Petition on Cancer, Epidemiology and Overview of Mechanisms of Carcinogenesis

Elizabeth Ward, PhD
Request from Dr. Howard

“I request that the STAC review the available information on cancer outcomes associated with exposures resulting from the September 11, 2001 terrorist attacks, and provide advice on whether to add cancer, or a certain type of cancer, to the List (of WTC related health conditions) specified in the Zadroga Act.”
It is _______ that exposure to WTC dust may cause cancer

a) unlikely
b) possible
c) biologically plausible
d) probable
e) proven

What is the scientific rationale?
Scientific rationale

• What we know
• What don't we know
• What we believe
Review of Data

(1) Epidemiologic studies

(2) Potential carcinogens present in WTC dust

(3) Mechanisms of carcinogenesis
# Epidemiologic Cohorts
(adopted from Perlman et al., 2011)

<table>
<thead>
<tr>
<th>Name or sponsor</th>
<th>Groups Studied</th>
<th>Size (12/31/2010)</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fire Department of New York</td>
<td>Firefighters and EMS Workers</td>
<td>15,415</td>
<td>Employer-based medical program</td>
</tr>
<tr>
<td>NY &amp; NJ WTC Clinical Consortium</td>
<td>Law enforcement &amp; other responders, sanitation &amp; construction workers, volunteers</td>
<td>29,572</td>
<td>Provides screening, monitoring and treatment</td>
</tr>
<tr>
<td>WTC Environmental Health Center</td>
<td>Area workers, residents, students</td>
<td>5,130</td>
<td>Monitors &amp; treats, includes children</td>
</tr>
<tr>
<td>WTC Health Registry</td>
<td>Rescue &amp; recovery workers, area workers, residents, students</td>
<td>71,437</td>
<td>30% recruited from employers &amp; govt. agencies, others self-enrolled</td>
</tr>
</tbody>
</table>
FDNY Study

- 9,853 firefighters employed on 1/1/1996; 8,927 WTC-exposed starting on 9/11/2001
- Standardized incidence ratio for all cancers among WTC-exposed firefighters of 1.10 based on general population rates and 1.19–1.32 based on unexposed firefighters
- Elevated or borderline excesses for stomach, colon, melanoma, prostate, thyroid, NHL compared to general population rates
Other epidemiologic findings related to cancer

- No excess of all cancers combined or 8 major organ systems in first follow-up of WTC Health Registry Cohort
- Case reports suggesting possible excess of multiple myeloma
Limitations of Epidemiologic Evidence

- Misclassification difficult to accurately estimate exposure reduced strength of association lack of clear "exposure-response" trend
- Complex and multiple exposures difficult to attribute causality lack of consistency in findings among exposed populations & studies insufficient to rule out small risks and risks for rarer cancers
- Population sizes
Limitations of Epidemiologic Evidence, cont.

Cancer's latent period → cancer risk may not appear until 20 or more years after first exposure.

Latent period is most relevant in epidemiologic studies when results are negative and follow-up period may be too short to observe an effect.
If epidemiologic data are not definitive, what can we learn from exposure data?

• Interpreting air sampling data from WTC site is difficult and controversial; no data in the critical first week after the building collapse

• (Belief) Relatively low air levels measured in some early studies at the WTC site inconsistent with observed high rates of respiratory symptoms

• One approach to evaluating potential cancer hazard is to examine composition of the initial dust/smoke (as reflected in the dust samples collected)
Who could have been or could be exposed to the materials present in the *initial* dust/smoke?*

**Initial collapse of the WTC**
- Local and downwind residents
- Rescue workers
- Commuters
- Shop/business owners, operators & customers

**Re-suspension of the dust/smoke during the following week**
- Professional & volunteer rescue workers
- Outdoor & indoor cleanup workers
- Residents & workers in Wall Street area downwind

**Re-suspension of dust/smoke during the next weeks/months**
- Workers not wearing respiratory protection at WTC site
- Indoor cleanup workers not wearing respiratory protection
- Residents & workers returning to poorly cleaned buildings

*Although not measured, gases would be associated with many of these exposures
Adapted from Lioy, 2006
What materials were present in the initial dust/smoke?

- Gypsum (major component of drywall)
- Concrete dust (cement dust, crystalline silica)
- Glass fragments and man-made vitreous fibers
- Asbestos
- Polycyclic aromatic hydrocarbons (PAH's)
- Metals (hexavalent chromium, nickel, arsenic)
- Volatile organic compounds (benzene)
Which materials appear to be of most concern for cancer?

- Gypsum (major component of drywall)
- Concrete dust (cement dust, crystalline silica)
- Glass fragments and man-made vitreous fibers
- Asbestos
- Polycyclic aromatic hydrocarbons (some PAH's)
- Metals (hexavalent chromium, nickel, arsenic)
- Volatile organic compounds (benzene)

RED = IARC Group 1, NTP human carcinogen
Understanding Cancer and Related Topics

Understanding Cancer

Developed by:
Lewis J. Kleinsmith, Ph.D.
Donna Kerrigan, M.S.
Jeanne Kelly
Brian Hollen

Discusses and illustrates what cancer is, explains the link between genes and cancer, and discusses what is known about the causes, detection, and diagnosis of the disease.


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Loss of Normal Growth Control

Normal cell division

Cell damage — no repair

Cell Suicide or Apoptosis

Cancer cell division

First mutation
Second mutation
Third mutation
Fourth or later mutation

Uncontrolled growth
### Microscopic Appearance of Cancer Cells

<table>
<thead>
<tr>
<th>Normal</th>
<th>Large number of irregularly shaped dividing cells</th>
<th>Large, variably shaped nuclei</th>
<th>Small cytoplasmic volume relative to nuclei</th>
<th>Variation in cell size and shape</th>
<th>Loss of normal specialized cell features</th>
<th>Disorganized arrangement of cells</th>
<th>Poorly defined tumor boundary</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cancer</td>
<td><img src="image1.png" alt="Image" /></td>
<td><img src="image2.png" alt="Image" /></td>
<td><img src="image3.png" alt="Image" /></td>
<td><img src="image4.png" alt="Image" /></td>
<td><img src="image5.png" alt="Image" /></td>
<td><img src="image6.png" alt="Image" /></td>
<td><img src="image7.png" alt="Image" /></td>
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</table>

*Image credits:* [Image1](image1.png), [Image2](image2.png), [Image3](image3.png), [Image4](image4.png), [Image5](image5.png), [Image6](image6.png), [Image7](image7.png)
Lag Time

20-Year Lag Time Between Smoking and Lung Cancer

Cigarette consumption (men)

Cigarettes Smoked per Person per Year

Lung cancer (men)

Lung Cancer Deaths (per 100,000 people)

Year

1900 1920 1940 1960 1980

4000 3000 2000 1000

150 100 50
Genes and Cancer

Viruses

Chemicals

Radiation

Heredity

Chromosomes are DNA molecules
Oncogenes

Normal genes regulate cell growth

Oncogenes accelerate cell growth and division

Mutated/damaged oncogene

Normal cell

Cancer cell
Tumor Suppressor Genes

Normal cell

Normal genes prevent cancer

Remove or inactivate tumor suppressor genes

Cancer cell

Mutated/inactivated tumor suppressor genes

Damage to both genes leads to cancer
DNA Repair Genes

Normal DNA repair

Base pair mismatch

Cancer

No cancer

No DNA repair
Cancer Tends to Involve Multiple Mutations

Benign tumor cells grow only locally and cannot spread by invasion or metastasis.

Malignant cells invade neighboring tissues, enter blood vessels, and metastasize to different sites.

Time

- Mutation inactivates suppressor gene
- Cells proliferate
- Mutations inactivate DNA repair genes
- Proto-oncogenes mutate to oncogenes
- More mutations, more genetic instability, metastatic disease
Process of Carcinogenesis

Many cancers take a long time to develop

Most tumors evolve through a number of stages

Time

Initiation  Promotion  Malignant transformation  Progression, invasion and metastasis
Inflammation and Cancer

- Inflammation is a normal response to tissue damage resulting from infection, chemical irritation and/or wounding. When it becomes chronic, it can damage the body and lead to illness.

- Inflammatory diseases associated with cancer include certain immunologic disorders, infections and chronic chemical and mechanical irritation.

- Inflammation can lead to cancer through a variety of mechanisms: increased cell proliferation, generating mutagens from releasing reactive oxygen and nitrogen species, and producing biologically active chemicals that influence the cellular/tissue microenvironment.
Other considerations

- **Duration of exposure**: Since inhaled fibers and dusts may remain in the body for a long time, a short-term environmental exposure can lead to a long-term biological exposure.

- **Latent period**: Although on average it takes 20 or more years for a solid tumor to develop after, most carcinogens can act at during multiple stages of the carcinogenic process, and can impact cancer risk in a shorter time frame; this is most evident when an exposure is withdrawn.
Lag Time

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Lung Cancer Deaths (per 100,000 people)

Cigarettes Smoked per Person per Year

Year

1900 1920 1940 1960 1980

1000 2000 3000 4000

50 100 150
Relative risk of lung cancer falls rapidly after smoking cessation


*Rates are per 100,000, age-adjusted to the US standard population.
Data Source: Surveillance, Epidemiology, and End Results (SEER) Program, SEER 9 registries, National Cancer Institute.
Metals and VOC's
Particulates
PAH's
Asbestos

Moving on
Concrete dust

- Concrete is a mixture of Portland cement, sand, gravel and water

- Pulverized concrete contains crystalline silica and cement dust, including Portlandite (Ca(OH)$_2$) which is highly caustic

- Crystalline silica causes lung cancer in humans (IARC); most common health effect is lung disease (silicosis); also associated with renal disease, scleroderma, rheumatoid arthritis
Cement dust

• Most (but not all) studies of respiratory health among cement manufacturing workers have found *increased symptoms* (cough, phlegm and dyspnea) and *reduced lung function* (FEV<sub>1</sub>, FVC and FEV<sub>1</sub>/FVC ratio)

• One study found *increased prevalence* of ulcer-like and reflux-like dyspepsia among cement workers vs. unexposed controls and high- vs. low-exposed cement workers

• Cohort and case-control studies have *suggested associations* between cement-exposed occupations and cancer of the lung, stomach, colon and head & neck, including pharynx and larynx
Carcinogenicity of cement dust

- Has not been reviewed by IARC or NTP

- Although the UK Health and Safety Executive (2006) did not find that epidemiologic evidence was convincing of a causal association between cement dust exposure and cancer, they noted that:

"As a highly alkaline substance, cement can cause irritation at sites of contact, such as the mouth, throat and lungs. Persistent chronic irritation will cause repeated cycles of cell death, cell proliferation and other inflammatory responses. It is recognized that this process can be a step on the pathway to cancer. Thus it is biologically plausible that cement dust could have the potential to cause cancers at sites of contact."
Preview

• After the 4 presentations and discussion (before the public comment period that will begin at 3:45 pm) we will poll the committee
It is _______ that exposure to WTC dust may cause cancer.

a) unlikely
b) possible
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d) probable
e) proven
Framing tomorrow's discussion

• Identify critical evidence not presented
• Discussion of opposing positions...?
• Discussion of scientific rationale...?
• Discussion of cancer sites...

• Cautions and perspectives
• Draft letter of response