Executive Summary of Meeting

November 18, 2021

World Trade Center (WTC) Health Program
Scientific/Technical Advisory Committee (STAC)

The World Trade Center (WTC) Health Program Scientific/Technical Advisory Committee (STAC) was convened for its 13th meeting on November 18, 2021 from 11:00 a.m. to 4:00 p.m., EST. This was a virtual meeting conducted via Zoom. The public was welcome to follow the proceedings via live webcast on the World Wide Web. No registration was required.

Committee Members Present

Dr. Elizabeth Ward (chairperson)
Dr. Sophie Balk
Dr. Thomas Dydek
Ms. Mariama James
Dr. Anita Jose
Dr. Michael Larrañaga
Ms. Catherine McVay Hughes
Dr. Debra Milek
Dr. Lawrence Mohr
Dr. Jason Ostrowe
Dr. Robin Sassman
Dr. Leigh Wilson

The roll call confirmed that 12 members in attendance constituted a quorum for the STAC to conduct the meeting. Ms. Chandra Davis, Dr. John Meyer and Dr. Nicholas Newman were unable to attend the meeting. The roll was called subsequent to each break and lunch, with quorum established each time throughout the day. During the roll call, each committee member confirmed that they did not have conflicts of interest, and that no changes since they last filed the OGE 450 forms have occurred.

Employees of the U.S. Deptartment of Health and Human Services Present

Dr. Tania Carreón-Valencia, Senior Scientist and Designated Federal Officer
Dr. John Howard, Administrator, WTC Health Program and Director, National Institute for Occupational Safety and Health (NIOSH)

Dr. Dori Reissman, Deputy Administrator, WTC Health Program
Ms. Jessica Bilics, Policy Coordinator and Governmental Affairs Liaison, WTC Health Program
Dr. Geoffrey Calvert, Senior Medical Advisor, WTC Health Program
Ms. Emily Howell, Senior Attorney, Office of the General Counsel

Public Comments

The following persons provided oral public comments via Zoom during the public comment period from 1:30 p.m. to 2:00 p.m., EST: Kimberly Flynn on behalf of the WTC Health Program Survivors Steering Committee, Jennifer Waddleton, Matthew McCauley, Anne-Marie Principe, Piera Greathouse-Cox, and Gary Smiley. In addition, written public comments from the following persons and organizations were received and posted on the Federal eRulemaking Portal: https://www.regulations.gov: Ann Ajana, SHARE, Bethany Hardwig, StuyHealth, and Jennifer Lee.

Administrator's Opening Remarks

Dr. John Howard, Administrator of the WTC Health Program and Director of the National Institute for Occupational Safety and Health, welcomed the committee. He reminded the STAC that in the previous meeting they were charged 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. Finally, he thanked those members that would complete their terms after the meeting.

Updated Policy and Procedures for Adding Cancer Conditions

Ms. Jessica Bilics, Policy Coordinator and Governmental Affairs Liaison for the WTC Health Program provided an overview of the *Updated Policy and Procedures for Adding Cancer Conditions to the List of WTC-Related Health Conditions* (Appendices A and B). This policy governs the evaluation of evidence of a causal association between 9/11 agents and a type of cancer. The policy updates presented by Ms. Bilics fell under three categories. The first category of updates involved the concurrent identification of peer-reviewed published epidemiologic studies regarding the type of cancer among 9/11-exposed populations and regarding potential causal association between a condition already on the List and that cancer, which previously involved two non-concurrent steps. The second category of updates provided consistency throughout the document, as well as alignment to the *Policy and Procedures for Adding Non-Cancer Conditions to the List of WTC-Related Health Conditions*. The third category of updates involved clarification of the four methods. These methods were not changed but more detail was provided on the role of the WTC Health Program in the application of Methods 1 through 3 versus the role of the committee in Method 4, the review of information by the STAC.

STAC Workgroup Report

Dr. Ward reported on behalf of the workgroup that wrote a draft report describing the committee's conclusion, scientific rationale, and supporting evidence for adding uterine cancer as a WTC-related health condition (Appendix C). Members of the workgroup included Dr. Sophie Balk, Dr. Michael Larrañaga, Dr. Nicholas Newman, Dr. Robin Sassman, and Dr. Elizabeth Ward. Upon evaluation of the evidence, the workgroup stated that because "[m]echanisms for carcinogenesis resulting from endogenous and exogenous exposures are similar for most cancer types ... it is ... highly implausible that uterine cancer would be the only cancer not related to WTC exposures." In fact, in reviewing the literature, the workgroup found that uterine cancer "shares many of the same genetic mechanisms with cancers already included in [the] List of WTC-Related Health Conditions." Because exposure to endogenous and exogenous hormones is associated with both uterine and breast cancer, the STAC found exposure to endocrine disrupting chemicals in WTC dust to be "particularly relevant." The STAC recommendation includes additional evidence supporting the association between endocrine disrupting chemicals and uterine cancer.

The workgroup also commented on the inability of existing and future epidemiologic studies in the 9/11-exposed responder population – the most studied 9/11-exposure cohort – to accurately capture uterine cancer incidence because of the small number of female responders. Moreover, the report noted that studies of carcinogens by the World Health Organization's International Agency for Research on Cancer often include industrial cohorts, which regularly include few or no females, making finding an association between a 9/11 agent with uterine cancer highly unlikely.

Finally, the workgroup considered public comment as well as the strong support of the WTC Health Program Clinical Centers of Excellence for the addition of uterine cancer to the List, noting that many Program members and advocates feel the exclusion of uterine cancer from the List is "illogical and unfair and may cause tangible harm."

Committee's Deliberations

Following deliberation and minor edits to the draft report, all members present voted to approve the report (Appendix D) and recommended that the Administrator add uterine cancer to the List. The STAC concluded that, "[i]n 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".

Certification Statement

I hereby certify that, to the best of my knowledge and ability, the foregoing executive summary of the November 18, 2021, meeting of the World Trade Center Health Program Scientific/Technical Advisory Committee (STAC) is accurate and complete.

Elizabeth Ward, PhD
Chair, STAC

Appendix A

Policy and Procedures for Adding Types of Cancer to the List of WTC-Related Health Conditions

Policy and Procedures for Adding Types of Cancer to the List of WTC-Related Health Conditions

John Howard, M.D., Administrator
World Trade Center Health Program

May 14, 2014
Revised May 11, 2016
Updated May 1, 2019
Updated November 18, 2021

Note for May 11, 2016 Revision: This version (1) clarifies that a type of cancer can be added if the criteria of *any* of the four methods are met; and (2) adds peer review procedures when the Administrator proposes to add a type of cancer to the List of WTC-Related Health Conditions.

Note for May 1, 2019 Update: This version incorporates non-substantive changes to update the definition of "9/11 agents" and describe the Inventory of 9/11 agents as established in the "Development of the Inventory of 9/11 Agents," published July 17, 2018.

Note for November 18, 2021 Update: This version clarifies the role of the WTC Health Program in the application of Methods 1-3 versus the role of the Scientific/Technical Advisory Committee (STAC) in Method 4, the Review of Information by the STAC.

I. Authority

The *Policy and Procedures for Adding Types of Cancer to the List of WTC-Related Health Conditions* is based on the James Zadroga 9/11 Health and Compensation Act of 2010 ("Act"),[1] the Final Rule, "*World Trade Center Health Program: Addition of Certain Types of Cancer to the List of WTC-Related Health Conditions*,"[2] and the World Trade Center (WTC) Health Program regulations.[3]

II. Introduction

[1] Pub. L. 111-347, as amended by Pub. L. 114-113 and Pub. L. 116-59, codified at 42 U.S.C. § 300mm *et seq*.

[2] 77 Fed. Reg. 56138 (Sept. 12, 2012). *See* http://www.gpo.gov/fdsys/pkg/FR-2012-09-12/pdf/2012-22304.pdf.

[3] 42 C.F.R. Part 88.

The Act provides two pathways to initiate the process to propose adding a health condition, including types of cancer, to the List of WTC-Related Health Conditions ("List").[4] The Administrator of the WTC Health Program initiates the process either (1) at his own discretion,[5] or (2) after receiving a valid petition[6] from an interested party.[7] Regardless of which pathway is taken, a health condition may only be added to the List by rulemaking.

III. Initial Review of Scientific and Medical Information and Administrator Determination on whether to Proceed with Assessment

Once the process of determining whether to propose adding a type of cancer to the List is initiated, the WTC Health Program's Science Team reviews the scientific literature to determine if the available scientific information[8] has the potential to provide a basis for a decision on whether to add the type of cancer to the List.

A. Literature Search

The literature search identifies and gathers information from the following sources for review:

1. Peer-reviewed,[9] published,[10] epidemiologic studies[11] of the cancer in 9/11-

[4] 42 U.S.C. § 300mm-22(a)(6)(B).

[5] 42 U.S.C. § 300mm-22(a)(6)(A).

[6] When the Administrator receives a submission from an interested party to add a health condition to the List, he follows the steps outlined in the "Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions" (available at: http://www.cdc.gov/wtc/policies.html) and determines whether the submission meets the requirements for a petition specified in 42 C.F.R. § 88.16(a)(1).

[7] 42 U.S.C. § 300mm-22(a)(6)(E); 42 C.F.R. § 88.1 ("Interested party means a representative of any organization representing WTC responders, a nationally recognized medical association, a WTC Health Program CCE or Data Center, a State or political subdivision, or any other interested person").

[8] Information may be gathered by the Program in a search of the peer-reviewed, published scientific literature of epidemiologic studies of 9/11 populations or supplied to the Administrator by a petitioner. The Program then evaluates the information to determine whether it meets the standard of scientific evidence necessary for the Administrator to make a determination. Scientific evidence is a subtype of information that supports, refutes, or has no impact on a determination whether an association exists between a specified exposure and a specific health effect.

[9] The Administrator has determined that articles and reports published in CDC's *Morbidity and Mortality Weekly Report* (MMWR) are also eligible for review for their potential to provide a basis for deciding whether to propose adding a condition to the List. MMWR publications undergo a review process that has been independently evaluated and found to be similar or equivalent to peer review.

[10] Published studies include those published online ahead of print.

[11] Epidemiologic studies include "descriptive epidemiologic studies" which describe the "what, who, where, when and why/how of a situation," as well as analytic epidemiologic studies which involve the use of a comparison group. *See* Centers for Disease Control and Prevention, HHS, *Principles of Epidemiology in Public Health Practice* (3rd ed. 2012), at 1-46. The WTC Health Program reviews these epidemiologic studies to determine if they identify causal

exposed populations;

2. Peer-reviewed, published, epidemiologic studies regarding the potential causal association between a condition already on the List and that cancer; and

3. The most recent classifications of the World Health Organization's International Agency for Research on Cancer (IARC) *Monographs on the Identification of Carcinogenic Hazards to Humans* (Monographs)[12] and the National Toxicology Program (NTP) *Report on Carcinogens* (RoC).[13]

B. Literature Review

The studies found in the literature search[7] are then further reviewed for quantity and quality[14] and their potential to provide a basis for deciding whether to propose adding the type of cancer to the List. In addition, any medical basis provided in the valid petition is included in this review.[15] The findings of this literature review, including any information about IARC classifications and the NTP *RoC*, are documented and discussed with the Administrator.

C. Administrator Determination on whether to Proceed with Assessment

The Administrator determines whether the information gathered in the literature review has the potential to provide a basis for a decision on whether to add the type of cancer and whether to proceed with an assessment of that information.

1. Where the Administrator determines that the information does not provide a sufficient basis for a decision:

   a. The evaluation is documented and archived according to document management requirements; and

   b. If the evaluation was initiated by a valid petition, then the Administrator:

      i. Publishes a determination in the *Federal Register* that the

associations between exposures and health outcomes with the potential to provide a basis for deciding whether to propose adding a condition to the List.

[12] WHO International Agency for Research on Cancer (IARC) Monographs on the Identification of Carcinogenic Hazards to Humans (Monographs). http://monographs.iarc.fr/. Accessed October 13, 2021.

[13] NTP Report on Carcinogens (RoC). https://ntp.niehs.nih.gov/go/roc14. Accessed October 13, 2021.

[14] The evaluation of quantity and quality includes consideration of any limitations, such as bias or confounding, of the reviewed studies.

[15] *See* 42 C.F.R. § 88.16(a)(1)(iv); *see also* "Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions" (available at: http://www.cdc.gov/wtc/policies.html).

available information is insufficient to take action;[16] and

ii. Notifies the petitioner in writing of the decision concurrently with the publication of the determination in the *Federal Register*.

2. Where the Administrator determines that the available information has the potential to provide a basis for a decision, the Administrator may:

a. Direct the Science Team to conduct a full assessment of the scientific and medical information and provide input on whether the available information supports a causal association between 9/11 exposures and the type of cancer [*see* Section IV.A.1.], and

b. In addition, the Administrator may request advice from the WTC Health Program Scientific/Technical Advisory Committee (STAC) [*see* Sections IV.A.1. Method 4 and V.A.].

IV. Assessment of Scientific and Medical Information

A. Assessment Process

1. Administrator's Review Criteria

The Administrator of the WTC Health Program has developed four methods for determining whether to add a type of cancer to the List. In order to propose adding a type of a cancer to the List, the Administrator's review of the information must demonstrate fulfillment of at least one of the four methods.

The Administrator will direct the Science Team to assess the available information under Methods 1 through 3. If the Administrator requests a recommendation from the STAC, Method 4 may be used to determine whether to add a type of cancer to the List.

Method 1. Epidemiologic Studies of September 11, 2001 Exposed Populations.

The peer-reviewed, published, epidemiologic studies of 9/11-exposed populations are assessed by applying the following criteria extrapolated from the Bradford Hill criteria,[17] as appropriate:

a. Strength of the association between a 9/11 exposure and a type of cancer (including the precision of the risk estimate[18]);

[16] 42 U.S.C. § 300mm-22(a)(6)(B)(iv).

[17] *See* Hill AB [1965]. The environment and disease: association or causation? Proc R Soc Med 58:295–300.

[18] A precision of the risk estimate describes the uncertainty inherent in estimating the strength of association (the effect size) between exposure and health effect from observational data. It is often expressed as a confidence

b. Consistency of the findings across multiple studies. If only a single published epidemiologic study is available for assessment, the consistency of findings cannot be evaluated and more emphasis will be placed on evaluating the strength of the association and the precision of the risk estimate;

c. Biological gradient, or dose-response relationships between 9/11 exposures and the type of cancer; and

d. Plausibility and coherence with known facts about the biology of the type of cancer.

Method 2. Established Causal Associations.

A type of cancer may be added to the List if there is well-established scientific support published in multiple peer-reviewed epidemiologic studies for a causal association between a condition already on the List and that cancer.

Method 3. Review of Evaluations of Carcinogenicity in Humans.

A type of cancer may be added to the List under Method 3 only if both of the following criteria are satisfied:

3A. Published Exposure Assessment Information. A 9/11 agent[19] included in the Inventory of 9/11 Agents[20] is identified; and

3B. Evaluation of Carcinogenicity in Humans from Scientific Studies. NTP has determined that the 9/11 agent is *known to be a human carcinogen* or is *reasonably anticipated to be a human carcinogen*, and IARC has determined there is *sufficient* or *limited* evidence in humans that the 9/11 agent causes the type of cancer.

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interval illustrating a range of values that contains the true effect size. A narrow confidence interval indicates a more precise measure of the effect size and a wider interval indicates greater uncertainty.

[19] Chemical, physical, biological, or other hazards reported in a published, peer-reviewed exposure assessment study of responders, recovery workers, or survivors who were present in the New York City disaster area, or at the Pentagon site, or the Shanksville, Pennsylvania site, as those locations are defined in 42 C.F.R. § 88.1, as well as those hazards not identified in a published, peer-reviewed exposure assessment study, but which are reasonably assumed to have been present at any of the three sites. WTC Health Program, "Development of the Inventory of 9/11 Agents," published July 17, 2018, available at: https://wwwn.cdc.gov/ResearchGateway/Content/pdfs/Development_of_the_Inventory_of_9-11_Agents_20180717.pdf.

[20] The Inventory of 9/11 Agents is composed of those agents identified in Tables 1-4 of the document, "Development of the Inventory of 9/11 Agents." *See* WTC Health Program, "Development of the Inventory of 9/11 Agents," published July 17, 2018, available at: https://wwwn.cdc.gov/ResearchGateway/Content/pdfs/Development_of_the_Inventory_of_9-11_Agents_20180717.pdf.

Method 4. Review of Information by the WTC Health Program Scientific/Technical Advisory Committee (STAC).

A type of cancer may be added to the List if the STAC recommends the addition and provides a reasonable basis for the recommendation.[21] To assist the Administrator in understanding whether the STAC's recommendation has a reasonable basis, the STAC must describe in detail the basis for its recommendation and, if applicable, any evidentiary sources it has used to support its recommendation.

2. Administrator's Consideration

The Science Team ensures that the results of their assessment are documented and provided to the Administrator (additional discussion between the Science Team and the Administrator may occur). If applicable, the Designated Federal Officer for the STAC ensures that the STAC's recommendation and basis are documented and provided to the Administrator. The Administrator will review the findings and determine whether one or more of the four methods have been met.

B. Administrator Actions

1. If the assessment was performed in response to a valid petition, the Administrator takes one of the following actions:[22]

   a. If a review of the information demonstrates fulfillment of at least one of the four methods described in IV.A.1. above, the Administrator publishes in the *Federal Register* a notice of proposed rulemaking (NPRM) to add the type of cancer to the List;[23] or

   b. If a review of the information does not demonstrate fulfillment of at least one of the four methods described in IV.A.1. above and does demonstrate that 9/11 exposures are not causally related to the type of cancer, the Administrator publishes in the *Federal Register* a determination not to propose a rule and the basis for such determination;[24] or

   c. If a review of the information indicates the information is insufficient to take either of the actions in IV.B.1.a. or b. above, then the Administrator

[21] The STAC may base its recommendation and reasonable basis on criteria other than those outlined in Methods 1-3.

[22] If the Administrator exercises his discretion to request review and recommendation from the STAC, he will also take the STAC's recommendation into consideration in determining which of the actions described in Section IV.B.1. to take [*see* Section V].

[23] 42 U.S.C. § 300mm-22(a)(6)(B)(ii).

[24] 42 U.S.C. §300mm-22(a)(6)(B)(iii).

publishes that determination in the *Federal Register*.[25]

2. If the assessment was initiated by the Administrator, the Administrator may take one of the actions described in Section IV.B.1. above.

V. WTC Health Program Scientific/Technical Advisory Committee (STAC)

A. Convening the STAC

The Administrator may convene the STAC to request a recommendation on whether to add a type of cancer to the List [*see* Section IV.A.1. Method 4].

B. Meeting Procedures

If the Administrator decides to request a recommendation from the STAC regarding a type of cancer, the Designated Federal Officer (DFO) works with the STAC to schedule meetings and assemble information needed to develop recommendations on whether there is a reasonable basis to support adding the type of cancer to the List. The Administrator provides a charge to the STAC and all proceedings are conducted in accordance with the Federal Advisory Committee Act.[26]

C. Time Limits

1. If a valid petition to add a type of cancer to the List has been received and the Administrator decides to exercise his discretion to convene the STAC, then the Administrator must make his request for a STAC recommendation within 90 days of receipt of the petition.

2. If the Administrator requests a recommendation from the STAC, whether following the receipt of a valid petition or as part of an Administrator-initiated review, the Administrator will send a letter to the STAC Chair requesting advice on whether to add the type of cancer and establishing a period of 90 days, with potential extension up to 180 days, for the committee to provide recommendations and their reasonable basis for those recommendations.

3. After receiving the recommendations from the STAC, the Administrator evaluates the STAC's recommendation and takes appropriate action under Section IV.B. not later than 90 days after receipt of the recommendation.

Exception: The option found in Section IV.B.1.c. above is not an option for the Administrator when advice has been requested from the STAC in response to a valid petition.

VI. Rulemaking

[25] 42 U.S.C. §300mm-22(a)(6)(B)(iv).

[26] 5 U.S.C. App.

A. Notice of Proposed Rulemaking (NPRM)

If the Administrator decides to propose adding the health condition to the List, he publishes an NPRM in the *Federal Register* to that effect. The NPRM solicits public comments. The Administrator also conducts an independent peer review of the Program's evaluation of the scientific and technical evidence supporting the addition of the condition.[27]

1. Public comments. All public comments received are considered and responded to, as appropriate, in the final rule preamble. The public comment period will remain open no less than 45 days after publication of the NPRM in the Federal Register to allow the public an additional 15 days to comment after peer reviewers' comments are posted. The public comments are posted to the rulemaking docket.

2. Independent Peer Review. The Program requests peer review from three subject matter experts for the health condition to be added.

    a. Identification of peer reviewers. The Administrator identifies qualified peer reviewers who are outside of NIOSH, with input provided by the STAC.[28]

    b. Charge to peer reviewers. Peer reviewers are asked to review the evaluation of the evidence for adding the health condition to the List within the context of this policy, and provide a brief written report answering the following questions:[29]

        i. Are you aware of any other studies which should be considered? If so, please identify them.

        ii. Have the requirements of this *Policy and Procedures* been fulfilled? If not, please explain which requirements are missing or deficient.

        iii. Is the interpretation of the available information appropriate, and does it support the conclusion to add the health condition, as described in the regulatory text, to the List? If not, please explain why.

    c. All peer reviewers' comments are considered and responded to in the final rule preamble. The peer reviews are compiled without attribution and posted to the rulemaking docket at the end of 30 days.

[27] 42 U.S.C. § 300mm-22(a)(6)(F).

[28] 42 U.S.C. § 300mm-22(a)(6)(G)(ii).

[29] The questions given to the peer reviewers may be modified by the Administrator, as necessary, for the specific health condition being considered.

B. Final Rule

After reviewing the public comments and peer reviews, the Administrator determines whether the rationale discussed in the NPRM is changed by the information supplied by commenters. If the evidence continues to support the addition of the type of cancer:

1. A final rule is developed and published in the *Federal Register*;

2. The condition is added to the List; and

3. Implementation procedures are developed, which may include:

    a. Exposure qualifications;

    b. Time intervals/latency; and

    c. Other procedures as appropriate to the type of cancer.

Appendix B

Presentation

Updates to the Policy and Procedures for Adding Cancer Conditions

WORLD TRADE CENTER HEALTH PROGRAM

Shanksville


New York City


Pentagon

Updates to the Policy and Procedures to Add Cancer Conditions

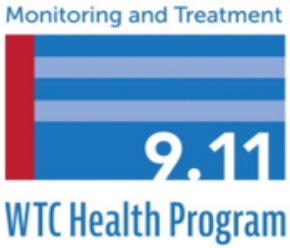
Jessica Bilics, MPH
Policy Coordinator and Governmental Affairs Liaison

World Trade Center Health Program
National Institute for Occupational Safety and Health

Monitoring and Treatment 9.11 WTC Health Program

Pentagon photo courtesy of FEMA. Shanksville photo by vlashton, courtesy of Flickr

Updates to the Policy and Procedures



Policy and Procedures for Adding Types of Cancer to the List of WTC-Related Health Conditions

John Howard, M.D., Administrator
World Trade Center Health Program

May 14, 2014
Revised May 11, 2016
Updated May 1, 2019
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Note for November 18, 2021 Update: This version clarifies the role of the WTC Health Program in the application of Methods 1-3 versus the role of the Scientific/Technical Advisory Committee (STAC) in Method 4, the Review of Information by the STAC.

Categories of Updates to the Policy

- Identification of peer-reviewed, published, epidemiologic studies
- Consistency and alignment with the policy for adding a non-cancer condition to the List of WTC-Related Health Conditions (List)
- Clarification of the four Methods and roles

Identification of Studies Updates

- **May 2019 Policy**
  - **Section III.A. and B.**
  - **First step: Literature search**
    - Studies regarding the type of cancer among 9/11-exposed populations
    - Studies regarding potential causal association between a condition already on the List and that cancer
    - The most recent classifications of the World Health Organization's International Agency for Research on Cancer (IARC) and the National Toxicology Program (NTP) Report on Carcinogens
  - **Second step: Literature review**
    - Identify peer-reviewed, published, epidemiologic studies found among the results of the above literature search
    - Evaluate peer-reviewed, published, epidemiologic studies for quantity and quality

Identification of Studies Updates (continued)

- **November 2021 Policy**
  - **Section III.A. and B.**
  - **First step: Literature search**
    - Peer-reviewed, published, epidemiologic studies regarding the type of cancer among 9/11-exposed populations
    - Peer-reviewed, published, epidemiologic studies regarding potential causal association between a condition already on the List and that cancer
    - The most recent classifications of the IARC and NTP Report on Carcinogens
  - **Second step: Literature review**
    - Evaluate peer-reviewed, published, epidemiologic studies for quantity and quality

Consistency and Alignment Updates

- Specified IARC's *Monographs on the Identification of Carcinogenic Hazards to Humans* and added citations in footnotes for both IARC's Monographs and NTP's *Report on Carcinogens*

- "Information" and "Evidence" – both used throughout May 2019 policy
  - Updated to "Information" in November 2021 policy and defined the term in a footnote:

"Information may be gathered by the Program in a search of the peer-reviewed, published scientific literature of epidemiologic studies of 9/11 populations or supplied to the Administrator by a petitioner. The Program then evaluates the information to determine whether it meets the standard of scientific evidence necessary for the Administrator to make a determination. Scientific evidence is a subtype of information that supports, refutes, or has no impact on a determination whether an association exists between a specified exposure and a specific health effect."

Consistency and Alignment Updates (continued)

- Updated section references from prior versions
- Specified public comment period and timing of posting of peer reviewers' comments, in event of Notice of Proposed Rulemaking (NPRM)
  (45 days total with peer reviewers' comments posted after 30 days)

Clarification of Methods and Roles Updates

- **Method 1:** Peer-reviewed, published, epidemiologic studies of the cancer in 9/11-exposed populations;
- **Method 2:** Peer-reviewed, published, epidemiologic studies of causal associations between a health condition already on the List of WTC-Related Health Conditions (List) and the cancer;
- **Method 3:** Review of evaluations of carcinogenicity in humans based on classifications from National Toxicology Program (NTP) and International Agency for Research on Cancer (IARC); and
- **Method 4:** Review of information provided by the Scientific/Technical Advisory Committee (STAC).

Clarification of Methods and Roles Updates (continued)

- **Section IV.A.1.**
- **Methods 1 – 3**
  - Administrator directs Science Team to assess information
- **Method 4**
  - STAC recommends addition and provides reasonable basis
  - Added "recommendation," and clarified the details that should be provided regarding the STAC's reasonable basis. Added the following footnote:
    - The STAC may base its recommendation and reasonable basis on criteria other than those outlined in Methods 1 – 3.
- Administrator reviews findings from Methods 1 – 4 and determines whether one or more of the Methods have been met

Questions?

Appendix C

Presentation

Summary of WTC Health Program STAC Recommendations Regarding Uterine Cancer

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.

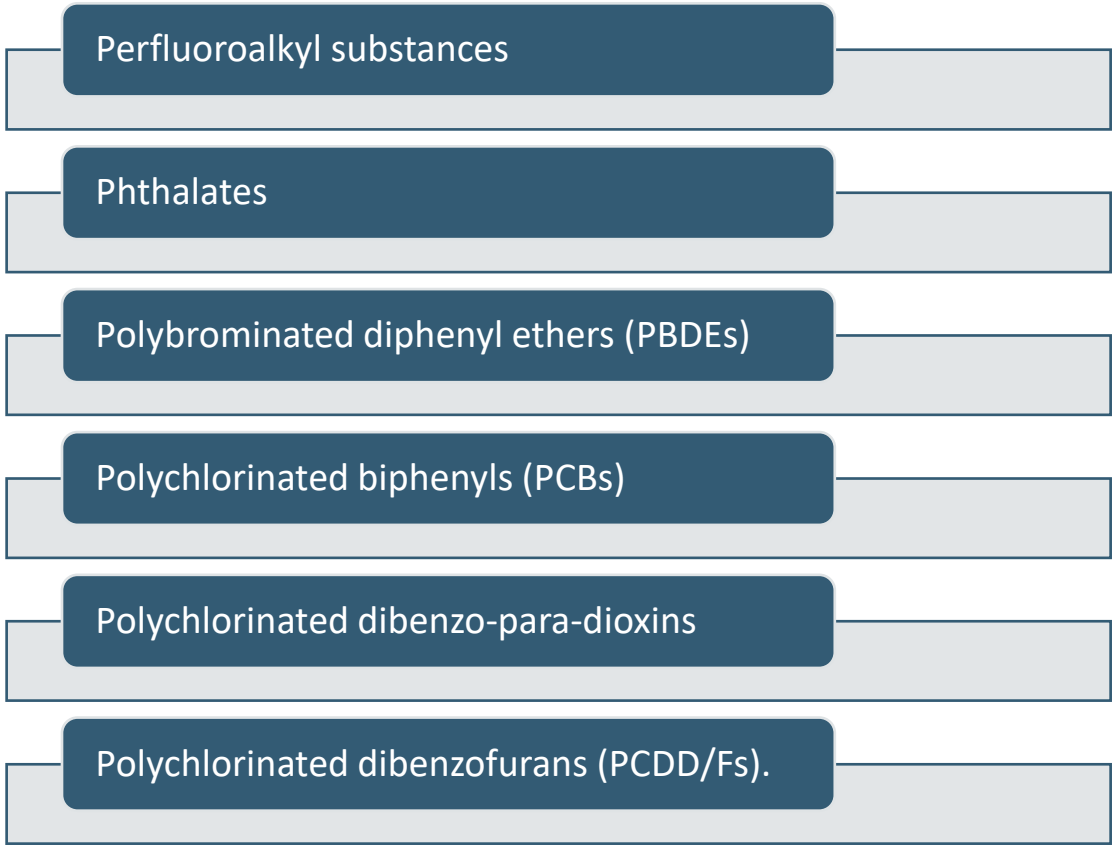
In the 2012 recommendations, the STAC focused on several classes of WTC exposures which have substantial evidence regarding cancer in animals and humans. These include asbestos, polycyclic aromatic hydrocarbons (PAHs), polychlorinated biphenyls, dioxins and furans, metals, and volatile and semi-volatile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

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

Appendix D

Committee Recommendation

Letter from Dr. Elizabeth Ward, Chair of the STAC, to the Administrator, regarding the STAC's resolution on the addition of uterine cancer to the List of WTCHP Covered Conditions

November 18, 2021

John Howard, MD
Administrator, World Trade Center Health Program
Centers for Disease Control and Prevention (CDC)
National Institute for Occupational Safety and Health (NIOSH)
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Patriots Plaza
Washington, D.C. 20201

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 1 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

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[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]
>
> "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]
>
> "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.[20] 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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