Priorities to Reduce Environmental Cancer

Mechanisms of Carcinogenesis to Identify Priority Carcinogens

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HAZARD IDENTIFICATION

BITUMENS AND BITUMEN EMISSIONS, AND SOME N- AND S-HETEROCYCLIC POLYCYCLIC AROMATIC HYDROCARBONS
VOLUME 103

IARC MONOGRAPHS ON THE EVALUATION OF CARCINOGENIC RISKS TO HUMANS
Hazard Identification by IARC

Does this agent have the capacity to cause cancer in humans?

- Evidence of cancer causation in humans (epidemiological data)
- Evidence of carcinogenicity in experimental animals, usually rodents (experimental evidence)
- Mechanism of action

Categorization of agents in relation to

- **Group 1** – *carcinogenic to humans*
- **Group 2A** – *probably carcinogenic to humans*
- **Group 2B** – *possibly carcinogenic to humans*
- **Group 3** – *not classifiable as to its carcinogenicity to humans*
  - PS. Group 4. *Probably not carcinogenic to humans*

But what of exposure to low concentrations? Mechanistic data?
Mechanism of action of (chemical) carcinogens

Genotoxic

- Direct acting
- Procarcinogen
- Inorganic carcinogen

Non-genotoxic

- Solid state carcinogen
- Hormone
- Immunosuppressors
- Promoter

Weisburger, J. H., and Williams, G. M. (1981). Carcinogen testing:
“An enabling characteristic:” Genomic instability and mutation
Mechanisms of chemical carcinogenesis

Genotoxic

Non-genotoxic

- **Peroxisome proliferators** (hypolipidemic drugs, phthalates, trichloroethylene)
  - Gap junction inhibitors
  - DNA methylating agents

- **Compounds interacting with the Aryl Hydrocarbon receptor - AhR** (polychlorinated biphenyls, dibenzo-\(p\)-dioxins including TCDD)

- **Inducers of oxidative stress** (pentachlorophenol, quercetin-type flavenoids)

- **Inducers of hormone imbalance** (imidizole, dimethylpyridine, benzensulfonic ethers)

A small-cell lung cancer genome with complex signatures of tobacco exposure

Erin D. Pleasance¹, Philip J. Stephens¹, Sarah O’Meara¹,², David J. McBride¹, Alison Meynert³, David Jones¹,
Comprehensive molecular characterization of urothelial bladder carcinoma

The Cancer Genome Atlas Research Network*

Seventy-two per cent of the cancers in this study were from current or past smokers, consistent with extensive epidemiological studies indicating an association between smoking and urothelial cancer risk. In contrast with lung cancer, however, there was no statistically significant association between smoking status and the mutational spectrum, frequency of mutation in any significantly mutated gene, occurrence of focal somatic CNAs or expression subtype (Supplementary Tables 2.9.1
### Exogenous

<table>
<thead>
<tr>
<th>Factor</th>
<th>Mutation</th>
<th>Cancer Type</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ultraviolet light</td>
<td>C → T, CC → TT</td>
<td>Skin cancer</td>
</tr>
<tr>
<td>Benzo[a]pyrene</td>
<td>G → T</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>NNK</td>
<td>G → A</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>Aflatoxin B₁</td>
<td>AGG → AGT</td>
<td>Liver cancer</td>
</tr>
</tbody>
</table>

### Endogenous

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<th>Factor</th>
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</thead>
<tbody>
<tr>
<td>Spontaneous deamination</td>
<td>C → T</td>
<td>Stomach cancer</td>
</tr>
<tr>
<td>Apurinic site generation</td>
<td>C → T, G → T</td>
<td>Multiple cancers</td>
</tr>
<tr>
<td>Oxidative damage and ROS generation</td>
<td>G → T</td>
<td>Lung cancer</td>
</tr>
<tr>
<td>DNA polymerase error</td>
<td>G → T, T → C</td>
<td>Brain cancer, colon cancer</td>
</tr>
<tr>
<td>APOBEC</td>
<td>C → T</td>
<td>Cervical, breast, head and neck and bladder cancers</td>
</tr>
</tbody>
</table>

Abbreviations: 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone, NNK; reactive oxygen species, ROS; apolipoprotein B mRNA editing enzyme, catalytic polypeptide-like, APOBEC.

Asian Lung Cancer Genome Sequencing: Secondhand smoke not accounting for Lung Cancer in Never-Smokers

Mechanistic data complementing sufficient epidemiological data

Outdoor air pollution and particulate matter from outdoor air pollution – Group 1 (Vol 109 – October 2013)

• Increased lung cancer in exposed populations

Mechanistic data includes

• In humans, exposure associated with changed expression of DNA repair enzymes
• Somatic and germ cell mutations, cytogenetic abnormalities and DNA damage observed in mammals and other species exposed.
Recognized categories of pollutants

Genotoxins or compounds sometimes exhibiting genotoxicity
• Polycyclic aromatic hydrocarbons: benzo[a]pyrene
• Polychlorinated biphenyls
• Halogenated hydrocarbons: trichloroethylene, 1,2-dibromo-methane, chloroform, dichlorodiphenyltrichloroethane

Compounds often exhibiting non-genotoxic characteristics
• Polychlorinated biphenyls
• Estrogen analogues: bisphenol-A, alkylphenol ethoxylates)
• Phthalates: di(2-ethylhexyl)phthalate, dibutylphthalate
• Doixins: 2,3,7,8-tetrachlorodibenzo[\(p\)]dioxin and many others
• Perfluorinated compounds and brominated flame retardants

Epidemiological data typically focus on high, even highest, exposure: contrast the ‘Occupational’ papers with ‘Environmental’ papers in Occup Environ Med
Relative risks of 1.2 or less are typical

- Mechanistic studies specifically addressing low levels of exposure are rare; most
  - Mechanistic studies specifically addressing low levels of exposure are rare; most studies address mechanisms operative irrespective of exposure level
- Once mechanism is establish (or reasonably inferred) broadly accepted principles apply
  - For genotoxic agents, no ‘safe level of exposure’
  - For non-genoxic agents, early perceptions included the possibility of threshold;
Non-genotoxic agents: Bisphenol-A & TCDD

- Complex epidemiological findings: TCDD at Seveso and risk of breast cancer
- Inferences properly drawn from adverse health effects apart from cancer incidence

Commentary:
The Learning Curve
Evidence-based Public Health Policy in Relation to
Evidence-based Public Health Policy in Relation to

Scant prospects in relation to epidemiological evidence

Epidemiological assessment of occupational cancer may involve a relative risk as low as 1.20 (corresponding to an excess risk of $10^{-2}$) which, in a retrospective cohort mortality study, would require approximately 4,000 workers involved.

Detecting at excess risk of $10^{-4}$ under the same circumstances may be calculated to require 40 million workers.


On mechanistic grounds, no preventable exposure to a genotoxic agent can be specified as involving an acceptable risk: “no safe dose”

Evidence of biological effects caused by very low concentrations of endocrine disrupting compounds now preclude reference to non-genotoxic mechanisms as justifying

Sometimes, novel circumstances provide insight

Cancer risk following occupational exposure to pesticides has
Organic food consumption and the incidence of cancer in a large prospective study of women in the United Kingdom

K E Bradbury, A Balkwill, E A Spencer, A W Roddam, G K Reeves, J Green, T J Key, V Beral, K Pirie and The Million Women Study Collaborators

Conclusions: In this large prospective study there was little or no decrease in the incidence of cancer associated with consumption of organic food, except possibly for non-Hodgkin lymphoma.
Disaggregating Data on Asian American and Pacific Islander Women to Provide New Insights on Potential Exposures to Hazardous Air Pollutants in California

Thu Quach¹,², Ruiling Liu¹, David O. Nelson¹,², Susan Hurley¹, Julie Von Behren¹, Andrew Hertz¹, and Peggy Reynolds¹,²

Abstract

Background: The Asian American and Pacific Islander (AAPI) population is heterogeneous and rapidly growing in the United States, with a high proportion concentrated in California. Although traditionally assumed to have lower rates of breast cancer than non-Hispanic white women, recent studies have suggested considerable variation in incidence by AAPI ethnic group, with rates in some exceeding those in non-Hispanic whites. The potential role of environmental toxicants has not been well explored and may provide insights into these patterns.
A public health quandary
Evidence of exposure in the absence of evidence of an adverse cancer (health?) outcome.

Exposure to many exogenous chemicals is widespread. Certain polychlorinated biphenyls, organochlorine pesticides, perfluorinated compounds, phenols, polybrominated diphenyl ethers, phthalates, and perchlorate were detected in 99-100% of the US population.

Centre for Disease Control and Prevention 4th National Report on Human Exposure to Environmental Chemicals
In conclusion

Granted that
Primary cancer prevention involves identification of carcinogens and risk consequent upon particular exposures then

• Currently available data establish priorities for (IARC Monograph) evaluations
• In respect of low levels of exposure and certain complex risk factors, clear epidemiological findings cannot be anticipated
• Prospects for epidemiological uncertainties to be resolved by mechanistic data are limited
• Increasing understanding of epigenetic change in cancer etiology is the most encouraging prospect.