Carcinogens – What Should You Know While Waiting for IARC

Paul Blanc MD MSPH
Division of OEM
UCSF

No conflicts of interest to disclose

Chemical Carcinogens:
What Cancers Matter A Priori?

• Respiratory Tract
  – Asbestos, silica
  – Selected metals [Cr, Ni, Arsenic]
• Bladder
  – Dyestuffs
• Liver
  – Vinyl chloride; other halogenated hydrocarbons?
• Skin
  – Polycylics
• Bone marrow
  – Benzene
Physical Carcinogens: What Cancers Matter *A Priori*?

- **Respiratory Tract**
  - Radon progeny
  - Other Radionuclides

- **Skin**
  - Solar radiation
  - Other UV

- **Brain**
  - Non-ionizing radiation?

---

U.S. Cancer Trends Over Time: Male
Inferences from Temporal Trends

Lung cancer incidence and mortality ↓
Breast cancer incidence →; mortality ↓
Pancreas mortality ↑ (slowly)
Liver mortality ↑ (slowly, males)
Leukemia mortality ↓ then ↑ (slowly, males)
Bladder incidence ↑ (slowly; males)
Melanoma incidence ↑ (steeply)
Thyroid incidence ↑ (slope female > male)
Inferences for Carcinogens

Lung cancer ↓ from smoking ↓; will occupational carcinogens become more important?
Liver mortality ↑ (slowly, males); chlorinated or other workplace chemicals?
Leukemia mortality ↓ then ↑ (slowly, males); benzene better controlled; other chemicals?
Bladder incidence ↑ (slowly; males); other continued industrial occupational sources?
Melanoma incidence ↑ (steeply); only UV?
Thyroid incidence ↑ (slope female > male) Pancreas mortality ↑ (slowly); missed environmental factors?

What is IARC? What Does it Do?

• 1965: IARC established in 1965, soon receives frequent requests for advice on the carcinogenic risk of chemicals.
• 1970: IARC Advisory Committee on Environmental Carcinogenesis recommends “a compendium on carcinogenic chemicals be prepared by experts.”
• 1971: Criteria established to evaluate carcinogenic risks to humans in a series of monographs.
IARC Carcinogen Classification through Volume 115

<table>
<thead>
<tr>
<th>Cancer in Humans</th>
<th>Cancer in Experimental Animals</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sufficient</td>
<td>Sufficient</td>
</tr>
<tr>
<td>Limited</td>
<td>Limited</td>
</tr>
<tr>
<td>Inadequate</td>
<td>Inadequate</td>
</tr>
</tbody>
</table>

Carcinogenicity of some industrial chemicals

In February 2016, 24 experts from eight countries met at the International Agency for Research on Cancer (IARC), Lyon, France, to assess the carcinogenicity of seven industrial chemicals (appendix). These assessments will be published as volume 115 of the IARC Monographs.
Lung Cancer as a Paradigm

• What exposures are in IARC Group 1?
• What occupations?
• What are substances are not?
• What should we worry about waiting for IARC?

Group I  IARC Lung Carcinogens

• Arsenic
• Asbestos
• BCME
• Beryllium
• Cadmium
• Chromium VI
• Silica dust, crystalline
• Nickel
• Ionizing radiation
• Polyaromatic hydrocarbons
• Sulfur mustard
• Soot
• Coal tar pitch
• Diesel Exhaust

Occupations
• Aluminum production
• Coal gasification
• Coke production
• Hematite mining
• Iron and steel founding
• Painting

Important to note that the time lag until Group 1 classification was considerable for some key exposures, including silica and diesel exhaust
Group 2  IARC Lung Carcinogens

- Bitumen (Asphalt)
- Creosote
- Cobalt-tungsten
- Dioxin
- Inorganic acid mists
- Hydrazine (new)

**Occupations**
- Printing Processes
- Welding

What substances or occupations on this list should be Group 1?
What may not be on this list at all?

Other Examples of Potential Gaps

<table>
<thead>
<tr>
<th>Organ</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Liver</td>
<td>Vinyl chloride; 1,2 Dichloropropane</td>
<td>Arsenic; DDT; Troiholoethylene; Dichloromethane</td>
</tr>
<tr>
<td>Melanoma</td>
<td>PCBs; Solar; Tanning salons</td>
<td>No other chemicals</td>
</tr>
<tr>
<td>Other Skin</td>
<td>Coal Tar Pitch; Soot; Mineral oil</td>
<td>Creosote</td>
</tr>
<tr>
<td>Larynx</td>
<td>Tobacco smoke</td>
<td>Secondhand smoke</td>
</tr>
<tr>
<td>Pancreas</td>
<td>Tobacco smoke</td>
<td>Red meat; Ethanol; No other chemicals;</td>
</tr>
<tr>
<td>Nasal Cavity</td>
<td>Leather Dust; Wood Dust</td>
<td>Formaldehyde; Carpentry and Joinery; Chromium VI</td>
</tr>
</tbody>
</table>
Bladder Cancer as a Paradigm

- What does the history dye-caused bladder cancer teach us?

- What how does the experience of IARC in relation to this teach us?

Dyestuffs

- 1856: William Henry Perkin synthesizes mauveine (aniline purple; Tyrian purple)
- 1857: Sets up commercial manufacturing
- 1859-60: Fuschine/roseine (magenta) synthesized by Hofmann and others
<table>
<thead>
<tr>
<th>Early Perkins Factory</th>
<th>Queen Victoria in Mauve dress</th>
</tr>
</thead>
</table>

## Dye Chemistry

- These dyes are not a single moiety
- Mauveine is a mix of 4 major entities
- Magenta/Fuchsine also has 4 components (Basic Red 9 (Magenta 0), Magenta I (Rosanilin), Magenta II, and Magenta III (New Fuchsin))
- Multiple synthetic pathways for Magenta:
  - Aniline $\text{Hg}_2\text{Cl}_2$
  - Aniline+Arsenous acid, boiled
  - Aniline+Nitrobenzene+HCl+Fe
Germany

• 1870-1900: Rapid expansion of dye industry

• One site: Hoechst paint works near Frankfurt

• 1878: Nitze introduces cystoscope

• 1886: Dr. Ludwig Rehn begins practice in Frankfurt

• 1895: Bladder cancer in 3/45 dye workers
Bladder Cancer in the 20th Century

• Rehn was challenged by Friedrich Wilhelm Grandhomme [1st chief physician at Hoechst]: He asked, “Why only 3/45?”

• 1906: Rehn f/u - 33 more cases

• 1912: Leuenberger in Basel – 18 more cases

• 1920: 177 total cases from Germany/Switzerland

Alice Hamilton Critique, May 1921

• We don’t know the denominator of cases (but the population attributable risk near 50%!)

• Variable latency and stage

• Not related to pure aniline production, but multiple suspect compounds [ß-napthylamine, benzidine]

• No animal model

• Suspects arsine/arsenicals as the cause
Jump Ahead - 1950s
Aniline Dye Workers

- Large British study (1954) benzidine, ß-napthylamine +; Magenta + in sub-analysis
- Animal model for some dyes
- Wilhelm Hueper (1894 - 1978) 1st director, Environmental Cancer Section of the U.S. National Cancer Institute argues forcefully on occupational bladder cancer
- Exposure continues

MAGENTA AND MAGENTA PRODUCTION

Magenta and magenta production were considered by previous IARC Working Groups in 1973, 1986, 1987, and 2008 [IARC, 1974; 1987a, b, 2010]. Since that time new data have become available, which have been incorporated in this Monograph, and taken into consideration in the present evaluation.

5. Evaluation

There is sufficient evidence in humans for the carcinogenicity of magenta production. Magenta production causes cancer of the urinary bladder. There is sufficient evidence in experimental animals for the carcinogenicity of CI Basic Red 9.

There are insufficient mechanistic data relevant to the carcinogenicity of magenta in humans or experimental animals.

Magenta production is carcinogenic to humans (Group 1).

Magenta is possibly carcinogenic to humans (Group 2B).
Bladder Carcinogen IARC Gap

<table>
<thead>
<tr>
<th>Organ</th>
<th>Group 1</th>
<th>Group 2</th>
</tr>
</thead>
</table>
| Bladder | 2-Naphthylamine
Benzidine
Ortho toluidine
Magenta production
Auramine production | 4-Chloro-ortho-toluidine
2-Mercaptobenzothiazole (new)
Printing
Hair dressing, barbers (occupation) |

But maybe this is all semantics?
Does Group 1 vs. Group 2 really impact regulation?
Does identification of a discrete substance as opposed to a process matter?

Jean from Lissner, Queensland, Australia asked:
Does Castellani’s paint cause cancer?

“Castellani’s paint or magenta paint has been used to treat fungal skin infections since the 1920s. Magenta has also been used in hair dyes, cosmetic products and artist paints. Several studies have shown that people who work in dye-making factories that produce magenta have a higher risk of bladder cancer than the general population. The International Agency for Research into Cancer (IARC) classifies different things according to their cancer risk – they have listed the production of magenta as high risk, meaning there is conclusive evidence that working in such as job could cause cancer, likely because of exposure in the production process to a chemical called ortho-toluidine. However, evaluations by IARC have found no evidence of magenta as a product increasing cancer risk. There is also no clear evidence that other ingredients in Castellani’s paint, aside from the dyes that make up magenta, pose any risk of cancer.”
Waiting for IARC: Interpret the Data

• The IARC process is inherently “conservative.”

• If IARC Group 1, the human evidence is strong.

• Do not discount IARC Group 2, especially Group 2A.

• IARC Group 3 does not = good negative data.

Waiting for IARC: Interrogate the Data

• When was the substance in question last reviewed?

• What are the assessments of other agencies?
  National Toxicology Program
  California EPA (OEHHA):
  Proposition 65 List [12/04/15]

• Are there other relevant data, especially meta-analyses?
Waiting for IARC: Bottom Line

- IARC classifications are a major metric and should not be ignored
- IARC Group 2, not just 1, matters
- IARC is not the sole arbiter of carcinogenicity

Q&A

* A substance for which there is strong epidemiologic evidence of cancer causation but experimental data are lacking would most likely be assessed by IARC as:
  A. Category 2A
  B. Category 2B
  C. Category 1
  D. Decision would be deferred pending more data
Q&A

*Magenta is the name for a group of dyes for which:*

A. IARC has determined that some of the components are Category 1 human carcinogens
B. IARC has determined that all of its components are at least 2B
C. IARC has not carried out an assessment
D. IARC has categorized the manufacturing process but not the product as carcinogenic

---

Q&A

*Which of the following is not considered a definite (Group 1) lung carcinogen by IARC:*

A. Asbestos
B. Silica
C. Hydrazine
D. Arsenic