December 13, 2022

WTC Health Program

Scientific Considerations for Addition of Uterine Cancer to the List of Covered Conditions by the World Trade Center Health Program (Final)

The final version of the white paper includes updates made in response to peer reviews provided to the notice of proposed rulemaking published in the *Federal Register* on May 10, 2022, and a summary of the WTC Health Program's actions since receipt of the STAC recommendation on November 29, 2021.

Changes to the second revised version of the white paper include:

- The definition of EDC by the Endocrine Society, including a reference to the Society's position statement on EDCs.
- Revised Table 3 to include an additional 84 agents, mixtures, and categories of agents known and potential EDCs. The Table is sorted in alphabetical order and no longer includes the EPA classifications of carcinogenicity.

Changes to the first revised version of the white paper, published on September 16, 2021, include:

- Summaries of three additional studies on 9/11 exposures and cancer (Boffetta et al. [2016], Shapiro et al. [2020], and Li et al. [2021]).
- Table 2 and the corresponding study summaries are organized by study design and year of publication.
- 3,3',4,4',5-Pentachlorobiphenyl is listed as an IARC Group 1 carcinogen on Table 3. It has also been added to the list of carcinogenic endocrine disruptors listed on page 30.
- Summaries of two additional studies on asbestos exposure and uterine cancer (Germani et al. [1999] and Magnani et al. [1993]). In addition, clarification was provided that the study by Magnani et al. [2007] was likely to include uterine and cervical cancer cases combined.
- URLs and minor corrections on some references.

None of these additions and changes affected the conclusions of the original White Paper.

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I. Executive Summary

The World Trade Center (WTC) Health Program provides medical monitoring and treatment benefits for health conditions on the List of WTC-Related Health Conditions (the List). The List currently includes aerodigestive disorders, mental health conditions, musculoskeletal disorders, and cancers. The List was established in the James Zadroga 9/11 Health and Compensation Act of 2010 (Pub. L. 111–347, as amended by Pub. L. 114-113 and Pub. L. 116-59), which requires that new health conditions be added to the List by rulemaking. In addition to the Program's regulatory provisions in 42 C.F.R. Part 88, the WTC Health Program *Policy and Procedures for Adding Types of Cancer to the List of WTC-Related Health Conditions* governs the evaluation of evidence supporting the potential addition of a type of cancer to the List.

Uterine cancer is currently the only type of cancer not included in the WTC Health Program's List of WTC-Related Health Conditions (List). In September 2020, the WTC Health Program received a submission to add uterine cancer to the List. The medical basis for the submission was the contributing role of endocrine disrupting chemicals (EDCs) on the incidence rate of uterine cancers. Although this submission did not meet the Program's petition requirements, the Administrator instructed WTC Health Program staff to review the evidence for uterine carcinogenicity by EDCs and other 9/11 agents. This document provides the WTC Health Program's assessment of the currently available evidence to support adding uterine cancer to the List.

In addition to directing the Science Team to assess the available evidence supporting the addition of uterine cancer to the List, the Administrator asked the WTC Health Program Scientific/Technical Advisory Committee (STAC) for a recommendation regarding whether there was a reasonable basis for adding uterine cancer to the List.

The Administrator reviewed the available body of evidence, including the evidence presented in this White Paper and the STAC's comprehensive rationale and recommendation, and concluded that the totality of the available information provided a sufficient evidentiary basis to propose adding uterine cancer to the List. Subsequently, the Administrator and HHS Secretary published a notice of proposed rulemaking (NPRM) to propose the addition of uterine cancer to the List.

II. Background

The WTC Health Program provides medical monitoring and treatment benefits for health conditions on the List. The List currently includes aerodigestive disorders, mental health conditions, musculoskeletal disorders, and cancers. Currently, uterine cancer is the only type of cancer not included on the List.[1]

Uterine cancer is often referred to as endometrial cancer because more than 90 percent of cases occur in the endometrium. Known risk factors for uterine cancer include endometrial hyperplasia, hormone therapy with estrogen, selective estrogen receptor modulators, and obesity. Protective factors include increasing parity (number of pregnancies) and lactation, hormonal contraceptives, physical activity, and smoking.

A subtype of uterine cancer, uterine sarcoma, is covered by the WTC Health Program as a rare cancer – those cancers that have an incidence rate of less than 15 cases per 100,000 per year in the U.S. based on 2005-2009 average annual data age-adjusted to the 2000 U.S. population.[2] In addition, uterine cancers that arise from the use of tamoxifen to treat a WTC-certified cancer may be covered as a medically associated condition (MAC).

A. Procedures for Adding Cancers for Coverage in the WTC Health Program

The Zadroga Act established the List and permits the addition of more health conditions through rulemaking. The Zadroga Act provides two pathways to initiate the process of adding a health condition, including types of cancer, to the List: (1) the Administrator of the WTC Health Program initiates the rulemaking process and publishes a proposed rule or requests a recommendation from the STAC at his discretion; or (2) the Administrator initiates the process after receiving a petition from an interested party.[3]

In addition to the Program's regulatory provisions in 42 C.F.R. Part 88, the WTC Health Program *Policy and Procedures for Adding Types of Cancer to the List of WTC-Related Health Conditions* governs the evaluation of evidence supporting the potential addition of a type of cancer to the List.[4] The Policy and Procedures establishes that a review of the evidence must demonstrate fulfillment of at least one of four methods as basis to propose adding a condition to the List:

Method 1 – Epidemiologic studies of September 11, 2001 exposed populations

The WTC Health Program evaluates the "weight of evidence" from peer-reviewed, published, epidemiologic studies of 9/11-exposed populations, by following four following criteria of Bradford Hill's guidelines for assessing causation:[5]

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

b. Consistency of the findings across multiple studies;

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 casual association

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

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 included in the Inventory of 9/11 Agents is identified;[6] and
- *3B. Evaluation of carcinogenicity in humans from scientific studies*. The National Toxicology Program (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 the International Agency for Research on Cancer (IARC) has determined there is sufficient or limited evidence that the 9/11 agent causes a type of cancer.

Method 4 – Review of information provided by the WTC Health Program Scientific/Technical Advisory Committee (STAC)

A type of cancer may be added to the List if the STAC provides a reasonable basis for adding it.

B. Uterine Cancer: Definition, Types, and Risk Factors

Cancer of the uterine corpus (uterine cancer) is a type of cancer that begins to develop in the uterus. The uterus is the hollow, pear-shaped pelvic organ where a fetus develops. Uterine cancer is often referred to as endometrial cancer because more than 90 percent of cases occur in the endometrium (lining of the uterus); most of the remainder of uterine cancers originate in the myometrial muscle or, less commonly, the endometrial stroma.[7, 8]

Table 1 lists all subtypes of uterine cancer and their codes, according to the International Classification of Diseases, 10th Edition (ICD-10).[9]

Table 1. Classification of uterine cancers according to the International Classification of Diseases, 10th Edition (ICD-10)

ICD-10 Code	Name
C54	Malignant neoplasm of corpus uteri
C54.0	Malignant neoplasm of isthmus uteri
C54.1	Malignant neoplasm of endometrium
C54.2	Malignant neoplasm of myometrium
C54.3	Malignant neoplasm of fundus uteri

ICD-10 Code	Name
C54.8	Malignant neoplasm of overlapping sites of corpus uteri
C54.9	Malignant neoplasm of corpus uteri, unspecified
C55	Malignant neoplasm of uterus, part unspecified

According to the American Cancer Society,[10] in 2022 an estimated 65,950 cases of uterine cancer will be diagnosed in the United States and 12,550 women are expected to die from the disease. Endometrial cancer is the fourth most common cancer in U.S. women after cancers of the breast, lung/bronchus, and colon/rectum. The incidence peaks between ages 60 and 70 years, but 2 to 5 percent of cases occur before age 40 years.

The National Cancer Institute (NCI)[11] identifies the following as known factors that increase the risk of uterine cancer and provides a basis for their identification:

- *Endometrial hyperplasia*

  Based on solid evidence in prospective cohort studies, endometrial hyperplasia is associated with concurrent or subsequent development of cancer.

- *Hormone therapy with estrogen: Unopposed estrogen*

  Based on solid evidence in randomized controlled trials, cohort, and case-control studies, unopposed estrogen (estrogen therapy alone without the counterbalancing effects of progesterone) is associated with an increased risk of endometrial cancer. This excess risk can be eliminated by adding continuous progestin to estrogen therapy, but this combination is associated with an increased risk of breast cancer.

- *Selective estrogen receptor modulators (SERMs)*

  Based on solid evidence in multiple randomized controlled trials, use of tamoxifen (a SERM) for more than 2 years is associated with an increased risk of uterine cancer.

- *Obesity*

  Based on solid evidence in multiple randomized controlled trials, being overweight or obese, and adult weight gain are associated with an increased risk of uterine cancer.

NCI also indicates that the following factors decrease the risk of uterine cancer and provides a basis for their identification:

- *Increasing parity and lactation*

  Based on solid evidence in a prospective cohort study and case-control studies, increased number of pregnancies and duration of lactation are associated with a decreased risk of uterine cancer.

- *Hormonal contraceptives*

  Based on solid evidence in case-control studies and cohort studies, at least 1-year use of oral contraceptives containing estrogen and progesterone decreases uterine cancer risk, proportionate to duration of use.

- *Physical activity*

  Based on solid evidence in multiple cohort and case-control studies, increased physical exercise is associated with a decreased risk of uterine cancer.

- *Smoking*

  Based on evidence in prospective cohort and case-control studies, cigarette smoking is associated with a decreased risk of uterine cancer. This reduction in risk contrasts with the increased risks observed with many other non-respiratory-tract cancers, including those of the bladder, pancreas, and cervix uteri.

NCI also concluded that the following intervention has adequate evidence of no association with uterine cancer:

- *Fruits, vegetables, and vitamins*

  Cohort and case-control studies provide adequate evidence of no association between uterine cancer and diet or vitamin intake.

C. Previous Consideration of Uterine Cancer by the WTC Health Program

To date, the WTC Health Program has received eight submissions to add uterine cancer or uterine cancer subtypes to the List; seven of these submissions did not meet the requirements of the *Policy and Procedures for Handling Submissions and Petitions to Add a Health Condition to the List of WTC-Related Health Conditions* to qualify as petitions.[12] Submission 117 received in 2019 was determined to qualify as a petition (Petition 023); however, following a thorough review and evaluation of published, peer-reviewed epidemiologic evidence in 9/11 populations, the Administrator determined that the evidence was insufficient to add uterine cancer to the List.[13] In September 2020, the WTC Health Program received Submission 166 from the WTC Health Program Clinical Centers of Excellence (CCEs) to add uterine cancer to the List. The basis for the submission was that the WTC Health Program should consider the contributing role of endocrine disrupting chemicals (EDCs) on the incidence rate of uterine cancers. The submission did not meet the criteria to qualify as a petition, since no new medical basis was provided.

Although the submission from the CCEs did not qualify as a petition, the Administrator found that the issues raised regarding the contributing role of EDCs and the low number of women included in study populations with occupational 9/11 exposure merit further consideration. As a result, the Administrator exercised his discretion to initiate the process of deciding whether to propose adding uterine cancer to the List[4] and directed the WTC Health Program's Science Team to review the available scientific evidence for EDCs causing uterine cancer to determine if it has the potential to provide a basis for a decision on whether to add uterine cancer to the List.

III. WTC Health Program Evaluation of Available Evidence Regarding Uterine Cancer Among 9/11 Exposed Populations

Pursuant to the *Policy and Procedures for Adding Types of Cancer to the List of WTC-Related Health Conditions*,[4] the WTC Health Program conducted a literature review and assessed the available evidence using Methods 1, 2, and 3. The results of that assessment are summarized below:

Method 1 – *Epidemiologic Studies of September 11, 2001 Exposed Populations*. Five relevant peer-reviewed, published, epidemiologic studies were identified and reviewed. The studies do not provide consistent evidence of elevated uterine cancer incidence or mortality among WTC responders and survivors. The studies also do not report a dose-response relationship between 9/11 exposures and uterine cancer and the study designs may be susceptible to selection bias. As a result, collectively, these studies do not demonstrate a potential to provide a basis for a decision on whether to add uterine cancer to the List.

Method 2 – *Established Casual Association*. A thorough review of the scientific literature found that estrogen-secreting tumors are associated with endometrial cancer, but that these estrogen-secreting tumors are rare. Because estrogen-secreting tumors fall under the category of "rare cancers" in the List, uterine cancer can be added to the List only for members who have a certified estrogen-secreting tumor.

Method 3 – *Review of Evaluations of Carcinogenicity in Humans*. Four EDCs listed in the Inventory of 9/11 Agents are considered carcinogenic to humans by NTP or IARC: (1) 2,3,7,8-tetrachlorodibenzodioxin (TCDD); (2) 2,3,4,7,8-pentachlorodibenzofuran; (3) polychlorinated biphenyls (PCB); and (4) cadmium. None of these agents is considered to have sufficient or even limited evidence of uterine carcinogenicity. Further review of epidemiologic studies published after the NTP and IARC reports did not identify additional evidence of carcinogenicity to the uterus.

A complete discussion of the studies identified, and the Program's assessment follows.

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

The Science Team reviewed the epidemiologic studies of 9/11-exposed populations to determine if the body of evidence has the potential to provide a basis for a decision on whether to add uterine cancer to the List. In general, this review followed five key steps: (1) define the causal questions of interest and develop criteria for study selection; (2) develop a literature search protocol and conduct the search; (3) review, identify, and select the relevant information from available studies; (4) evaluate and integrate the evidence across studies; and (5) synthesize and interpret findings.

The epidemiological studies considered in the evaluation were focused on evaluating the health effects of 9/11 exposures among two groups of people, as described by the WTC Health Program:[14]

- WTC Responders: workers or volunteers who provided rescue, recovery, debris cleanup, and related support services on or in the aftermath of the September 11, 2001, attacks for certain amounts of time during the period between September 11, 2001, and July 31, 2002. There are four types of responders: Fire Department of the City of New York (FDNY) Responders; New York City (NYC) General Responders (including New York City Police Department (NYPD)); and Pentagon and Shanksville, PA, Responders.
- WTC Survivors: individuals who were present in the NYC Disaster Area in the dust or dust cloud on September 11, 2001; who worked, resided, or attended school, childcare, or adult daycare in the NYC Disaster Area from September 11, 2001, to July 31, 2002; who were eligible for certain residential grants or whose place of employment was eligible for certain grants following the September 11, 2001, attacks.

Some studies considered in this method have been conducted among enrollees of the WTC Health Registry, a registry developed in 2002 to document and evaluate the long-term physical and mental

health effects of September 11, 2001. More than 71,000 responders and survivors voluntarily enrolled in the Registry during 2003-2004.[15]

As indicated above, in 2019 the WTC Health Program received a petition to add uterine cancer to the List. At the time, the Administrator instructed the Science Team to search the literature and review the available published, peer-reviewed epidemiologic studies of uterine cancer in 9/11-exposed populations. Databases searched included: CINAHL, Embase, NIOSHTIC-2, ProQuest Health & Safety, PsycINFO, Ovid MEDLINE, Scopus, Toxicology Abstracts/TOXLINE, and WTC Health Program Bibliographic Database. The following keywords were used to conduct the search: endometrial neoplasm, endometrial cancer, endometrial carcinoma, malignant neoplasm of endometrium, adenocarcinoma of endometrium, cancer of the endometrium, uterine neoplasm, malignant neoplasm of corpus uteri, uterine cancer, uterine carcinoma; and the terms: World Trade Center, WTC, September 11, September 11 terrorist attacks. The literature search was conducted in English-language journals on May 23, 2019.

As part of the current assessment, a new literature search using the same search terms and databases as in Petition 023 was conducted on April 19, 2021. In addition to the two articles identified for that Petition,[16, 17] the new search identified one additional epidemiologic article that reports uterine cancer as an outcome.[18] This study reported a case series of cancers identified by the WTC Environmental Health Center, the Clinical Center of Excellence (CCE) for survivors. A total of 2,999 cancer diagnoses (excluding non-melanoma skin cancer) were identified in 2,561 patients. Primary cancer diagnoses confirmed by a pathology/cytology report, among participants who were enrolled in the CCE from May 2002 through December 2019, were included in the analysis. Among women, 1,305 cancers were identified. Breast cancer (46%) was the most common cancer diagnosis, followed by lung (11%), thyroid (9%), and lymphoma (6%); uterine cancer was found in only 0.76% of all cases. Since this study provided only cancer counts and did not directly assess cancer incidence or mortality, it was not further used in the evaluation.

In addition, the Program is aware of prospective cohort studies being conducted in several 9/11-exposed subpopulations.[19-27] The studies follow these subpopulations with the intent to compare them with groups of individuals without 9/11 exposures (usually using U.S. or New York state rates) to evaluate cancer incidence (the number of new cases) and cancer mortality. These prospective cohort studies often perform internal comparisons in which higher exposed cohort members are compared with those that have lower exposures. These studies might include findings on uterine cancer incidence or mortality, but unless the abstract, title, or keywords include these findings, they could be missed in literature searches like the one described above. Therefore, published findings from these studies were reviewed to ascertain if they report findings on uterine cancer.

Twelve scientific articles were identified and were further reviewed, including the two articles identified through the literature search. Four studies were excluded from further evaluation. Two of them were conducted among men only and are therefore not relevant for uterine cancer outcomes.[19, 20] One study was excluded because even though it identified three police officers who developed uterine cancer after the September 11, 2001 attacks, background rates of uterine cancer in this population were not provided and the Science Team was not able to interpret this finding.[28]

The following nine articles were considered relevant and were used for the evaluation. Their main characteristics are summarized in Table 2.

Table 2. Summary of studies included in the evaluation of evidence between 9/11 exposure and uterine cancer

Study	Study design	Study population	Exposure assessment	Outcome	Main findings
Jordan et al. [2011][21]	Prospective cohort mortality study.	Enrollees in the WTC Health Registry who were residents of New York City when enrolled in Registry. Study included 13,337 (3,188 women) rescue/recovery workers and 28,593 (16,733 women) survivors.	Using questionnaire data, they developed 9/11-related exposure levels (high, intermediate, or low) separately for rescue/recovery workers and survivors.	Deaths were ascertained through linkage to death certificates in NYC vital records through 12/31/2009 and NDI through 12/31/2007.	All-cause SMRs were statistically significantly lower than that expected for rescue/recovery workers (SMR=0.45, 95% CI 0.38-0.53) and survivors (SMR=0.61, 95% CI 0.56-0.66). There were no statistically significantly elevated SMRs for any category of cancer examined, including cancer of female genital organs among Registry enrollees (SMR=0.82, 95% CI 0.49-1.28), rescue/recovery workers (SMR=0.67, 95% CI 0.08-2·43), or survivors (SMR=0.84, 95% CI 0.49-1.35). SMRs for uterine cancer were not provided.
Stein et al. [2016][22]	Prospective cohort mortality study.	28,918 general responders who worked or volunteered onsite in rescue, recovery, demolition, debris cleanup, or related duties (4,286 women).	9/11 exposure was self-reported in questionnaires. Exposure was categorized as very high, high, intermediate, and low to reflect the intensity and duration of exposure to the dust, smoke, and debris.	Cause of death was ascertained through linkage to the NDI through 12/31/2011.	Overall cancer deaths were not elevated (SMR 0.43, 95% CI 0.39-0.48). No cause specific SMRs were elevated, including cancers of the female genital organs (SMR=0.65, 95% CI 0.08-2.37). An SMR for uterine cancer was not reported. Overall mortality hazard ratios showed no linear trend with exposure.

Study	Study design	Study population	Exposure assessment	Outcome	Main findings
Jordan et al. [2018][23]	Prospective cohort mortality study.	Update of the Jordan et al. (2011)[21] study. Included the full cohort of WTC Health Registry enrollees, not only those living in New York City at enrollment, and adding five years of follow-up. This study included 29,280 (6,422 women) rescue/recovery workers and 39,643 (21,126 women) survivors.	Same as in the previous study.	Data were linked to the NDI through 12/31/2014.	Overall cancer SMRs were not elevated for rescue/recovery workers (SMR=0.94, 95% CI 0.84-1.05), but were statistically significantly elevated among survivors (SMR=1.14, 95% CI 1.06-1.24) when compared to the New York City population; no elevated SMRs were reported for all cancers using the general US population as reference. Cancer of the female genital organs were not statistically significantly elevated among rescue/recovery workers or survivors (SMR=0.67, 95% CI 0.27-1.39 and SMR=1.17, 95% CI 0.85-1.58, respectively). The authors also examined 119 sub-categories of the major causes of death, but only reported statistically significant results; uterine cancers were not among the reported causes of death. No statistically significant elevations and no statistically significant trends were observed in the analyses of the association between 9/11-related exposures and overall cancer mortality. Dose-response findings were not provided for uterine cancer nor female genital organs.
Li et al. [2012][16]	Prospective cohort cancer incidence study.	Enrollees in the WTC Health Registry who were residents of New York State on 9/11 and had no history of cancer at the time of enrollment. A total of 55,778 individuals were eligible for the study, including 21,850 (4,185 women) involved in rescue/recovery and 33,928 (18,922 women) survivors not involved in rescue/recovery.	Classified exposure as high, intermediate, or low, using qualitative descriptions of WTC exposures. Separate analyses were reported for rescue/recovery workers and for survivors and separate results were reported for cases identified in two calendar periods, i.e., through 2006 and from 2007 through 2008.	Cancers were ascertained by linkage to 11 state cancer registries based on the state of residence of the cohort member. Expected numbers of cancers were based on New York state rates.	Among rescue/recovery workers, the SIR for all cancer sites combined in 2007-2008 was not statistically significantly elevated (SIR=1.14; 95% CI, 0.99-1.30). Also, among rescue/recovery workers, uterine cancer incidence was not elevated during the early period (less than five cases, SIR=0.97, 95% CI 0.2-2.83), and no cases were reported during the later period. Among survivors, no statistically significantly increased cancer incidence was observed in 2007-2008. Uterine cancer incidence was not elevated during the earlier nor the late period (SIR=1.01, 95% CI 0.58-1.65 and SIR=1.01, 95% CI 0.55-1.69, respectively). Results of analyses to assess the risk of uterine cancer as a function of 9/11 exposure levels were not presented.

Study	Study design	Study population	Exposure assessment	Outcome	Main findings
Solan et al. [2013][24]	Prospective cohort cancer incidence study.	20,984 general responders (3,203 women) involved in rescue, recovery, and cleanup efforts at Ground Zero after 9/11.	Self-reported exposures were categorized based on four variables: occupation, extent of exposure to the dust cloud on 9/11, duration working at the site, and work on the debris pile during four time periods.[29] An integrated exposure variable was created using a 4-point scale (very high, high, intermediate, and low) based on total time spent working at Ground Zero, exposure to the dust cloud, and work on the debris pile.[30]	Cases were identified through linkage with state tumor registries in New York, New Jersey, Connecticut, and Pennsylvania. Vital status obtained through linkage with NDI and next-of-kin reports. Cancer SIRs were calculated based on state rates and national rates.	Overall cancer was elevated for all cancer sites combined (SIR=1.15; 95% CI 1.06-1.25). Fewer than six cases of uterine cancer were observed, and no elevated incidence was reported for this type of cancer. No exposure-response results were reported for uterine cancer.
Boffetta et al. [2016][25]	Report of 3 prospective cohort cancer incidence studies to evaluate the feasibility of conducting parallel or pooled analyses.	Only 2 cohorts included women. The cohort previously reported by Li et al. [2012][16] included 21,850 (19% women) rescue/recovery workers. The cohort previously reported by Solan et al. [2013][24] included 20,984 (15% women) rescue/recovery workers.	Same as reported in previous studies.	Both studies included cancer data until 2008. Data were linked to state cancer registries as reported in previous studies. Expected numbers of cases in the Li et al. cohort were based on New York state rates. Expected numbers of cases in the Solan et al. cohort were based on New York, New Jersey, and Connecticut rates, and national data for Pennsylvania.	For the Li et al. cohort, SIR for all first primary cancers for 2007-2008 (late period) was 1.14 (95% CI 0.99-1.30). For the Solan et al. cohort, SIR for all multiple primary cancers for 2002-2008 was 1.06 (95% CI 0.94-1.18). Findings for uterine cancer were not reported.

Study	Study design	Study population	Exposure assessment	Outcome	Main findings
Li et al. [2016][17]	Prospective cohort cancer incidence study.	Update of the Li et al. [2012][16] study. Enrollees in the WTC Health Registry, including 60,339 eligible individuals; 24,863 (5,015 women) rescue/recovery workers and 35,476 (18,845 women) survivors not involved in rescue/recovery.	Used recalibrated exposure categories based on potential contaminants containing carcinogens. For rescue/recovery workers, they developed a WTC exposure matrix based on date of arrival, duration of work at the site, dates or period working on the pile, and being near the WTC site.	The analysis focused on cancers occurring from 2007 through 2011. Data were linked to 11 cancer registries as described in the Li et al. [2012] study.	Overall cancer incidence was statistically significantly greater than the reference population among both rescue/recovery workers (SIR=1.11, 95% CI 1.03-1.20), and survivors (SIR=1.08, 95% CI 1.02-1.15). Uterine cancer incidence was not statistically significantly elevated among rescue/recovery workers nor among survivors (observed uterine cancers=8, SIR=0.82, 95% CI 0.35-1.62 and observed uterine cancers=37, SIR=1.03, 95% CI 0.72-1.41, respectively). Comparisons among exposure groups were not reported for uterine cancer.
Shapiro et al. [2020][26]	Prospective cohort cancer incidence study.	Update of the Solan et al. [2013][24] study. Study population included 28,729 (4,161 women) members of the General Responder Cohort enrolled from 2002 to 2013.	Developed 9/11 exposure indexes using self-reported exposure to the dust cloud (direct, significant, some, none) combined with arrival time (between 9/11and 9/14, and after 9/14); cumulative days working on the WTC; and working directly on the debris pile at any time. A four-level (low, medium, high, very high) composite of these exposure measures was also used.	Incident cancer cases were ascertained by linkage with cancer registries of New York, New Jersey, Pennsylvania, Connecticut, Florida, and North Carolina. In a restricted analysis, person-years of observation and observed counts began 6 months after member enrollment; in an unrestricted analysis, follow-up time and cancer cases started 9/11/2001. Expected counts were derived through indirect standardization to the age, sex, race and/or ethnicity, diagnosis year, and residency-state-specific population rates.	In the restricted analysis, overall cancer incidence was statistically significantly greater than the reference population (SIR=1.09, 95% CI 1.02-1.16). Similar findings were observed in the unrestricted analysis. No elevation in uterine cancer incidence was observed in the restricted analysis (SIR=0.82, 95% CI 0.35-1.61), and no findings were presented for the unrestricted analysis. None of the three separate exposure measures (dust exposure and arrival time, length of work time, or work on the pile) and none of the levels of the four-level 9/11 exposure index showed a statistically significant association with cancer risk for all cancer sites combined. Internal analyses by exposure measures were not reported for uterine cancer.

Study	Study design	Study population	Exposure assessment	Outcome	Main findings
Li et al. [2021][27]	Prospective cohort cancer incidence study.	A cohort of rescue and recovery workers who were members of any these 9/11-exposed cohorts: FDNY, GRC, or WTC Health Registry. The study included 69,102 workers (9,151 women).	Used self-reported information to classify exposures by 1) date of first arrival to the WTC site (on 9/11, on 9/12, between 9/13-17, or after 9/17); 2) worked on debris pile at Ground Zero (yes, no, or unknown); and 3) exposed to the dust cloud on 9/11 (yes, no, or unknown).	Cancers diagnosed during 2002-2015 were identified through linkages with 13 state cancer registries where 93% of the members resided. Expected numbers of cancers were based on New York state rates. SIRs were estimated using two approaches: multiple primaries (MP-SIR) examined all cancers diagnosed after follow-up began; and first primary cancer (FP-SIR) in which only first primary cancer diagnoses were counted.	Incidence for all MP and FP cancers combined was below expected (MP-SIR=0.95 95% CI 0.92-0.98; FP-SIR=0.96, 95% CI 0.93-0.99). No elevation in uterine cancer incidence was observed (MP-SIR=0.66, 95% CI 0.45-0.94; FP-SIR=0.67, 95% CI 0.45-0.96). Compared with those arriving after 9/17, workers arriving on 9/11, 9/12, or 9/13-17 were at increased risk of all-cancers (adjusted hazard ratio [aHR]=1.47, 95% CI 1.32-1.64; aHR=1.34, 95% CI 1.19-1.51; aHR=1.32, 95% CI 1.17-1.48, respectively). All-cancer risk was not increased among those working on the pile compared with those that did not (aHR=1.03, 95% CI 0.95-1.11). Dust cloud exposure was associated with an increased risk of all cancers (aHR=1.21, 95% CI 1.12-1.31). Comparisons among exposure groups were not reported for uterine cancer.

Abbreviations: FDNY – New York City Fire Department, GRC – General Responder cohort, NDI – National Death Index, NYC – New York City, SIR – Standardized Incidence Ratio, SMR – Standardized Mortality Ratio, WTC – World Trade Center

Jordan et al. [2011] conducted a mortality study among the cohort of WTC Health Registry enrollees, including 3,188 rescue/recovery female workers and 16,733 women survivors living in New York City at time of enrollment.[21] The authors used questionnaire data to develop 9/11-related exposure levels (high, intermediate, or low) separately for rescue/recovery workers and survivors. Deaths were ascertained through linkage to death certificates in New York City vital records through 12/31/2009 and NDI through 12/31/2007. All-cause SMRs were statistically significantly lower than that expected for rescue/recovery workers (SMR=0.45, 95% CI 0.38-0.53) and survivors (SMR=0.61, 95% CI 0.56-0.66). There were no statistically significantly elevated SMRs for any category of cancer examined, including cancer of female genital organs among all studied Registry enrollees (SMR=0.82, 95% CI 0.49-1.28), rescue/recovery workers (SMR=0.67, 95% CI 0.08-2·43), or survivors (SMR=0.84, 95% CI 0.49-1.35). SMRs for uterine cancer were not reported.

Stein et al. [2016] conducted a mortality study among 28,918 general responders who worked or volunteered onsite in rescue, recovery, demolition, debris cleanup, or related duties, of which 4,286 were women.[22] The authors ascertained cause of death by linkage to the National Death Index (NDI) through December 31, 2011. Exposure information was obtained through self-report in exposure assessment questionnaires. The authors categorized exposure as very high, high, intermediate, and low to reflect the intensity and duration of exposure to the dust, smoke, and debris. Overall cancer deaths were not elevated (standardized mortality ratio (SMR)=0.43, 95% CI 0.39-0.48). No cause specific SMRs were elevated, including cancers of the female genital organs (SMR=0.65, 95% CI 0.08-2.37). SMRs for uterine cancer were not reported. Mortality hazard ratios did not show a linear trend with exposure.

Jordan et al. [2018] updated their 2011 study by including the full cohort of WTC Health Registry enrollees (not only those living in New York City at enrollment, which was a requirement to be included in their 2011 study), and adding five years of follow-up.[23] This study included rescue/recovery workers (6,422 women) and survivors (21,126 women). The authors conducted exposure assessment as in their earlier study.[21] They linked their records to NDI through 12/31/2014. Overall cancer SMRs were not elevated for rescue/recovery workers (SMR=0.94, 95% CI 0.84-1.05), but were statistically significantly elevated among survivors (SMR=1.14, 95% CI 1.06-1.24) when compared with the New York City population; no elevated SMRs were reported for all cancers using the general U.S. population as reference. Cancer of the female genital organs were not statistically significantly elevated among rescue/recovery workers or survivors (SMR=0.67, 95% CI 0.27-1.39 and SMR=1.17, 95% CI 0.85-1.58, respectively). The authors also examined 119 sub-categories of the major causes of death, but only reported statistically significant results; uterine cancers were not among the reported causes of death, suggesting that the risk of uterine cancer was not statistically significantly elevated. No statistically significant elevations and no statistically significant trends were observed in the analyses of the association between 9/11-related exposures and overall cancer mortality.

Li et al. [2012] conducted a cancer incidence study among enrollees in the WTC Health Registry who were residents of New York state on September 11, 2001 and had no history of cancer at the time of enrollment.[16] Persons eligible for the study included 4,185 women involved in rescue/recovery and 18,922 women survivors not involved in rescue/recovery. Cancers were ascertained by linkage to 11 state cancer registries based on the state of residence of the cohort member. Expected numbers of cancers were based on New York state rates. The authors used qualitative descriptions of WTC exposures to classify exposure as high, intermediate, or low. They conducted separate analyses for rescue/recovery workers and for survivors and presented separate results for the period of enrollment through 2006 and 2007 through 2008. Among rescue/recovery workers, the SIR for all cancer sites combined was not statistically significantly elevated in any period of Registry enrollment (early period, SIR=0.94; 95% CI, 0.82-1.08; later period SIR=1.14; 95% CI, 0.99-1.30). Uterine cancer incidence was not

elevated during the early period (five cases or less), SIR=0.97, 95% CI 0.2-2.83), and no cases were reported during the later period. Among survivors, no significantly increased incidence for cancer sites combined was observed in either period. Uterine cancer incidence was not elevated during the early or late periods (early: observed uterine cancers=16, SIR=1.01, 95% CI 0.58-1.65 and late: observed uterine cancers=14, SIR=1.01, 95% CI 0.55-1.69, respectively). Results of analyses to assess the risk of uterine cancer as a function of WTC exposure levels were not reported.

Solan et al. [2013] conducted a cancer incidence study among workers, including 3,203 women, involved in rescue, recovery, and cleanup efforts at Ground Zero after 9/11, but who were not part of the FDNY.[24] Cancer cases were identified through linkage with state tumor registries in New York, New Jersey, Connecticut, and Pennsylvania. Vital status was obtained through linkage with the National Death Index (NDI) and next-of-kin reports. The authors categorized self-reported exposures using occupation, extent of exposure to the dust cloud on 9/11, duration working at the site, and work on the debris pile during four time periods. They created an integrated exposure variable using a four-point scale (very high, high, intermediate, and low) based on total time spent working at Ground Zero, exposure to the dust cloud, and work on the debris pile. The standardized incidence ratio (SIR) (based on New York state rates for New York residents, state-specific incidence data for New Jersey and Connecticut residents; and national data for Pennsylvania residents) was elevated and statistically significant for all cancer sites combined (SIR=1.15; 95% confidence interval (CI), 1.06-1.25). Fewer than six cases of uterine cancer were observed, and no additional information was reported for this type of cancer. It is unknown how many cases of uterine cancer were identified. Furthermore, no SIRs were reported for uterine cancer nor were relative risks reported for the association between 9/11 integrated exposure variables (i.e., a 4-point scale based on total time spent working at Ground Zero, exposure to the dust cloud, and work on the debris pile) and uterine cancer.

Boffetta et al. [2016] reported preliminary results of three prospective cohort cancer incidence studies.[25] The purpose was to compare their methods and findings to evaluate the feasibility of conducting parallel or pooled analyses. Of the three cohorts, only two included women and will be summarized here. The cohort previously reported by Li et al. [2012][16] included 21,850 (19% women) rescue/recovery workers, while the cohort previously reported by Solan et al. [2013][24] included 20,984 (15% women) rescue/recovery workers. The Li et al. cohort used an exposure summary index based on time of first arrival to the WTC site, duration on site, work on the pile, and being in the WTC site before noon on 9/11. The Solan et al. cohort exposure measurements included dust cloud exposure, duration on site, location of work; and an exposure index based on dust, duration, and location. Both studies conducted linkages with state cancer registries to identify incident cancer cases. Expected numbers of cases in the Li et al. cohort were based on New York state rates, while expected numbers of cases in the Solan et al. cohort were based on New York, New Jersey, and Connecticut rates, and national data (SEER 17) for Pennsylvania. For the Li et al. cohort, SIR for all first primary cancers for 2007-2008 (late period) was 1.14 (95% CI 0.99-1.30). For the Solan et al. cohort, SIR for all multiple primary cancers for 2002-2008 was 1.06 (95% CI 0.94-1.18). Findings for uterine cancer were not reported.

Li et al. [2016] updated the 2012 study,[16] adding three years of follow-up and using recalibrated exposure categories based on potential contaminants containing carcinogens.[17] They also expanded the study population by including enrollees who lived in any of the 11 states selected for cancer registry linkage between September 11, 2001 and December 31, 2011. The study included 5,015 female rescue/recovery workers and 18,845 women survivors not involved in rescue/recovery. The authors recalibrated exposure categories based on potential contaminants containing carcinogens. For rescue/recovery workers, they developed a WTC exposure matrix based on date of arrival, duration of work at the site, time working on the pile, and being near the WTC site. The analysis focused on cancers

occurring from 2007 through 2011. Data were linked to 11 cancer registries as described by Li et al. [2012].[16] The overall cancer incidence was statistically significantly greater than the reference population of New York state among both rescue/recovery workers (SIR=1.11, 95% CI 1.03-1.20) and survivors (SIR=1.08, 95% CI 1.02-1.15). Uterine cancer incidence was not statistically significantly elevated among rescue/recovery workers nor among survivors (observed uterine cancers=8, SIR=0.82, 95% CI 0.35-1.62 and observed uterine cancers=37, SIR=1.03, 95% CI 0.72-1.41, respectively). Comparisons among exposure groups were not reported for uterine cancer.

Shapiro et al. [2020] updated the prospective cohort cancer incidence study conducted by Solan et al. [2013], adding an additional 5 years of follow-up.[26] The study population included 28,729 (4,161 women) members of the General Responder Cohort enrolled from 2002 to 2013. The authors developed 9/11 exposure indexes using self-reported exposure to the dust cloud (direct, significant, some, none) combined with arrival time (between 9/11and 9/14, and after 9/14); cumulative days working on the WTC; and working directly on the debris pile at any time. A four-level (low, medium, high, very high) composite of these exposure measures was also used; low- and medium-exposure groups included those who were not directly in the dust cloud, with the low-exposure group also working less than 40 days on the response and not having worked at any time on the debris pile. The high and very high groups included those who were directly in the dust cloud, with the very high group also working 90 or more days on the response and working at some point on the debris pile. Incident cancer cases were ascertained by linkage with cancer registries of New York, New Jersey, Pennsylvania, Connecticut, Florida, and North Carolina. In a restricted analysis, person-years of observation and observed counts began 6 months after member enrollment; in an unrestricted analysis, follow-up time and cancer cases started 9/11/2001. Expected counts were derived through indirect standardization to the age, sex, race and/or ethnicity, diagnosis year, and residency-state-specific population rates. In the restricted analysis, overall cancer incidence was statistically significantly greater than the reference population (SIR=1.09, 95% CI 1.02-1.16). Similar findings were observed in the unrestricted analysis. No elevation in uterine cancer incidence was observed in the restricted analysis (SIR=0.82, 95% CI 0.35-1.61), and no findings were presented for the unrestricted analysis. None of the three separate exposure measures (dust exposure and arrival time, length of work time, or work on the pile) and none of the levels of the four-level 9/11 exposure index showed a statistically significant association with cancer risk for all cancer sites combined. Internal analyses by exposure measures were not reported for uterine cancer.

Li et al. [2022] conducted a prospective cohort cancer incidence study among a combined and deduplicated cohort of rescue and recovery workers who were members of any three 9/11-exposed cohorts: New York Fire Department, General Responders, or WTC Health Registry.[27] The study included 69,102 workers (9,151 of which were women). The authors used self-reported information collected at study enrollment to classify exposures by 1) date of first arrival to the WTC site (on 9/11, on 9/12, between 9/13-17, or after 9/17); 2) worked on debris pile at Ground Zero (yes, no, or unknown); and 3) exposed to the dust cloud on 9/11 (yes, no, or unknown). Cancers were diagnosed during 2002-2015 and were identified through linkages with 13 state cancer registries where 93% of the members resided based on last known residence. Expected numbers of cancers were based on New York state rates. SIRs were estimated using two approaches: multiple primaries (MP-SIR) examined all cancers diagnosed after follow-up began; and first primary cancer (FP-SIR) in which only first primary cancer diagnoses were counted. For internal analyses, Cox regression models were used to estimate hazard ratios for FP cancer risk associated to 9/11 exposure. Incidence for all MP and FP cancers combined was below expected (MP-SIR=0.95, 95% CI 0.92-0.98; FP-SIR=0.96, 95% CI 0.93-0.99). No elevation in uterine cancer incidence was observed (MP-SIR=0.66, 95% CI 0.45-0.94; FP-SIR=0.67, 95% CI 0.45-0.96). Compared with those arriving after 9/17, workers arriving on 9/11, 9/12, or 9/13-17 were at increased risk of all-cancers

(adjusted hazard ratio [aHR]=1.47, 95% CI 1.32-1.64; aHR=1.34, 95% CI 1.19-1.51; aHR=1.32, 95% CI 1.17-1.48, respectively). All-cancer risk was not increased among those working on the pile compared with those that did not (aHR=1.03, 95% CI 0.95-1.11). Dust cloud exposure was statistically significantly associated with an increased risk of all cancers (aHR=1.21, 95% CI 1.12-1.31). Comparisons among exposure groups were not reported for uterine cancer.

Prospective cohort studies, like those described above, have the advantage that study participants are known to be disease-free at the beginning of the observation period when their exposure occurred; therefore, it is possible to establish the temporal sequence between exposure and outcome. However, since some slow-growing cancers become apparent only after long periods of time after exposure, it is possible that such cancers might have been present but undetected before September 11, 2001. In addition, all of the studies described above have had a relatively short period of follow-up since September 11, 2001. The studies discussed above might not have sufficient statistical power to detect excesses in uterine cancer due to their small size. This is especially a concern with studies of rescue/recovery workers since those cohorts are only approximately 15 percent female. Another limitation of the studies reviewed is their overlap in participation, which limits the interpretation of consistency of findings among them. Approximately 20 percent of rescue/recovery workers enrolled in the WTC Health Program are also enrolled in the WTC Health Registry.[22] These two cohorts also might be prone to selection bias, because enrollment in their respective programs was voluntary. For the WTC Health Registry cohort, it is possible that differential participation due to race/ethnicity, socioeconomic status, age, or their perception of being affected by the September 11, 2001 attacks, might have occurred. For the rescue/recovery worker cohort enrolled in the WTC Health Program, their health status, including their cancer diagnosis, might have prompted them to enroll. Study findings are available for both rescue/recovery workers and survivors. Another limitation is that only external comparisons were made. Thus, differences between the population of interest and the referent (control) group may have distorted risk estimates. It is likely that the 9/11 population is generally healthier than the referents used in existing studies.

The studies by Jordan et al. [2011],[21] Li et al. [2012],[16] and Solan et al. [2013][24] were updated by Jordan et al. [2018],[23] Li et al. [2016],[17] and Shapiro et al. [2020],[26] respectively, and were therefore not further considered for evaluation. The findings reported by Boffetta et al. [2016][25] have been updated by Li et al. [2016],[17] and Shapiro et al. [2020][26] and were likewise not further considered. Of the five remaining studies, Jordan et al. [2018][23] and Stein et al. [2016][22] did not report findings for uterine cancer, and Li et al. [2016],[17] Shapiro et al. [2020],[26] and Li et al. [2022][27] did not report elevated uterine cancer risks as a result of 9/11 exposures.

The Science Team concluded that the above studies do not provide consistent evidence that uterine cancer incidence or mortality is elevated among WTC responders and survivors. The Science Team concluded that the requirements of Method 1 were not met because collectively the studies do not demonstrate a potential to provide a basis for a decision on whether to add uterine cancer to the List.

B. Method 2 – Established Casual Association

Pursuant to ***Method 2***, the Program explored whether there is an established casual association between uterine cancer and a condition already on the List of WTC-Related Health Conditions. A thorough review of the scientific literature found that estrogen-secreting tumors are associated with endometrial cancer, but these tumors are rare. The most common type of estrogen-secreting tumor are granulosa cell tumors of the ovary.[31] Among women with granulosa cell tumors of the ovary, 5-10 percent also have endometrial cancer. Granulosa cell tumors of the ovary account for approximately 4–6

percent of all ovarian malignancies (i.e., approximately 4 cases of granulosa cell tumors of the ovary per million women per year).[31, 32]

Other types of estrogen-secreting tumors are adrenocortical cancers. Adrenocortical cancers are very rare (0.7–2.0 cases per million population per year), and those that are estrogen-secreting comprise a rare subset of all adrenocortical cancers.[33] However, no scientific evidence was found linking estrogen-secreting adrenocortical cancer with uterine cancer. Instead, such estrogen-secreting adrenocortical cancers in women produce breast tenderness and dysfunctional uterine bleeding. A single case report was found that described a 32-year-old woman who had co-occurring adrenocortical cancer, uterine adenocarcinoma, and ovarian adenocarcinoma.[34] The authors of that report conducted a literature search for similar cases but found none. The authors of that report could not explain why three tumors co-occurred in this patient.

Because estrogen-secreting tumors fall under the category of "rare cancers" in the List, uterine cancer can be added to the List only for members who have a certified estrogen-secreting tumor.

C. Method 3 – Review of Evaluations of Carcinogenicity in Humans

Pursuant to ***Method 3***, the Science Team first reviewed the definitions of EDCs. The following authoritative organizations have defined EDCs as follows:[35]

- **U.S. Environmental Protection Agency (EPA)**: "An endocrine disruptor is an exogenous agent that interferes with the production, release, transport, metabolism, binding, action, or elimination of natural hormones in the body responsible for the maintenance of homeostasis and the regulation of developmental processes."
- **European Union**: "An endocrine disruptor is an exogenous substance that causes adverse health effects in an intact organism, or its progeny, secondary to changes in endocrine function. A potential ED is a substance that possesses properties that might be expected to lead to endocrine disruption in an intact organism."
- **World Health Organization**: "An endocrine disruptor is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse effects in an intact organism, or its progeny, or (sub)populations."
- **National Institute of Environmental Health Sciences (NIEHS)**: "Many chemicals, both natural and man-made, may mimic or interfere with the body's hormones, known as the endocrine system. Called endocrine disruptors, these chemicals are linked with developmental, reproductive, brain, immune, and other problems."
- **The Endocrine Society**: "An exogenous chemical, or mixture of chemicals, that interferes with any aspect of hormone action." According to The Endocrine Society, EDCs simulate or block hormones and disrupt the body's normal functions. This disruption can occur by altering normal hormone levels, inhibiting or stimulating the production of hormones, or changing the way hormones travel through the body. EDCs have key characteristics that affect to their ability to interact with hormone systems.[36]

The following agents are identified as common endocrine disruptors by NIEHS:[37]

- **Bisphenol A (BPA)** — used to make polycarbonate plastics and epoxy resins, which are found in many plastic products including food storage containers.

- **Dioxins** — produced as a byproduct in herbicide production and paper bleaching, they are also released into the environment during waste burning and wildfires.
- **Perchlorate** — a by-product of aerospace, weapon, and pharmaceutical industries found in drinking water and fireworks.
- **Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS)** — used widely in industrial applications, such as firefighting foams and non-stick pan, paper, and textile coatings.
- **Phthalates** — used to make plastics more flexible, they are also found in some food packaging, cosmetics, children's toys, and medical devices.
- **Phytoestrogens** — naturally occurring substances in plants that have hormone-like activity, such as genistein and daidzein that are in soy products, like tofu or soy milk.
- **Polybrominated diphenyl ethers (PBDE)** — used to make flame retardants for household products such as furniture foam and carpets.
- **Polychlorinated biphenyls (PCB)** — used to make electrical equipment like transformers, and in hydraulic fluids, heat transfer fluids, lubricants, and plasticizers.
- **Triclosan** — might be found in some anti-microbial and personal care products, like liquid body wash.

An additional EDC was identified by Mallozzi et al.,[38] but not identified by NIEHS or others:

- **Cadmium and cadmium compounds** — Common industrial uses for cadmium today are in batteries, alloys, coatings (electroplating), solar cells, plastic stabilizers, and pigments.

The Endocrine Society also has a list of classes of EDCs that are the most commonly studied.[39]

In the absence of an internationally harmonized list of EDCs, each agent listed in the Inventory of 9/11 Agents was matched against publicly available lists of known and potential endocrine disruptors. The Inventory was matched against the European Union's (EU) List of Substances Identified as Endocrine Disruptors at EU Level (EU List I), the List of Substances Under Evaluation for Endocrine Disruption Under an EU Legislation (EU List II), and the List of Substances Considered by the Evaluating National Authority to Have Endocrine Disrupting Properties (EU List III).[40] The Endocrine Disruptor Lists are compiled by the national authorities of Belgium, Denmark, France, The Netherlands, Sweden, and Spain. Altogether, these three lists include 194 chemicals; they are updated at least bi-annually, and the most recent update was in June 2022. The Inventory of 9/11 Agents was also matched against the United Nations Environment Programme's List of Identified Endocrine Disrupting Chemicals.[41] This list, developed by The International Panel on Chemical Pollution (IPCP), includes 45 chemical substances and was last updated in July 2017. The Inventory was also matched against the TEDX List of Potential Endocrine Disruptors, a master list of 1,482 chemicals with at least one study demonstrating endocrine disrupting properties. This list was developed by TEDX, a nonprofit research institute that ended its operations in 2019, was last updated in September 2018.[42] Finally, the Inventory of 9/11 Agents was also matched against 32 EDCs included in the SIN ("Substitute It Now") List developed by the non-profit The International Chemical Secretariat (ChemSec).[43] The SIN List, whose name implies that ChemSec desires the prompt removal from use of these chemicals because of their threat to human health and the environment, was last updated in 2014.

Table 3 includes 136 individual agents, one mixture (diesel exhaust), and 10 categories of agents that may be evaluated as a group. Of the agents and categories of 9/11 agents identified in the Inventory of 9/11 Agents that have also been evaluated by IARC, 12 are classified in Group 1 (carcinogenic to

humans), 8 in Group 2A (probably carcinogenic to humans), 20 in Group 2B (possibly carcinogenic to humans), and 38 in Group 3 (not classifiable as to its carcinogenicity to humans); the rest have not been evaluated. Likewise, 7 agents and categories are classified in NTP's 15th Report on Carcinogens as *Known to be human carcinogens* and 23 agents and categories as *Reasonably anticipated to be human carcinogens*. Nonetheless, none are listed in IARC's List of classifications by cancer sites with *sufficient* or *limited* evidence in humans of uterine carcinogenicity. Among 9/11 Agents that are known or potential EDCs and that have been evaluated for their carcinogenicity by NTP and IARC, none are currently known to cause or be reasonably anticipated to cause uterine cancer.

Table 3. Substances on the Inventory of 9/11 Agents that are known or potential endocrine disruptors, and their reported carcinogenicity by authoritative bodies

Name	CAS	IARC*		NTP-RoC	
Individual Agents					
Acenaphthylene	208-96-8		Not listed		Not listed
Acetone	67-64-1		Not listed		Not listed
Acrylonitrile	107-13-1	Monograph 71 [1999]	Group 2B	1981	*Reasonably anticipated to be a human carcinogen*
Aluminum	7429-90-5		Not listed		Not listed
Ammonia	7664-41-7		Not listed		Not listed
Anthracene	120-12-7	Supplement 7, Monograph 92 [2010]	Group 3		Not listed
Barium	7440-39-3		Not listed		Not listed
Benzaldehyde	100-52-7		Not listed		Not listed
Benz[a]acridine	225-11-6	Monograph 32, Supplement 7, Monograph 103 [2013]	Group 3		Not listed
Benz[c]acridine	225-51-4	Monograph 32, Supplement 7, Monograph 103 [2013]	Group 3		Not listed
Benz[a]anthracene (*see* PAHs)	56-55-3	Supplement 7, Monograph 92 [2010]	Group 2B	1981	*Reasonably anticipated to be a human carcinogen*
Benzene	71-43-2	Monograph 29, Supplement 7, Monographs 100F, 120 [2018]	Group 1 [lung, childhood acute myeloid leukemia, acute myeloid leukemia, other acute non-lymphocytic leukemia, chronic myeloid leukemia, chronic lymphocytic leukaemia, non-Hodgkin lymphoma; multiple mieloma][†]	1980	*Known to be a human carcinogen*
Benzo[b]fluoranthene (*see* PAHs)	205-99-2	Monograph 92 [2010]	Group 2B	1981	*Reasonably anticipated to be a human carcinogen*
Benzo[k]fluoranthene (*see* PAHs)	207-08-9	Monograph 92 [2010]	Group 2B	1989	*Reasonably anticipated to be a human carcinogen*
Benzo[b]fluorene	243-17-4	Supplement 7, Monograph 92 [2010]	Group 3		Not listed

Name	CAS	IARC*		NTP-RoC	
Benzo[jk]fluorene	206-44-0	Supplement 7, Monograph 92 [2010]	Group 3		Not listed
Benzo[b]naphtho[2,1-d]thiophene	239-35-0	Monograph 103 [2013]	Group 3		Not listed
Benzo[c]phenanthrene	195-19-7	Supplement 7, Monograph 92 [2010]	Group 2B		Not listed
Benzo[a]pyrene (*see* PAHs)	50-32-8	Supplement 7, Monographs 92, 100F [2012]	Group 1. Overall evaluation upgraded based on mechanistic and other relevant data	1981	*Reasonably anticipated to be a human carcinogen*
Benzo[e]pyrene	192-97-2	Supplement 7, Monograph 92 [2010]	Group 3		Not listed
Benzyl butyl phthalate (*see* Phthalates)	85-68-7	Supplement 7, Monograph 73 [1999]	Group 3		Not listed
Benzyl Chloride (*see* alpha-Chlorinated toluenes)	100-44-7		Not listed		Not listed
Biphenyl	92-52-4		Not listed		Not listed
Bromomethane	74-83-9	Monograph 41, Supplement 7, Monograph 71 [1999]	Group 3		Not listed
1,3-Butadiene	106-99-0	Supplement 7, Monographs 54, 71, 97, 100F [2012]	Group 1 [leukemia, lymphoma, multiple myeloma]	1989	*Known to be a human carcinogen*
2-Butanone	78-93-3		Not listed		Not listed
Cadmium (*see* Cadmium compounds)	7440-43-9	Monographs 58, 100C [2012]	Group 1 [lung, prostate, kidney]	2016	*Known to be a human carcinogen*
Carbon tetrachloride	56-23-5	Monograph 20, Supplement 7, Monograph 71 [1999]	Group 2B	1981	*Reasonably anticipated to be a human carcinogen*
cis-Chlordane	5103-71-9		Not listed		Not listed
trans-Chlordane	5103-74-2		Not listed		Not listed
Chloroform	67-66-3	Supplement 7, Monograph 73 [1999]	Group 2B	1981	*Reasonably anticipated to be a human carcinogen*
Chromium	7440-47-3	Supplement 7, Monograph 49 [1990]	Group 3		Not listed
Chrysene	218-01-9	Monograph 92 [2010]	Group 2B		Not listed

Name	CAS	IARC*		NTP-RoC	
Cyclopenta[cd]pyrene (*see* PAHs)	27208-37-3	Supplement 7, Monograph 92 [2010]	Group 2A		Not listed
Decabromodiphenyl ether	1163-19-5	Monographs 48, 71 [1999]	Group 3		Not listed
Dibenz[a,c]anthracene (*see* PAHs)	215-58-7	Supplement 7, Monograph 92 [2010]	Group 3		Not listed
Dibenz(a,h)anthracene (*see* PAHs)	53-70-3	Supplement 7, Monograph 92 [2010]	Group 2A. Overall evaluation upgraded with supporting evidence from other relevant data	1981	*Reasonably anticipated to be a human carcinogen*
Dibenzothiophene	132-65-0	Monograph 103 [2013]	Group 3		Not listed
Dibutyl phthalate (*see* Phthalates)	84-74-2		Not listed		Not listed
1,2-Dichlorobenzene	95-50-1	Supplement 7, Monograph 73 [1999]	Group 3		Not listed
1,3-Dichlorobenzene	541-73-1	Monograph 73 [1999]	Group 3		Not listed
Dichlorodiphenyldichloroethane	72-54-8		Not listed		Not listed
4,4-Dichlorodiphenyldichloroethylene	72-55-9		Not listed		Not listed
2,4-Dichlorodiphenyltrichloroethane (DDT)	50-29-3	Supplement 7, Monographs 53, 113 [2018]	Group 2A [liver, bile duct, testis, non-Hodgkin lymphoma]	1985	*Reasonably anticipated to be a human carcinogen*
Dichloromethane	75-09-2	Supplement 7, Monographs 71, 110 [2017]	Group 2A [bile duct, non-Hodgkin lymphoma]	1989	*Reasonably anticipated to be a human carcinogen*
Dicyclohexyl phthalate (*see* Phthalates)	84-61-7		Not listed		Not listed
Didodecyl phthalate (*see* Phthalates)	2432-90-8		Not listed		Not listed
Dieldrin	60-57-1	Monograph 5, Supplement 7, Monograph 117 [2019]	Group 2A [breast]		Not listed
Diethyl phthalate (*see* Phthalates)	84-66-2		Not listed		Not listed
Diisobutyl phthalate (*see* Phthalates)	84-69-5		Not listed		Not listed
Endosulfan	115-29-7		Not listed		Not listed
Ethyl benzene	100-41-4	Monograph 77 [2000]	Group 2B		Not listed
Fluorene	86-73-7	Supplement 7, Monograph 92 [2010]	Group 3		Not listed

Name	CAS	IARC*		NTP-RoC	
Formaldehyde	50-00-0	Supplement 7, Monographs 62, 88, 100F [2012]	Group 1 [nasopharynx, nasal cavity and paranasal sinus, acute myeloid leukemia, other acute non-lymphocytic leukemia, chronic myeloid leukemia][§]	1981	*Known to be a human carcinogen*
2,2',3,4,4',5',6-Heptabromodiphenyl ether	207122-16-5		Not listed		Not listed
Heptachlor	76-44-8	Supplement 7, Monographs 53, 79 [2001]	Group 2B		Not listed
Heptachlor epoxide	1024-57-3		Not listed		Not listed
***n*-Heptane**	142-82-5		Not listed		Not listed
2,2',3,4,4',5,5'- Heptachlorobiphenyl (*see* PCBs)	35065-29-3		Not listed		Not listed
1,2,3,4,6,7,8-Heptachlorodibenzodioxin (*see* Dioxins)	35822-46-9	Monograph 69 [1997]	Group 3		Not listed
1,2,3,4,6,7,8-Heptachlorodibenzofuran (*see* Dibenzofurans)	67562-39-4	Monograph 69 [1997]	Group 3		Not listed
1,2,3,4,7,8,9-Heptachlorodibenzofuran (*see* Dibenzofurans)	55673-89-7	Monograph 69 [1997]	Group 3		Not listed
2,2',4,4',5,5'-Hexabromodiphenyl ether	68631-49-2		Not listed		Not listed
2,2',4,4',5,5'-Hexachlorobiphenyl (*see* PCBs)	35065-27-1		Not listed		Not listed
2,2',3,4,4',5'- Hexachlorobiphenyl (*see* PCBs)	35065-28-2		Not listed		Not listed
1,2,3,6,7,8-Hexachlorodibenzodioxin (*see* Dioxins)	57653-85-7	Monograph 69 [1997]	Group 3		Not listed
1,2,3,4,7,8-Hexachlorodibenzofuran (*see* Dibenzofurans)	70648-26-9	Monograph 69 [1997]	Group 3		Not listed

Name	CAS	IARC*		NTP-RoC	
1,2,3,6,7,8-Hexachlorodibenzofuran (*see* Dibenzofurans)	57117-44-9	Monograph 69 [1997]	Group 3		Not listed
1,2,3,7,8,9-Hexachlorodibenzofuran (*see* Dibenzofurans)	72918-21-9	Monograph 69 [1997]	Group 3		Not listed
2,3,4,6,7,8-Hexachlorodibenzofuran (*see* Dibenzofurans)	60851-34-5	Monograph 69 [1997]	Group 3		Not listed
***n*-Hexane**	110-54-3		Not listed		Not listed
Hexachlorobenzene	118-74-1	Supplement 7, Monograph 79 [2001]	Group 2B	1983	*Reasonably anticipated to be a human carcinogen*
2,2',4,4',5,6'-Hexabromodiphenyl ether	207122-15-4		Not listed		Not listed
1,2,3,4,7,8-Hexachlorodibenzodioxin (*see* Dioxins)	39227-28-6	Monograph 69 [1997]	Group 3		Not listed
1,2,3,7,8,9-Hexachlorodibenzodioxin (*see* Dioxins)	19408-74-3	Monograph 69 [1997]	Group 3		Not listed
1,2,3,4,6,7-Hexachloronaphthalene	103426-96-6		Not listed		Not listed
1,2,3,5,6,7-Hexachloronaphthalene	103426-97-7		Not listed		Not listed
Hydrogen sulfide	7783-06-4		Not listed		Not listed
1-Hydroxypyrene	5315-79-7		Not listed		Not listed
Indeno[1,2,3-cd]pyrene (*see* PAHs)	193-39-5	Supplement 7, Monograph 92 [2010]	Group 2B	1981	*Reasonably anticipated to be a human carcinogen*
Iron	7439-89-6		Not listed		Not listed
Lead (*see* Lead compounds)	7439-92-1	Monograph 23, Supplement 7 [1987]	Group 2B [stomach]	2004	*Reasonably anticipated to be a human carcinogen*
Lindane	58-89-9	Monograph 113 [2018]	Group 1 [non-Hodgkin lymphoma]	1981	*Reasonably anticipated to be a human carcinogen*
Manganese	7439-96-5		Not listed		Not listed
Mercury	7439-97-6	Monograph 58 [1993]	Group 3		Not listed
Methyl tert butyl ether	1634-04-4	Monograph 73 [1999]	Group 3		Not listed
Metribuzin	21087-64-9		Not listed		Not listed
Mirex	2385-85-5	Monograph 20, Supplement 7 [1987]	Group 2B	1981	*Reasonably anticipated to be a human carcinogen*
Monobutyl phthalate (*see* Phthalates)	131-70-4		Not listed		Not listed

Name	CAS	IARC*		NTP-RoC	
Naphthalene	91-20-3	Monograph 82 [2002]	Group 2B	2004	*Reasonably anticipated to be a human carcinogen*
2,2',3,3',4,4',5,6,6'-Nonabromodiphenyl ether	437701-79-6		Not listed		Not listed
cis-Nonachlor	5103-73-1		Not listed		Not listed
trans-Nonachlor	39765-80-5		Not listed		Not listed
1,2,3,4,6,7,8,9-Octachlorodibenzodioxin (*see* Dioxins)	3268-87-9	Monograph 69 [1997]	Group 3		Not listed
1,2,3,4,6,7,8,9-Octachlorodibenzofuran (*see* Dibenzofurans)	39001-02-0	Monograph 69 [1997]	Group 3		Not listed
***n*-Octane**	111-65-9		Not listed		Not listed
2,2',4,4',5-Pentabromodiphenyl ether	60348-60-9		Not listed		Not listed
2,3,3',4',6- Pentachlorobiphenyl (*see* PCBs)	38380-03-9		Not listed		Not listed
3,3',4,4',5-Pentachlorobiphenyl (*see* PCBs)	57465-28-8		Not listed		Not listed
1,2,3,7,8-Pentachlorodibenzodioxin (*see* Dioxins)	40321-76-4	Monograph 69 [1997]	Group 3		Not listed
1,2,3,7,8-Pentachlorodibenzofuran (*see* Dibenzofurans)	57117-41-6		Not listed		Not listed
2,3,4,7,8-Pentachlorodibenzofuran (*see* Dibenzofurans)	57117-31-4	Monograph 100F [2012]	Group 1. Overall evaluation upgraded based on mechanistic and other relevant data		Not listed
Perfluorodecanoic acid (*see* PFAS)	335-76-2		Not listed		Not listed
Perfluorohexanesulfonate acid (*see* PFAS)	355-46-4		Not listed		Not listed
Perfluoroisobutylene (*see* PFAS)	382-21-8		Not listed		Not listed
Perfluorononanoic acid (*see* PFAS)	375-95-1		Not listed		Not listed
Perfluorooctanoic acid (*see* PFAS)	335-67-1	Monograph 110 [2017]	Group 2B [kidney, testis]		Not listed
Perfluoroundecanoic acid (*see* PFAS)	2058-94-8		Not listed		Not listed
Perylene	198-55-0	Supplement 7, Monograph 92 [2010]	Group 3		Not listed

Name	CAS	IARC*		NTP-RoC	
Phenanthrene	85-01-8	Supplement 7, Monograph 92 [2010]	Group 3		Not listed
Silver	7440-22-4		Not listed		Not listed
Styrene	100-42-5	Monographs 60, 82, 121 [2019]	Group 2A [lymphoma, multiple myeloma, leukemia]	2011	*Reasonably anticipated to be a human carcinogen*
Sulfur dioxide	7446-09-5	Monograph 54 [1992]	Group 3		Not listed
2,2',4,4'-Tetrabromodiphenyl ether	5436-43-1		Not listed		Not listed
2,3,7,8-Tetrachlorodibenzodioxin (*see* Dioxins)	1746-01-6	Supplement 7, Monographs 69, 100F [2012]	Group 1 [lung, soft tissue, leukemia and lymphoma, all cancer sites (combined)]	1999	*Known to be a human carcinogen*
2,3,7,8-Tetrachlorodibenzofuran (*see* Dibenzofurans)	51207-31-9	Monograph 69 [1997]	Group 3		Not listed
Tetrachloroethylene	127-18-4	Supplement 7, Monographs 63, 106 [2014]	Group 2A [urinary bladder]	1989	*Reasonably anticipated to be a human carcinogen*
Tetrahydrofuran	109-99-9	Monograph 119 [2019]	Group 2B		Not listed
Toluene	108-88-3	Monographs 47, 71 [1999]	Group 3		Not listed
1,2,3-Tribromo-4-(2,4-dibromophenoxy)benzene	182346-21-0		Not listed		Not listed
1,3,5-Tribromo-2-(2,4-dibromophenoxy)benzene	189084-64-8		Not listed		Not listed
Trichloroethylene	79-01-6	Supplement 7, Monographs 63, 106 [2014]	Group 1 [liver, bile duct, kidney, non-Hodgkin lymphoma]	2000	*Known to be a human carcinogen*
Vinyl acetate	108-05-4	Monograph 101 [2013]	Group 2B		Not listed
***p*-Xylene**	106-42-3		Not listed		Not listed
Zinc	7440-66-6		Not listed		Not listed
Agent Categories and Mixtures					
alpha-Chlorinated toluenes (benzal chloride, benzotrichloride, benzyl chloride) and benzoyl chloride (combined exposures)		Monograph 29, Supplement 7, Monograph 71 [1999]	Group 2A [lung]		Not listed
Cadmium compounds		Monographs 58, 100C [2012]	Group 1 [lung, prostate, kidney]	2016	*Known to be a human carcinogen*

Name	CAS	IARC*		NTP-RoC	
Dibenzofurans		Monograph 69 [1997]	Group 3, except 2,3,4,7,8-pentachlorodibenzofuran		
Diesel exhaust		Monographs 46, 105 [2014]	Group 1 [lung, urinary bladder]	2000	*Reasonably anticipated to be a human carcinogen*
Dioxins		Monograph 69 [1997]	Dibenzodioxins, except 2,3,7,8-tetrachlorodibenzodioxin, are Group 3		Not listed
Hexachlorocyclohexanes		Monograph 20, Sup 7 [1987]	Group 2B	1981	*Reasonably anticipated to be a human carcinogen*
Lead compounds		Monograph 23, Supplement 7 [1987]	Group 2B [stomach]	2004	*Reasonably anticipated to be a human carcinogen*
Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS)			Only perfluorooctanoic acid (PFOA) listed		Not listed
Phthalates			Only benzyl butyl phthalate listed		Only di(2-ethylhexyl) phthalate listed (not on Inventory)
Polychlorinated biphenyls (PCBs)		Monograph 107 [2015]	Group 1 [melanoma, breast, lymphoma and leukemia]	2016	*Reasonably anticipated to be human carcinogens*
Polycyclic Aromatic Hydrocarbons (PAHs)			Not listed	1981, 1989	*Reasonably anticipated to be a human carcinogen*

Abbreviations: CAS - Chemical Abstract Service (CAS) Registry Number, IARC – International Agency for Research on Cancer, NTP-RoC – National Toxicology Program's Report on Carcinogens.

*IARC classifies agents as: Group 1 - Carcinogenic to humans; Group 2A - Probably carcinogenic to humans; Group 2B - Possibly carcinogenic to humans; and Group 3 - Not classifiable as to its carcinogenicity to humans.

[†]Square brackets include the organs for which the agents have *sufficient* or *limited* evidence of carcinogenicity in humans.[44]

The WTC Health Program identified studies on carcinogenicity of TCDD/dioxin and cadmium that were published after the IARC evaluations were conducted. The findings of these studies are shown in Tables 4 and 5, respectively. No new evidence on uterine cancer was identified.

It is relevant to note that TCDD/dioxin is classified by IARC as having *sufficient evidence of carcinogenicity in humans* for all cancers combined. However, IARC does not interpret this as meaning that every cancer may be caused by TCDD.

Table 4. Studies of TCDD and cancer published after the latest IARC Monograph (2012):

Study design	Study population	Reference population(s)	Outcome, uterine cancer risk estimate	Reference
Ecological	Michalovce District, the Slovak Republic (~ 112,000 inhabitants) and Uherske Hradiste, the Czech Republic (146,000 inhabitants)	Slovak Republic (~ 5 M inhabitants) and the Czech Republic (10,3 M inhabitants)	Cancer incidence, NR	Bencko et al. [2009][45]
Retrospective cohort	1,615 workers who worked 1 or more days in a department with potential TCDD exposure	US population	Mortality, NR	Collins et al. [2009][46]
Retrospective cohort	Subjects resident and those who migrated into (or newborn in) the area in the 10-year period after the Seveso accident in three contaminated zones with decreasing TCDD soil levels: 723 (high), 4,821 (medium), 31,643 (low)	181,574 residents of the surrounding non-contaminated zone	RR (95% CI) = 1.24 (0.17-8.82) (high exposure); 0.6 (0.19-1.87) (medium exposure); 0.73 (0.49-1.10) (low exposure)	Pesatori et al. [2009][47]
Retrospective cohort	777 Ranch Hand veterans exposed to Agent Orange, contaminated with TCDD	737 comparison veterans	Cancer incidence, men only	Buffler et al. [2011][48]
Retrospective cohort	2122 pentachlorophenol (PCP) production workers from four plants exposed to PCP and to polychlorinated dibenzo-p-dioxin and dibenzofuran contaminants of PCP production.	US population	Mortality, NR	Ruder and Yiin [2011][49]
Retrospective cohort	180,639 Korean Vietnam war veterans (no indication if women were included)	7,973 low exposed veterans	Mortality, NR	Yi et al. [2014][50]
Retrospective cohort	180,251 Korean Vietnam veterans (no indication if women were included).	Low and no-exposed veterans	Cancer incidence, NR	Yi et al. [2014][51]

Study design	Study population	Reference population(s)	Outcome, uterine cancer risk estimate	Reference
Meta-analysis	45 cases from 2 mortality studies	Pooled reference populations.	Mortality, NR	Xu et al. [2016][52]
Retrospective cohort	1,599 men and women working at a New Plymouth, New Zealand plant producing the herbicide 2,4,5-trichlorophenoxyacetic acid (2,4,5-T) with TCDD as a contaminant	New Zealand population	Mortality, SMR (95% CI) = 0.0 (0.0-17.78)	McBride et al. [2018][53]
10-year period cancer prevalence ratio study	631 endometrial cancer cases diagnosed between 2010-2020 among Vietnam War era deployed Veterans	Non-Vietnam War deployed veterans	Adjusted period prevalence ratio (95% CI) = 0.72 (0.33-1.11)	Hastings [2021][54]

Abbreviations: NR – uterine cancer risk not reported; RR – relative risk; SMR – standardized mortality ratio.

Only the Pesatori et al. [2009] study reported an elevated, albeit not statistically significant, risk of uterine cancer associated with TCDD exposure.[47] Study participants were exposed to very high levels of TCDD as a result of a chemical explosion close to their residence. TCDD levels in serum collected at the time of the accident were shown to be of similar magnitude to those reported in 2,4,5-trichlorophenol production workers, and some were among the highest ever reported. An analysis of 232 stored samples from girls who were age 0-10 at the time of the incident showed a median TCDD concentration that ranged from 123 ppt for those age >5–10 years to 288 for those age >0-2 years, with higher concentrations among those in the most contaminated zone: 322 ppt for those age >5-10 years to 553 ppt for those age >0-2 years. In comparison, the median TCDD serum concentration in a WTC cohort of 110 adolescents at the time of the attack was 10 ppt, 12 years after exposure.[55] In this study, mean TCDD levels were 14.2 pg/g lipid among 60 9/11-exposed study participants and 2.10 pg/g lipid among 50 non-exposed participants.

Table 5. Studies of cadmium and cancer published after the latest NTP evaluation (2016):

Study design	Study population	Reference population(s)	Outcome, uterine cancer risk estimate	Reference
Prospective cohort	7348 individuals from the Jinzu River basin, the heaviest Cd-polluted area in Japan	2098 residents of non-polluted areas	Adjusted HR for death from all cancers or from renal and uterine cancers were statistically significantly higher in subjects with proteinuria, glucosuria, and glucoproteinuria	Nishijo et al. [2018][56]
Retrospective cohort	229 individuals from the Taisi Village in Taiwan living nearby a petrochemical complex	1333 individuals from the Dacheng Township, and 372 individuals from the Zhutang Township	All cancer IRR higher in Taisi than non-exposed populations, NR	Chen et al. [2018][57]
Nested case-control	1,200 cancer cases who, at some time between the years 1979–2004 lived within a 2 km radius of a glassworks emission source in Sweden	7,000 cancer-free control individuals	NR	Helmfrid et al. [2019][58]
Prospective cohort	1161 men and 1812 women from non- Cd polluted areas in Japan	Individuals with urinary Cd levels below limit of detection	Mortality, one uterine cancer case observed, NR	Watanabe et al. [2020][59]
Retrospective cohort	Copper metallurgy waste workers (exposed to metals, included Cd)	Not reported in abstract	Article in Russian. Mortality, NR among cancers elevated in women	Adrianovsky et al. [2020][60]
Prospective cohort	26,056 participants from NHANES	Not indicated	Cadmium in urine was associated with all cancer mortality, NR	Duan et al. [2020][61]

Study design	Study population	Reference population(s)	Outcome, uterine cancer risk estimate	Reference
Prospective cohort	4,573 individuals with type 2 diabetes from Shiyan City, China	Individuals with plasma metals concentrations at the 10th percentile	Plasma cadmium was statistically significantly higher among participants with higher cancer incidence, NR	Li et al. [2020][62]

Abbreviations: IRR – Incidence rate ratio; NR – uterine cancer risk not reported.

No reports of elevated uterine cancer incidence or mortality associated with cadmium exposure were found in the available literature. An editorial opinion suggests that cadmium might be a risk factor for uterine cancer among women with obesity and diabetes.[63] The authors describe a case-control study that adjusted the regression model to account for obesity and diabetes mellitus and found a 22 percent statistically significant increased risk of uterine cancer with cadmium exposure.[64] This evidence suggests a relationship between cadmium exposure and uterine cancer, but is inconclusive; more research is needed to explore a potential causal relationship including elucidating a mechanism of carcinogenicity.

IV. Additional Considerations

In addition to the three methods outlined above, a type of cancer may be added to the List if the STAC provides a reasonable basis for adding it. The Administrator has requested a STAC recommendation regarding whether 9/11 exposures have a causal association with uterine cancer.

The Zadroga Act allows the STAC 90 days, with potential extension up to 180 days, to give its recommendation to the Administrator. The STAC may consider any scientific evidence it deems relevant to determining whether or not there is sufficient support for the addition of uterine cancer to the List of WTC-Related Health Conditions. As outlined below, the Science Team has accumulated additional information that the STAC may wish to consider in its deliberations.

1. Mechanisms of endometrial cancer development

   The review by Banno et al. [2014] describes the currently proposed mechanisms of carcinogenesis in endometrial cancer.[65] These mechanisms include estrogen, an abnormal mismatch repair (MMR) system, genetic abnormalities, and aberrant methylation of DNA and microRNA. The mechanisms of Type I endometrial cancer development (which accounts for 80 percent of all endometrial cancers) do not markedly differ from those at other cancer sites. The mechanisms of type II endometrial cancers remain largely unknown. What follows is a summary of the commonalities in mechanisms for uterine (type I and II) and other cancers.

   - The mismatch repair (MMR) system is responsible for repairing base mismatches that arise during DNA replication. Aberrations in MMR genes are involved in carcinogenesis of type I endometrial cancer. MMR genes are also causative genes in Lynch syndrome (hereditary nonpolyposis colorectal cancer), a typical familial tumor with autosomal dominant inheritance.
   - Gene mutations found in type I endometrial cancer include those in *PTEN*, *β-catenin* and *K-ras*. *PTEN* inactivation is also found in malignant melanoma, brain tumors, and endometrial, ovarian,

thyroid, breast, and prostate cancers. *β-catenin* and *K-ras* mutations are found in various human cancers.

- Mutations in type II endometrial cancer are thought to be linked to the oncogene *HER-2/neu* and tumor suppressor gene *p53*. Mutations of the *HER-2/neu* gene are also found in breast and ovarian cancers. A *p53* gene mutation is the most frequent mutation in human cancer.
- *RB* and *cyclin* might also be involved in the carcinogenesis of endometrial cancer. *RB* gene mutations have been found in small cell lung, bladder, and esophageal cancers.
- Many tumor suppressor genes in cancer cells are inactivated by aberrant DNA methylation in different cancer pathways. An example is *RSK4* expression, that has been shown to be downregulated by methylation in atypical endometrial cancer, as well as in rectal, breast and kidney cancers. Another example is *CHFR* downregulation by aberrant hypermethylation that increases the paclitaxel sensitivity of gastric and endometrial cancers.
- microRNAs (miRNAs) are short noncoding RNAs that regulate gene expression. miRNAs that inhibit DNA methylation in cancers are referred to as tumor suppressor miRNAs (TSmiRNA). One microRNA, *miR-152* is also a TS-miRNA in endometrial cancer. *miR-152* methylation levels are also changed in acute lymphoblastic leukemia, gastrointestinal cancer, and cholangiocarcinoma.

2. Other evidence from studies of uterine cancer from exposure to the 9/11 agents TCDD, PCBs, cadmium, asbestos, and chloroethane:

   a. The retrospective cohort study by Pesatori et al. [2009] among residents and those who migrated into the area in the 10-year period after the Seveso accident.[47] The study compared people in three contaminated zones with decreasing TCDD soil levels: 723 (high TCDD soil levels), 4,821 (medium), 31,643 (low) with 181,574 residents of the surrounding non-contaminated zone. Incident cancer cases were ascertained through 120 hospital-network of the Lombardy region between 1977 and 1996. Sex-, age-, and period-adjusted rate ratios (RR) and 95% confidence intervals (95% CI) for uterine cancer were: RR (95% CI) = 1.24 (0.17-8.82) (high exposure); 0.6 (0.19-1.87) (medium exposure); 0.73 (0.49-1.10) (low exposure).

   b. The findings by Kogevinas et al. [1997] from the International Cohort Study.[66] This is a retrospective mortality study of 21,863 male and female workers exposed to phenoxy herbicides, chlorophenols, and dioxins in 12 countries. The authors reconstructed exposure using job records, company exposure questionnaires, and serum and adipose tissue dioxin levels. Follow-up period varied in each cohort; overall, it extended from 1939 to 1992. The study found an SMR for uterine cancer among workers exposed to TCDD or higher chlorinated dioxins of 3.41 (95% CI 0.7–9.96).

   c. The prospective population-based Swedish Mammography Cohort study of dietary PCB exposure, by Donat-Vargas et al. [2016].[67] This study included 36,777 cancer-free women at baseline. Validated estimates of dietary PCB exposure were obtained via a food frequency questionnaire. Incident cancer cases were ascertained through register linkage. The study found a non-statistically significant increased risk of endometrial cancer (adjusted RR in the highest tertile of PCB exposure=1.21, 95% CI: 0.73–2.01; p_{trend}=0.54).

   d. The study by Akesson et al. [2008], also conducted in the population-based Swedish Mammography Cohort.[68] This study is a prospective cohort of 30,210 postmenopausal women who were cancer-free at baseline (1987) and who completed a food frequency questionnaire at baseline and in 1997. The authors estimated dietary cadmium intake based on the questionnaire

data and cadmium content in all foods. They found an adjusted RR=1.39 (95% CI 1.04–1.86, p_{trend}=0.019) of post-menopausal endometrial cancer in the highest tertile of dietary cadmium consumption.

e. The retrospective mortality study by Magnani et al. [2007] in a cohort of 3,434 Italian asbestos cement workers (2657 men and 777 women).[69] The authors ascertained vital status and cause of death though registrar offices; diagnoses for five out of 15 observed uterine cancer cases could not be confirmed. When compared with the population of Piedmont, an excess uterine cancer mortality was observed among female workers (SMR=25.7, 95% CI 1.44-4.24). The number of uterine cancer cases increased after at least 10 years of latency, but no trend by duration of exposure was observed. Since the authors did not provide ICD codes, it is not possible to know if their definition of uterine cancer also included cervical cancers, as occurred in other studies by the same group, described below. Another study is the retrospective cohort mortality study conducted by Germani et al. [1999] among 631 Italian women compensated for asbestosis.[70] Cause of death was obtained from the Registry Office of the municipality of residence or death. When compared with the national population, uterine cancer mortality was elevated (SMR=2.56, 95% CI 1.03-5.28); however, cases of uterine and cervical cancer were not differentiated. In contrast, a retrospective cancer incidence study by Reid et al. [2009] followed up 2,552 women, residents of Wittenoom, Australia, and 416 workers of the local asbestos company.[71] When compared with the Western Australian population, no increased incidence of uterine cancer was observed. With the exception of intensity of exposure, risk decreased with increases in time since first exposure, year of arrival, age of first exposure, and duration of exposure. In another study, Magnani et al. [1993] did not find an excess mortality of uterine cancer among the wives of workers in the asbestos cement industry (SMR=0.68, 95% CI 0.22-1.59).[72] This study also failed to separate cancers of the uterus and cervix.

f. The study by Holder [2008], who exposed male and female F344 rats and B6C3F1 mice (50/sex/group) chronically to either 0 or 15,000 ppm chloroethane gas for 6 h/day, 5 days/week for 102 weeks (rats) or 100 weeks (mice).[73] Chloroethane was associated with uterine cancer in mice (but not rats). The author indicates that the mechanism appears to be through chloroethane-stimulated adrenal production of corticosteroids, which adversely promotes endometrial cells to cancer in mice −a mechanism that is also observed in humans.

3. Sex Disparities in Occupational Cohort Studies, and other cancers causally associated with EDCs

Most studies of exposures to EDCs have been conducted in occupational cohorts, which included a small number of women or no women at all. Furthermore, there are other cancers that are associated with EDCs (e.g., breast, prostate, and ovarian cancers).

In addition, the following evidence from Table 3 shows that other cancers are causally associated with endocrine disrupting agents included in the Inventory of 9/11 agents:

- **2,3,7,8-Tetrachlorodibenzodioxin**, classified by IARC in Group 1 (carcinogenic to humans).[74] It is an agent with limited evidence in humans for cancers of the lung, soft tissue sarcoma, and non-Hodgkin lymphoma, and sufficient evidence in humans for all cancer sites (combined).[44] It is also listed as a Known to Be a Human Carcinogen on NTP's Fourteenth Report on Carcinogens.[75]
- **2,3,4,7,8-Pentachlorodibenzofuran**, classified by IARC in Group 1.[74] There is no evidence in humans of its carcinogenicity; however, there is sufficient evidence in experimental animals, as well as mechanistic and other relevant data that support this classification.

- **Perfluorooctanoic acid**, classified by IARC in Group 2B (possibly carcinogenic to humans).[76] It is an agent with limited evidence in humans for cancers of the kidney and testis.[44]
- **Polychlorinated biphenyls (PCBs)**, classified by IARC in Group 1.[77] PCBs have sufficient evidence in humans for skin cancer (melanoma) and limited evidence for breast cancer, and leukemia and lymphoma. They are considered Reasonably Anticipated to Be a Human Carcinogen by NTP and classified in Group B2 (probable human carcinogen, based on sufficient evidence of carcinogenicity in animals) by EPA.[75, 78]
- **3,3',4,4',5-Pentachlorobiphenyl**, classified by IARC in Group 1.[74] There is no evidence in humans of its carcinogenicity; however, there is sufficient evidence in experimental animals, as well as mechanistic and other relevant data that support this classification.
- **Cadmium and cadmium compounds**, classified by IARC in Group 1.[79] Cadmium and its compounds have sufficient evidence in humans for lung cancer and limited evidence for cancers of the prostate and kidney.[44]

V. WTC Health Program's Actions after Receipt of the STAC Recommendation

After receiving the recommendations from the STAC on November 29, 2021,[80] the Administrator evaluated the Committee's advice and published a Notice of Proposed Rulemaking (NPRM) in the *Federal Register*.[81] The Administrator ultimately relied on the Committee's recommendation to propose the addition of uterine cancer to the List. The following excerpt from the May 2022 NPRM contains the Administrator's evaluation of the information and advice provided by the STAC:

> ... the Administrator reviewed the recommendation of the STAC to determine if uterine cancer could be added to the List pursuant to Method 4, which permits an addition where the STAC recommends such an addition and provides a reasonable basis for the recommendation. The Administrator finds that the STAC's recommendation provides a reasonable basis for the addition of uterine cancer under Method 4 and this recommendation is further supported by the supplemental information presented by the Science Team in the White Paper.
>
> Specifically, the Administrator agrees with the STAC's finding that mechanisms of initiation and progression of uterine cancer are similar to those for several other cancers on the List. In particular, the evidence showing similar gene mutations and abnormal mismatch repair proteins among many cancers, including uterine cancer, strongly supports shared etiology and pathogenesis between uterine cancer and other cancer types on the List. For example, gene mutations found in low-grade, endometrioid endometrial cancer (which accounts for 80 percent of all endometrial cancers) include those in *PTEN* (phosphatase and tensin homolog deleted on chromosome 10), *CTNNB1* (b-catenin), and *K–RAS. PTEN* inactivation is similarly found in malignant melanoma, brain tumors, and ovarian, thyroid, breast, and prostate cancers, while *CTNNB1* and *K–RAS* mutations are found in a variety of human cancers. High-grade endometrial cancers are associated with mutations in oncogene *ERBB2* (HER–2/neu) and tumor suppressor gene *TP53. ERBB2* gene mutations are also found in breast and ovarian cancers; likewise, *TP53* is frequently mutated in a variety of human cancers, including high-grade serous ovarian and basal-like breast cancers. Finally, studies have shown that several microRNAs (miRNAs), including miR–152 which plays a role as a tumor suppressor, can be epigenetically silenced by hypermethylation of their respective DNA locus in endometrial cancer. Aberrant methylation of miR–152 has also been reported for other cancers, including acute lymphoblastic leukemia,

gastrointestinal cancer, and cholangiocarcinoma. Recent pan-cancer molecular studies have found shared molecular features among invasive breast carcinoma and several gynecologic tumors, such as high-grade serous ovarian cystadenocarcinoma, uterine corpus endometrial carcinoma, cervical squamous cell carcinoma and endocervical adenocarcinoma, and uterine carcinosarcoma. The Administrator agrees with the STAC's finding that the shared etiology and pathogenesis described in the scientific literature suggest it would be unlikely that uterine cancer would be the only cancer type not related to 9/11 exposures.

The Administrator also finds that an association between exposure to EDCs in WTC dust and uterine cancer risk is plausible. EDCs can mimic endogenous hormones and interfere with endogenous hormone homeostasis, which may lead to a variety of adverse health outcomes, including cancer (*e.g.,* estrogen imbalances are a key risk factor for uterine cancer). There is extensive evidence from human studies of an etiologic role of estrogens in cancer. However, finding a causal association between an EDC 9/11 agent and uterine cancer is highly unlikely given the potentially long latency between exposure and disease. Moreover, the low number of women included in epidemiologic studies examining EDC carcinogenic risks in occupational cohorts increases the difficulty in finding conclusive evidence of a causal association with uterine cancer. Given the growing body of scientific evidence suggesting that exposure to EDCs may be a risk factor for female reproductive organ cancers (*e.g.,* breast, ovarian, and endometrial cancers), it is reasonable to assume that exposure to EDCs in WTC dust may contribute to uterine cancer risk.

Finally, the Administrator recognizes that the disproportionally low representation of women in the most studied cohorts of exposed responders makes it epidemiologically unlikely that a definitive association between 9/11 exposures and the occurrence of uterine cancer will be identified during the lifetime of even the most highly exposed Program members.

The Administrator has determined that the available scientific evidence and rationale provided by the STAC in its recommendation, supported by the supplemental information presented by the Science Team in the White Paper, offers a plausible rationale for an association between uterine cancer and EDCs in the *Inventory of 9/11 Agents.* Moreover, the cohorts relevant to understanding uterine cancer in the 9/11-exposed population are too small to allow a definitive decision about whether uterine cancer is causally associated with 9/11 exposure. For these reasons, the Administrator finds that a reasonable basis has been provided by the STAC under Method 4 and, accordingly, proposes to add uterine cancer to the List of WTC-Related Health Conditions.

After publication of the NPRM, the Administrator solicited an assessment of the WTC Health Program's evaluation of evidence supporting the proposal to add uterine cancer to the List by three independent peer reviewers who are subject matter experts in endocrine disruption and cancer. The three peer reviewers were asked to respond to the following questions:

1. Are you aware of any other studies which should be considered? If so, please identify them.
2. Have the requirements of this *Policy and* Procedures[4] been fulfilled? If not, please explain which requirements are missing or deficient.
3. 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.

Comments received from the three peer reviewers were de-identified and compiled into one document which was published in the docket on June 9, 2022, 30 days after the NPRM publication.[82] Members of the public also provided comments. These comments were generally supportive of the addition of uterine cancer to the List.

The following is the Science Team's evaluation of the comments and references provided by peer reviewers to supplement the STAC's discussion of some potential mechanisms of action through which EDCs might cause uterine cancer in humans:

> Much of the available research on EDCs' mechanisms of action has focused on EDCs which are not also identified 9/11 agents in the Inventory of 9/11 Agents. Indeed, some of the specific chemicals and toxins identified as EDCs by the peer reviewers based on supplemental sources have not been identified by the Program as 9/11 agents. The Science Team has recognized, however, that the list of 9/11 agents identified by the Program in the Inventory may not be complete and that WTC-related uterine cancer may be associated with chemicals and toxins that exhibit estrogenic properties that may be identified as 9/11 agents in the future. Regardless of whether there are EDCs that may be associated with uterine cancer that may be added to the Inventory of 9/11 Agents in the future, the Science Team has found it instructive to examine mechanisms of action for endocrine disruption even for those EDCs that have not been recognized as 9/11 agents. The supplemental references' descriptions of mechanisms of endocrine disruption illustrate the various ways in which exposure to EDCs could impact the female reproductive system and result in uterine cancer. The similar mechanisms of action for other EDCs help provide a complete picture of the possible causal relationship between the September 11, 2001, terrorist attacks, and uterine cancer among WTC responders and survivors.
>
> Most endometrial tumors are hormonally driven through estrogen signaling via estrogen receptors α and β acting as an oncogenic signal. The main risk factors (i.e., estrogen therapy without progestins, tamoxifen for the treatment of breast cancer, parity, oral contraceptive use, age at menarche) and some treatment options (i.e., progestin therapies) for endometrial cancer patients underscore a key role for estrogen signaling in the disease.[83] Estrogen-like chemicals have been shown to mimic the estrogen pathway and affect the normal function of female sex hormones. This mechanism is suspected to lead to carcinogenesis in women, including the development of endometrial cancer, breast and ovarian cancers, and prostate cancer in men.[84] EDCs can interfere with the function and metabolism of estrogen; breast and ovarian cancers are associated with EDCs and their current known mechanisms of action are similar to those of uterine cancer.[85] For example, experimental studies in animals exposed to endocrine-disrupting alkylphenols such as nonylphenol and oxylphenol, as well as a case-control study, suggest an association between exposure to EDCs and endometrial cancer.[86-88] Experimental animal and *in vitro* studies have shown that exposure to the EDCs bisphenol A (BPA) and 2,4-dichlorodiphenyltrichloroethane (DDT) result in changes that could lead endometrial cells towards malignancy.[89]
>
> Studies in animal models show that exposure to some EDCs can cause endometrial hyperplasia (a proliferation of endometrial glands) and other alterations to the uterine lining.[90-96] Endometrial hyperplasia with atypia is of clinical significance because it may progress to, or coexist with, endometrial carcinoma. However, no human studies that showed an association between EDCs and endometrial hyperplasia were identified. Nonetheless, experimental animal studies have identified some evidence that suggests the likelihood of occurrence in humans.

EDCs such as di(2-ethylhexyl)phthalate (DEHP) and cadmium have also been associated with uterine leiomyoma (a benign smooth muscle tumor, also known as a fibroid, that causes symptoms such as uterine bleeding and severe pelvic pain, resulting in infertility or major surgery). A meta-analysis of five studies showed that urinary DEHP metabolites were statistically significantly associated with an increased risk of uterine leiomyoma, although the mechanism is still not well understood.[97] Moreover, an *in vitro* study showed that fibroid cells subjected to cadmium exposure for two months show enhanced migration potential, augmented anchorage-independent growth, and increased DNA synthesis, suggesting EDC-induced potential progression towards uterine cancer.[98]

In addition to interacting with estrogen receptors α and β, EDCs are known to bind to and activate the estrogen-related receptor gamma (ERRγ). BPA has weak estrogenic activity due to its limited capacity to bind to nuclear estrogen receptors α and β. Nonetheless, ERRγ is activated by BPA and interacts with the ligand domain of estrogen receptors.[99] Multiple studies show that BPA may increase the risk of estrogen-related cancers.[100]

EDCs are also known to play a role in endocrine disruption leading to epigenetic changes. An instructive example is a study among Michigan residents accidentally exposed to the EDC polybrominated biphenyl (PBB). The study's authors found differences in epigenetic marks (chemicals which turn genes "on" and "off") that suggest that PBB acts similarly to estrogen and is associated with dysregulated immune system pathways. The authors also found evidence that PBB could be acting like an estrogen, impacting gene expression.[101] Furthermore, EDCs may increase uterine sensitivity to estrogens due to epigenetic alterations. Another example is a study in female mice in which BPA administered *in utero* increased the expression of the developmental homeobox gene *Hoxa10* that controls uterine organogenesis. Alterations in methylation of *Hoxa10* have been associated with several human cancers.[89, 102]

In addition, endocrine disruption caused by some 9/11 agents alters reproductive and sexual development, and may lead to other health outcomes such as obesity and diabetes that affect the risk of uterine cancer development.[103] The following identified EDC 9/11 agents may pose such risks for the development of uterine cancer: polyvinyl chloride plastics, which contain phthalates;[104-107] trichloroethylene and its major metabolites;[108] TCDD, which is an EDC that has antiestrogenic properties;[109] and pesticides such as chlordane, DDT, dieldrin, endosulfan, hexachlorobenzene (HCB), lindane, heptachlor, metribuzin, and mirex.[110]

Finally, the development of most endocrine cancers is likely to be the result of low-dose exposures to complex chemical mixtures in the environment throughout a person's life.[111] WTC dust is a complex mixture of EDCs and other environmental chemicals. Exposure to WTC dust, when added to the usual low-dose environmental chemical exposures experienced in a person's lifetime, may directly or indirectly influence the development of uterine cancer. Combined exposures have simultaneous effects on the endocrine system that could affect the development of uterine cancer and its risk factors.[85]

The Science Team finds that the evaluations and supplemental information provided by the peer reviewers in response to the NPRM provide additional support for the STAC recommendation and rationale provided to the Administrator under Method 4.

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