WORLD TRADE CENTER HEALTH PROGRAM

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Pentagon

Scientific Considerations for Adding Uterine Cancer to the List of WTC-Related Health Conditions

Geoff Calvert, MD, MPH
Associate Director for Clinical Quality
WTCHP/NIOSH/CDC

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Disclaimer: This presentation provides only summary background information on the WTC Health Program; it does not replace the official statutes, regulations, policies, and/or procedures governing the Program.

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Monitoring and Treatment 9.11 WTC Health Program

This presentation is a summary of the White Paper, "Scientific Considerations for Potential Addition of Uterine Cancer to the List of Covered Conditions by the World Trade Center Health Program," [updated] that was distributed to STAC members and the public before this meeting.

Outline

1. Background
2. Procedures for Adding Cancers to the List of WTC-Related Health Conditions
   - Four methods to assess available evidence
3. Uterine Cancer: Definition, Types, and Risk Factors
4. Previous consideration of uterine cancer by the WTC Health Program
5. WTC Health Program Evaluation of Available Evidence Regarding Uterine Cancer Among 9/11 Exposed Populations
   - Evidence for Method 1
   - Evidence for Method 2
   - Evidence for Method 3
6. Additional considerations
   a) Mechanisms of endometrial cancer development
   b) Sex disparities in occupational cohort studies
   c) Observed associations between 9/11 agents and increased uterine cancer risk
   d) Other cancers causally associated with endocrine disrupting chemicals (EDCs) that are 9/11 agents

Background: Uterine Cancer

- Uterine cancer is the *only* cancer type not included in the World Trade Center (WTC) Health Program's List of WTC-Related Conditions
  - Uterine sarcoma, a rare subtype of uterine cancer, is covered as a rare cancer (rare cancers are those with a US incidence rate <15 cases/100K/yr)
  - Uterine cancers that arise from the use of tamoxifen to treat a WTC-certified cancer may be covered as a medically associated condition (MAC)
  - Uterine cancers that arise from estrogen-secreting tumors, which are rare cancers, may also be covered as a MAC

Background: Uterine Cancer

- Often referred to as endometrial cancer
  - Since >90% of cases occur in the endometrium
- Endometrial cancer is the fourth most common cancer in U.S. women
  - After cancers of the breast, lung/bronchus, and colon/rectum
- In 2021, ~66,570 cases of uterine cancer will be diagnosed in the US (ACS, 2021)
  - 12,940 women are expected to die from this disease
- Incidence peaks between ages 60 and 70 years, but 2%-5% of cases occur before age 40 years

Background: Uterine Cancer

- Known risk factors
  - Endometrial hyperplasia
  - Estrogen hormone therapy with estrogen (unopposed estrogen)
  - Selective estrogen receptor modulators (e.g., tamoxifen)
  - Obesity
  - Protective factors include increasing parity (number of pregnancies) and lactation, hormonal contraceptives, physical activity, and smoking

Previous Consideration of Uterine Cancer by the WTC Health Program

- WTC Health Program has received eight submissions to add uterine cancer or uterine cancer subtypes to the List
  - Seven of these did not meet the requirements to qualify as petitions
  - One submission qualified as a petition
    - Received in 2019
    - Program reviewed the available evidence and determined it was insufficient to add uterine cancer to the List
- Most recent submission was received in 2020
    - Submitted by several Clinical Centers of Excellence (CCEs)
    - Requested that the WTC Health Program consider the contributing role of endocrine disrupting chemicals (EDCs)
    - Submission did not meet the requirements to qualify as a valid petition because no new medical basis was provided

Current Consideration of Uterine Cancer by the WTC Health Program

- The Administrator determined that the issues raised in the 2020 submission merited further consideration
  - The contributing role of EDCs
  - The low number of women included in study populations with exposures to 9/11 agents
- The Administrator directed the WTC Health Program's Science Team to:
  - Review the available scientific evidence for EDCs causing uterine cancer
  - Determine if that scientific evidence has the potential to provide a basis for adding uterine cancer to the List

Four methods to assess available evidence for adding a cancer to the List*

- At least one of these four methods must be fulfilled to add a cancer
  - Method 1: Assessment of peer-reviewed, published, epidemiologic studies of 9/11-exposed populations satisfies the causal criteria adapted from Bradford Hill
  - Method 2: An established causal association exists between the cancer and a condition already on the List
  - Method 3: Review of Evaluations of Carcinogenicity in Humans
    - Must meet both of the following criteria
      - A chemical, physical, biological, or other hazard must be included in the Inventory of 9/11 Agents, AND
      - NTP determined that the 9/11 agent is known to be a *human carcinogen* or is *reasonably anticipated to be a human carcinogen*, AND IARC has determined there is sufficient or limited evidence that the 9/11 agent causes the cancer type of interest
  - Method 4: STAC provides a reasonable basis for adding the cancer type

*List=List of WTC-Related Health Conditions

Methodology

- WTC Health Program's Science Team conducted a literature review and assessed the available evidence using Methods 1, 2, and 3
- Databases searched included: CINAHL, Embase, NIOSHTIC-2, ProQuest Health & Safety, PsycINFO, Ovid MEDLINE (PubMed), Scopus, Toxicology Abstracts/TOXLINE, and WTC Health Program Bibliographic Database
- The results of that assessment are summarized in the following slides

<u>Method 1</u>: Assessment of peer-reviewed, published, epidemiologic studies of 9/11-exposed populations satisfies the causal criteria adapted from Bradford Hill

- Nine relevant peer-reviewed, published, epidemiologic studies were identified and reviewed
  - Three other studies excluded
    - Two included only men (Moir et al 2016; Zeig-Owens et al 2011)
    - One didn't provide a comparison population or background rates (Klineman et al 2015)
- The Program concluded that these studies do not provide a sufficient basis to add uterine cancer to the List
  - No consistent evidence of elevated uterine cancer incidence or mortality among WTC responders and survivors
  - A dose-response relationship between 9/11 exposures and uterine cancer not provided
  - Study designs may be susceptible to selection bias
  - Only external comparisons were made. 9/11 population is considered healthier than external comparison groups. Differences between the 9/11 population and these comparison groups may have under-estimated risk estimates

<u>Method 1</u>: Assessment of peer-reviewed, published, epidemiologic studies of 9/11-exposed populations satisfies the causal criteria adapted from Bradford Hill

Li et al 2021, Cancer Incidence in World Trade Center Rescue and Recovery Workers: 14 Years of Follow-Up. J Natl Cancer Inst. 2021 Sep 9:djab165. Epub ahead of print. PMID: 34498043

- Prospective cohort cancer incidence study (linkages with 13 statewide cancer registries)
- Study of three responder cohorts: General Responder Cohort; FDNY; and WTC Registry
- Included 9,151 women (among 57,402 total participants). All were involved in rescue, recovery, and cleanup efforts at Ground Zero after the 9/11 attack
- Expected cancer rates based on New York State data
- Findings for Uterine CA , 2002-2015 : SIR=0.66, 95%CI=0.45-0.94, based on 31 cases
- No dose-response analyses reported for uterine cancer

<u>Method 1</u>: Assessment of peer-reviewed, published, epidemiologic studies of 9/11-exposed populations satisfies the causal criteria adapted from Bradford Hill

Shapiro et al 2019, Cancer in General Responders Participating in World Trade Center Health Programs, 2003-2013. JNCI Cancer Spectr. Nov 6;4(1)

- Prospective cohort cancer incidence study (linkages with six statewide cancer registries)
- Study of the General Responder Cohort (update of Solon et al., Environ Health Perspect 2013;121:699-704)
- Included 4,161 women (among 28,729 total participants). All were involved in rescue, recovery, and cleanup efforts at Ground Zero after 9/11 (but were not part of FDNY)
- Expected cancer rates based on state level cancer incidence data
- Findings for Uterine CA, 2003-2013: SIR=0.82, 95%CI=0.35-1.91, based on 8 cases
- No dose-response analyses reported for uterine cancer

<u>Method 1</u>: Assessment of peer-reviewed, published, epidemiologic studies of 9/11-exposed populations satisfies the causal criteria adapted from Bradford Hill

Li et al 2016, Ten-year cancer incidence in rescue/recovery workers and civilians exposed to the September 11, 2001 terrorist attacks on the World Trade Center. Am J Ind Med. 2016;59(9):709-21

- Prospective cohort cancer incidence study (linkages with 11 state cancer registries, based on the state of residence of the cohort member)
  - Update of an earlier study (Li et al 2012, JAMA. 2012;308(23):2479-88)
  - Expected cancer rates based on New York State data
- Study Population: Enrollees in the WTC Health Registry (did <u>not</u> need to reside in New York State on 9/11)
- A total of 60,339 individuals eligible for the study, including 24,863 (5,015 women) involved in rescue/recovery and 35,476 (18,845 women) survivors not involved in rescue/recovery
- Findings provided only for uterine cancers that occurred between 2007 and 2011 (Li et al 2012 reported similar findings for 2003-2007)
- Rescue/Recovery workers
  - 2007-2011:8 cases, SIR=0.82, 95% CI 0.35-1.62
- Survivors
  - 2007-2011: 37 cases, SIR=1.03, 95% CI 0.72-1.41
- No dose-response analyses reported for uterine cancer

<u>Method 1</u>: Assessment of peer-reviewed, published, epidemiologic studies of 9/11-exposed populations satisfies the causal criteria adapted from Bradford Hill

Stein et al 2016, Mortality among World Trade Center Rescue and Recovery Workers, 2002 – 2011. Am J Ind Med. 2016;59(2):87-95

- Prospective cohort mortality study,
- Study of the General Responder Cohort
- A total of 28,918 (4,286 women) involved in rescue/recovery/demolition/debris clean-up
- Deaths ascertained through linkage with the National Death Index (NDI) through 12/31/2011
- Findings for all female genital cancers combined were reported
  - 2 cases, SMR= 0.65, 95% CI 0.08-2.37
- Findings for uterine cancer not reported

<u>Method 1</u>: Assessment of peer-reviewed, published, epidemiologic studies of 9/11-exposed populations satisfies the causal criteria adapted from Bradford Hill

Jordan et al 2018, Mortality among rescue and recovery workers and community members exposed to the September 11, 2001 World Trade Center terrorist attacks, 2003–2014. Environ Res. 2018;163:270-279

- Prospective cohort mortality study, update of Jordan et al 2011 (Lancet. 2011;378[9794]:879-87)
- Study Population: Enrollees in the WTC Health Registry (enrolled in 2003/2004)
- A total of 68,923 individuals were eligible for the study, including 29,280 (6,422 women) involved in rescue/recovery and 39,643 (21,126 women) survivors not involved in rescue/recovery.
- Deaths ascertained through linkage to death certificates in NYC vital records and the National Death Index (NDI) through 12/31/2014
- The authors examined 119 minor categories of causes of death, one of which was for uterine cancer. But they only reported statistically significant results for the minor categories; uterine cancer was not among those with reported results, suggesting that the risk of uterine cancer was not significantly elevated.
- Findings for all female genital cancers combined were reported
  - Rescue/Recovery workers
    - 2003-2014: 7 cases, SMR= 0.67, 95% CI 0.27-1.39
  - Survivors
    - 2003-2014: 43 cases, SMR=1.17, 95% CI 0.85-1.58
  - No dose-response analyses reported for uterine cancer or female genital cancers

<u>Method 1</u>: Assessment of peer-reviewed, published, epidemiologic studies of 9/11-exposed populations satisfies the causal criteria adapted from Bradford Hill

Conclusion

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

<u>Method 2</u>: Established causal association exists between the cancer and a condition already on the List

- Estrogen-secreting tumors are associated with endometrial cancer
  - However, these tumors are rare
- Granulosa cell tumors of the ovary
  - Most common type of estrogen-secreting tumor
  - Account for 4-6% of all ovarian malignancies
  - Annual Incidence = ~4 cases/million women
- Adrenocortical cancers
  - Annual incidence= 0.7–2.0 cases/million
  - Estrogen-secreting variety is a rare subset of all adrenocortical cancers
    - Generally produce breast tenderness and dysfunctional uterine bleeding
    - Other than a single case report, no scientific evidence was found linking estrogen-secreting adrenocortical cancer with uterine cancer
- **Conclusion**: Estrogen-secreting tumors are considered “rare cancers”. Uterine cancer can be covered only for members who have a certified estrogen-secreting tumor

Method 3: Review of Evaluations of Carcinogenicity in Humans

- Must meet both of the following criteria:
  - A chemical, physical, biological, or other hazard must be included in the Inventory of 9/11 Agents, AND
  - NTP determined that the 9/11 agent is known to be a *human carcinogen* or is *reasonably anticipated to be a human carcinogen*, AND IARC has determined there is *sufficient* or *limited evidence* that the 9/11 agent causes the cancer type of interest (IARC Groups 1, 2A or 2B)

<u>Method 3</u>: Review of Evaluations of Carcinogenicity in Humans

- Review the available scientific evidence for endocrine disrupting chemicals (EDCs) causing uterine cancer
- EDC Definition
  - Many authoritative organizations have defined EDCs (EPA, NIEHS, European Union, WHO)
    - Definitions are not identical, but similar
  - **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.

Method 3: Review of Evaluations of Carcinogenicity in Humans

- 9/11 Agents that are considered EDCs:
  - Dioxins
  - Perfluoroalkyl and Polyfluoroalkyl Substances (PFAS)
  - Phthalates
  - Polybrominated diphenyl ethers (PBDE)
  - Polychlorinated biphenyls (PCB)
  - Cadmium

- None of these EDCs have been found by IARC (or EPA) to cause uterine cancer

Additional Considerations

- Per the Zadroga Act, 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
- The Science Team has accumulated additional information that the STAC may wish to consider in its deliberations

Mechanisms of endometrial cancer development

- The mechanisms of Type I endometrial cancer development (accounts for 80% of all endometrial cancers) do not markedly differ from those at other cancer sites
  - The mechanisms of type II endometrial cancers are less well known
- Gene mutations found in type I endometrial cancer include those in PTEN, β-catenin and K-ras
  - PTEN inactivation 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 linked to oncogene *HER-2/neu* and tumor suppressor gene *p53*
  - *HER-2/neu* gene mutations are also found in breast and ovarian cancers
  - *p53* gene mutations are a frequent mutation in human cancer
- 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)
  - *miR-152* is a TS-miRNA in endometrial cancer
  - *miR-152* methylation levels are also changed in acute lymphoblastic leukemia, gastrointestinal cancer, and cholangiocarcinoma

Sex Disparities in Occupational Cohort Studies

- Many (most?) epidemiologic studies of EDC exposures involved occupational cohorts
  - In general, these studies of occupational cohorts included few or no women
  - Female is a “rare gender” in occupational epidemiologic studies
  - Does this explain the paucity of uterine cancer findings?

Observed associations between 9/11 agents and increased uterine cancer risk

Asbestos

Four relevant peer-reviewed epidemiologic studies were identified and reviewed

- Two found significantly elevated risks (asbestos-exposed workers)(Magnani et al, 2007; Germani et al. 1999)
- One found a non-significantly elevated risk (cohort included female residents of isolated mining town and its female asbestos workers)(Reid et al. 2009)
- One found a non-significantly reduced risk (wives of asbestos workers)((Magnani et al, 1993)
- Note that only one of these four studies reported separate findings for uterine cancer (Reid et al. 2009). The other three clearly or likely provided findings for uterine and cervical cancer combined

IARC Conclusion

- Group 1: Carcinogenic to humans
- Based on sufficient evidence in humans for mesothelioma, cancers of the lung, larynx, ovary, pharynx, stomach and colorectum.
- IARC made no mention of uterine cancer (or cervical cancer)

Observed associations between 9/11 agents and increased uterine cancer risk

Asbestos

Magnani et al. Cancer risk after cessation of asbestos exposure: A cohort study of Italian asbestos cement workers. Occup Environ Med. 2007;65(3):164-170.

- Retrospective mortality study of Italian asbestos cement workers. Cohort included 3434 blue-collar workers (2657 men and 777 women) employed between 1950 and 1986 (plant closed in 1986)
- Age-, and period-adjusted standardized mortality ratios (SMR) and 95% confidence intervals (95% CI) for uterine cancer (*not clear if outcome included cervical cancer*). Piedmont regional mortality rates were used for comparison
- Analyses were restricted to deaths that occurred between 1965 and 2003

Employment Duration	Observed	Expected	SMR (95%CI)
< 1 year	0	0.2	—
1-4 years	1	0.5	1.95
5-9 years	3	0.7	4.49
10-19 years	2	1.6	1.23
20-29 years	7	1.7	4.06*
≥ 30 years	2	1.1	1.75
Total	**15**	**5.8**	**2.57 (1.43-4.23)**

*=p<0.01

Trend was reported as unstable

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Observed associations between 9/11 agents and increased uterine cancer risk

Asbestos

Germani et al. Cohort Mortality Study of Women Compensated for Asbestosis in Italy. Am J Ind Med 1999;36:129-134

- Retrospective mortality study of women compensated for asbestosis in Italy
- Cohort included 631 women with asbestosis, 277 of whom died
- Vital status ascertained through the registrar's office of the town where the person lived or died
- Age-, and period-adjusted standardized mortality ratios (SMR) and 95% confidence intervals (95% CI) for uterine cancer (*outcome included cervical cancer*). National rates were used for comparison
- Analyses restricted to deaths that occurred between 1980 and 1997
- SMR for uterine cancer (including cervical cancer): 2.56 (95%CI=1.05, 5.28), based on 7 cases

Observed associations between 9/11 agents and increased uterine cancer risk

Asbestos

Reid et al. Gynecologic and breast cancers in women after exposure to blue Asbestos at Wittenoom. Cancer Epidemiol Biomark Prev. 2009;18(1):140-147

- Retrospective cancer incidence study of women in Wittenoom, Australia. 2,552 were residents and 416 worked at the asbestos mine/mill (mostly in company offices, hotel, and shop). Wittenoom was an isolated mining town, where working and living conditions were hard, and its population was largely transient with low SES
- Cancer incidence: Age-, and period-adjusted rate ratios (RR) and 95% confidence intervals (95% CI) for uterine cancer. Reference group were background cancer rates in Western Australia. Incident cancer cases ascertained from the Western Australian Cancer Registry between 1982 and 2006
- Nested case-control design to examine exposure-response relationships. Cases identified from 1960-2006 (cases from 1960-1981 identified through manual search of cancer registrations in Western Australia and hospital admission records of all Australian public hospitals)
- Cancer incidence, 1982-2006: SIR=1.23 (95% CI=0.56-1.90), 13 cases
- Nested case-control, 1960-2006:
  - Risk non-significantly increased with higher exposure intensity (not clear how intensity measured)(OR=2.3), and if lived with asbestos worker (OR=1.5)
  - Monotonic decrease in risk with increasing age at first exposure, and duration of exposure (trend not reported)
  - Odds ratios non-significantly below null for: increasing time since first exposure; washed clothes; was a former asbestos worker

Observed associations between 9/11 agents and uterine cancer risk

Asbestos

Magnani et al. A cohort study on mortality among wives of workers in the asbestos cement industry in Casale Monferrato, Italy. Br J Ind Med 1993;50:779-784

- Retrospective mortality study of wives of asbestos cement workers (same plant as the Magnani et al 2007 paper)
- Cohort included 1,740 women with domestic exposure and 3434 blue-collar workers (2657 men and 777 women) employed between 1950 and 1986 (plant closed in 1986)
- Vital status of ascertained through the registrar's office of the town where the person was living
- Age-, and period-adjusted standardized mortality ratios (SMR) and 95% confidence intervals (95% CI) for uterine cancer (*outcome included cervical cancer*). Piedmont regional mortality rates were used for comparison
- Analyses were restricted to deaths that occurred between 1965 and 1988
- SMR for uterine cancer (including cervical cancer): 0.68 (95%CI=0.22, 1.59), based on 5 cases
- No dose-response analyses reported for uterine cancer

Observed associations between 9/11 agents and increased uterine cancer risk

TCDD

Pesatori et al. [2009]

- Retrospective cohort study of Seveso, Italy residents after accident in 1976. Study compared people in three contaminated zones with decreasing TCDD soil levels: 723 resident in zone with high TCDD soil levels, 4,821 in zone with medium levels, 31,643 in zone with low levels, 181,574 in surrounding non-contaminated zone.
- Sex-, age-, and period-adjusted rate ratios (RR) and 95% confidence intervals (95% CI) for uterine cancer. Reference group was the non-contaminated zone
- Incident cancer cases were ascertained through 120 hospital-network of the Lombardy region between 1977 and 1996
- High Exposure: RR=1.24 (95% CI = 0.17-8.82), based on 1 case
- Medium Exposure: RR=0.6 (95% CI = 0.19-1.87), based on 3 cases
- Low Exposure: RR=0.73 (95% CI = 0.49-1.10), based on 27 cases

Kogevinas et al. [1997]

- International Cohort Study, retrospective mortality study of 21,863 male and female workers exposed to phenoxy herbicides, chlorophenols, and dioxins in 12 countries
- 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
- Uterine cancer among workers exposed to TCDD or higher chlorinated dioxins: SMR = 3.41 (95% CI 0.7–9.96), based on 3 cases

Observed associations between 9/11 agents and increased uterine cancer risk

PCBs

Donat-Vargas et al. [2016]

- Prospective population-based Swedish Mammography Cohort study of dietary PCB exposure
- Included 36,777 cancer-free women at baseline (1987)
- Validated estimates of dietary PCB exposure were obtained via a food frequency questionnaire at baseline
- Incident cancer cases were ascertained through linkage to Swedish Cancer Registries through 2012
- Endometrial cancer risk, highest tertile of PCB exposure: Adjusted RR=1.21, 95% CI: 0.73–2.01 (p trend=0.54)

Ruder et al. [2014. Int J Hyg Environ Health. 2014 Mar;217(2-3):176-87]

- Retrospective mortality study of 24,865 workers (female =13,077) exposed to PCBs at electrical capacitor manufacturing plants in Indiana, Massachusetts, and New York
- Followed for mortality through 2008
- Entire cohort: SMR for uterine cancer=1.07 (95%CI 0.74-1.5), 34 cases
- Short-term workers: SMR for uterine cancer =0.75 (95%CI 0.28-1.63), 6 cases
- Long-term workers: SMR for uterine cancer =1.18 (95%CI 0.78-1.7), 28 cases
- Dose response when examining cumulative PCB exposure (p trend <0.001)
  - Standardized rate ratio at highest exposure: 1.35 (95% CI=0.46-3.98)

Observed associations between 9/11 agents and increased uterine cancer risk

Cadmium

Adams et al. [Occup Environ Med. 2012 Feb;69(2):153-6]

- Prospective cohort mortality study using NHANES data from 1988-1994, nationally representative
- Included 10,636 women who were cancer-free at baseline
- Cd measured in spot urine
- Mortality assessed through 2006 via National Death Index linkage
- Adjusted Hazard Ratio for doubling of urinary CD level 1.48 (95%CI:1.09-2.00), 7 cases
- Adjusted Hazard Ratio for highest quartile (compared to lower quartiles) 1.03 (95%CI: 0.23-4.62). Three cases in highest quartile vs 4 in the other three quartiles

McElroy et al [PLoS One. 2017 Jul 24;12(7):e0179360]

- Case Control study using cancer registries in AR, IA and MO
- 631 incident cases diagnosed between 2010 and 2012
- 879 age-matched controls identified via voter registration roles
- Cd measured in urine (not clear how many subjects provided urine or when measured)
- Adjusted OR for doubling of urinary CD level 1.22 (95%CI:1.03-1.44)

Observed associations between 9/11 agents and increased uterine cancer risk

Cadmium

Akesson et al. [2008]

- Prospective population-based Swedish Mammography Cohort study of dietary cadmium exposure
- Included 30,210 postmenopausal women who were cancer-free at baseline (1987)
- Completed a food frequency questionnaire at baseline and in 1997
- Linkage of the study population to Swedish Cancer Registries through June 30, 2006
- Endometrial cancer risk, highest tertile of baseline dietary cadmium consumption: Adjusted RR= 1.39 (95% CI 1.04–1.86) (p trend=0.02)

Other cancers causally associated with EDCs included in the Inventory of 9/11 agents

Several 9/11 agents are EDCs and are known or suspected human carcinogens for the following cancers

- **TCDD**: IARC Group 1
  - All cancer sites combined, lung, soft tissue sarcoma, and non-Hodgkin lymphoma
  - IARC does not interpret that "all cancer sites combined" as meaning that every cancer may be caused by TCDD
- **PCBs**: IARC Group 1
  - Melanoma, breast cancer, and leukemia and lymphoma
- **Cadmium and cadmium compounds**: IARC Group 1
  - Lung, prostate and kidney cancers
- **2,3,4,7,8-Pentachlorodibenzofuran**: IARC Group 1
  - IARC classification, based on sufficient evidence in experimental animals (liver cancer, cholangiocarcinoma), and mechanistic and other relevant data. There is no evidence in humans of its carcinogenicity
- **Perfluorooctanoic acid** (a type of PFAS): IARC Group 2B
  - Based on limited evidence in humans for kidney and testicular cancer

IARC Group 1=Carcinogenic to humans
IARC Group 2B=Possibly carcinogenic to humans

The Administrator is seeking a recommendation from the STAC regarding whether there is a reasonable basis for adding uterine cancer to the List of WTC-Related Health Conditions