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Dear Dr. Howard:

We are writing in response to your request to the World Trade Center Health Program Scientific/Technical Advisory Committee (WTCHP STAC) to provide an evaluation and recommendation on whether there is a reasonable scientific basis to support adding uterine cancer to the List of WTC-Related Health Conditions.

The STAC recognizes that the WTC Health Program has established policies and procedures for the addition of specific types of cancer to the List of WTC-Related Health Conditions based on four methods, and that the Administrator has determined that uterine cancer does not meet the criteria based on Methods 1, 2, and 3.

We appreciate the opportunity to consider whether there is "reasonable scientific basis to support adding uterine cancer to the List of WTC-Related Health Conditions" as prescribed under Method 4. Method 4 relies on findings from other sources of information relevant to 9/11 exposures and the occurrence of cancer, including expert judgment, personal and professional experiences of STAC members, and comments from the public.

The STAC has concluded that there is a reasonable basis for adding all types of uterine cancer to the List of WTC-related cancers. This conclusion is based largely on the evidence and principles that were developed by the STAC in 2012[1] and considered by the Administrator in developing policies and procedures regarding the addition of specific types of cancer (as defined by body organ or region) as WTC-related conditions, as well as in subsequent rulemakings and amendments. In his deliberations, the Administrator has continued to place considerable weight on the recommendations and evidence provided by the STAC in 2012.[1-7] After nearly a decade of applying well-conceived and reasonable procedures for adding additional cancer types, the WTC Health Program finds itself in the unforeseen situation that only uterine cancer (all types) is not considered a WTC-related cancer condition. In the current context, it is useful to review the STAC's earlier considerations about whether to recommend that all cancers be covered:

> 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."[1]

Although the 2012 STAC ultimately recommended methods for adding specific cancer types rather than all cancers, we believe that the arguments for adding all cancers can apply to the question of whether to include all types of uterine cancer. Other than uterine cancer, all cancer types now are covered as WTC-related conditions. Mechanisms for carcinogenesis resulting from endogenous and exogenous exposures are similar for most cancer types. It is therefore highly implausible that uterine cancer would be the *only* cancer not related to WTC exposures.

Several lines of evidence demonstrate that uterine cancer shares common etiologies and mechanisms for development with other cancers. In reviewing this evidence, we refer to endometrial rather than uterine cancer as that is the term used in relevant articles.[1] Traditionally endometrial cancers have been classified into major subtypes; however, while the Type 1 and 2 classifications have provided an important framework for decades, heterogeneity and overlap between these subtypes has been recognized in recent years.[8] Type 1, which accounts for most endometrial cancers, consists of estrogen-dependent and low-grade lesions with endometroid morphology which often have mutations in the *PTEN* gene.[8, 9] Type 1 also frequently involves mutations in the beta-catenin and *KRAS* genes as well as deficiencies in mismatch repair.[9] The same mutations and abnormal mismatch repair are associated with many other cancers. Specifically, PTEN inactivation is found in melanoma, brain tumors, ovarian cancer, thyroid cancer, breast cancer, and prostate cancer; mutations in the beta-catenin gene are found in liver and colorectal cancers[10]; and *KRAS* mutations are found in non-small cell lung cancer, colorectal cancer, and pancreatic cancer. Mutations in mismatch repair genes cause hereditary nonpolyposis colorectal cancer and loss of mismatch repair is associated with a significant fraction of sporadic cancers.[11] Type 2 endometrial cancer is rarer than Type 1 and contains high-grade lesions of serous or clear cell histology with frequent mutations in p53 and high expression and/or amplification of HER2. A p53 gene mutation is the most frequent mutation in human cancer.[9] HER2/neu is a tyrosine kinase membrane receptor in the epidermal growth factor (EGF) receptor family. Mutations of this gene are also found in breast and ovarian cancers.[9] The STAC review of the literature suggests that endometrial cancer shares many of the same genetic mechanisms with cancers already included in List of WTC-Related Health Conditions.

Incidence rates of both endometrial cancer and breast cancer are strongly related to exposure to endogenous and exogenous hormones and, therefore, exposure to endocrine-disrupting chemicals (EDCs) in WTC dust and smoke are particularly relevant for these cancers. Estrogen receptor (ER), progesterone receptor (PR) human epidermal growth factor 2 (HER2) overexpression are

[1] Endometrial cancer is the most common type of uterine cancer, and the terms are sometimes used synonymously. Most of the scientific literature on uterine cancer relates specifically to endometrial cancer. However, in keeping with Dr. Howard's charge, the STAC recommendations pertain to all types of uterine cancers, which is the more inclusive term. The STAC also recognizes that uterine sarcomas, which are the second most common type of uterine cancers, are considered rare cancers and are already considered WTC-Related Health Conditions.

well recognized prognostic and predictive markers for breast cancer. Although the roles of ER, PR, and HER2 expression in endometrial cancer are less well understood, a recent study of biomarker expression in tissue samples from 360 women with endometrial cancer found that, among Type I tumors, 92.7% were positive for ER and 85.1% were positive for PR expression; smaller but significant proportions of Type II cancers were also ER- and PR-positive.[12]

The risks of developing breast and endometrial cancer are related to reproductive factors and hormonal therapies, and risks may vary by the age and stage of development at which the exposure occurred. Because endometrial cancers are clearly related to hormonal factors, the presence of multiple EDCs at the WTC sites and other exposure areas[2] is of special significance in evaluating risks associated with WTC exposures. In supporting documents to the 2012 STAC Committee recommendations,[1] the Committee focused on several classes of WTC exposures which have substantial evidence regarding cancer in animals and humans. These include asbestos, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls, dioxins and furans, metals, and volatile and semi-volatile organic compounds (VOCs). In this report, we provide additional evidence regarding the presence and toxicity of EDCs in WTC dust. EDCs present at the WTC site included cadmium, perfluoroalkyl substances, phthalates, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), polychlorinated dibenzo-para-dioxins, and polychlorinated dibenzofurans (PCDD/Fs).[13] Although data on the carcinogenicity of many of these substances in experimental animals and humans are extremely limited, recent review articles address the potential relationship between endocrine disruption and endometrial cancer.[14, 15] In addition, there is evidence that exposure to some EDCs in-utero and during early life are particularly hazardous, thus posing potential risks for uterine cancer among survivors with early life exposures. Exposure to diethylstilbestrol (DES) resulted in clear cell adenocarcinoma of the vagina and other reproductive abnormalities in adolescents and young adults who were exposed as fetuses, and increased risk of breast cancer among pregnant women who took the drug; the DES experience is one well-known example showing consequences of EDC exposure after long latency periods.[16] Reproductive abnormalities also occurred in grandchildren of women who took DES during pregnancy.[16] These data raise concern for the young people who attended schools and childcare centers in the WTC area, as well as area residents who were in utero, infants, children, adolescents, and young adults during the attack and its aftermath. These individuals have decades of life ahead during which they may experience effects of their earlier exposures.

The STAC provides additional documentation regarding potential exposures to EDCs at the WTC sites and other exposure areas in Attachment 1.

The STAC recognizes that increases in uterine cancer incidence or risk have not been observed in studies of WTC-exposed cohorts to date,[17] but believes that these studies may not be able to provide definitive evidence for associations of uterine cancer with WTC exposures now or in the future. Although the incidence rate of uterine cancer exceeds the threshold used by the Administrator to define rare cancers, because of the relatively small numbers of women in WTC cohorts, similar statistical power constraints apply to uterine cancer. In addition to the limited

[2] Locations covered by the WTC Health Program.

statistical power for generating overall estimates of risk, these small numbers limit the ability to evaluate exposure-response or to conduct highly relevant analyses by histological type, menopausal status, age at exposure, age at diagnosis, and other factors that may be critically important in investigating endometrial cancer risk. Many women in the cohorts under study are only now reaching the ages at which peak incidence of uterine cancer occurs in the population, so it is possible that elevated uterine cancer risks are yet to be observed.

Although none of the WTC carcinogenic agents reviewed in the WTCHP white paper have been found by IARC to be associated with uterine cancer, the epidemiologic evidence regarding these cancers comes primarily from studies of industrial cohorts, which often include very few or no women and therefore would be unable to detect an increased risk if it were present.[17] The STAC also recognizes that many epidemiological studies of these agents have significant limitations in sample size and methodology and do not account for other important risk determinants such as age at exposure and reproductive risk factors.

Prior decisions made by the Administrator have articulated the importance of balancing the degree of certainty regarding cancer associations with the importance of providing timely services to affected responders and survivors. The STAC has considered public comments from affected survivors, responders, and health care providers from WTCHP Centers of Excellence. Many comments reflect the perception that coverage of all types of cancer except uterine cancer as WTC-Related Health Conditions is illogical and unfair and may cause tangible harm. One such harm is that women diagnosed with uterine cancers may experience poorer health outcomes than their peers whose cancers are considered WTC-related. A recent study found better cancer survival among responders enrolled in WTC Medical Monitoring and Treatment Programs compared to the general population.[18] While some of these benefits may accrue from screening and diagnostic benefits, it is likely that coverage for treatment and access to high quality care among those with WTC-related cancers contribute to better outcomes. In addition, in public comments, WTC-exposed women who have been diagnosed with uterine cancer have stated that the lack of the social and clinical support and recognition that uterine cancer is a WTC-related condition has had a significant negative impact on their morale and quality of life.

The STAC has also considered comments from WTCHP providers who are ethically conflicted and deeply troubled by their role of explaining to individuals with uterine cancer that they are not eligible for benefits because their form of cancer is the only one not covered. The STAC notes the strong support of WTCHP Center directors and providers for inclusion of all types of uterine cancer as a WTC-related condition, as well as comments from the public and STAC members who are or have been WTCHP providers.

The STAC believes that the WTC Environmental Health Center Pan-Cancer Database will be an important tool for research on cancer in WTC survivors. This database contains information on cancer characteristics and emerging biomarkers for cancers in individuals enrolled in the WTC Environmental Health Centers.[19] The database does not appear to include uterine cancer, thus closing the door to future research that might provide greater insights into the role of WTC exposures for development of these cancers. Such research will be particularly important in

identifying risks associated with less common histologic subtypes of uterine cancer, such as clear cell carcinoma, a diagnosis mentioned in several public comments.

In view of the strong rationale for adding all types of uterine cancer to the list of WTC-related cancers and the potential benefits to affected WTC responders, WTC survivors, and providers caring for these patients, we recommend that all types of uterine cancer be added to the list of WTC-related cancers and urge the Administrator to make all feasible efforts to do so as quickly as policies and procedures allow.

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 Ward

Elizabeth Ward, PhD.
Chair, World Trade Center Health Program
Scientific/Technical Advisory Committee

Attachment 1: Supporting documentation for the Committee's recommendation

1. The STAC's understanding of WTC exposures

In developing the 2012 recommendation that certain cancers be listed as WTC-related conditions, the STAC investigated and described potential exposures at the site. Our understanding of the nature of these exposures provides an important foundation of the current STAC recommendation regarding uterine cancer:

> "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 2001 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]
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> "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. Dust 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]
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> "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.

"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.[24] 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."[1]

2. The STAC's understanding of potential exposures to endocrine-disrupting chemicals (EDCs) at the WTC sites and other exposure areas and their potential role in causing endometrial cancers

In discussing the potential that WTC exposures may cause cancer in 2012, the STAC focused on classes of agents for which there was substantial evidence regarding cancer in animals and humans. These included asbestos, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls, dioxins and furans, metals, and volatile and semi-volatile organic compounds (VOCs). Although some of these agents are EDCs, in its 2012 report the STAC did not specifically review this category of agents, which are of particular importance in evaluating WTC exposures that may be related to uterine cancer.[1]

As defined by The Endocrine Society: "An endocrine-disrupting chemical (EDC) is an exogenous chemical, or mixture of chemicals, that can interfere with any aspect of hormone action. The potential for deleterious effects of EDC must be considered relative to the regulation of hormone synthesis, secretion, and actions and the variability in regulation of these events across the life cycle. The developmental age at which EDC exposures occur is a critical consideration in understanding their effects. Because endocrine systems exhibit tissue-, cell-, and receptor-specific actions during the life cycle, EDC can produce complex, mosaic effects."[25]

Studying the potential health effects of exposure to EDCs is inherently challenging and much remains unknown despite decade of research. As described in a recent review: "Because they have multiple mechanisms of action, EDCs can act simultaneously at the level of the receptor, hormone synthesis, and hormone degradation. This can lead, for example, to estrogenic or antiandrogenic effects, sometimes creating integrated estrogenic signals not predicted by studying each action alone. Further complicating research, compounds that alter thyroid signaling can affect the actions of other hormones or EDCs. If EDCs interact like hormones, the most sensitive endpoint can change depending on the endocrine-active compounds present and even their pattern of exposure. The long time period between early exposures and the development of disease later in life makes it challenging to trace morbidity due to EDC exposure; this pattern is further complicated by the potential effects of developmental "windows of susceptibility," when any endocrine perturbation can have important effects."[26] A characteristic of EDCs is that they can act at very low levels of exposure, often showing a nonmonotonic exposure response curve with greater effects at very low and high doses.[26]

Disturbance of the balance in sex steroid hormones resulting from EDC exposure is a plausible mechanism for the development of endometrial cancer among WTC responders and survivors. Imbalances in sex steroid hormones producing excess stimulation of endometrial epithelium by estrogen relative to progesterone are thought to play a critical role in the etiology of endometrial carcinomas. Estrogen, when insufficiently opposed by progesterone, has proliferative effects on the endometrium, which may result in a higher probability of random mutations in oncogenes and tumor suppressor genes. Endometrial cells that acquire multiple mutations without appropriate repair mechanisms may gain a growth advantage and develop into clones of cancer

cells.[27] Although the relationship between exposure to EDCs and endometrial cancer risk is highly plausible, for the reasons described above, epidemiological studies have limited ability to detect such these complex associations. Hormonally related cancers which are potential target organs for carcinogenesis related to EDC exposures include thyroid cancer, breast cancer, testicular and prostate cancer, and all cancers of the female reproductive tract, all of which except for uterine cancer are considered WTC-related conditions.

Based on the inventory of 9/11 agents,[13] EDCs present the WTC site include cadmium, perfluoroalkyl substances, phthalates, polybrominated diphenyl ethers (PBDEs), polychlorinated biphenyls (PCBs), polychlorinated dibenzo-para-dioxins, and polychlorinated dibenzofurans (PCDD/Fs). In the analyses of settled dust and smoke samples collected in the first days after the collapse and fire, levels of PCBs, benzo-p-dioxins (PCDDs), and dibenzofurans (PCDFs) were in the nanograms per gram (ng/g) and picograms per gram (pg/g) range. Levels of PBDEs were in the micrograms per gram (μg/g) range.[28] Samples of ambient organic films deposited on exterior window surfaces from lower Manhattan and Brooklyn in New York City collected six weeks after 9/11 found orders of magnitude higher levels of PCDD/Fs compared to a background site 3.5 km away in Brooklyn.[28] Ash-laden runoff samples collected in Rector Street on 9/14 and 9/20 also demonstrated the release of PCBs, PBDEs, polybrominated dibenzo-para-dioxins and PBDD/Fs from the incident.[29]

Among the biomonitoring studies available to the STAC, two provide the clearest evidence for EDC exposure at the WTC site. A study of perfluorochemicals in plasma collected from New York State and National Guard personnel working in the vicinity of the WTC between September 11 and December 23, 2001 found that levels of perfluorooctanoic acid (PFOA) and perfluorohexanesulfonate (PFHxS) were approximately 2 times higher in WTC responders compared to the U.S. general population.[30] A study conducted among 110 adolescents who lived, attended school, or were present in lower Manhattan on 9/11 recruited from the WTC Health Registry (WTCHR) and unexposed youths found that median PCDD/F levels were statistically significantly higher among WTCHR participants compared to non-WTCHR participants for 16 out of 17 congeners. Mean and median TEQ concentrations in WTCHR participants were more than 7 times those in non-WTCHR participants (72.5 vs. 10.1 and 25.3 vs. 3.39 pg/g lipid, respectively).[31]

The potential toxicity of the high concentrations of PBDEs in WTC dust has received less attention than the presence and toxicity of other EDCs. Due to their bio persistence and toxicity, pentaBDE and octaBDE mixtures were voluntarily withdrawn from the U.S. marketplace by their manufacturers at the end of 2004, and decaBDE was not allowed to be manufactured or imported into the U.S. after December 31, 2013. Prior to their withdrawal from the market, the main use of decaBDE was for electronic enclosures, such as television cabinets, octaBDE was largely used in plastics for business equipment, and pentaBDE was principally used in foam for cushioning in upholstery, all of which were present in large quantities in WTC offices. PBDEs have been strongly associated with developmental neurotoxicity and thyroid hormone disruption, and recent studies in animals have shown that PBDEs interfere with estrogen- and androgen-mediated processes .[32] The highest concentration of PBDEs in WTC dust was for BDE-209

(3,3',4,4',5,5',6,6'-decabromodiphenyl ether), ranging from 1,330 μg/g at Sherry Street to 2,330 μg/g at Market Street; concentrations of BDE-47 (2,2',4,4'-tetrabromodiphenyl ether) ranged from 107 μg/g at Cortlandt Street to 174 μg/g at Market Street.[20] These concentrations are approximately 100 to 1000 times higher than levels of BDE-47 and BDE-209 measured in studies of dusts collected in U.S. residences during 2011 to 2014, which ranged from 1051 to 4204 ng/g for BDE-209 and 224-870 ng/g for BDE-47.[33]

The high levels of PBDEs in WTC dust are of substantial concern with respect to developmental effects as well as carcinogenicity. In 2009, the EPA released an Action Plan stating the concern that some PBDE congeners are persistent, bioaccumulative and toxic and that it intends to initiate a number of actions to limit the exposure and release of PBDE congeners and/or articles to which they have been added.[34] The EPA summarized animal studies of various commercial mixtures and individual congeners which suggested potential concerns about liver toxicity, thyroid toxicity, developmental toxicity, and developmental neurotoxicity. They stated that these findings and the presence of PBDEs in house dust and breast milk raise particular concerns about potential risks to children. In 2008, EPA published toxicological reviews of four PBDE congeners: tetraBDE (BDE-47), pentaBDE (BDE-99), hexaBDE (BDE-153), and decaBDE (BDE-209). Neurobehavioral effects were identified as the critical endpoint of concern for each of the four congeners. For decaBDE, EPA also proposed that the data support a finding of "suggestive evidence of carcinogenic potential".[34]

While there is no direct evidence relating the high levels of PBDEs in WTC dust to uterine cancer, some toxicologic studies provide indirect evidence for such an association. One study found that BDE-209 increased the viability and proliferation of cells in several types of cancer, including breast cancer, cervical cancer, and ovarian cancer.[35] Another study found that BDE-47 promoted cell growth, migration and chemoresistance of endometrial cancer cells both in vivo and in vitro.[36]

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