Priorities to Reduce Environmental Cancer

Mechanisms of Carcinogenesis to Identify Priority Carcinogens

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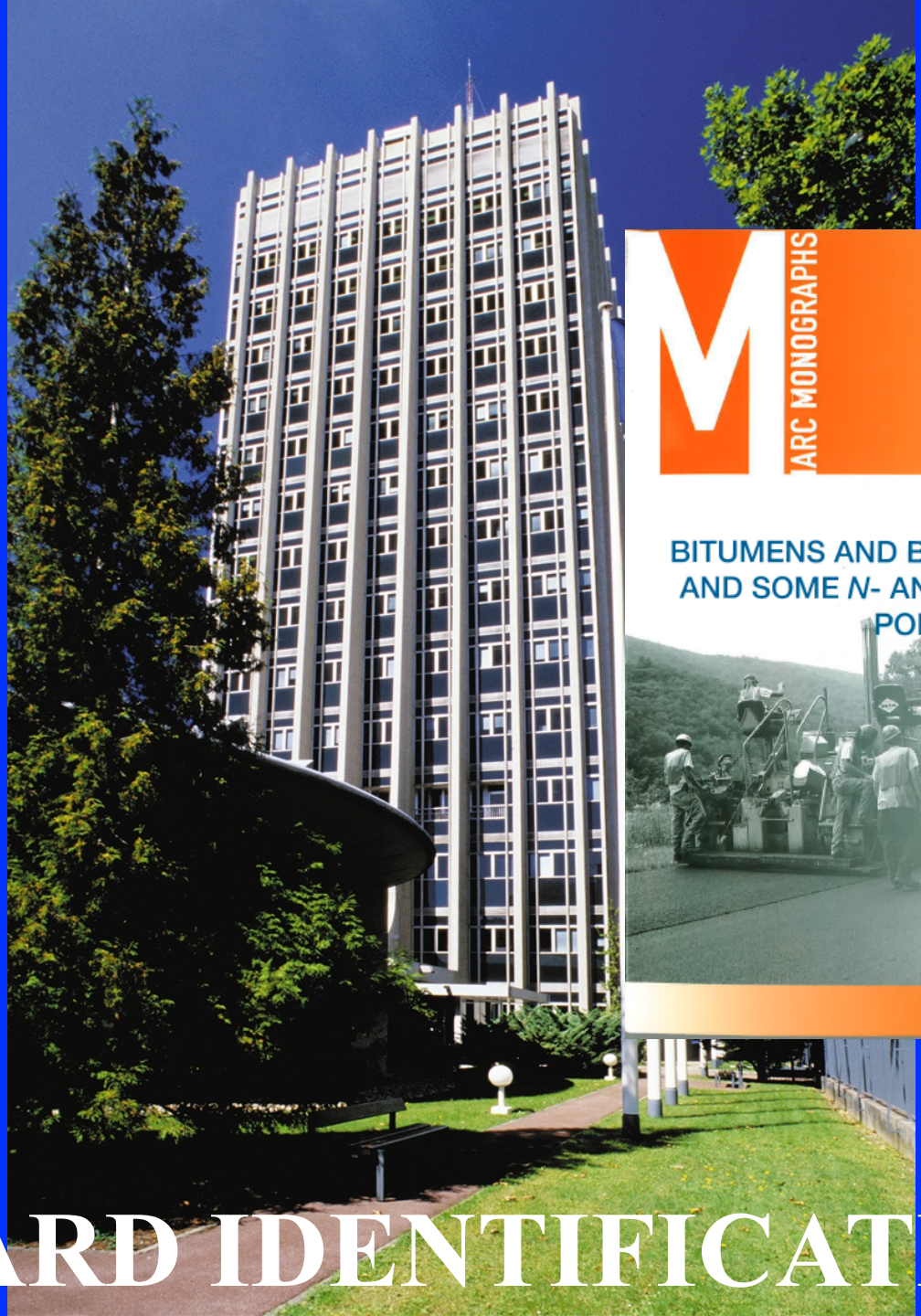
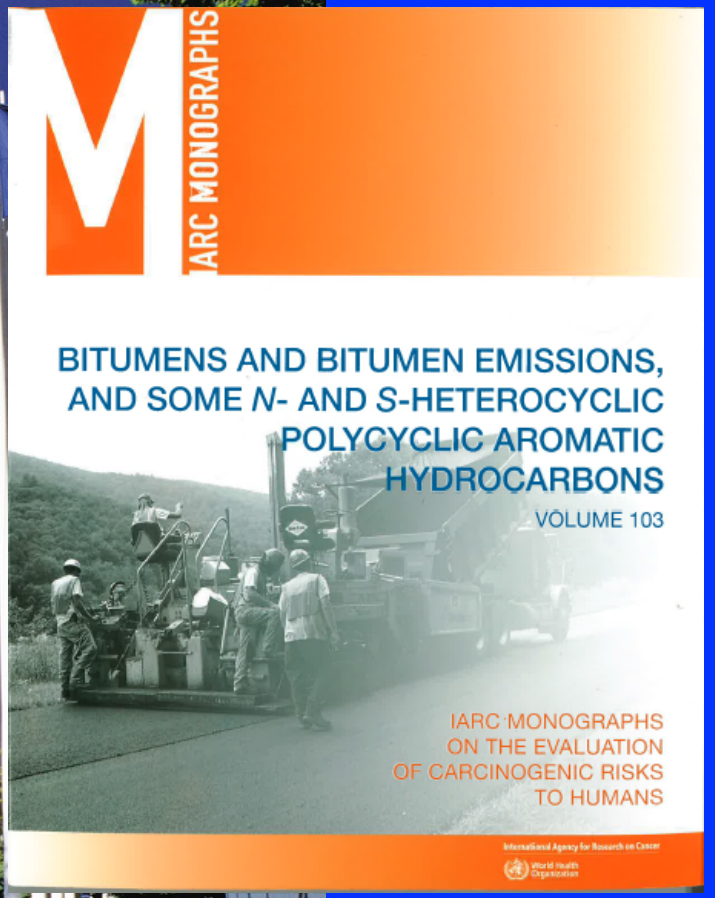
Lyon. France





HAZARD IDENTIFICATION

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

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Genotoxic

Genotoxic

- Direct acting
- Procarcinogen
- Inorganic carcinogen

Non-genotoxic

- Solid state carcinogen
- Hormone
- Immunosuppressor
- Promoter

Weisburger, J. H., and Williams, G. M. (1981). Carcinogen testing:

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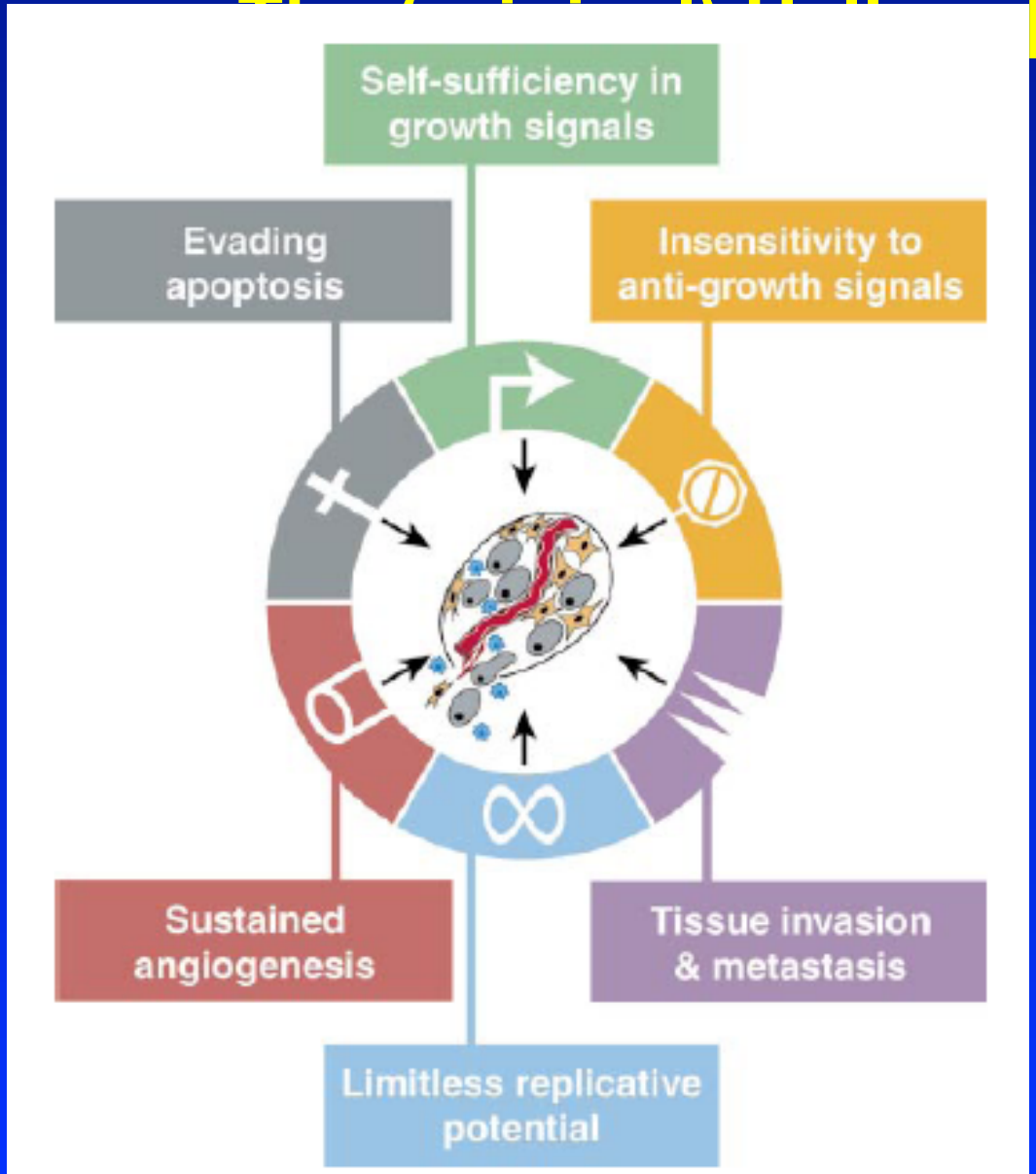
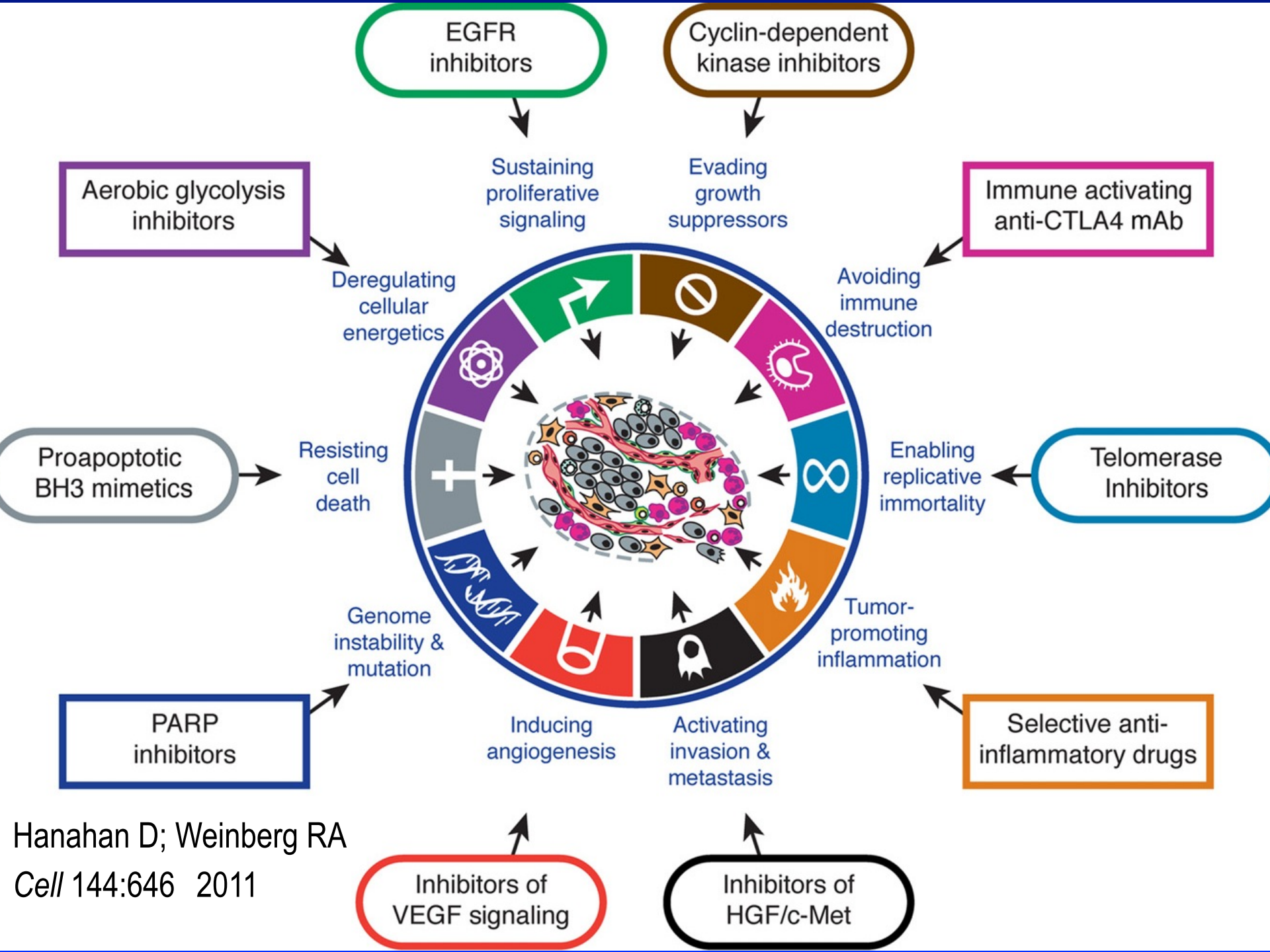
The (original) Hallmarks of Cancer



Hanahan & Weinberg
Cell 100 (2000) 57.

"An enabling characteristic:"
Genomic instability and mutation



Hanahan D; Weinberg RA

Cell 144:646 2011

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 inbalance** (imidizole, dimethyl-pyridine, benzensulfonic ethers)

Benigni R et al, *Chem Rev* **113**:2940-57, 2013

nature Vol 463|14 January 2010|doi:10.1038/nature08629

ARTICLES

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

Erin D. Pleasance[1], Philip J. Stephens[1], Sarah O'Meara[1,2], David J. McBride[1], Alison Meynert[3], David Jones[1],

Table 1 | Somatically acquired genomic variants of all classes in a SCLC genome

Variant	Number
Somatic substitution	22,910
Coding	134 (0.6%)
Nonsense	4
Non-synonymous	94
Synonymous	36
Non-coding, transcribed	182 (0.8%)
Untranslated region	119
Non-coding RNA	63
Intronic	6,463 (28%)
Splice site	5
Other intronic	6,458
Intergenic	16,131 (70%)

ARTICLE

20 MARCH 2014 | VOL 507 | NATURE | 315

OPEN

doi:10.1038/nature12965

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

CNAs: copy number alterations

Exogenous

Ultraviolet light	C → T, CC →TT	Skin cancer
Benzo[*a*]pyrene	G → T	Lung cancer
NNK	G → A	Lung cancer
Aflatoxin B_1	AGG → AGT	Liver cancer

Endogenous

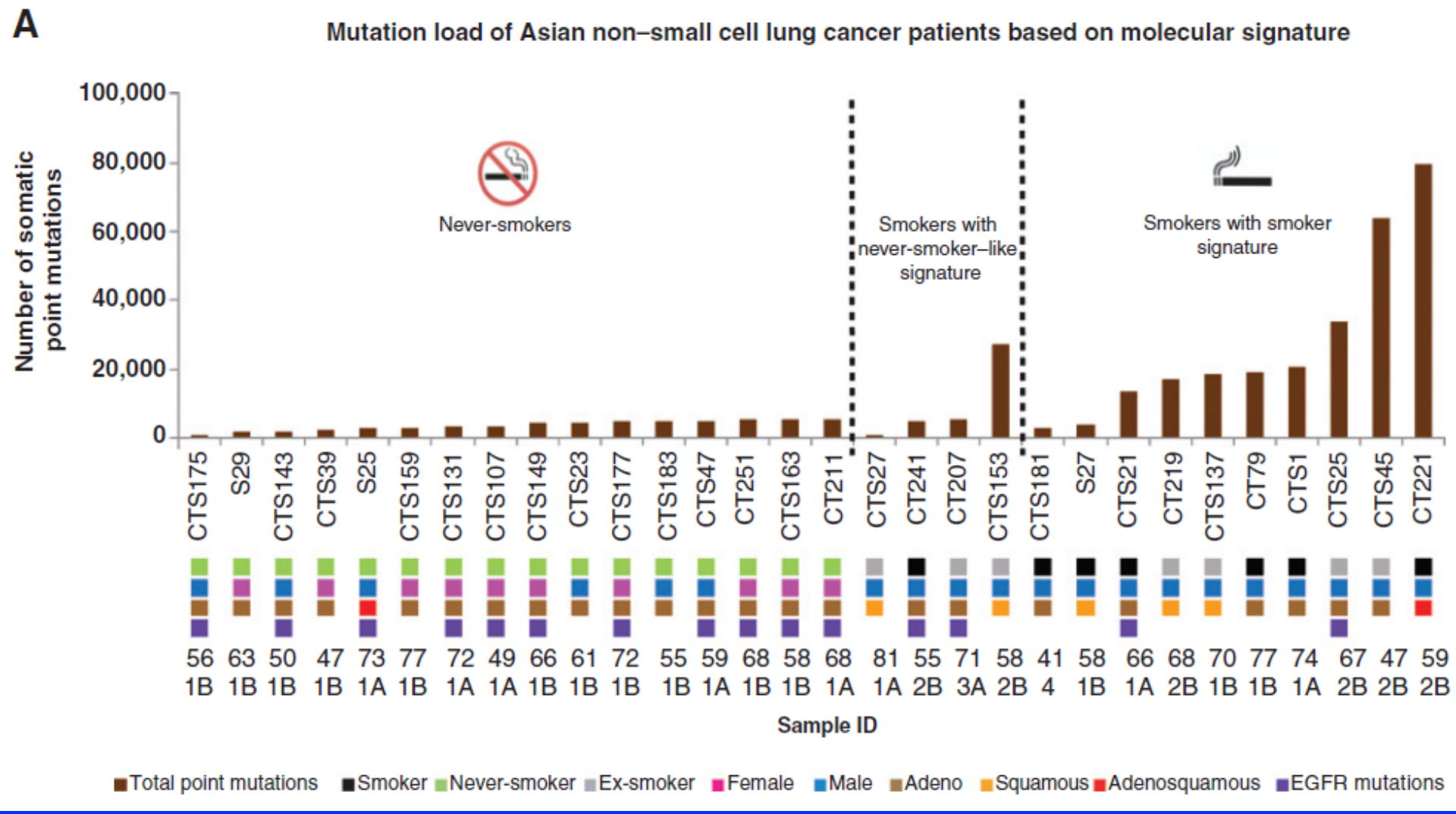
Spontaneous deamination	C → T	Stomach cancer
Apurinic site generation	C →T, G → T	Multiple cancers
Oxidative damage and ROS generation	G → T	Lung cancer
DNA polymerase error	G → T, T →C	Brain cancer, colon cancer
APOBEC	C → T	Cervical, breast, head and neck and bladder cancers

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

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

Based on Kuong KJ, Loeb LA, APOBEC3B mutagenesis in cancer, *Nat Genetics* 45:964-5, 2013 and other sources.

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



Krishnan VG et al. *Cancer Res* **74**:6071-81, 2014

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**

Manzetti S et al *Chem Res Toxicol* **2**7:713-37, 2014

Qualitative Risk Assessment
Qualitative Risk Assessment

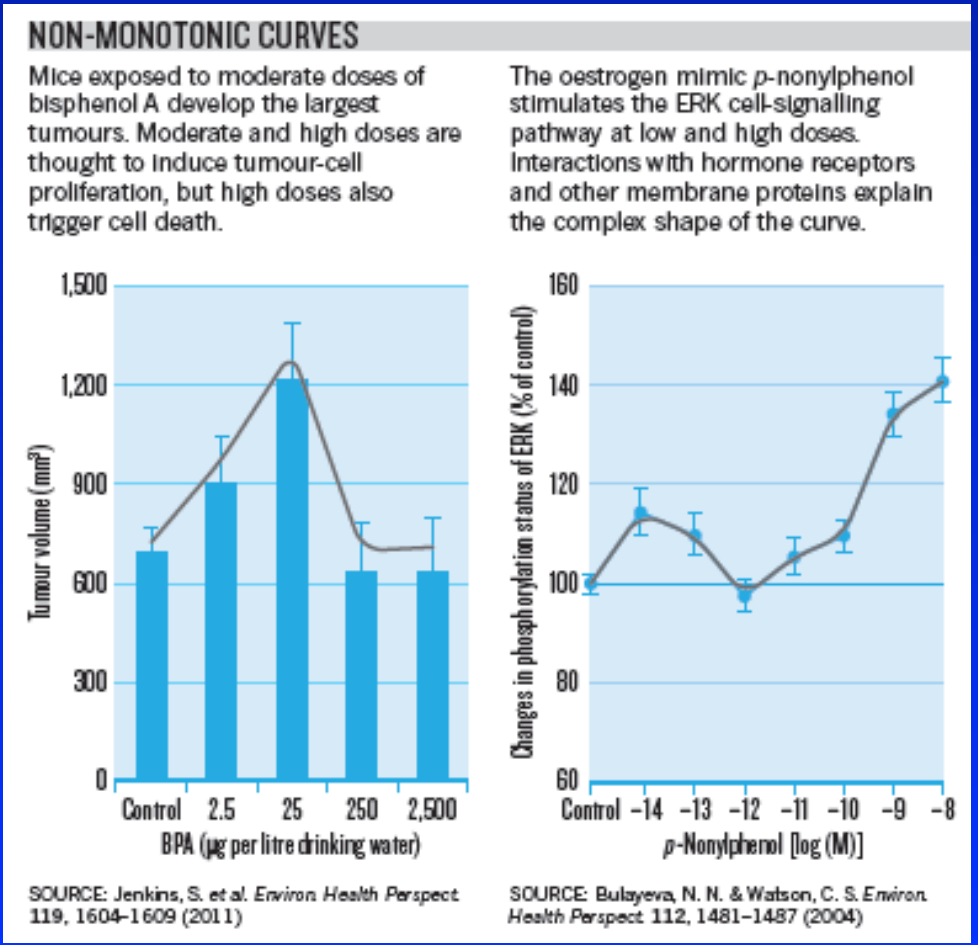
Epidemiological data typically focus on high, even highest, exposure: contrast the 'Occupational' papers with 'Environmental' papers in Occup Environ Med
Relative risks of 1.2 or less are typical

- 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

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
Nature
490:462-5, 2012

Evidence-based Public Health Policy in Relation to
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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.

Stayner L. et al. *Ann NY Acad Sci* **895**:212, 1999

On mechanistic grounds, no preventable exposure to a genotoxic agent can be specified

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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

Sometimes, novel circumstances provide insight

Cancer risk following occupational exposure to pesticides h

Carcinogenic risk from pesticide

Carcinogenic risk from pesticide

FULL PAPER

BJC

British Journal of Cancer (2014) 110, 2321–2326 | doi: 10.1038/bjc.2014.148

Keywords: organic food; cancer; cohort; women

Organic food consumption and the incidence of cancer in a large prospective study of women in the United Kingdom

K E Bradbury*[,1], A Balkwill[1], E A Spencer[2], A W Roddam[3], G K Reeves[1], J Green[1], T J Key[1], V Beral[1], K Pirie[1] and The Million Women Study Collaborators[4]

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.

Experimental/mechanistic data driving epidemiological studies

Disaggregating Data on Asian American and Pacific Islander Women to Provide New Insights on Potential Exposures to Hazardous Air Pollutants in California

Thu Quach[1,2], Ruiling Liu[1], David O. Nelson[1,2], Susan Hurley[1], Julie Von Behren[1], Andrew Hertz[1], and Peggy Reynolds[1,2]

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.

Cancer Epid Biomark Prev **23**: 2218-28, 2014

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.**