Introduction to the Public Meeting to Seek Comments on the Current NIOSH Policy to Classify Carcinogens and Establish Recommended Exposures Limits

December 12, 2011

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The findings and conclusions in this report are those of the author and do not necessarily represent the views of the National Institute for Occupational Safety and Health.

Purpose of the Policy Review

In recent years, there have been concerns by NIOSH and stakeholders about limitations in NIOSH's cancer policy:

- Use of the term "potential occupational carcinogen"
  - Conveys uncertainty not warranted with many known carcinogens (e.g. asbestos, benzene, and cadmium)
  - How to incorporate levels of uncertainty in the policy
- Technical questions on developing recommended exposure limits (RELs)
  - Levels of residual risk
  - Meaning of the phrase "to the extent feasible"
  - Utility of the "action level" concept in RELs
- How to incorporate advances in cancer science

Agenda for the Meeting

- Overview
- Public input to each of five questions posted in the Federal Register on August 23, 2011
- General comments

NIOSH Panel

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Overview

Background

- In 21st century, occupational cancer still a significant cause of morbidity, mortality, and societal burden
- Millions of workers currently exposed to OSHA regulated carcinogens
- Tens of millions with past exposure
- It is estimated that annually at least 4% (24,000) of the approximately 600,000 deaths from cancer result from workplace exposure

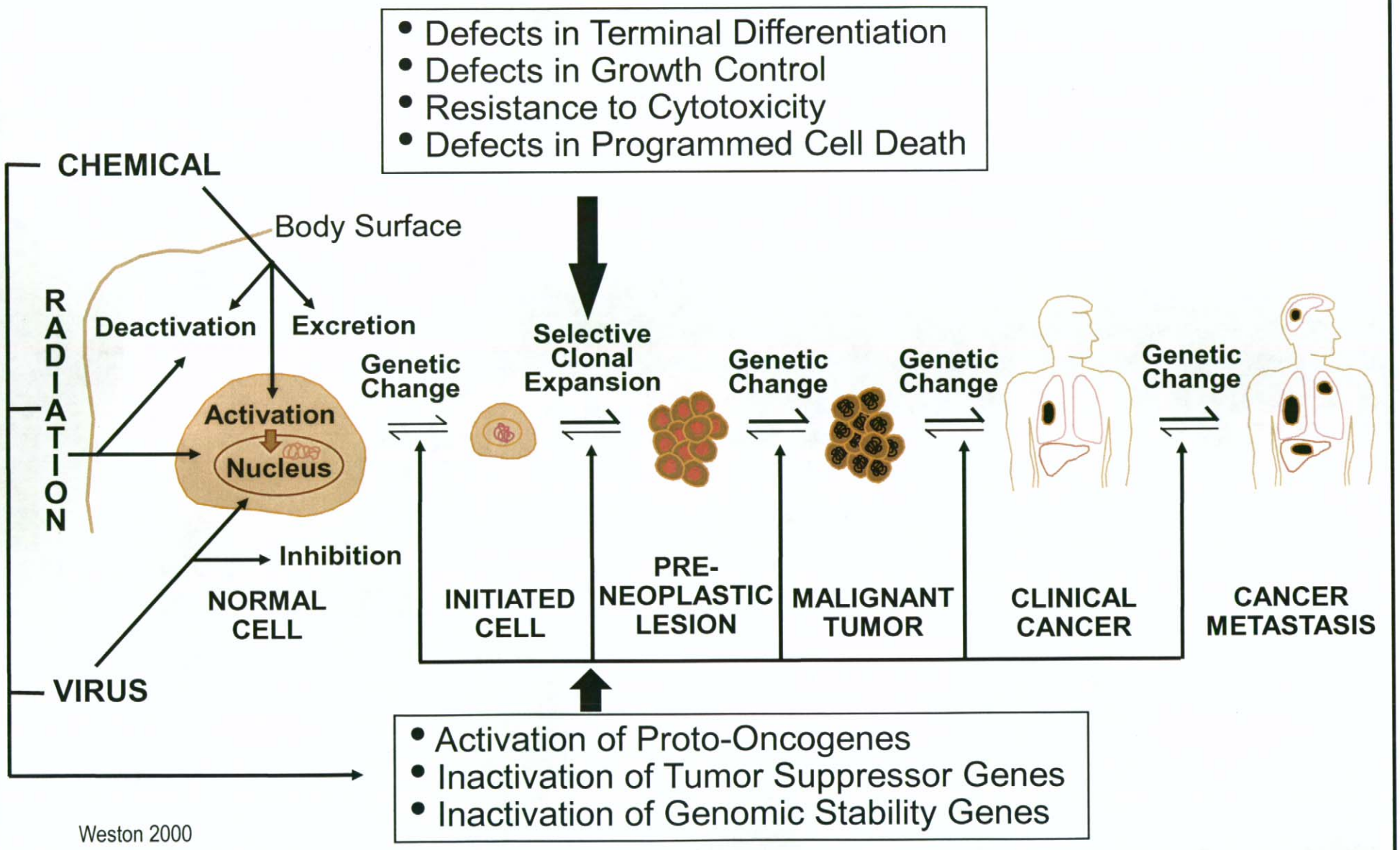
Overview (cont'd)

- Generally, these numbers are underestimated
  - Conducted only on a few carcinogens and cancer sites
  - Role of occupational carcinogenic exposures to women or sub-populations at high risk not widely studied
  - Other estimates of attributable risk range as high as 10%
- If 4% for deaths is the same as morbidity, an estimated 48,000 new cancer cases attributed to occupational exposures would occur per year
- This contribution of occupational exposures to cancer burden only exceeded by cigarette smoking and diet

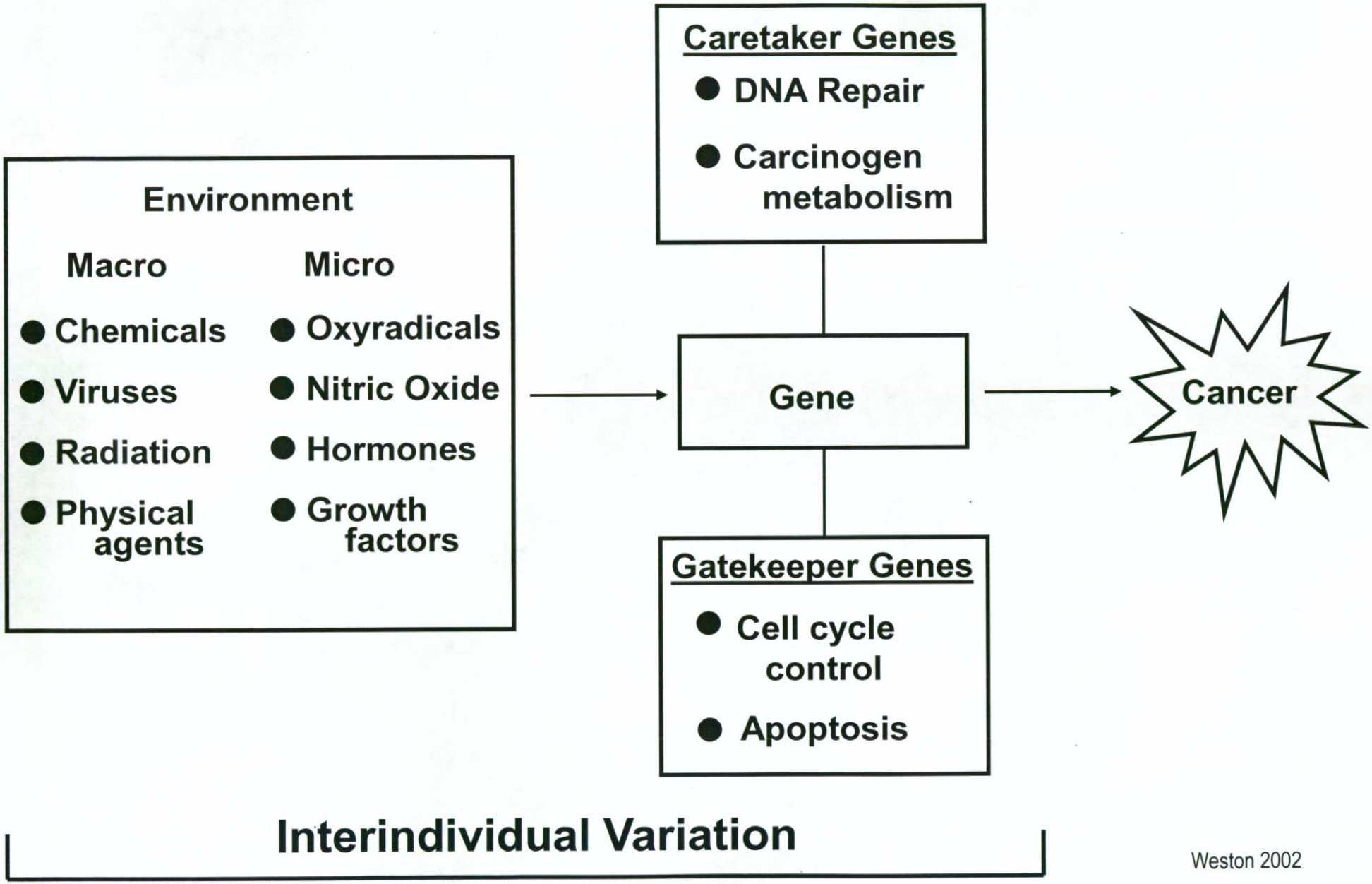
Chemical Carcinogenesis

- Suggested by Pott 200 years ago – chimney sweeps
- First experimental studies in animal about 100 years ago
- 1970-1990s large number of chemicals tested for carcinogen potency
- 271/451 synthetic chemicals tested positive for cancer in rats and mice (Ames and Gold, Mutat Res 447:3-13, 2000)
- Of the approximately 200 agents known to cause cancer in humans, nearly all have been shown to also cause cancer in rats and mice (atsdr.cdc.gov/risk/cancer/cancer-laboratory.html)
- Cancer is a multi-stage process
- Genotoxic and nongenotoxic modes of action

MULTISTEP CARCINOGENESIS



Weston 2000


Caretaker Genes
DNA Repair
Carcinogen metabolism
Environment
Macro
Micro
Chemicals
Viruses
Radiation
Physical agents
Oxyradicals
Nitric Oxide
Hormones
Growth factors
Gene
Cancer
Gatekeeper Genes
Cell cycle control
Apoptosis
Interindividual Variation

Weston 2002

Table 12.1. Selected Examples of Human Chemical Carcinogenesis

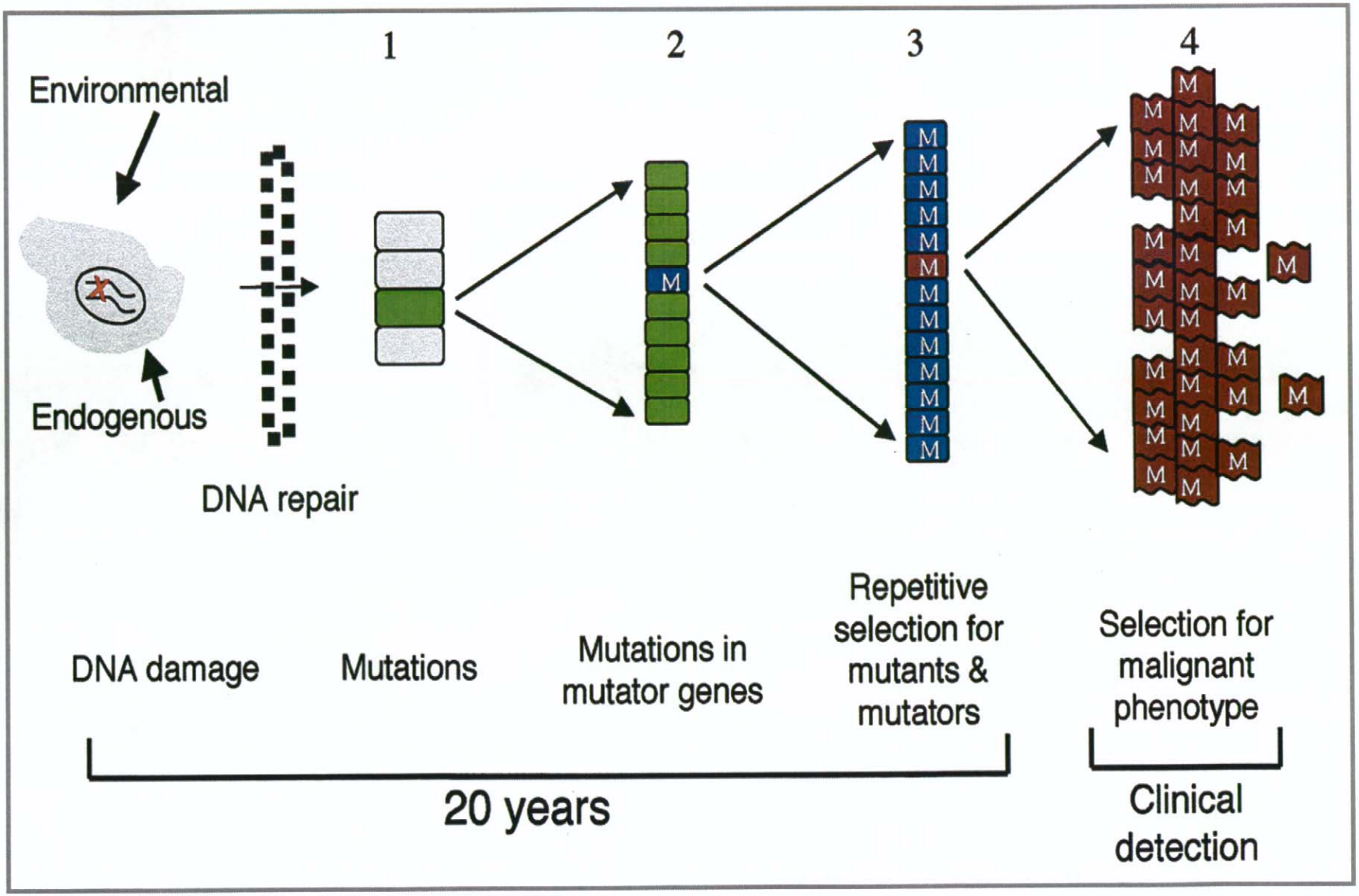
Organ System (specific pathology)	Chemical Carcinogen	Cocarcinogen
Lung	Metals: As, Be, Cd, Cr, Ni	
	BCME*	
(Small cell and squamous cell)	Tobacco smoke	Asbestos
	Diesel exhaust	
Pleural mesothelium	Asbestos	
Oral cavity	Smokeless tobacco	
	Betel quid	Slaked lime [$Ca(OH)_2$]
Esophagus	Tobacco smoke	Alcohol
Nasal sinuses	Snuff	Powdered glass
	Isopropylalcohol	
Skin	Cutting oil	
(Scrotum)	Coal soot†	
Liver	Aflatoxin B_1	HBV*
(Angiosarcoma)	Vinyl chloride	Alcohol
Bladder	Aromatic amines (e.g., 4-ABP* and benzidine)	
	Aromatic amines from tobacco smoke‡	
ALL*	Benzene	
Lymphatic and hemapoietic malignancies	Ethylene oxide	

*BCME = *Bis* chloromethyl ether; HBV = hepatitis B virus; 4-ABP = 4-aminobiphenyl; ALL = acute lymphoblatic leukemia.

† Early report of occupational chemical carcinogenesis from 225 years ago.[1]

‡ Strong circumstantial evidence.[2] A comprehensive treatise on the evaluation of the carcinogenic risk of chemicals to humans can be found in the ongoing IARC monograph program initiated in 1971.[3]

Weston & Harris 2000


1
2
3
4
Environmental
Endogenous
DNA repair
M
DNA damage
Mutations
Mutations in mutator genes
Repetitive selection for mutants & mutators
Selection for malignant phenotype
20 years
Clinical detection

Weston 2002

NIOSH is mandated to:

" … develop criteria dealing with toxic materials and harmful physical agents and substances which will describe exposure levels that are safe for various periods of employment, including but not limited to exposure levels at which no employee will suffer impaired health or functional capacities or diminished life expectancy as a result of his work experience."

OSH Act, Section 20 (a)(3)

Overview (cont'd)

- NIOSH assessment of workplace carcinogens and setting of recommended exposure limits (RELs) have been important tools
- To date, NIOSH pocket guide lists 135 substances as carcinogens
- And NIOSH has developed RELs for most of these

Selected Dates in Occupational Cancer Policy History

1932 Occupational cancer compensation in Ontario (coal tar exposure)

1942 German law to compensate for occupational lung cancer

1971 OSHA temporary standard for asbestos

1974 OSHA standards for 14 carcinogens and vinyl chloride

1976 Guidelines for a NIOSH Cancer Policy

1977 OSHA proposal for "identifying, classifying, and regulation of potential occupational carcinogens"

1980 CFR 1900.112 enacted

1985 NTP and IARC Cancer Classification Systems

1995 Revised NIOSH Cancer Policy

2010 Formation of NIOSH Carcinogen Policy Review Committee

1976

"Guidelines for a NIOSH policy on occupational carcinogenesis."
–Fairchild [NY Acad Sci 271:200–7]

- Concern about increase in unregulated number and quantities of synthetic chemicals
- Concern about human impact in the form of chronic occupational disease particularly, cancer

1976 Cancer Policy (cont'd)

- In the absence of solid evidence to the contrary, there is a possibility of carcinogenic effect in humans for any chemical conclusively shown to be carcinogenic in one animal species
- Since benign neoplasms can become frankly malignant—no distinction will be made
- Lowest feasible or no detectable levels for proven carcinogenic substances

1978

- NIOSH testified on the OSHA Notice of Proposed Rulemaking on the Identification, Classification, and Regulation of Toxic Substances Posing a Potential Occupational Carcinogenic Risk (i.e. the OSHA Cancer policy
- NIOSH testified to its general agreement with the definition of "potential occupational carcinogen" as stated in the OSHA Cancer Policy
- NIOSH used the term "potential occupational carcinogen" in the NIOSH Criteria for a Recommended Standard: Occupational Exposure to Glycidyl Ethers and other NIOSH documents
- This classification policy has continued to be followed to date

"Potential Occupational Carcinogen"

- Addressed in 29CFR 1990.112
- Any substance or combination
- Increased incidence
- Benign and/or malignant neoplasm
- In humans or one or more animal species
- Any oral, respiratory, or dermal exposure
- Results in tumor other than at site of administration
- Any substance metabolized into a chemical defined as a potential occupational carcinogen

NIOSH Recommended Exposure Limit (REL) Policy for Potential Occupational Carcinogens—1995

- Because of advances in science, in approaches to risk assessment, and in risk management, NIOSH adopted a more inclusive policy
  - NIOSH RELs will be based on human or animal health effects data
  - Measured by analytical techniques
  - Whether RELs can be feasibly achieved by engineering controls
  - NIOSH will project not only a no-effect exposure level … but also exposure levels where there may be residual risks

Advances in Cancer Science

- New understanding of mechanisms of chemical carcinogenesis
- Ability to screen large numbers of chemicals with high throughput technologies
- Ability to identify subgroups at high risk of cancer based on genetic or epigenetic data
- Ability to develop hazard and control bands for groups of chemicals based on available health effects data and exposure characteristics

Public Input

- NIOSH is seeking public input on the revision of its policy on cancer classification and development of recommended exposure limits for substances that may cause cancer in workers
- This public meeting and the electronic docket (cdc.gov/niosh/docket) are two means for obtaining that input. Ultimately, for most effective transfer of information from the public to NIOSH, the electronic docket is the best channel for communication. All electronic comments should be formatted for Microsoft Word (reference NIOSH 240).
- Docket will close for comments December 30, 2011.

Time Frame for Policy Review and Revision

Committee work	December 2010–present
Public meeting	Autumn 2011
Draft for public review	Spring 2012
Publication	Autumn 2012

Five Questions for the Public Meeting

1. Should there explicitly be a carcinogen policy as opposed to a broader policy on toxicant identification and classification (e.g. carcinogens, reproductive hazards, neurotoxic agents)?

2. What evidence should form the basis for determining that substances are carcinogens? How should these criteria correspond to nomenclature and categorizations (e.g., known, reasonably anticipated, etc.)?

3. Should 1 in 1000 working lifetime risk (for persons occupationally exposed) be the target level for a recommended exposure limit (REL) for carcinogens or should lower targets be considered?

4. In establishing NIOSH RELs, how should the phrase "to the extent feasible" (defined in the 1995 NIOSH Recommended Exposure Limit Policy) be interpreted and applied?

5. In the absence of data, what uncertainties or assumptions are appropriate for use in the development of RELs? What is the utility of a standard "action level" (i.e., an exposure limit set below the REL typically used to trigger risk management actions) and how should it be set? How should NIOSH address worker exposure to complex mixtures?