# Summary of WTC Health Program STAC recommendations regarding uterine cancer

**Draft report prepared by:**

Sophie Balk, Michael Larrañaga, Nicholas Newman, Robin Sassman, Elizabeth Ward

# Charge to the STAC

"As you are aware, the WTC Health Program currently covers all major types of cancer, except for uterine cancer. I welcome the Committee's evaluation and recommendation on whether there is a reasonable scientific basis to support adding uterine cancer to the List of WTC-Related Health Conditions."

# Material reviewed

- 2012 WTC Health Program STAC recommendations regarding cancer
- 2012 draft and final rulemaking regarding addition of certain types of cancers to the list of WTC-Related Health Conditions
- Subsequent rulemakings & amendments (breast/PCBs, prostate, rare cancers, cancer definitions)
- Literature regarding uterine cancer and endocrine disruptors

# Excerpts from 2012 WTC Health Program STAC conclusions regarding WTC 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.

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.

Exposures among community residents and those working and attending school in the area also have the potential to be significant. 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.

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.

# 2012 WTC Health Program STAC recommendations

- Made in the context that no cancers were yet covered
- Recommended criteria for deciding which cancer should be covered
- Recommended addition of specific cancers
- Gave serious consideration to the rationale for covering all cancers

# Is there a reasonable basis for covering all 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."

Excerpt from 2012 STAC Recommendation

# WTC Health Program Draft and Final Rulemaking (2012)

Method 1: Epidemiologic studies of 9/11-Exposed Populations

Method 2: Established causal association with a Health Condition Already on the List of WTC-Related Health Conditions

Method 3: Review of NTP and IARC Evaluations of Carcinogens in Humans/Cancer Types Identified by IARC as associated with a 9/11 exposure

Method 4: Review of Information Provided by the STAC Upon Request by the Administrator

# Is it biologically plausible that uterine cancer would be the only type of cancer not related to 9/11 exposures?

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.

- PTEN inactivation
- *KRAS* mutations
- Mutations in mismatch repair genes
- p53 mutations
- In common with breast and other hormonally-related cancers, endometrial cancers may exhibit estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor 2 (HER2) overexpression.

# Endocrine disruptors: breast and endometrial cancer

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 site is of special significance in evaluating risks associated with WTC exposures.

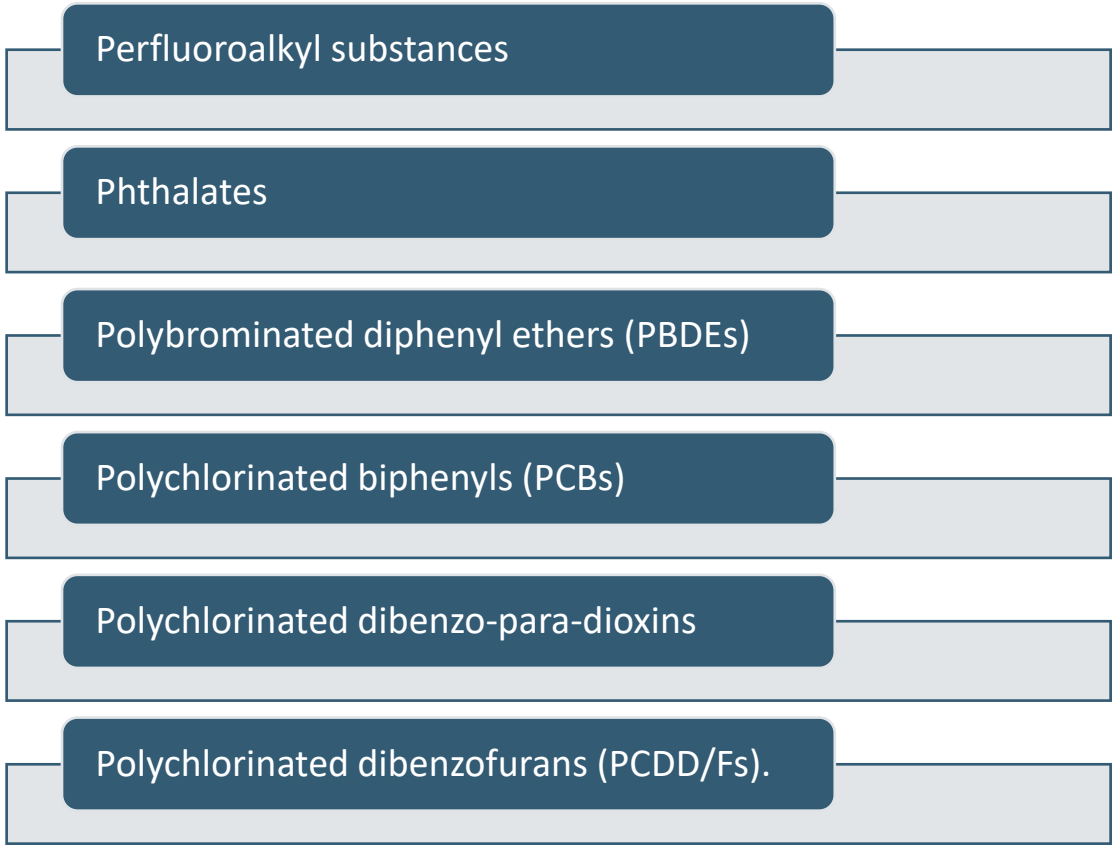
In the 2012 recommendations, the STAC focused on several classes of WTC exposures which have substantial evidence regarding cancer in animals and humans. These include asbestos, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls, dioxins and furans, metals, and volatile and semi-volatile organic compounds (VOCs).

In this report, we provide additional evidence regarding the presence and toxicity of EDCs in WTC exposures.

# Endocrine disruptors

"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."

# Endocrine disrupting chemical exposures: WTC site



# Challenges of studying and predicting effects of exposure to endocrine disruptors

- Multiple mechanisms of action; can act simultaneously at the level of the receptor, hormone synthesis and hormone degradation
- The most sensitive endpoint can change depending on the endocrine-active compounds present and even their pattern of exposure
- Long time period between early exposures and development of disease later in life; developmental windows of susceptibility
- EDCs can act at very low levels of exposure, often showing a non-monotonic exposure-response curve with greater effects at very low and high doses

# Evidence from epidemiological studies of WTC-exposed cohorts

The STAC recognizes that increases in uterine cancer risk have not been observed in studies of WTC-exposed cohorts 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.

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 understanding risks associated with WTC exposures.

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.

# Limitations of use of Method 3 with respect to reproductive cancers in women

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. 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.

# Additional considerations

- 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.
- Many comments from affected survivors, responders, and health care providers from WTCHP Centers of Excellence 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. There is strong support for inclusion of uterine cancer among WTC Health Program Center Directors and providers.
- 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.
- 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.
- Inclusion of uterine cancer in the WTC Environmental Health Center Pan-Cancer Database opens the door to future research that might provide greater insights into the role of WTC exposures in the development of uterine cancer, including the less common subtypes.

# WTC Health Program STAC Recommendation to the Administrator

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.