Carcinogenesis

Stephen W. Munday, MD, MPH, MS
Sharp Rees-Stealy Medical Group, Inc.
San Diego Division, CA Poison Control System
Objectives

- Provide a brief framework and terminology for understanding toxic carcinogenesis
- Provide an organized database to prepare for the board exam
Definitions

- Mutagen – A substance that alters DNA
- Carcinogen – A substance that increases the frequency or severity of cancer over background rates
- Proximate carcinogen – intermediate forms
- Procarcinogen – Requires metabolic activation
- Ultimate carcinogen – the form actually causing the injury
Carcinogen Activation

N-Hydroxylation

Benzidine (Procarcinogen)

N hydroxy dacetyl Benzidine (Proximate Carcinogen)

N Acetyl Benzidine Nitrenium ion (Ultimate Carcinogen)
Most widely accepted model of environmental carcinogenesis

Linear No-Threshold Effect Multistage Model of Carcinogenesis

- Developed from radiation exposure – not chemicals
- Not validated for low doses or low-dose rates
The advent of computed tomography (CT) has revolutionized diagnostic radiology. Since the inception of CT in the 1970s, its use has increased rapidly. It is estimated that more than 62 million CT scans per year are currently obtained in the United States, including at least 4 million for children.1

By its nature, CT involves larger radiation doses than the more common, conventional x-ray imaging procedures (Table 1). We briefly review the nature of CT scanning and its main clinical applications, both in symptomatic patients and, in a more recent development, in the screening of asymptomatic patients. We focus on the increasing number of CT scans being obtained, the associated radiation doses, and the consequent cancer risks in adults and particularly in children. Although the risks for any one person are not large, the increasing exposure to radiation in the population may be a public health issue in the future.
Computed Tomography and Radiation Exposure

TO THE EDITOR: Computed tomographic (CT) scans deliver a radiation dose of about 20 mSv. Brenner and Hall (Nov. 29 issue) assess the risk associated with CT radiation exposure by using the linear no-threshold extrapolation model, which assumes that cancer induction is proportional to dose even for the smallest doses. An excess of cancers has never been detected in laboratory animals or in humans for doses below 100 mSv. This model is used for analyzing data from cohorts including persons who have received doses higher than 100 mSv. This method is exposed to strong bias. Defense mechanisms against radiocarcinogenesis are much more effective at low doses, and the use of the linear no-threshold model in this dose range is highly debatable; it greatly overestimates the risk. After repeated x-ray examinations, induction of cancer has been observed only when the cumulative dose was above 500 mSv. In patients treated with radiotherapy, a threshold was reported for irradiation doses of 0.6 Sv delivered in 30 sessions. Overestimation of the risk may deprive patients of beneficial examinations.

Maurice Tubiana, M.D.
Institut Gustave-Roussy
94805 Villejuif, France
maurice.tubiana@inserm.fr


TO THE EDITOR: The report by Brenner and Hall is based on the effects of low levels of ionizing radiation from data on atomic-bomb survivors. A linear no-threshold hypothesis derived from the LSS data is not appropriate for the whole population.
Model’s Presumed Dose/Response Relationship

- Most closely describes initiating agents
- Assumes that the curve is linear to zero and that dose rates are unimportant
- Ignores experimental evidence for hormesis (Decreased rates at low doses presumably due to cellular repair mechanisms)
Classification of Chemical Carcinogens in Relation to their Action on One or More Stages of Carcinogenesis

• **Initiating agent**: an agent capable of initiating cells by producing a heritable DNA alteration (ex. Alkylating Agent, Radiation)

• **Promoting agent**: an agent capable of causing the expansion of initiated cell clones (ex. Hormones)

• **Progressor agent**: an agent capable of converting an initiated cell or a cell in the stage of promotion to a potentially malignant cell (increasing karyotypic instability)

*Complete carcinogen*: an agent possessing the capability of inducing cancer from normal cells, usually possessing properties of initiating, promoting and progressor agents
Initiation

- Initiation often occurs as the result of irreversible DNA alteration that either activates oncogenes or inactivates tumor suppression genes.
- Oncogenes primarily affect cellular growth, signal transduction and nuclear transcription (ex. ras).
- Tumor suppressor genes regulate cell growth and division (ex. p53, BRCA1).
- When the DNA alteration occurs in germ cells, it is then heritable. (2 Hit Theory)
Promotion

- A reversible process that works by altering gene expression often by interfering with signal transduction
- The process requires ligand-receptor interactions and therefore often demonstrates a sigmoid shaped dose/response relationship
- Some promoters demonstrate hormesis – a protective effect at low doses
Dose/Response Relationship

Increasing Dose

No response range

Range of increasing response with increasing dose

Maximum response range

Increasing Response

Threshold
Examples of Mechanism of Promotion
Steroid

G protein-linked

Plasma Membrane

Cytoplasm

Tyrosine Kinase

Receptor

HSP90

Dimerization

Nuclear Membrane

Nucleus

HRE

p19arf

E2F

Transcription

AC

G Protein

G Protein-linked

PKA

Phosphorylation

Ras

GDP ↔ GTP

Sos

B-raf

MEK

MAPK

RSK

PKA

Transcription

CREB

REB
Progression

• Irreversible progressive karyotype instability associated with further DNA alteration over time
Examples of Organizations with Carcinogenesis Classifications

- United Nations (WHO/IARC & GHS*)
  [*Globally Harmonized System]
- EPA (USA)
- NTP (USA) Publisher of Review of Carcinogens (RoC), 12th edition currently
- ACGIH (American Conference of Governmental Industrial Hygienists)
- OSHA/(IARC, NTP, 29CFR1910Hazcom subpart Z)
## Inter-Agency comparisons

<table>
<thead>
<tr>
<th>IARC</th>
<th>GHS</th>
<th>NTP</th>
<th>ACGIH</th>
<th>EU</th>
</tr>
</thead>
<tbody>
<tr>
<td>Group 1</td>
<td>Cat. 1A</td>
<td>Known</td>
<td>A1</td>
<td>Cat. 1</td>
</tr>
<tr>
<td>Group 2A</td>
<td>Cat. 1B</td>
<td>Reasonably suspected</td>
<td>A2</td>
<td>Cat. 2</td>
</tr>
<tr>
<td>Group 2B</td>
<td>Cat. 2</td>
<td></td>
<td>A3</td>
<td>Cat. 3</td>
</tr>
<tr>
<td>Group 3</td>
<td></td>
<td></td>
<td>A4</td>
<td></td>
</tr>
<tr>
<td>Group 4</td>
<td></td>
<td></td>
<td>A5</td>
<td></td>
</tr>
</tbody>
</table>
- FDA (National Center for Toxicology Research)
- NIEHS/(NIH)
- NIOSH/CDC
IARC International Agency for Research on Cancer (WHO/UN) [05/2012]
Carcinogen Classification

Group 1 Known Human Carcinogens (107)
Group 2A Probable Human Carcinogens (63)
Group 2B Possible Human Carcinogen (271)
Group 3 Not Classifiable (509)
Group 4 Probably Not Carcinogenic (1)
IARC Classification
Data Analysis

Based on:

• human epidemiology
• *in vitro*
• animal experiments
• Other relevant data (SAR, ADME, Dose/Response, Repair Mechanisms)
• They do not conduct the experiments, they just review the data.
IARC Classification, cont’d

• Human Epidemiology – frequently involves occupationally exposed cohorts but also case/control or ecologic studies
• Generally preferred for IARC 1 classification but exceptions exist (ethylene oxide, neutrons)
<table>
<thead>
<tr>
<th>Test</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gene mutation assays <em>in vitro</em></td>
<td></td>
</tr>
<tr>
<td>Prokaryote mutagenesis <em>in vitro</em> (Ames’ test, etc.)</td>
<td>Back or forward mutations in specific bacterial strains</td>
</tr>
<tr>
<td>Mouse lymphoma thymidine kinase (TK)</td>
<td>Mutations in TK</td>
</tr>
<tr>
<td>Chinese hamster ovary (CHO) &amp; V79 hypoxanthine guanine phosphoribosyltransferase (HGPRT)</td>
<td>Mutations in HGPRT</td>
</tr>
<tr>
<td>Test</td>
<td>Endpoint</td>
</tr>
<tr>
<td>------------------------------------</td>
<td>---------------------------------------------------</td>
</tr>
<tr>
<td>Chromosomal alterations <em>in vivo</em></td>
<td></td>
</tr>
<tr>
<td>Heritable translocation test (mice)</td>
<td>Translocations induced in germ cells</td>
</tr>
<tr>
<td>Rat bone marrow clastogenesis <em>in vivo</em></td>
<td>Chromosomal aberrations in bone marrow cells <em>in vivo</em></td>
</tr>
<tr>
<td>Micronucleus test</td>
<td>Appearance of micronuclei in bone marrow cells <em>in vivo</em></td>
</tr>
</tbody>
</table>
### IARC Classification, *in vitro* tests cont’d

<table>
<thead>
<tr>
<th>Test</th>
<th>Endpoint</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chromosomal alterations <em>in vitro</em></td>
<td></td>
</tr>
<tr>
<td>Mitotic recombination, mitotic crossing over, or mitotic gene conversion in yeast</td>
<td>Conversion of heterozygous alleles to homozygous state</td>
</tr>
<tr>
<td>Induced chromosomal aberrations in cell lines</td>
<td>Visible alterations in karyotype</td>
</tr>
<tr>
<td>Sister chromatid exchange</td>
<td>Visible exchange of differentially labeled sister chromatids</td>
</tr>
</tbody>
</table>
Ames’ Test

- Salmonella can normally synthesize histidine
- Ames’ salmonella strain is genetically unable to synthesize histidine
- The Ames’ test examines rate of loss of histidine-dependence due to mutation back to normal gene function allowing histidine synthesis
- Generally performed with and w/out microsomes (hepatic homogenate) to evaluate metabolic activation
IARC Classification, cont’d

Animal experiments
• Gold standard is the 2-year rodent bioassay
• Preferences are a minimum of 2 species and both sexes.
IARC Classification, cont’d

Problems

• Extrapolation from test tube to animal models
• Extrapolation from animals to humans
  – Dose/Response relationship
  – Cell type differences
  – Metabolic differences
Group 1 “Known Human Carcinogens” (107)

- Sufficient Human Evidence
- Less than sufficient in humans but sufficient in animals and strong evidence in humans of a relevant mechanism.
Group 2A “Probable” (63)

- Limited Human Evidence and sufficient animal evidence
- Inadequate human and sufficient animal evidence and a relevant mechanism in humans
- Rarely: limited Human Evidence Alone
Group 1: Agents and Groups of Agents (107 as of 05/12)

Benzo(a)pyrene
## Antineoplastic drugs and other drug evaluated by the IARC Monograph Working Group

<table>
<thead>
<tr>
<th>Group 1 Agent</th>
<th>Cancer on which sufficient evidence in humans is based</th>
<th>Established mechanistic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Busulfan</td>
<td>Acute myeloid leukemia</td>
<td>Genotoxicity (alkylating agent)</td>
</tr>
<tr>
<td>Chlorambucil</td>
<td>Acute myeloid leukemia</td>
<td>Genotoxicity (alkylating agent)</td>
</tr>
<tr>
<td>Cyclophosphamide</td>
<td>Acute myeloid leukemia, bladder</td>
<td>Genotoxicity (metabolism to alkylating agent)</td>
</tr>
<tr>
<td>Melphalan</td>
<td>Acute myeloid leukemia</td>
<td>Genotoxicity (alkylating agent)</td>
</tr>
<tr>
<td>Semustine (methyl-CCNU)</td>
<td>Acute myeloid leukemia</td>
<td>Genotoxicity (alkylating agent)</td>
</tr>
<tr>
<td>Thiotepa</td>
<td>Leukemia</td>
<td>Genotoxicity (alkylating agent)</td>
</tr>
<tr>
<td>Treosulfan</td>
<td>Acute myeloid leukemia</td>
<td>Genotoxicity (alkylating agent)</td>
</tr>
</tbody>
</table>
Antineoplastic drugs and other drug evaluated by the IARC Monograph Working Group

<table>
<thead>
<tr>
<th>Group 1 Agent</th>
<th>Cancer on which sufficient evidence in humans is based</th>
<th>Established mechanistic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>MOPP* combined therapy</td>
<td>Acute myeloid leukemia, lung</td>
<td>Genotoxicity (alkylating agent)</td>
</tr>
<tr>
<td>Etoposide in combination with cisplatin and bleomycin</td>
<td>Acute myeloid leukemia</td>
<td>Genotoxicity; translocation involving MLL gene (etoposide)</td>
</tr>
<tr>
<td>Etoposide (Group 2A in 2000)</td>
<td></td>
<td>Genotoxicity; translocation involving MLL gene</td>
</tr>
<tr>
<td>Chlomaphazine</td>
<td>Bladder</td>
<td>Genotoxicity (alkylating agent, metabolism to 2-naphthylamine derivatives)</td>
</tr>
<tr>
<td>Azathioprine</td>
<td>non-Hodgkin lymphoma, skin</td>
<td>Genotoxicity, immunosuppression</td>
</tr>
<tr>
<td>Cyclosporin</td>
<td>non-Hodgkin lymphoma, skin, multiple other sites</td>
<td>Immunosuppression</td>
</tr>
</tbody>
</table>

*MOPP= chlormethine (mechlorethamine), vincristine (oncovin), procarbazine, and prednisone
<table>
<thead>
<tr>
<th>Group 1 Agent</th>
<th>Cancer on which sufficient evidence in humans is based</th>
<th>Established mechanistic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methoxsalen+ultraviolet light</td>
<td>Skin</td>
<td>Genotoxicity following photo-activation</td>
</tr>
<tr>
<td>Plants containing aristolochic acid</td>
<td>Renal pelvis, ureter</td>
<td>Genotoxicity; DNA adducts in humans, A:T → T:A transversion in TP53 in human tumors</td>
</tr>
<tr>
<td>Aristolochic acid (Group 2A in 2000)</td>
<td></td>
<td>Genotoxicity; DNA adducts in animals are the same as those found in humans exposed to plants, A:T → T:A transversions in TP53, RAS activation</td>
</tr>
<tr>
<td>Analgesic mixtures containing phenacetin</td>
<td>Renal pelvis, ureter</td>
<td>(See phenacetin)</td>
</tr>
<tr>
<td>Phenacetin (Group 2A in 2000)</td>
<td>Renal pelvis, ureter</td>
<td>Genotoxicity, cell proliferation</td>
</tr>
</tbody>
</table>
Hormonal treatments assessed by the IARC Monograph Working Group

<table>
<thead>
<tr>
<th>Group 1 agent</th>
<th>Cancer on which sufficient evidence in humans is based</th>
<th>Established mechanistic events</th>
<th>Other likely mechanistic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diethylstilbestrol</td>
<td>Breast (exposure during pregnancy), vagina and cervix (exposure in utero)</td>
<td>Estrogen receptor-mediated events (vagina, cervix), genotoxicity</td>
<td>Epigenetic programming</td>
</tr>
<tr>
<td>Estrogen-only menopausal therapy</td>
<td>Endometrium, ovary</td>
<td>Estrogen receptor-mediated events</td>
<td>Genotoxicity</td>
</tr>
<tr>
<td>Combined estrogen-progestogen menopausal therapy</td>
<td>Endometrium (risk diseases with number of days/month of progestogen use), breast</td>
<td>Receptor-mediated events</td>
<td>Estrogen genotoxicity, hormone-stimulated expression of human papillomavirus genes</td>
</tr>
<tr>
<td>Combined estrogen-progestagen oral contraceptives</td>
<td>Breast, cervix, liver (endometrium &amp; ovary DECREASED)</td>
<td>Receptor-mediated events</td>
<td>Estrogen genotoxicity, hormone-stimulated expression of human papillomavirus genes</td>
</tr>
<tr>
<td>Tamoxifen</td>
<td>Endometrium (breast DECREASED)</td>
<td>Estrogen receptor-mediated events, genotoxicity</td>
<td></td>
</tr>
</tbody>
</table>
### Evidence for carcinogenicity in humans and for geotoxicity as the main mechanism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Tumor sites with sufficient evidence in humans</th>
<th>Evidence of genotoxicity as the main mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Aromatic amines</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4-Aminobiphenyl</td>
<td>Urinary bladder</td>
<td>Strong</td>
</tr>
<tr>
<td>Benzidine</td>
<td>Urinary bladder</td>
<td>Strong</td>
</tr>
<tr>
<td>Dyes metabolized to benzidine</td>
<td></td>
<td>Strong*</td>
</tr>
<tr>
<td>4.4’-Methylenebis(2-chloroaniline)</td>
<td></td>
<td>Strong*</td>
</tr>
<tr>
<td>2-Naphthylamine</td>
<td>Urinary bladder</td>
<td>Strong</td>
</tr>
<tr>
<td>Ortho-toluidine</td>
<td>Urinary bladder</td>
<td>Moderate</td>
</tr>
<tr>
<td>Auramine production</td>
<td>Urinary bladder</td>
<td>Weak / lack of data</td>
</tr>
<tr>
<td>Magenta production</td>
<td>Urinary bladder</td>
<td>Weak / lack of data</td>
</tr>
</tbody>
</table>

*Agents classified in Group 1 on the basis of mechanistic information*
Evidence for carcinogenicity in humans and for geotoxicity as the main mechanism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Tumor sites with sufficient evidence in humans</th>
<th>Evidence of genotoxicity as the main mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PAH-related exposures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Benzo(α)pyrene</td>
<td></td>
<td>Strong*</td>
</tr>
<tr>
<td>Soot (chimney sweeping)</td>
<td>Skin, lung</td>
<td>Moderate</td>
</tr>
<tr>
<td>Coal gasification</td>
<td>Lung</td>
<td>Strong</td>
</tr>
<tr>
<td>Coal-tar distillation</td>
<td>Skin</td>
<td>Strong</td>
</tr>
<tr>
<td>Coke production</td>
<td>Lung</td>
<td>Strong</td>
</tr>
<tr>
<td>Coal-tar pitches (paving, roofing)</td>
<td>Lung</td>
<td>Strong</td>
</tr>
<tr>
<td>Aluminum production</td>
<td>Lung, urinary bladder</td>
<td>Weak / moderate†‡</td>
</tr>
</tbody>
</table>

*Agents classified in Group 1 on the basis of mechanistic information
†Weak evidence in workers, but strong evidence for some chemicals in this industry
‡Due to the diversity and complexity of these exposure, other mechanisms may also be relevant
## Evidence for carcinogenicity in humans and for geotoxicity as the main mechanism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Tumor sites with sufficient evidence in humans</th>
<th>Evidence of genotoxicity as the main mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Aflatoxins</td>
<td>Hepatocellular carcinoma</td>
<td>Strong</td>
</tr>
<tr>
<td>Benzene</td>
<td>ANLL</td>
<td>Strong</td>
</tr>
<tr>
<td>Bis(chloromethyl)ether/chloromethyl methylether</td>
<td>Lung</td>
<td>Moderate/Strong</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>Haematolymphatic organs</td>
<td>Strong</td>
</tr>
<tr>
<td>Dioxin(2,3,7,8-TCDD)</td>
<td>All cancers combined**</td>
<td>§</td>
</tr>
<tr>
<td>2,3,7,8-Pentachlorodibenzofuran</td>
<td></td>
<td>*§</td>
</tr>
<tr>
<td>3,3’,4,4’,5-Pentachlorobiphenyl (PCB-126)</td>
<td></td>
<td>§</td>
</tr>
</tbody>
</table>

ANLL = acute non-lymphocytic leukemia  
*Agents classified in Group 1 on the basis of mechanistic information  
§Strong evidence for an aryl hydrocarbon receptor (AhR)-mediated mechanism  
**New epidemiological findings.
Evidence for carcinogenicity in humans and for geotoxicity as the main mechanism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Tumor sites with sufficient evidence in humans</th>
<th>Evidence of genotoxicity as the main mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other chemicals</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethylene oxide</td>
<td></td>
<td>Strong*</td>
</tr>
<tr>
<td>Formaldehyde</td>
<td>Nasopharynx</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Leukemia¶**</td>
<td>Moderate</td>
</tr>
<tr>
<td>Sulfur mustard</td>
<td>Lung</td>
<td>Strong</td>
</tr>
<tr>
<td>Vinyl chloride</td>
<td>Hepatic angiosarcoma</td>
<td>Strong</td>
</tr>
<tr>
<td></td>
<td>Hepatocellular carcinoma</td>
<td></td>
</tr>
</tbody>
</table>

*Agents classified in Group 1 on the basis of mechanistic information
¶Particularly myeloid leukemia
**New epidemiological findings.
## Evidence for carcinogenicity in humans and for genotoxicity as the main mechanism

<table>
<thead>
<tr>
<th>Agent</th>
<th>Tumor sites with sufficient evidence in humans</th>
<th>Evidence of genotoxicity as the main mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Other complex exposures</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iron and steel founding</td>
<td>Lung</td>
<td>Strong*</td>
</tr>
<tr>
<td>Isopropyl alcohol manufacture using strong acids</td>
<td>Nasal cavity</td>
<td>Moderate</td>
</tr>
<tr>
<td>Mineral oils</td>
<td>Skin</td>
<td>Strong</td>
</tr>
<tr>
<td>Occupational exposure as a painter</td>
<td>Lung, urinary bladder, pleural mesothelioma</td>
<td>Strong‡</td>
</tr>
<tr>
<td>Rubber manufacturing industry</td>
<td>Leukemia, lymphoma**, urinary bladder, lung**, stomach**</td>
<td>Strong‡</td>
</tr>
<tr>
<td>Shale oils</td>
<td>Skin</td>
<td>Weak / lack of data</td>
</tr>
<tr>
<td>Strong inorganic acid mists</td>
<td>Larynx</td>
<td>Weak / lack of data</td>
</tr>
</tbody>
</table>

*Agents classified in Group 1 on the basis of mechanistic information

**New epidemiological findings.

‡Due to the diversity and complexity of these exposure, other mechanisms may also be relevant
Metals, arsenic dusts and fibers assessed by the IARC Monograph Working Group

<table>
<thead>
<tr>
<th>Group 1 Agent</th>
<th>Tumor sites (or types) for which there is sufficient evidence in humans</th>
<th>Established mechanistic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Arsenic and inorganic arsenic compounds</td>
<td>Lung, skin, urinary bladder</td>
<td>Oxidative DNA damage, genomic instability, aneuploidy, gene amplification, epigenetic effects, DNA-repair inhibition leading to mutagenesis</td>
</tr>
<tr>
<td>Beryllium and beryllium compounds</td>
<td>Lung</td>
<td>Chromosome aberrations, aneuploidy DNA damage</td>
</tr>
<tr>
<td>Cadmium and cadmium compounds</td>
<td>Lung</td>
<td>DNA-repair inhibition, disturbance of tumor-suppressor proteins leading to genomic instability</td>
</tr>
<tr>
<td>Chromium (VI) compounds</td>
<td>Lung</td>
<td>Direct DNA damage after intracellular reduction to Cr (III), mutation, genomic instability, aneuploidy, cell transformation</td>
</tr>
<tr>
<td>Group 1 Agent</td>
<td>Tumor sites (or types) for which there is sufficient evidence in humans</td>
<td>Established mechanistic events</td>
</tr>
<tr>
<td>---------------------------------------------------</td>
<td>------------------------------------------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Nickel compounds</td>
<td>Lung, nasal cavity, and paranasal sinuses</td>
<td>DNA damage, chromosome aberrations, genomic instability, micronuclei, DNA-repair inhibition, alteration of DNA methylation, histone modification</td>
</tr>
<tr>
<td>Asbestos (chrysotile, crocidolite, amosite, tremolite, actinolite and anthrophyllite)</td>
<td>Lung, mesothelioma, larynx, ovary</td>
<td>Impaired fiber clearance leading to macrophage activation, inflammation, generation of reactive oxygen and nitrogen species, tissue injury, genotoxicity, aneuploidy and polyploidy, epigenetic alteration, activation of signaling pathways, resistance to apoptosis</td>
</tr>
</tbody>
</table>
Metals, arsenic dusts and fibers assessed by the IARC Monograph Working Group

<table>
<thead>
<tr>
<th>Group 1 Agent</th>
<th>Tumor sites (or types) for which there is sufficient evidence in humans</th>
<th>Established mechanistic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Erionite</td>
<td>Mesothelioma</td>
<td>Genotoxicity</td>
</tr>
<tr>
<td>Silica dust, crystalline in the form of quartz or crystobalite</td>
<td>Lung</td>
<td>Impaired particle clearance leading to macrophage activation and persistent inflammation</td>
</tr>
<tr>
<td>Leather dust</td>
<td>Nasal cavity and paranasal sinuses</td>
<td></td>
</tr>
<tr>
<td>Wood dust</td>
<td>Nasal cavity and paranasal sinuses, nasopharynx</td>
<td></td>
</tr>
</tbody>
</table>
Evidence for carcinogenicity in humans of Groups 1 agents assessed – Personal Health

<table>
<thead>
<tr>
<th></th>
<th>Tumor sites for which there is sufficient evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tobacco Smoking</td>
<td>Oral cavity, oropharynx, nasopharynx, and hypopharynx, esophagus (adenocarcinoma and squamous-cell carcinoma), stomach, colorectum*, liver, pancreas, nasal cavity and paranasal sinuses, larynx, lung, uterine, cervix, ovary (mucinous)*, urinary bladder, kidney (body and pelvis), ureter, bone marrow (myeloid leukemia)</td>
</tr>
<tr>
<td>Parental smoking (cancer in the offspring)</td>
<td>Hepatoblastoma*</td>
</tr>
</tbody>
</table>

*New sites
Evidence for carcinogenicity in humans of Groups 1 agents assessed – Personal Health

<table>
<thead>
<tr>
<th>Agent</th>
<th>Tumor sites for which there is sufficient evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Second hand smoke</td>
<td>Lung</td>
</tr>
<tr>
<td>Smokeless tobacco</td>
<td>Oral cavity, esophagus*, pancreas</td>
</tr>
<tr>
<td>Areca nut</td>
<td></td>
</tr>
<tr>
<td>Betel quid w/added tobacco</td>
<td>Oral cavity, pharynx, esophagus</td>
</tr>
<tr>
<td>Betel quid w/o added tobacco</td>
<td>Oral cavity, esophagus*</td>
</tr>
<tr>
<td>Alcohol consumption</td>
<td>Oral cavity, pharynx, larynx, esophagus, liver, colorectum, female breast</td>
</tr>
</tbody>
</table>

*New sites
### Evidence for carcinogenicity in humans of Groups 1 agents assessed – Personal Health

<table>
<thead>
<tr>
<th>Agent</th>
<th>Tumor sites for which there is sufficient evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acetaldehyde associated with alcohol consumption</td>
<td>Esophagus*, head and neck*</td>
</tr>
<tr>
<td>Chinese style salted fish</td>
<td>Nasopharynx</td>
</tr>
<tr>
<td>Indoor emissions from household combustion of coal</td>
<td>Lung</td>
</tr>
</tbody>
</table>

*New sites
Radiation exposures with sufficient evidence in humans

<table>
<thead>
<tr>
<th>Radiation type</th>
<th>Major study populations</th>
<th>Tumor sites (and types) on which sufficient evidence is based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-particle and beta-particle emitters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Radon-222 and decay products</td>
<td>General population (residential exposure), underground miners</td>
<td>Lung</td>
</tr>
<tr>
<td>Radium-224 and decay products</td>
<td>Medical patients</td>
<td>Bone</td>
</tr>
<tr>
<td>Radium-226, radium-228, and decay products</td>
<td>Radium-dial painters</td>
<td>Bone, paranasal sinus and mastoid process (radium-226 only)</td>
</tr>
<tr>
<td>Thorium-232 and decay products</td>
<td>Medical patients</td>
<td>Liver, extrahepatic bile ducts, gall bladder, leukemia (excluding CLL)</td>
</tr>
<tr>
<td>Plutonium</td>
<td>Plutonium-production workers</td>
<td>Lung, liver, bone</td>
</tr>
</tbody>
</table>

CLL: chronic lymphocytic leukemia
## Radiation exposures with sufficient evidence in humans

<table>
<thead>
<tr>
<th>Radiation type</th>
<th>Major study populations</th>
<th>Tumor sites (and types) on which sufficient evidence is based</th>
</tr>
</thead>
<tbody>
<tr>
<td>Alpha-particle and beta-particle emitters</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phosphorus-32</td>
<td>Medical patients</td>
<td>Acute leukemia</td>
</tr>
<tr>
<td>Fission products, including strontium-90</td>
<td>General population following nuclear reactor accident</td>
<td>Solid cancers, leukemia</td>
</tr>
<tr>
<td>Radioiodines, including iodine-131</td>
<td>Children and adolescents following nuclear reactor accident</td>
<td>Thyroid</td>
</tr>
</tbody>
</table>
# Radiation exposures with sufficient evidence in humans

<table>
<thead>
<tr>
<th>Radiation type</th>
<th>Major study populations</th>
<th>Tumor sites (and types) on which sufficient evidence is based</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-radiation or gamma-radiation</td>
<td>Atomic bomb survivors, medical patients, in-utero exposure (offspring of pregnant medical patients and of atomic bomb survivors)</td>
<td>Salivary gland, esophagus, stomach, colon, lung, bone, skin (BCC), female breast, urinary bladder, brain and CNS, leukemia (excluding CLL), thyroid, kidney (atomic bomb survivors, medical patients), multiple sites (in-utero exposure)</td>
</tr>
<tr>
<td>Solar radiation</td>
<td>General population</td>
<td>Skin (BCC, SCC, melanoma)</td>
</tr>
<tr>
<td>UV-emitting tanning device</td>
<td>General population</td>
<td>Skin (melanoma), eye (melanoma, particularly choroid and ciliary body)</td>
</tr>
</tbody>
</table>

**CLL:** chronic lymphocytic leukemia  
**BBC:** basal-cell-carcinoma  
**SCC:** squamous-cell-carcinoma
Biological agents assessed by the IARC Monograph Working Group

<table>
<thead>
<tr>
<th>Group 1 Agent</th>
<th>Cancers for which there is sufficient evidence in humans</th>
<th>Established mechanistic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Epstein-Barr Virus (EBV)</td>
<td>Nasopharyngeal carcinoma, Burkitt’s lymphoma, extranodal NK/T-cell lymphoma (nasal type), Hodgkin’s lymphoma</td>
<td>Cell proliferation, inhibition of apoptosis, genomic instability, cell migration</td>
</tr>
<tr>
<td>Hepatitis B virus (HBV)</td>
<td>Hepatocellular carcinoma</td>
<td>Inflammation, liver cirrhosis, chronic hepatitis</td>
</tr>
<tr>
<td>Hepatitis C virus (HCV)</td>
<td>Hepatocellular carcinoma, non-Hodgkin’s lymphoma*</td>
<td>Inflammation, liver cirrhosis, liver fibrosis</td>
</tr>
</tbody>
</table>

* Newly identified link between virus and cancer
### Biological agents assessed by the IARC Monograph Working Group

<table>
<thead>
<tr>
<th>Group 1 Agent</th>
<th>Cancers for which there is sufficient evidence in humans</th>
<th>Established mechanistic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Kaposi’s sarcoma herpes virus (KSHV)</td>
<td>Kaposi’s sarcoma*, primary effusion lymphoma*</td>
<td>Cell proliferation, inhibition of apoptosis, genomic instability, cell migration</td>
</tr>
<tr>
<td>Human immunodeficiency virus type 1 (HIV-1)</td>
<td>Kaposi’s sarcoma, non-Hodgkin’s lymphoma*, cancer of the cervix*, anus*, conjunctiva*</td>
<td>Immunosuppression (indirect action)</td>
</tr>
<tr>
<td>Human papillomavirus type 16 (HPV-16)</td>
<td>Carcinoma of the cervix, vulva, vagina, penis, anus, oral cavity, and oropharynx &amp; tonsil</td>
<td>Immortalisation, genomic instability, inhibition of DNA damage response, anti-apoptotic activity</td>
</tr>
</tbody>
</table>

*Newly identified link between virus and cancer
`For other types, see next slide
## Group HPV types

<table>
<thead>
<tr>
<th>Group</th>
<th>HPV Types</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Alpha HPV types</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>16</td>
<td>Most potent HPV type, known to cause cancer at several sites</td>
</tr>
<tr>
<td>1</td>
<td>18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59</td>
<td>Sufficient evidence for cervical cancer</td>
</tr>
<tr>
<td>2A</td>
<td>68</td>
<td>Limited evidence in humans and strong mechanistic evidence for cervical cancer</td>
</tr>
</tbody>
</table>
## Biological agents assessed by the IARC Monograph Working Group

<table>
<thead>
<tr>
<th>Group 1 Agent</th>
<th>Cancers for which there is sufficient evidence in humans</th>
<th>Established mechanistic events</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human T-cell lymphotrophic virus, type-1 (HTLV-1)</td>
<td>Adult T-cell leukemia and lymphoma</td>
<td>Immortalisation and transformation of T cells</td>
</tr>
<tr>
<td><em>Heliobacter pylori</em></td>
<td>Non-cardia gastric carcinoma, low-grade B-cell mucosa-associated lymphoid tissue (MALT) gastric lymphoma*</td>
<td>Inflammation, oxidative stress, altered cellular turnover and gene expression, methylation mutation</td>
</tr>
<tr>
<td><em>Clonorchis sinensis</em></td>
<td>Cholangiocarcinoma*</td>
<td></td>
</tr>
<tr>
<td><em>Opisochis viverrini</em></td>
<td>Cholangiocarcinoma</td>
<td>Inflammation, oxidative stress, cell proliferation</td>
</tr>
<tr>
<td><em>Schictosoma haematobium</em></td>
<td>Urinary bladder cancer</td>
<td>Inflammation, oxidative stress,</td>
</tr>
</tbody>
</table>

*Newly identified link between virus and cancer*
Oral Cavity

- Alcoholic beverages
- Betel quid with tobacco
- Betel quid without tobacco
- Human papillomavirus type 16
- Tobacco, smokeless
- Tobacco smoking
Tonsil

- Human papillomavirus type 16
Pharynx

- Alcoholic beverages
- Betel quid with tobacco
- Human papillomavirus type 16
- Tobacco smoking
Nasopharynx

- Epstein-Barr virus
- Formaldehyde
- Salted fish, Chinese-style
- Wood dust
Digestive tract, upper

- Acetaldehyde associated with consumption of alcoholic beverages
Esophagus

- Acetaldehyde associated with consumption of alcoholic beverages
- Alcoholic beverages
- Betel quid with tobacco
- Betel quid without tobacco
- Tobacco, Smokeless
- Tobacco smoking
- X-radiation, Gamma-radiation
Stomach

- *Heliobacter pylori*
- Rubber production industry
- Tobacco, Smokeless
- Tobacco smoking
- X-radiation, Gamma-radiation
Colon and rectum

- Alcoholic beverages
- Tobacco smoking
- X-radiation, Gamma-radiation
Anus

- Human immunodeficiency virus type 1
- Human papillomavirus type 16
Liver and bile duct

- Aflatoxins
- Alcoholic beverages
- *Clonorchis sinensis*
- Estrogen-progestogen contraceptives
- Hepatitis B virus
- Hepatitis C virus
- *Opisthorchis viverrini*
- Plutonium
- Thorium-232 and its decay products
- Tobacco smoking (in smokers and in smokers’ children)
- Vinyl chloride
Gall bladder

- Thorium-232 and its decay products
Pancreas

- Tobacco, Smokeless
- Tobacco smoking
Nasal cavity and paranasal sinus

- Isopropyl alcohol production
- Leather dust
- Nickel compounds
- Radium-226 and its decay products
- Radium-228 and its decay products
- Tobacco smoking
- Wood dust
Larynx

- Acid mists, strong inorganic
- Alcoholic beverages
- Asbestos (all forms)
- Tobacco smoking
Lung

- Aluminum production
- Arsenic and inorganic arsenic compounds
- Asbestos (all forms)
- Beryllium and beryllium compounds
- Bis(chloromethyl)ether; chloromethyl methyl ether (technical grade)
- Cadmium and cadmium compounds (cont’d)
Lung

- Chromium(VI) compounds
- Coal, indoor emissions from household combustion
- Coal gasification
- Coal-tar pitch
- Coke production
- Hematite mining (underground) (cont’d)
Lung

- Iron and steel founding
- MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)
- Nickel compounds
- Painting
- Plutonium
- Radon-222 and its decay products (cont’d)
Lung

- Rubber production industry
- Silica dust, crystalline
- Soot
- Sulfur mustard
- Tobacco smoke, secondhand
- Tobacco smoking
- X-radiation, gamma-radiation
Bone

- Plutonium
- Radium-224 and its decay products
- Radium-226 and its decay products
- Radium-228 and its decay products
- X-radiation, gamma-radiation
Skin Melanoma

- Solar radiation
- Ultraviolet-emitting tanning devices
Skin (non-melanoma malignant neoplasms)

- Arsenic and inorganic arsenic compounds
- Azathioprine
- Coal-tar distillation
- Coal-tar pitch
- Cyclosporine
- Methoxsalen plus Ultraviolet A
- Mineral oils, untreated or mildly treated
- Shale oils
- Solar radiation
- Soot
- X-radiation, gamma-radiation
Mesothelium (pleura and peritoneum)

• Asbestos (all forms)
• Erionite
• Painting
Endothelium (Kaposi sarcoma)

- Human immunodeficiency virus type 1
- Kaposi sarcoma herpes virus
Breast

- Alcoholic beverages
- Diethylstilbestrol
- Estrogen-progestogen contraceptives
- Estrogen-progestogen menopausal therapy
- X-radiation, gamma-radiation
Vulva

- Human papillomavirus type 16
Vagina

• Diethylstilbestrol (exposure in utero)
• Human papillomavirus type 16
Uterine cervix

- Diethylstilbestrol (exposure in utero)
- Estrogen-progestogen contraceptives
- Human immunodeficiency virus type 1
- Human papillomavirus types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59
- Tobacco smoking
Endometrium

- Estrogen menopausal therapy
- Estrogen-progestogen menopausal therapy
- Tamoxifen
Ovary

- Asbestos (all forms)
- Estrogen menopausal therapy
- Tobacco smoking
Penis

- Human papillomavirus 16
Kidney

- Tobacco smoking
- X-radiation, gamma-radiation
Renal pelvis and ureter

- Aristolochic acid, plants containing
- Phenacetin
- Phenacetin, analgesic mixtures containing
- Tobacco smoking
Urinary bladder

- Aluminum production
- 4-Aminobiphenyl
- Arsenic and inorganic arsenic compounds
- Auramine production
- Benzidine
- Chlornaphazine
- Cyclophosphamide

(cont’d)
Urinary bladder

- Magenta production
- 2-Naphthylamine
- Painting
- Rubber production industry
- *Schistosoma haematobium*
- Tobacco smoking
- *ortho*-Toluidine
- X-radiation, gamma-radiation
Eye

- Human immunodeficiency virus type 1
- Ultraviolet-emitting tanning devices
- Welding
Brain and central nervous system

- X-radiation, gamma-radiation
Thyroid

- Radioiodines, including Iodine-131
- X-radiation, gamma-radiation
Lymphoid, hematopoietic and related tissue: Leukemia &/or lymphoma

- Azathioprine
- Benzene
- Busulfan
- 1,3-Butadiene
- Chlorambucil
- Cyclophosphamide
- Cyclosporine

(cont’d)
Lymphoid, hematopoietic and related tissue: Leukemia &/or lymphoma

- Epstein-Barr virus
- Etoposide with cisplatin and bleomycin
- Fission products, including Strontium-90
- Formaldehyde
- *Heliobacter pylori*
- Hepatitis C virus
- Human immunodeficiency virus type 1 (cont’d)
Lymphoid, hematopoietic and related tissue: Leukemia &/or lymphoma

- Human T-cell lymphotrophic virus type 1
- Kaposi sarcoma herpes virus
- Melphalan
- MOPP (vincristine-prednisone-nitrogen mustard-procarbazine mixture)
- Phosphorus-32
- Rubber production industry

(cont’d)
Lymphoid, hematopoietic and related tissue: Leukemia &/or lymphoma

- Semustine (methyl-CCNU)
- Thiotepa
- Thorium-232 and its decay products
- Tobacco smoking
- Treosulfan
- X-radiation, gamma-radiation
Multiple sites (unspecified)

- Cyclosporine
- Fission products, including Strontium-90
- X-radiation, gamma-radiation (exposure in utero)
All cancer sites (combined)

- 2,3,7,8-Tetrachlorodibenzo-\textit{para}-dioxin