Environmental Exposures and Cancer Hazards

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Outline

• Cancer
• Environment exposures
• Identifying cancer hazards and risk characterization
• Report on Carcinogens
• Examples of environmental carcinogens
Cancer is a group of diseases

- Characterized by uncontrolled growth and spread of abnormal cells, which if not controlled can result in death.

<table>
<thead>
<tr>
<th>Men Case</th>
<th>Men Deaths</th>
<th>Women Cases</th>
<th>Women Deaths</th>
</tr>
</thead>
<tbody>
<tr>
<td>Prostate (28%)</td>
<td>Lung (28%)</td>
<td>Breast (29%)</td>
<td>Lung (26%)</td>
</tr>
<tr>
<td>Lung (14%)</td>
<td>Prostate (10%)</td>
<td>Lung (14%)</td>
<td>Breast (14%)</td>
</tr>
<tr>
<td>Colon &amp; rectum (9%)</td>
<td>Colon &amp; rectum (9%)</td>
<td>Colon &amp; rectum (9%)</td>
<td>Colon &amp; rectum (9%)</td>
</tr>
<tr>
<td>Urinary bladder (6%)</td>
<td>Pancreas (6%)</td>
<td>Uterine corpus (6%)</td>
<td>Pancreas (7%)</td>
</tr>
<tr>
<td>Melanoma of the skin</td>
<td>Liver (5%)</td>
<td>Thyroid (6%)</td>
<td>Ovary (5%)</td>
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</tbody>
</table>
Cancer is the 2\textsuperscript{nd} leading cause of death in the United States

- Approximately 1 out of 2 men and 1 out of 3 women living in the United States will develop cancer at some point in his or her lifetime
  - 1.5 million new cases of cancer are expected to be diagnosed in the United States
  - Estimated 562,000 Americans will die from this disease.

- Cancer cost the nation $243.4 billion
  - $99 billion for direct medical cost
  - $19.6 billion for indirect morbidity costs
  - $124.8 billion for indirect mortality costs

The environment is a major contributor to cancer development

- Environment can be defined as anything that people interact with
  - Lifestyle choices, naturally occurring exposures, medical treatment, household exposures, occupational exposures, pollution

- Specific environmental exposures can increased cancer risk (e.g., tobacco smoking)

- Combinations of exposures can have a synergistic effect

- Critical windows of exposure exists when individual are more susceptible

- Genetic factors can cause people to respond to the same exposure differently

Cancer can be prevented

• The World Health Organization estimates that 30 to 40% of deaths due to cancer are considered preventable
  – Estimated 12 million deaths worldwide by 2030

• Primary prevention – prevent cancer cases
  • Reduction or elimination of exposure

• Secondary prevention – prevent cancer deaths
  • Early detection via screening and treatment of any diagnosed precancerous conditions or early malignancies
Tobacco Use in the US, 1900-2006

Per Capita Cigarette Consumption

Year

Male lung cancer death rate

Female lung cancer death rate

Surgeon General Report 1964

Per capita cigarette consumption

Age-Adjusted Lung Cancer Death Rates*

*Age-adjusted to 2000 US standard population.


American Cancer Society
Identify carcinogens and characterizing risks is key to preventing cancer
First step is high quality research

• Cancer studies in humans
  – Most are observational epidemiologic studies
  – Studies of workers, who are exposed to higher levels of an agent, have been informative in identifying environmental carcinogens

• Cancer studies in experimental animals
  – All known human carcinogens have been shown to cause cancer in experimental animals when tested adequately

• Alternative testing methods
  – Molecular toxicology, computational sciences

• Other relevant data – e.g., metabolism
Risk assessment
Characterize potential carcinogenic effects resulting from exposure

- **Hazard Identification**
  - Does the agent cause cancer?

- **Exposure Assessment**
  - What is the level of exposure to people?

- **Dose-Response Assessment**
  - What is the risk of cancer at different doses?

- **Risk Characterization**
  - What is the level of potential risk to humans from exposure?
Risk analysis: Communication and decision making

- Risk management
  - Selecting the most appropriate regulatory action
  - Weighing the results of risk assessment with social, economic, and political concerns

- Risk communication
  - Exchanging information on risk assessment and risk management to the public and private sector including legislators, lawyers, judges, industry and businesses, environmental and community groups
# Agencies classifying carcinogens

<table>
<thead>
<tr>
<th>Activity</th>
<th>IARC</th>
<th>U.S. EPA (IRIS)</th>
<th>NTP (RoC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hazard Identification</td>
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<td>Hazard Identification</td>
</tr>
<tr>
<td>Classification</td>
<td>Group 1: carcinogenic</td>
<td>Group A: carcinogenic</td>
<td>Known to be a human carcinogen</td>
</tr>
<tr>
<td></td>
<td>Group 2A: probably</td>
<td>Group B: likely</td>
<td>Reasonably anticipated to be a human carcinogen</td>
</tr>
<tr>
<td></td>
<td>Group 2B: possibly</td>
<td>Group C: suggestive</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 3: unclassifiable</td>
<td>Group D: inadequate information</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Group 4: probably not</td>
<td>Group E: not likely</td>
<td></td>
</tr>
</tbody>
</table>

IARC – International Agency for Cancer Research, World Health Organization
IRIS – Integrated Risk Information System
NTP – National Toxicology Program
RoC – Report on Carcinogens
The RoC is congressionally mandated

- Public Health Services Act, Section 301(b)(4) (1978, amended 1992)
  - Directs HHS Secretary to annually publish a list of carcinogens
- Preparation of the RoC is delegated to the National Toxicology Program (NTP)
- The RoC is cumulative – each addition adds newly listed substances to current list
  - 1st Report published in 1980 had 26 listings
  - 12th RoC published in 2011 has 240 listing

http://ntp.niehs.nih.gov/go/roc
The RoC is a science based public health document

- Identifies substances that may pose a cancer hazard for people living in the United States
  - Lists substances as “known” or “reasonably anticipated human carcinogens”

- A listing in the Report on Carcinogens does not by itself establish that a substance will cause cancer in an individual.
  - Many factors, including the amount and duration of an exposure, and an individual’s susceptibility to a substance, impact whether a person will develop cancer or not.
Substances are listed in the RoC using a rigorous scientific process and established criteria

- Cancer evaluation is captured in the RoC monograph
  - Cancer evaluation component
  - Substance profile

- Key elements in the scientific review process
  - Scientific and public input
  - Peer review of scientific information

http://ntp.niehs.nih.gov/go/rocprocess
RoC Listing Criteria: Two listing categories

• Known to be a human carcinogen:
  – Sufficient evidence of carcinogenicity from studies in humans

• Reasonably anticipated to be a human carcinogen
  – Limited evidence in humans
  – Sufficient evidence in experimental animals
  – Belongs to well-defined structurally related class of substances listed in the RoC or convincing mechanistic evidence

Conclusions based on scientific judgment using all relevant information, such as metabolism, pharmacokinetics, genetic effects, mode of action.

http://ntp.niehs.nih.gov/go/15209
Each listed substance has a profile containing:

- Listing status
  - Known or reasonably anticipated human carcinogen

- Summary of studies that support the listing
  - Humans
  - Laboratory animals
  - Mechanisms

- Information on
  - Physical properties
  - Use and production
  - Sources of exposure
  - Current Federal regulations and guidelines to limit exposures

### 1,8-Dinitropropene

**CAS No:** 42397-05-9

**Listing status**
- Known or reasonably anticipated human carcinogen

**Carcinogenicity**
1,8-Dinitropropene is reasonably anticipated to be a human carcinogen based on sufficient evidence of carcinogenicity from studies in experimental animals.

**Cancer Studies in Experimental Animals**
- Dinitropropene caused tumors in different species, at several different tissue sites, and by several different routes of exposure. Subcutaneous injection of 1,8-dinitropropene caused cancer at the injection site (sarcoma) in male mice and in rats of both sexes and leukemia in female rats (IARC 1988). Exposure by intraperitoneal injection caused myeloid leukemia and cancer of the peritoneal cavity (sarcoma) and mammary gland (adenocarcinoma) in female rats. Administration of 1,8-dinitropropene to female rats by stomach tube also caused mammary gland cancer (adenocarcinoma).

**Cancer Studies in Humans**
The absence of consistent epidemiological studies is inadequate to evaluate the relationship between human cancer and exposure specifically to 1,8-dinitropropene.

**Studies on Mechanisms of Carcinogenesis**
Pathways of 1,8-dinitropropene metabolism leading to mutagenic and clastogenic metabolites and formation of DNA adducts have been described (IARC 1988). Reactive products of 1,8-dinitropropene are formed by metabolism through two reductions of a 1-nitro group to form first a nitroso and then a N-hydroxy amino group at the 1-position (Beland 1986). Activation occurs by O-acetylation of the N-hydroxylamine group followed by removal of the acetate to create the active nitrenium ion, which reacts with deoxyguanosine at C-8 to form the DNA adduct.

1,8-Dinitropropene is genotoxic in a wide variety of assays in bacteria and mammalian cells (IARC 1989). In Salmonella typhimurium, the most frequent mutations were C->G to A->T or G->C transitions (Watanabe et al. 1987), and a metabolite of 1,8-dinitropropene, 1-nitrosotoluene, caused mutagenic G->C base pairs and frameshift mutations (Lambert et al. 2001). 1,8-Dinitropropene also caused morphological transformation of cultured hamster embryo cells (IARC 1988). Exposure of SV40-transformed hamster ovary cells to 1,8-dinitropropene caused formation of DNA adducts and amplified SV40 DNA (Nott 1993).

There is no evidence to suggest that the mechanisms by which 1,8-dinitropropene causes tumors in experimental animals would not also operate in humans.

**Properties**
1,8-Dinitropropene is a nitro-substituted polycyclic aromatic hydrocarbon that exists at room temperature as a yellow fluffy or light-brown crystalline solid (IARC 1989). It has a molecular weight of 292.3 and a melting point of over 300°C (HSDB 2009).

**Use**
1,8-Dinitropropene has been reported to be a photosensitizer; however, there is no evidence that it has ever been used commercially for this or any other purpose (IARC 1989). 1,8-Dinitropropene is available for research purposes at a purity of at least 99% and in 14C- or 3H-labeled form at a radiocisually purity of at least 98%.

**Production**
In both commercial producers of 1,8-dinitropropene were identified worldwide, but 1,8-dinitropropene was available from two U.S. suppliers (ChemSources 2009). No data on U.S. imports or exports of 1,8-dinitropropene were found.

**Exposure**
The minimal human exposure to 1,8-dinitropropene is inhalation, ingestion, and dermal contact (IARC 1989). In Japan, 1,8-dinitropropene was detected in soil samples in various regions of the country (Watanabe et al. 1998, 1999, 2000, 2003, 2005). No data were found on occupational exposure to 1,8-dinitropropene. (See also the discussion of exposure in the Introduction for Nitroarenes [Selected], above.)

**Regulations**
No specific regulations or guidelines relevant to reduction of exposure to 1,8-dinitropropene were identified.

**References**


Who uses the RoC?

• Regulatory and health research agencies to inform public health decisions, some examples
  – OSHA Hazard Communication Standard
  – California Proposition 65 (Safe Drinking Water Act 1986)

• Public
  – Provides information about potential cancer hazards so they can make informed decisions about limiting exposures

• Scientific community
  – Report and background documents available on PubMed

• Stakeholders such as industry
Release of the 12th RoC generated public interest

- Approximately 500 news articles published in the first 10 days from release
- High website traffic (http://ntp.niehs.nih.gov/go/roc12)
- 8 substances reviewed
  - Two known human carcinogens – aristolochic acid and formaldehyde
  - Six reasonably anticipated human carcinogens – captafol, cobalt-tungsten carbide hard metals and powers, certain glass wool fibers, ortho-nitrotoluene, riddelliine, and styrene
Some environmental exposures listed as known to be a human carcinogens

<table>
<thead>
<tr>
<th>Exposure type</th>
<th>Exposure</th>
<th>Cancer site</th>
<th>Listing date*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Resulting from lifestyle choice</td>
<td>Environmental tobacco smoke</td>
<td>Lung</td>
<td>2000</td>
</tr>
<tr>
<td>Naturally occurring agent</td>
<td>Ultraviolet radiation</td>
<td>Skin</td>
<td>2000</td>
</tr>
<tr>
<td>Medical treatments</td>
<td>Aristolochic acid</td>
<td>Urothelial</td>
<td>2011</td>
</tr>
<tr>
<td>Occupational chemicals</td>
<td>Asbestos</td>
<td>Mesothelioma</td>
<td>1980</td>
</tr>
<tr>
<td>Consumer products</td>
<td>Formaldehyde</td>
<td>Sinonasal, Nasopharyngeal myeloid leukemia</td>
<td>2011</td>
</tr>
<tr>
<td>Pollution</td>
<td>Tetrachlorodibenzo-p-dioxin</td>
<td>All cancer mortality</td>
<td>2000</td>
</tr>
</tbody>
</table>

* First listed as known to be a human carcinogen
Environmental tobacco smoke

- People are exposed in the home and the workplace
- Estimated 9 million to 12 million children aged six or younger are exposed to environmental tobacco smoke in their homes
- Levels of cotinine (the primary metabolite of nicotine) in nonsmokers exposed to secondhand smoke fell by 44.7% from 1988 to 2004
- Scientific evidence supporting the listing
  - Human cancer studies showing increased incidences of lung cancer
    - Nonsmoking spouses living with individuals who smoke
    - Non-smokers in occupational setting
    - Exposure from parents who smoke during childhood
  - Sufficient evidence in studies in experimental animals
Ultraviolet Radiation  (UVA, UVB, UVC)

• People are exposed to ultraviolet radiation from solar radiation or from artificial sources such as sunlamps or sunbeds.

• Scientific evidence supporting the listing
  – Studies in humans exposed to sunlight showing increased incidences of skin tumors (melanocytic and non-melanocytic).
  – Studies of humans exposed to UVR emitting sources, such as sunlamps and sunbeds.
  – Mechanistic studies showing UVR causes DNA damage, DNA mutations in tumor suppression genres and immunosuppression.
Aristolochic Acids

- Aristolochic acids are a family of chemicals that occur naturally in plants in the family Aristolochiaceae.
- People exposed via intentional or inadvertent use of herbal remedies containing these acids:
  - Still can be purchased on the Internet despite FDA warning and bans in other countries.
- Scientific evidence supporting the listing:
  - Increased risks of urothelial cancer (upper urinary tract and urinary bladder) in individuals consuming botanical products containing aristolochic acids:
    - Key studies on individuals with renal disease who had consumed pills for weight loss:
    - Mechanistic studies showing aristolochic acids are the carcinogenic components of the botanical products.
Asbestos

- People are or were exposed to asbestos in the workplace and from the environment
  - Current occupational limited to end-user products
  - Past occupational exposure during mining, milling, manufacture of products.
  - Environmental exposure can occur from release of demolition of buildings and vehicle brake linings

- Scientific evidence supporting the listing
  - Increased risk of lung cancer and mesothelioma found among workers
  - People living near asbestos factories or mines or living with asbestos workers also developed mesothelioma
  - Since RoC listing, IARC concluded there was significant evidence for larynx and ovary, and limited evidence for cancer of the colorectal, pharynx, and stomach
Formaldehyde

• People are exposed to formaldehyde in the workplace, indoor air and consumer products
  – In the workplace, including industrial workers (manufacturers and users), and in occupations such as embalmers and health professionals
  – In the home from off-gassing of construction products and home-furnishings, and from consumer goods such as hair straighteners

• Scientific evidence supporting the listing
  – Studies of formaldehyde-exposed workers show elevated rates of myeloid leukemia and nasopharyngeal and sinonasal cancers
    • Industrial workers such as formaldehyde producers and textile workers, and professional workers, such as embalmers
  – Formaldehyde causes genetic damage (DNA adducts, DNA-protein cross links)
Tetrachlorodibenzo-p-dioxin “Dioxin”

- Dioxins are by products of industrial and natural processes
  - Paper and pulp industry
  - Municipal, hospital and toxic waste
  - Chlorophenoxy herbicides (Agent Orange)
  - Manufacture of polychlorinated phenols
  - Persistent environmental pollutants and accumulate in the food chain

- Exposure to people can occur via inhalation of contaminated air, ingestion of food and drinking water, and dermal contact
  - Times Beach and Love Canal evacuated

- People can also be exposed in the workplace
  - Military – spraying of Agent Orange
TCDD: Sufficient evidence in humans

- RoC listing criteria allows consideration of mechanistic evidence in humans

- Human epidemiology studies
  - Occupational cohort studies showing increase in overall mortality; risks of NHL and lung cancer also increased

- Mechanistic studies
  - Initial binding to aromatic hydrocarbon (Ah) receptor
  - Wide spectrum of biological responses – changes in gene expression, altered metabolism, altered cell growth and differentiation, disruption of steroid-hormone and growth-factor signal-transduction pathways
Summary

• Cancer is one of the leading causes of death in the United States

• Environmental exposures contribute significantly to cancer risk.

• Cancer can be prevented

• Hazard identification is an important step in preventing cancer

• Report on Carcinogens provides information to the public, and government agencies so that they can use it to make informed decisions that protect the health