. Benzo(a)pyrene is listed by IARC in Group 1 (carcinogenic), Dibenz[a,h]anthracene is listed in Group 2A (probably carcinogenic), and Benz[a]anthracene, Benzo[b]fluoranthene and Benzo[k]fluorenthene are listed in 2B (possibly carcinogenic). PAHs are absorbed by the body and metabolized to compounds that can bind to DNA. The major metabolites of PAHs excreted in urine are the monohydroxy PAHs, which typically have relatively short biological half-lives (4.4 to 35 hours) [35]. Sources of PAH's at the WTC included the burning of about 90,000 liters of jet fuel, 500,000 liters of transformer oil, 380,000 liters of fuel oil and approximately the same amount of gasoline plus any and all burning items. Heavy machinery and power tool brought to the site added to particulate and PAH exposures.

Sampling data regarding PAH's are extremely limited; area samples were collected at the fence line beginning 9/16/2001. It was reported that PAH levels from the fires after 9/11 were among the highest ever reported from an outdoor sources[36]. Unfortunately, the samples were stationary area samples designed not to estimate exposures of workers on the pile, but the levels at or near ground level at the periphery to capture what might be leaving the site. It is documented that when area samples are not designed to capture the worst exposure case, they can underestimate personal worker exposure by from 3- to 40-fold[37,38]. The vertical velocity of the smoke from the fires at the site would be the major reason that samples anywhere from 4–6 blocks from the pile itself would be lower than the personal exposures of the workers on the pile. As the authors state in their paper, "…workers engaged in the cleanup efforts could have been exposed to much higher levels of PAHs than those in our samples and, thus, could bear higher cancer risks"[36] Indeed, another set of samples taken 13 blocks from the pile were approximately 50% lower than the average of the 3 sites at the fence line. Pliel et al.[36] also did not

report whether there were any consistent differences in PAH levels between the 3 fence line sites, which would have occurred if there were spatial differences consistent with wind patterns or absolute distance from the pile.

The analysis of PAH levels by Pliel et al.[36] in $PM_{2.5}$ was also retrospective and opportunistic. Analysis was limited completely to PAH remaining in the particulate phase captured on filters and not intended specifically for PAH analysis. Thus, any PAH in the vapor phase would not have been included in the analysis. Burstyn et al. (2002)[39] reported that the PAH in the vapor and particulate phases contributed equally to total PAH exposure in other workers.

Pliel et al. used non-linear regression to estimate the levels of PAH exposure on September 11, 2001 from the sampling data that was collected beginning September 16, 2001. They estimate that maximal exposure would have been 35 ng/m^3 [36]. Butt et al. (2004)[10] measured the PAH levels in window films from buildings that varied in distances and orientation from the ground zero pile. They reported that upwind sites greater than 2 km from the pile had levels of 6000 ng/m^3. This could be considered background. In contrast, those sites that were within 1km averaged 77,100 ng/m^3, and those within 1 km and downwind from the site averaged 130,000 ng/m^3. While these data cannot be used for exposure estimates they do give an indication of the variation due to proximity and whether or not an window was in the overall plume.

Thus, it would appear that the PAH exposure estimates taken from the area samples probably underestimated the exposure of worker s on the pile. The magnitude of the underestimation is impossible to estimate, but indications are that it could be an order of magnitude or greater.

When done appropriately, biological monitoring can be a very useful in estimating exposure. Biomonitoring integrates exposure by all routes, including the use or misuse of personal protective equipment. Biomonitoring can also be used to reconstruct exposures, provided the half-life of the biomarker and the time since the last exposure are documented. The half-life for the most widely used PAH biomarker, 1-hydroxypyrene (1HP), is effectively ~24 hours for persons without chronic exposure [40,41]. This means that 1HP largely represents the exposure of only the last 24 hours. Biological samples for PAH were also taken for exposure analysis[42]. Unfortunately these samples were obtained for 365 firefighters 22–24 days after 9/11/01. Assuming that the shape of the exposure curve estimated by Pliel et al.[36] are correct (however, as discussed above, the absolute values are likely underestimated for workers on the pile), then the 1HP levels measured are estimates of exposures that were much, much lower than the peaks that occurred 9/11–9/14. Nonetheless, the 1HP levels remained significantly increased over what was seen in firefighters who were not at the WTC site. Since more than 99.99% of

the 1HP resulting from exposures immediately after 9/11 would have been eliminated well before the samples were collected, the Edelman data cannot be used to estimate exposure for that time. Rather they will reflect the exposure during the previous 24-hour period. The other shortcoming of the Edelman paper was that there was no indication of when the samples were taken relative to the person's last exposure. In addition, there is no indication of the distribution of the data within the groups, and only the mean data are given without an idea of the variance. The important questions—namely, were there some individuals with higher exposure in the previous 24 hours and what tasks did they perform—cannot be addressed either, since this information is not provided.

There are also concerns that PAH may have been adsorbed unto particulates and form large masses in the lung from which the PAH would only be slowly absorbed into the body [43]. Unfortunately the biomonitoring data provided by Edelman et al.[42] cannot be used to determine if this possibility was in fact real, since only one sample was collected from each worker.

c. Polychlorinated biphenyls, dioxins, furans

Polychlorinated biphenyls (PCBs) were present in the transformer oil in the electrical power substation that was located in the World Trade Center. In the area air sampling results reported by Lorber et al.[9], a large number of chemically different congeners, which contain different amounts of chlorine substituted at different places in the biphenyl rings, are treated as the same material. These samples were taken to characterize outdoor inhalation exposures incurred by the "general population" defined as individuals living and working in neighborhoods surrounding GZ, and specifically did not address exposures that could have occurred to workers on the site or in indoor environments. Among the hundreds of samples analyzed for PCBs, only one sample was above 100 ng/m^3, and only three were greater than 50 ng/m^3 [9]. Air levels around GZ were said to be reduced fairly quickly to "normal" ambient urban levels of 1–8 ng/m^3. This might be expected since PCBs have an extremely low vapor pressure and dermal absorption of PCB's from contaminated surfaces is thought to be a significant route of exposure. Once absorbed, PCBs have a fairly long half-life in the body, so biological monitoring should capture the exposure. Edelman et al. [42] sampled for 31 PCB congeners 21 days after 9/11 and found that there was not a statistically significant difference between any of the mean values of firefighters on or who never entered the GZ site. On the other hand, Dalgren et al.[11] saw that certain PCB levels were markedly elevated in the sera of seven first responders compared to general population norms. For example, all seven were above the median value found in the CDC NHANES study, three were above the 75th percentile, two above the 90th and one above the 95thpercentile. For several measured congeners the 2

highest firefighters had levels above the NHANES detection limit, where 95% of the unexposed population was below it. These data indicate that PCB levels in the sera of at least some first responders were elevated relative to the general population. Dioxin-like compounds were present at elevated levels in the air immediately after 9/11/01. These compounds are formed when chlorinated plastics like PVC are burned under certain conditions of temperature, oxygen and pressure. The levels of dioxin and dioxin-like compounds (furans and various congeners) were markedly elevated in initial area samples taken at the periphery of the WTC site (Ground Zero, GZ) [9]. (Please see the discussion of PAH for the limitations of these samples to estimate exposure for those at GZ itself.) At least 6 samples taken in late September or early October yielded levels of total TCDD equivalents greater than 100 pg TEQ/m^3, with the highest levels measured being 170 pg TEQ/m^3 . These were the highest ambient levels ever recorded [9]. In comparison, typical urban ambient measurements or approximately 0.1 pgTEQ/m^3 and levels reported downwind from incinerators are on the order 1-5 pgTEQ/m^3. This would indicate substantial exposure to dioxin-like compounds. The USEPA did not find elevated levels of TCDD in house dusts. However, analyses of window films obtained from buildings at various distances from the WTC found that concentrations of 2,3,7,8-TCDD were 400 times higher in a sample from Church and Warren Street than samples taken at New York University and in Brooklyn [44].

Dioxins have relatively long half-lives in the human body; for TCDD half-life is estimated to be 7 years (MMWR, 1988). Edelman et al. (2004)[42] measured 15 dioxin-like compounds in the sera of ~350 firefighters. Only one congener was higher in the exposed firefighters compared to those who did not enter the site. The mean values were 27.8 ppt for all on site firefighters, 30.1 ppt for those present at the collapse, 26.2 ppt for those arriving after the collapse (day 1 and 2) and 30.6 ppt for those in Special Operations Command. Firefighters not at the site had an average level of 19.2 ppt. There was no increase in TCDD levels compared to controls (please see PAH discussion for the limitations of the data presented in Edelman et al., 2004). In contrast, the average levels reported in blood samples drawn approximately ten years after exposure for military personnel involved in spraying Agent Orange was 49 ppt and ranged to 313 ppt. This work reported that 20 ppt was the highest level generally seen in the general population. Again, no significant increase in TCDD levels were reported by Edelman, et al. 2004.[42,45]

d. Particulates

Particulates include non-fibrous and fibrous inorganic particles. The non-fibrous are silica, coal mine dust, and a variety of metallic and non-metallic crustal silicates. Silica (quartz) is an IARC Group 1

carcinogen based on *sufficient* evidence for cancer of the lung in humans and also causes silicosis, a non-malignant lung disease characterized by scarring and inflammation. The fibrous particles include the commercial types of asbestos, which are all known carcinogens (chrysotile, amosite, crocidlite, anthophyllite). These are all hydrated magnesium silicates, and the main non-asbestos fiber that is a known carcinogen is the fibrous zeolite erionite. Erionite is a fibrous aluminum silicate. Other fibers may contaminate commercial products and be a cause of cancer, including tremolite and possibly other fibers in vermiculite. Man-made vitreous fibers, rock wool, fibrous glass, glass shards, and other fiber-like fragments either have no association with cancer or very limited data. Air pollution epidemiological studies have shown that PM less than 2.5 microns is associated with increased mortality for lung cancer in studies of the cohort formed by the American Cancer Society[46] and studied using time-series in Metropolitan Statistical Areas with PM measurements over time, and corroborated by the Harvard six-cities study[47] followed prospectively. In addition, biomass indoor air pollution from poorly ventilated cooking stoves has been noted to increase lung cancer in women[48]. Diesel exhaust has been implicated as a cause of lung cancer in large mortality studies of railroad workers [49]and recently in non-metallic underground miners[50]. This latter cohort of more than 10,000 miners exposed to high diesel exhaust concentrations without confounding by radon had more than a 25% increase in lung cancer mortality. A subsequent case–control study corroborated this increase and differentiated the risk from cigarette smoking[45]. A small body of evidence exists on lung particulate burden based on sputum, bronchoalveolar lavage and tissue analysis, primarily from symptomatic WTC-responders. A bronchoalveolar lavage study of a firefighter who developed eosinophilic pneumonia after worked on the pile for the first two weeks after 9/11 found 305 fibers per million alveolar macrophages, including chrysotile and amosite asbestos fibers, chromium, degraded glass fibers, fly ash and many silicates[51,52]. Sputum samples obtained from 39 WTC-exposed FDNY firefighters ten months after 9/11 found a higher proportion of large and irregularly shaped particles and many more metallic elements compared to firefighters from Tel Aviv[53]. Minerologic analyses of biopsy samples from lungs of seven symptomatic responders who were exposed to WTC dust on 9/11 and 9/12 found variable amounts of sheets of aluminum and magnesium silicates, chrysotile asbestos, calcium phosphate and calcium sulfate, small shards of glass and carbon nanotubes of various sizes and lengths[54]. A study of twelve WTC-exposed patients local workers, residents and clean up workers) found opaque and bi refringent particles within macrophages, with particles containing silica, aluminum silicates, titanium dioxide, talc and metals undergoing lung biopsy[55].

e. Carcinogenic metals

As noted in Table 1 and 2, five metals measured in ETC dust and air samples are listed as known human carcinogens by IARC; all increase risk for lung cancer with other cancer sites of sufficient or limited evidence in humans varying by metal. As with other WTC exposures, varying exposure levels have been reported and monitoring was limited[9,56]. In general, however, the concentration of carcinogenic metals in settled dust and smoke samples was low compared to concentrations of non-carcinogenic metallic elements. For example, in dust samples collected at Cortland, Cherry and Market Street, concentrations of titanium and zinc were over 40 times the concentration of nickel, the most common of the carcinogenic metals measured[27]. Cahill and colleagues developed the "incinerator hypothesis" to explain the presence several carcinogenic metals in aerosol plumes in October 2011, apparently liberated from burning debris at temperatures at which they would not normally volatilize[57].

Groups at risk for metal exposures include workers at the WTC site (plume lofting was thought to protect wider areas of NYC) and responders and survivors with short-term exposure to the initial dust cloud and those with longer-term exposure to dusts in homes, schools and offices or during cleanup[58]. Some metals, such as cadmium, bioaccumulate in the body, resulting in persistent exposure from endogenous sources. Further factors raising concern for metals include the potentially large load deposited in the lungs of those in the initial WTC collapse, with uncertain impact on half-life and interaction with high dust pH.

f. Volatile organic compounds (VOCs)

As noted in Table 1, three VOCs, benzene, 1,3 butadiene and formaldehyde, are listed as known human carcinogens by IARC; all increase risk for lymphatic and hematopoietic cancer. Formaldehyde also increases risk for nasopharyngeal cancer with limited evidence for nasal cavity and paranasal sinus cancer. Hematopoetic cancers, such as leukemia, have the shortest latency of the chemically-related cancers, so it is biologically plausible that leukemias diagnosed to date in exposed WTC populations are related to 9/11. Other VOCs, such as tetrachloroethylene and trichloroethylene, are considered group 2A probable human carcinogens that impact the hematopoetic system.

Benzene, 1,3 butadiene and formaldehyde are common exposures present in combustion products. Groups with potential for exposure to these VOCs include workers on the pile and those exposed to diesel exhaust. VOCs are not persistent in environment and do not accumulate in the body.

As with other WTC exposures, varying exposure levels have been reported and monitoring was limited[9,27,59]. Benzene and 1,3-butadiene were among the 11 VOCs monitored in and near GZ to

determine if the area was safe for entry by rescue workers and firefighters [9]. These samples were mainly 4-minute samples, with a few 24-hour samples. Of the VOCs monitored, benzene levels were noted to be measureable the greatest distance from GZ, with levels approaching the ATSDR Intermediate (>14–364 days) MRL, although for a duration likely less than 45 days[9]. Descriptions of air in lower Manhattan and diesel exhaust[60] suggest that more frequent air monitoring would have indicated higher levels.

2. Mechanisms of carcinogenesis and role of inflammation

a. Overview of Carcinogenesis

As presented by Committee member Dr. Elizabeth Ward and elaborated on by Dr. Julia Quint, carcinogenesis is characterized by four stages: initiation, promotion, malignant transformation, and tumor progression. Initiation occurs when a carcinogen interacts with DNA, most often by forming a DNA adduct (a specific type of chemical bond) between the chemical carcinogen or one of its functional groups and a nucleotide in DNA, or by producing a strand break. If the cell divides before the damage is repaired, an alteration can become permanently fixed as a heritable error that will be passed on to daughter cells. Such heritable changes in DNA structure are called mutations. Many mutations have no apparent effect on gene function. However, when mutations occur in critical areas of genes that regulate cell growth, cell death, or DNA repair, they may predispose clonal expansion and accumulation of further genetic damage. Promoters are substances or processes that contribute to clonal expansion by stimulating initiated cells to replicate, forming benign tumors or hyperplastic lesions. Promotion is thought to be completely reversible. The process of promotion does not cause heritable alterations or mutations. It stimulates cell turnover, so that mutated cells can exploit their selective growth advantage and proliferate, increasing the probability that a cell will acquire additional mutations and become malignant. Unlike promotion, the end result of malignant transformation is irreversible. Tumor progression involves the further steps of local invasion and/or metastasis.

b. Mechanistic Data on Chemical Carcinogenesis and Current Uses of the Data

Advances in the scientific understanding of cancer biology and the use of bioanalytical approaches (transcriptomics, proteomics, metabolomics, and toxicogenomics) have significantly improved research on the mechanisms of chemical carcinogenesis. In addition to using established short-term tests to determine whether chemicals damage DNA or cause genotoxic effects, scientists are now determining the effects of chemicals on epigenetic mechanisms such as DNA methylation, apoptotic response, and

cell signaling pathways. This is an important advancement because altered DNA methylation in key regulatory genes may be an early and significant event in the development of human cancer[61,62].

Cancer mechanistic data and information are currently used to predict carcinogenicity, to inform the hazard identification process of cancer risk assessments, and to identify and classify agents that cause cancer. Gene expression biomarkers can distinguish between carcinogens and non-carcinogens in acute and subchronic *in vivo* and *in vitro* studies, and can predict carcinogenicity with high degrees of specificity and sensitivity[63-67]. Tests based on toxicogenomic and classification methods eventually may replace the two-year rodent cancer bioassays that currently are used to identify chemical carcinogens. In its *Guidelines for Carcinogen Risk Assessment* [68](US EPA, 2005), the US EPA emphasizes the use of mechanistic data in evaluating the modes of actions of chemicals. IARC relies on mechanistic and other relevant data, in addition to epidemiological studies and cancer bioassays, in assessing carcinogenicity. An agent is identified as carcinogenic to humans if there is sufficient evidence in animal bioassays and "strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity"[69]. The NTP, US EPA, and Germany have adopted IARC's approach of using information on mechanisms of carcinogenicity[68,70]. Information obtained from mechanistic studies also may be used to classify cancer and predict its clinical course[67,71] and to identify new cancer therapies[71]).

c. Mechanisms of Specific WTC Human Carcinogens and the Role of Inflammation

Table 5 shows established mechanistic events related to causing human cancer for seven WTC human carcinogens [72]. The data support the view that chemicals agents act through multiple mechanisms or modes of action to induce cancer. Based on the strength of existing evidence, arsenic, chromium VI compounds, nickel compounds and asbestos induce cancer through both genotoxic and epigenetic modes of action. Beryllium acts through genotoxic modes of action, and cadmium and silica act through epigenetic modes of action. Chromium VI compounds, nickel compounds, beryllium, and asbestos can damage DNA through direct interactions, whereas arsenic increases oxidative DNA damage and does not interact directly with DNA.

Inflammation is an established mechanism of asbestos and silica-induced cancer in humans (Table 5). Based on several lines of evidence, inflammation also is postulated as a mechanism for human cancers caused by exposures to arsenic, nickel compounds, chromium VI, and beryllium (IARC, 2011). Inflammation can accelerate multiple stages of carcinogenesis and is thought to be an important factor in the development of cancer. It is a normal physiologic process in response to tissue damage resulting from chemical irritation and/or wounding. Inflammation usually is a self-limited process that results in

repair of damaged tissue. However, when inflammatory processes become chronic they may lead to persistent tissue damage that can predispose to cancer development. Critical evidence for the role of inflammation in carcinogenesis comes from clinical conditions that involve both inflammation and increased cancer risk. Examples include the inflammatory diseases, ulcerative colitis and Crohn's disease, and predisposition to cancer of the large bowel; and chemical injury caused by chronic reflux of gastric acid and bile into the distal esophagus, and development of Barrett's esophagus and esophageal adenocarcinoma [73,74]. Extensive experimental data on several WTC human carcinogenic agents also provide evidence for the role of inflammation in carcinogenesis.

Studies in animals show that asbestos fibers induce macrophage activation and persistent inflammation that contribute to tissue injury and cell proliferation. In a similar manner, rats exposed to crystalline silica develop a severe, prolonged inflammatory response that is characterized by elevated neutrophils, proliferation of epithelial cells, and lung tumors. Consistent with the effects of silica in rodents, a recent study showed significant, dose-related secretion of cytokines and alterations in gene expression by human lung epithelial cells exposed for 24 hours to crystalline silica, but not to amorphous silica[75].

Arsenic-induced increases in inflammation have been reported in numerous studies[76]. The inflammatory process involves arsenic activation of the transcription factor, NF-kB[77]. In mice, low levels of arsenic promote progressive inflammatory angiogenesis, which provides a blood supply to tumors[76]. The NF-kB inflammatory signaling pathway is activated in infants born to mothers exposed to high levels of arsenic in drinking water [78]. A single exposure to particulate chromium VI results in inflammation of lung tissue in mice that persists for up to 21 days. Repetitive exposure induces chronic lung injury and an inflammatory microenvironment that is consistent with the promotion of chromium VI-induced lung cancer[79]. Evidence that inflammation may contribute to nickel-induced carcinogenesis is based on studies which show that nickel compounds cause significant increases in oxidative DNA damage with concomitant inflammation in the lungs of rats[80]. In a review of the available studies on beryllium-induced cancer, IARC concluded that "the inflammatory processes associated with the development of acute or chronic beryllium disease could plausibly contribute to the development of lung cancer by elevating the rate of cell turnover, by enhancing oxidative stress, and by altering several signaling pathways involved in cell replication"[72].

d. WTC-Related Respiratory Conditions and WTC Dust—Evidence of Inflammatory Processes

A number of studies have documented the role of inflammatory processes in WTC-related respiratory conditions. A bronchoalveolar lavage (BAL) study recovered significant quantities of fly ash, degraded fibrous glass, and asbestos fibers along with evidence for a significant inflammatory response (70% eosinophils and increased levels of interleukin-5) in one FDNY firefighter hospitalized with acute eosinophilic pneumonitis several weeks after WTC exposure[51] . Fireman et al.[53], studied induced sputum samples obtained 10 months after the attack from 39 highly exposed firefighters and found evidence for higher percentages of eosinophils and neutrophils (compared to controls) that increased with exposure intensity. A study conducted in a cohort of 801 never-smokers with normal pre-9/11 FEV(1) found that elevated serum granulocyte macrophage stimulating factor(GM-CSF) and macrophage-derived chemokine (MDC) factor soon after WTC exposure were associated with increased risk of airflow obstruction in subsequent years. Surgical lung biopsies of twelve symptomatic WTC-exposed local workers, residents, and cleanup workers enrolled in a treatment program found interstitial fibrosis, emphysematous change, and small airway abnormalities were seen. All cases had opaque and birefringent particles within macrophages, and examined particles contained silica, aluminum silicates, titanium dioxide, talc, and metals[57]. Elevated prevalence of sarcoid-like granulomatous disease has also been observed among firefighters and other first responders[81]. Granulomatous diseases arise from inflammatory processes including infection (tuberculosis) and beryllium exposure (chronic beryllium disease) [81].

Studies of the effects of WTC dust particles on mice and on cultured human cells provide mechanistic evidence for the role of inflammatory processes in WTC-related respiratory conditions. Gavett et al. found significant neutrophilic inflammation in the lungs of mice and an increase in airway hyper-responsiveness to methacholine challenge following exposure to a single oropharyngeal aspiration of fine WTC dust (mass-median aerodynamic diameter of less than 2.5 µm or $PM_{2.5}$)[82]. Exposure of human primary alveolar marcrophages and type II epithelial cells, key lung cell populations, to WTC dust particles (WTC $PM_{2.5}$) caused time- and dose-related increases in the formation/release of pro-inflammatory cytokines/chemokines that contribute to inflammation and airway remodeling processes[83]. A recent study of WTC $PM_{2.5}$ exposure in lung epithelial cells demonstrated that activation of mitogen-activated protein kinase signaling pathway(s) likely played an important role in the dose-dependent increase of cytokine formation by the cells[84]. The authors postulate that WTC-induced cytokine induction at low doses (0-200 µg/mL) and short time intervals (5 hr) in their study compared to the Payne et al. study (500–2000 µg/mL and 24 hr)[83] may help to explain why the incidence of asthma

and other inflammation-associated diseases were increased both in First Responders as well as among metropolitan area residents 20–30 miles away from Ground Zero.

Many exposures that cause cancer in the upper and lower respiratory tracts also cause non-malignant respiratory diseases. Examples include tobacco smoking, silica, asbestos, beryllium, particulate air pollution, and indoor exposures to the burning of biomass fuels.

3. Evidence regarding cancer from completed incidence studies

One study has been published regarding cancer outcomes among 9,853 men who were employed as firefighters as of January 1, 1996, and were or would have been less than 60 years of age on 9/11/2001.[1] Of these, 8927 were WTC-exposed. Cancers (excluding basal cell skin cancers) diagnosed between 1996 and 2008 were identified from five state cancer registries and from self-reports on questionnaires administered during routine mandatory FDNY wellness evaluations performed every 12–18 months and subsequently verified by review of medical records.

Risks of cancer were compared by calculating expected numbers of cancers during non-exposed person-years (never-exposed firefighters and period before 9/11 for exposed firefighters) and post-exposure person years, based on sex, age, race, and ethnicity-specific cancer rates in the SEER-13 registries. WTC-exposed and non-exposed SIR's were calculated for the exposed and non-exposed groups based on the ratios of observed and expected cancers in the general population each group. In addition, because firefighters constitute an unusually fit and healthy population who might be expected to have lower age-adjusted cancer rates than the general population, SIR Ratios were calculated to assess differences in cancer rates between the two groups. Among a number of secondary analyses reported, the one considered the most relevant was an adjustment for early diagnosis (surveillance bias) through lagging the diagnosis dates for two years for all cancers potentially identified by WTC-related medical screening in the FDNY medical surveillance program.

Strengths of the study included probably near-complete case-finding, reliable (albeit crude) exposure information, lack of selection bias, and inclusion of a control population with equivalent non-WTC environmental and occupational exposures. Limitations include lack of representativeness for women, children, and elderly persons; insufficient power to detect differences in most specific cancer types; insufficient exposure data and insufficient variability in exposure to evaluate for a dose-response effect; and short follow-up time relative to cancer latency.

A total of 263 cancers were documented in 61,884 person-years after WTC exposure, where 238 would have been expected from SEER-13 data, yielding a Standardized incidence ratio (SIR) of 1.10, with

95% confidence interval spanning 0.98 to 1.25—just missing statistical significance. For the 60,761 unexposed person-years, however, the SIR estimate was 0.84 (0.71 to 0.99), indicating that, absent WTC exposure, firefighters have a lower than predicted cancer incidence (an example of the healthy worker effect). Comparing exposed to unexposed, the estimated SIR ratio was 1.32, with confidence intervals 1.07 to 1.62, demonstrating that WTC exposure increased risk of cancer approximately 32% over that expected in this worker population.

After introducing an artificial 2-year lag time in cancer diagnosis for thyroid, lung, and prostate cancers and for lymphoma (to "correct" for possible surveillance bias), the total number of diagnosed cancers in the exposed population would have been 242 and the estimated SIR ratio would have been 1.21, with confidence interval spanning 0.98 to 1.49, again just missing statistical significance, but still far more likely than not reflecting a small excess of cancers among exposed firefighters. Arguing against a more severe surveillance bias is that cancer staging did not demonstrate an earlier stage of diagnosis in the exposed as compared to the unexposed.

For each individual type of cancer, too few cases were expected to have statistical power to detect moderate increases (or decreases) in cancer risk. However, for thyroid cancer, melanoma, and non-Hodgkin Lymphoma, SIRs were substantially higher than 1.0 and approached statistical significance. Regarding prostate cancer, consistent with prior studies[85], even the unexposed firefighters had slightly and statistically significantly higher incidence than predicted, with SIR 1.35. The WTC-exposed FDNY group did not show an increased risk over the unexposed, with estimated SIR ratio 0.90 (after correction for possible surveillance bias). Therefore, despite the statistically significant SIR for prostate cancer in WTC-exposed firefighters compared to the general population, the overall results do not support an increased risk of prostate cancer associated with WTC exposures. Data from the Zeig-Owens study are presented in Table 4 for cancer sites with some evidence of increased risk. Some of the cancer sites with excess risk in this study have been observed in prior studies of firefighters[85].

Additional post-WTC cancer incidence results are expected to come from the non-FDNY WTC Responder Consortium, the WTC registry cohorts, and the FDNY EMS cohort in the near future. The STAC has not had access to those studies and therefore has not based current recommendations on them. Given the paucity of epidemiological studies to date, additional studies can be expected to inform the body of knowledge on the issue of WTC and cancer risk, though the limitations of surveillance bias, sample size, selection bias, limited follow-up and others are likely to persist.

4. Inclusion of rare cancers

Excesses in rare cancers are difficult to detect in epidemiologic studies. Even large studies may have very low numbers of expected cases of rare cancers, and thus very low statistical power to detect any but very large effects. In addition, most cancer studies analyze data by organ site, and not by site and histology. This can result in inability to detect rare site and histology combinations, such as angiosarcoma of the liver, associated with vinyl chloride monomer exposure,[86] and small cell carcinoma of the lung, associated with bis chloromethyl ether[87]. Cancers can also be defined as rare based on the patient's gender (male breast cancer), age (prostate cancer in men under 40) or race (melanoma in African Americans). Since customary study methods are unlikely to identify increased risks for rare cancers among WTC-exposed populations unless they occur in sizable clusters. Nonetheless, given the sizable number of carcinogens (and related cancer sites) present in WTC smoke and dust, it is reasonable to consider the possibility that an increased risk of specific rare cancers may occur or that the incidence of common cancers would be increased at younger ages in WTC-exposed populations. One approach that has been used is to consider rare cancers as cancers with age-adjusted incidence rates less than 15 per 100,000, which would result in defining 25% of all adult cancers in the US as rare[88]. Additional definitions— 10 cases per million per year, or 1 case per million per year— have also been examined[88].

For the purposes of defining rare cancers for the WTC Health Program, one approach would be construct a matrix of on age-specific incidence rates by gender, decade of age, site and histology and to consider as rare any cancer with an incidence rate of < 5 or <10 per 100,000 in the appropriate gender age stratum for the site/histology combination. If this approach is adopted, site/histology combinations to be considered as unique cancers should be determined *a priori* in consultation with appropriate experts. However, it is clear that there are many reasonable approaches that could be used to define rare cancers and the STAC is not endorsing a specific approach at this time.

5. Inclusion of childhood cancers

The unique vulnerability of children to synthetic chemicals commonly found in the environment has been documented in the landmark 1993 US National Academy of Sciences report.[6] Children drink more water, breathe more air and eat more food per pound, and have higher exposures than adults.[7,8] Their developing organ systems are also more vulnerable to many chemicals, and are less well able to detoxify or eliminate them.[89,90] Together, these aspects of early life development increase the likelihood of lifelong organ system impairment following exposure to environmental chemicals.[91] Children also have more years of life in which chronic conditions can occur as a result of early life exposures.[92]

Epidemiologic studies have associated exposure to benzene[93,94], certain pesticides[95,96], polychlorinated biphenyls[97,98], and 1,3-butadiene with increases in childhood malignancies.

Children who attended schools and lived near the World Trade Center site experienced exposures in the range of responder populations [86]. Given the baseline relative infrequency in which cancer occurs in children, and the limited statistical power of even a study of all 14,000 children who lived south of 14th Street on September 11, 2001, no negative study will eliminate the possibility of causation. Indeed, this is an area of need for research, yet such research should not preclude a measure of caution taken in including coverage for all cancers incident before age 21 insofar as a health care provider confirms substantial likelihood of association with World Trade Center exposures.

I. Summary of Cancer Classifications for COPC and Select Other Agents

IARC Group 1—Carcinogenic to Humans

This category is used when there is sufficient evidence of carcinogenicity in humans. Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than sufficient but there is sufficient evidence of carcinogenicity in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.

Agent	Category		
	IARC	NTP	
Arsenic	**1**	**A**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Arsenic.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol84/mono84-6E.pdf		
Asbestos	**1**	**A**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Asbestos.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/suppl7/Suppl7-20.pdf		
Benzene	**1**	**A**	
NTP hyperlink:	http://monographs.iarc.fr/ENG/Monographs/suppl7/Suppl7-24.pdf		
IARC hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Benzene.pdf		
Benzo[a]pyrene (PAHs)	**1**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/PolycyclicAromaticHydrocarbons.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol92/mono92-10.pdf		
Beryllium	**1**	**A**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Beryllium.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol58/mono58-6.pdf		

Agent	Category		
	IARC	NTP	
1,3-Butadiene	**1**	**A**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Butadiene.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol97/mono97.pdf		
Cadmium and compounds	**1**	**A**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Cadmium.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol58/mono58-7E.pdf		
Chromium VI	**1**	**A**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/ChromiumHexavalentCompounds.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol49/mono49-6.pdf		
Formaldehyde	**1**	**A**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Formaldehyde.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol88/mono88-6.pdf		
Nickel compounds	**1**	**A**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Nickel.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol49/mono49-7.pdf		
Quartz	**1**	**A**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Silica.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol68/mono68-6.pdf		
Soot[1]	**1**	**B**	
NTP hyperlink	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Soots.pdf		
IARC hyperlink	http://monographs.iarc.fr/ENG/Monographs/vol35/volume35.pdf		
Sulfuric Acid	**1**	**A**	

[1] As found in occupational exposure of chimney sweeps.

Agent	Category		
	IARC	NTP	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/StrongInorganicAcidMists.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol54/mono54-6.pdf		
Vinyl chloride	**1**	**A**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/VinylHalides.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol97/mono97-8.pdf		

IARC Group 2A—Probably Carcinogenic to Humans

This category is used when there is limited evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals. In some cases, an agent may be classified in this category when there is inadequate evidence of carcinogenicity in humans and sufficient evidence of carcinogenicity in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of limited evidence of carcinogenicity in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one of more members have been classified in Group 1 or in Group 2A.

Agent	Category		
	IARC	NTP[2]	
Benzyl Chloride	**2A**	**NL**	
NTP hyperlink:	Not applicable		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-19.pdf		
Biomass fuel **(primarily wood, indoor emissions from household combustion)**	**2A**	**NL**	
NTP hyperlink	Not applicable		
IARC hyperlink	http://monographs.iarc.fr/ENG/Monographs/vol95/mono95-6A.pdf		
Dibenz[a,h]anthracene	**2A**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/PolycyclicAromaticHydrocarbons.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol92/mono92-10.pdf		
Engine Exhaust, diesel	**2A**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/DieselExhaustParticulates.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol46/volume46.pdf		

[2] NL = not listed

Agent	Category		
	IARC	NTP[2]	
Ethylene Dibromide	**2A**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Dibromoethane.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-28.pdf		
Lead (inorganic)	**2A**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Lead.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol87/index.php		
Nitrate ion (ingested)	**2A**	**NL**	
NTP hyperlink:	Not applicable		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol94/mono94-6F.pdf		
Polychlorinated Biphenyls	**2A**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/PolychlorinatedBiphenyls.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/suppl7/suppl7.pdf		
Tetrachloroethylene	**2A**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Tetrachloroethylene.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol63/volume63.pdf		
Trichloroethylene	**2A**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Trichloroethylene.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol63/mono63-6.pdf		

IARC Group 2B—Possibly Carcinogenic to Humans

This category is used for agents for which there is limited evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals. It may also be used when there is inadequate evidence of carcinogenicity in experimental animals. In some instances, an agent for which there is inadequate evidence of carcinogenicity in humans and less than sufficient evidence of carcinogenicity in experimental animals, together with supporting evidence from mechanistic and other relevant data, may be placed in this group. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Agent	Category		
	IARC	NTP[3]	
Acrylonitrile	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Acrylonitrile.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-7.pdf		
Antimony trioxide	**2B**	**NL**	
NTP hyperlink:	Not applicable		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol47/volume47.pdf		
Benzene Hexachloride **(syn: lindane)**	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Lindane.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/suppl7/Suppl7-88.pdf		
Benz[a]anthracene	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/PolycyclicAromaticHydrocarbons.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol92/mono92-10.pdf		
Benzo[b]fluoranthene	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/PolycyclicAromaticHydrocarbons.pdf		

[3] NL = not listed

Agent	Category		
	IARC	NTP[3]	
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol92/mono92-10.pdf		
Benzo[k]fluoranthene	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/PolycyclicAromaticHydrocarbons.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol92/mono92-10.pdf		
Bromodichloromethane	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Bromodichloromethane.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-73.pdf		
Carbon tetrachloride	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/CarbonTetrachloride.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol71/volume71.pdf		
Cobalt sulfate and soluble cobalt	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/CobaltSulfate.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol86/mono86-6E.pdf		
Chlordane	**2B**	**NL**	
NTP hyperlink:	Not applicable		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol79/mono79-17.pdf		
4-Chloroaniline	**2B**	**NL**	
NTP hyperlink:	Not applicable		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol57/mono57-21.pdf		
Chloroform	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Chloroform.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol73/mono73-10.pdf		
Chrysene	**2B**	**NL**	

Agent	Category		
	IARC	NTP[3]	
NTP hyperlink:	Not applicable		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol92/mono92-10.pdf		
DDT	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Dichlorodiphenyltrichloroethane.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol53/mono53-9.pdf		
1,4-Dichlorobenzene	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Dichlorobenzene.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol73/mono73-13.pdf		
3,3'-Dichlorobenzidine	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Dichlorobenzidine.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol99/mono99-10.pdf		
p,p'-Dichlorodiphenyl-dichloroethane (TDE)	**2B**	**NL**	
NTP hyperlink:	Not applicable		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol53/mono53-9.pdf		
p,p'-Dichlorodiphenyl-dichloroethylene (DDE)	**2B**	**NL**	
NTP hyperlink:			
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol53/mono53-9.pdf		
1,2-Dichloroethane **(syn: Ethylene dichloride)**	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Dichloroethane.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-21.pdf		
2,4-Dinitrotoluene	**2B**	**NL**	
NTP hyperlink:	Not applicable		

Agent	Category		
	IARC	NTP[3]	
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol65/mono65-9.pdf		
2,6-Dinitrotoluene	**2B**	**NL**	
NTP hyperlink:	Not applicable		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol65/volume65.pdf		
1,4-Dioxane	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Dioxane.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-25.pdf		
Ethylbenzene	**2B**	**NL**	
NTP hyperlink:	Not applicable		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol77/mono77-10.pdf		
Heptachlor	**2B**	**NL**	
NTP hyperlink:	Not applicable		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol79/mono79-17.pdf		
Hexachlorobenzene	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Hexachlorobenzene.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol79/mono79-18.pdf		
Hexachloroethane	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Hexachloroethane.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol73/mono73-15.pdf		
Indeno[1,2,3-cd]pyrene	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/PolycyclicAromaticHydrocarbons.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol32/volume32.pdf		
Methylene chloride	**2B**	**B**	

Agent	Category		
	IARC	NTP[3]	
(syn: dichloromethane)			
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Dichloromethane.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol32/volume32.pdf		
Mirex	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Mirex.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol20/volume20.pdf		
Naphthalene	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Naphthalene.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol82/mono82-8.pdf		
Nickel metallic	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Nickel.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol49/mono49-7.pdf		
Nitrobenzene	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Nitrobenzene.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol65/mono65-11.pdf		
N-Nitroso-Di-n-propylamine	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Nitrosamines.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol17/volume17.pdf		
Pentachlorophenol	**2B**	**NL**	
NTP hyperlink:	Not applicable		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-34.pdf		
Styrene	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Styrene.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol82/mono82-9.pdf		

Agent	Category		
	IARC	NTP[3]	
Titanium Dioxide	**2B**	**NL**	
NTP hyperlink:	Not applicable		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol93/mono93-7F.pdf		
Toxaphene	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Toxaphene.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol79/mono79-19.pdf		
2,4-Toluenediisocyanate	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/TolueneDiisocyanates.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-37.pdf		
2,6-toluene diisocyanate	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/TolueneDiisocyanates.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-37.pdf		
2,4,6-Trichlorophenol	**2B**	**B**	
NTP hyperlink:	http://ntp.niehs.nih.gov/ntp/roc/twelfth/profiles/Trichlorophenol.pdf		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol71/mono71-34.pdf		
Vanadium Pentoxide	**2B**	**NL**	
NTP hyperlink:	Not applicable		
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol86/mono86-10.pdf		
Vinyl acetate	**2B**	**NL**	
NTP hyperlink:			
IARC hyperlink:	http://monographs.iarc.fr/ENG/Monographs/vol63/mono63-19.pdf		

Table 2. Selected agents that IARC has classified as *carcinogenic to humans* and related cancer sites with *sufficient* or *limited* evidence in humans [99].

Carcinogenic agent	**Cancer sites with *sufficient evidence* in humans**	**Cancer sites with *limited evidence* in humans**
Acid mists, strong inorganic (Sulfuric acid)	Larynx	Lung
Arsenic and inorganic arsenic compounds	Lung Skin Urinary bladder	Kidney Liver Prostate
Asbestos (all forms)	Larynx Lung Mesothelioma Ovary	Colorectum Pharynx Stomach
Benzene	Leukemia (acute nonlymphocytic)	Leukemia (acute lymphocytic, chronic lymphocytic, multiple myeloma, non-Hodgkin lymphoma)
Beryllium and beryllium compounds	Lung	
1,3-Butadiene	Hematolymphatic organs	
Cadmium and cadmium compounds	Lung	Kidney Prostate
Chromium(VI) compounds	Lung	Nasal cavity and paranasal sinus
Formaldehyde	Leukemia Nasopharynx	Nasal cavity and paranasal sinus
Nickel compounds	Lung Nasal cavity and paranasal sinus	
Silica dust, crystalline (in the form of quartz or crystobalite)	Lung	
Soot	Lung Skin	Urinary bladder
2,3,7,8-Tetrachlorodibenzo-*para*-dioxin	All cancers combined	Lung Non-Hodgkin lymphoma Soft-tissue sarcoma
Vinyl Chloride	Liver (angiosarcoma, hepatocellular carcinoma)	

Table 2. Agents that IARC has classified as *probably carcinogenic* or *possibly carcinogenic* to hu*mans* and cancer sites with *limited* evidence [99]

Suspected carcinogenic agent	Cancer sites with *limited evidence* in humans
Engine exhaust, diesel	Lung Urinary bladder
Lead compounds, inorganic	Stomach
Polychlorinated biphenyls	Hepatobiliary tract
Polychlorophenols or their sodium salts (combined exposures)	Non-Hodgkin lymphoma Soft-tissue sarcoma
Tetrachloroethylene	Cervix Non-Hodgkin Lymphoma Esophagus
Trichloroethylene	Liver and biliary tract Non-Hodgkin Lymphoma

Table 3. WTC-related health conditions specified in the Zadroga Act that may be associated with cancer through chronic inflammation or irritation

Upper airway
• Chronic rhinosinusitis
• Chronic nasopharyngitis
• Chronic laryngitis
• Chronic airway hyperreactivity
• Cough
• Sleep apnea
Lower airway
• Asthma
• Chronic reactive airway dysfunction syndrome
• Chronic obstructive pulmonary disease
• Other chronic respiratory disorder due to fumes and vapors
• Interstitial lung disease
Gastrointestinal
• Gastroesophageal reflux

Table 4. Summary of evidence regarding potential carcinogenicity of WTC exposures by cancer site

Cancer site	Carcinogenic agents at WTC with *sufficient or limited evidence* in humans [99]	WTC-related Conditions	FDNY Study Cancers with Elevated Standardized Incidence Ratios (SIR's) [1]. **Statistically significant effects
Lip, Oral Cavity, and Pharynx			
Lip			
Oral cavity			
Salivary gland			
Tonsil			
Pharynx	*Limited:* Asbestos (all forms)	Chronic nasopharyngitis	
Nasopharynx	*Sufficient:* Formaldehyde	Chronic nasopharyngitis	
Digestive Organs			
Esophagus	*Limited:* Tetrachloroethylene	GERD	
Stomach	*Limited:* Asbestos (all forms) *Limited:* Lead compounds, inorganic	GERD	**Stomach (including gastro-esophageal junction)** **Observed / Expected / SIR (95% CI)** Exposed: 8 / 4 / 2.24 (0.98–5.25)** Non-exposed: ≤5 / 2 / 1.23 (0.40–3.83) SIR ratio*: 1.82 (0.44–7.49
Colon and rectum	*Limited:* Asbestos (all forms)		**Colon (excluding rectum)** **Observed / Expected / SIR (95% CI)** Exposed: 21 / 14 / 1.52 (0.99–2.33 Non-exposed: 9 / 9 / 1.01 (0.53–1.94) SIR ratio*: 1.50 (0.69–3.27)
Anus			
Liver and bile duct	*Sufficient:* Vinyl chloride *Limited:* Arsenic and inorganic arsenic compounds *Limited:* Polychlorinated biphenyls *Limited:* Trichloroethylene		
Gall bladder			
Pancreas			
Digestive tract, unspecified			
Respiratory Organs			

<table>
<tr><td>Nasal cavity and paranasal sinus</td><td>Sufficient: Nickel compounds
Limited: Chromium(VI) compounds
Limited: Formaldehyde</td><td>Chronic nasopharyngitis
Upper airway hyperreactivity</td><td></td></tr>
<tr><td>Larynx</td><td>Sufficient: Acid mists, strong inorganic
Sufficient: Asbestos (all forms)</td><td>Chronic laryngitis</td><td></td></tr>
<tr><td>Lung</td><td>Sufficient: Arsenic and inorganic arsenic compounds
Sufficient: Asbestos (all forms)
Sufficient: Beryllium and beryllium compounds
Sufficient: Cadmium and cadmium compounds
Sufficient: Chromium(VI) compounds
Sufficient: Nickel compounds
Sufficient: Silica dust, crystalline
Sufficient: Soot
Limited: Acid mists, strong inorganic
Limited: Engine exhaust, diesel
Limited: 2,3,7,8-Tetrachlorodibenzo-para-dioxin
Limited: Welding fumes</td><td>Interstitial lung disease
Chronic respiratory disorder – fumes/vapors
Reactive airways disease syndrome (RADS)
Chronic cough syndrome</td><td></td></tr>
<tr><td colspan="4">Bone, skin, and mesothelial and soft tissue</td></tr>
<tr><td>Bone</td><td></td><td></td><td></td></tr>
<tr><td>Skin (melanoma)</td><td></td><td></td><td>Melanoma
<table><tr><th></th><th>Observed</th><th>Expected</th><th>SIR (95% CI)</th></tr><tr><td>Exposed</td><td>33</td><td>21</td><td>1.54 (1.08–2.18)**</td></tr><tr><td>Non-exposed</td><td>15</td><td>16</td><td>0.95 (0.57–1.58)</td></tr><tr><td>SIR ratio*</td><td></td><td></td><td>1.61 (0.87–2.99</td></tr></table></td></tr>
</table>

Skin (other malignant neoplasms)	*Sufficient:* Arsenic and inorganic arsenic compounds *Sufficient:* Soot		
Mesothelioma (pleura and peritoneum)	*Sufficient:* Asbestos (all forms)		
Kaposi sarcoma			
Soft tissue	*Limited:* Polychlorophenols or their sodium salts (combined exposures) *Limited:* 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin		
Breast and Female Genital Organs			
Breast			
Vulva			
Vagina			
Uterine cervix	*Linited:* Tetrachloroethylene		
Endometrium			
Ovary	*Sufficient:* Asbestos (all forms)		
Male Genital Organs			
Penis			
Prostate	*Limited:* Arsenic and inorganic arsenic compounds *Limited:* Cadmium and cadmium compounds		
Testis			
Urinary Tract			
Kidney	*Limited:* Arsenic and inorganic arsenic compounds *Limited:* Cadmium and cadmium compounds		
Renal pelvis and ureter			

	Observed	Expected	SIR (95%CI)
Prostate			
Exposed	90	60	1.49 (1.20–1.85)**
Non-exposed	45	33	1.35 (1.01–1.81)**
SIR ratio*			1.11 (0.77–1.59)
Prostate, corrected (diagnosis date lagged 2 years)			
Exposed	73	60	1.21 (0.96–1.52)
Non-exposed	45	33	1.35 (1.01–1.81)**
SIR ratio*			0.90 (0.62–1.30)

Urinary bladder	*Sufficient:* Arsenic and inorganic arsenic compounds *Limited:* Engine exhaust, diesel *Limited:* Soot		
Eye, Brain, and Central Nervous System			
Eye	*Sufficient:* Welding	Extensive foreign body washout required	
Brain and central nervous system			
Endocrine Glands			
Thyroid			**Thyroid** Exposed: 17 / 6 / 3.07 (1.86-5.08)** Unexposed: ≤5 / 3 / 0.59 (0.15–2.36) SIR ratio*: 5.21 (1.19–22.74)** **Thyroid, corrected (diagnosis date lagged 2 years)** Exposed: 12 / 6 / 2.17 (1.23–3.82)** Unexposed: ≤5 / 3 / 0.59 (0.15–2.36) SIR ratio*: 3.67 (0.82–16.42)
Lymphoid, Hematopoietic, and Related Tissue			
Leukemia and/or lymphoma and multiple myeloma*	*Sufficient:* Benzene *Sufficient:* 1,3-Butadiene *Sufficient:* Formaldehyde *Limited:* Polychlorophenols or their sodium salts (combined exposures) *Limited:* Styrene *Limited:* 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin	Sarcoidosis	**Non-Hodgkin lymphoma** Exposed: 21 / 13 / 1.58 (1.03–2.42)** Non-exposed: 9 / 11 / 0.83 (0.43–1.60) SIR ratio*: 1.90 (0.87–4.15) **NHL, corrected (diagnosis date lagged 2 years)** Exposed: 20 / 13 / 1.50 (0.97–2.33) Non-exposed: 9 / 11 / 0.83 (0.43–1.60) SIR ratio*: 1.81 (0.82–3.97)
Multiple sites (unspecified)			
All cancers combined	*Sufficient:* 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin		

*Studies of associations between occupational and environmental carcinogens have been complicated by inaccuracies of death certificate diagnosis and changes in classification of cancers of the lymphatic and hematopoietic system (LHC's) over time. Epidemiologic and animal studies may report morphologically distinct hematological cancers as separate endpoints even though they may share common cellular origins. Over time, there has been growing recognition of close relationships and overlap of such morphologically diverse disorders as chronic lymphocytic leukemia and multiple myeloma, now considered sub classifications of mature B-cell neoplasms (Swerdlow et al. 2008). For this reason, LHC's are considered as a combined category in this table.

Table 5. WTC Human Carcinogens with established mechanistic events for tumor sites (or types) for which there is sufficient evidence in humans (adapted from IARC Monograph Working Group, 2009)

WTC Human Carcinogen	**Tumor sites (or types) for which there is sufficient evidence in humans**	**Other sites with limited evidence in humans**	**Established mechanistic events**
Arsenic and Inorganic arsenic compounds	Lung, skin, urinary bladder	Kidney, liver, prostate	Oxidative DNA damage, genomic instability, aneuploidy, gene amplication, epigenetic effects, DNA-repair inhibition leading to mutagenesis
Asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite, and anthophyllite)	Lung, mesothelioma, larynx, ovary	Colorectum, pharynx, stomach	Impaired fiber clearance leading to macrophage activation, inflammation, generation of reactive oxygen and nitrogen species, tissue injury, genotoxicity, aneuploidy and polyploidy, epigenetic alteration, activation of signaling pathways, resistance to apoptosis
Beryllium and beryllium compounds	Lung	--	Chromosome aberrations, aneuploidy, DNA damage
Cadmium and Cadmium compounds	Lung	Prostate, kidney	DNA-repair inhibition, disturbance of tumor-suppressor proteins leading to genomic stability
Chromium (VI) compounds	Lung	Nasal cavity and paranasal sinuses	Direct DNA damage after intracellular reduction to Cr(III), mutation, genomic instability, aneuploidy, cell transformation
Nickel compounds	Lung, nasal cavity, and paranasal	--	DNA damage, chromosome aberrations, genomic instability, micronuclei, DNA-repair inhibition,

	sinuses		alteration of DNA methylation, histone modification
Silica dust, crystalline in the form of quartz or crystobalite	Lung	--	Impaired particle clearance leading to macrophage activation and persistent inflammation

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