# CANCER ET TRAVAIL

Cancer@Work

## Les Monographies du CIRC/OMS.

## Procédure d'évaluation de la cancérogénicité d'une substance.

Kurt Straif, MD MPH PhD

SYMPOSIUM

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((S)).((M)).((T))
Val de Loire

# Identifying occupational causes of cancer

- Bernadino Ramazzini *De morbis artificium*,1700
  Increased risk of breast cancer among nuns
- Percival Pott, 1775
  Scrotal cancer in chimney sweeps
- Haerting & Hesse, 1879
  Schneeberg lung cancer
- Rehn, 1895


Blasengeschwülste bei Fuchsin-Arbeitern

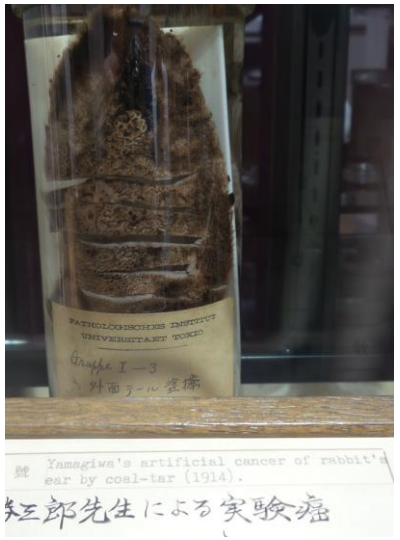
Von

Dr. L. Rehn,

Three bladder tumours in 45 workers involved in the manufacture of fuchsin

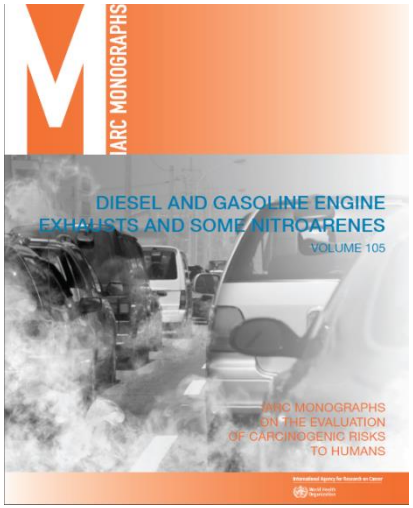
# PAHs, the Histories of Occupational Cancer and Carcinogenesis

| | |
|---|---|
| 1775 Percival Pott | Scrotal cancer in chimney sweeps |
| 1912 Yamagiwa & Itchikawa | Skin Cancer induced by application of coal tar |
| 1925 1. Ordinance of Occupational Diseases, Germany | Skin cancer related to soot paraffin, tar, anthracene & pitch |
| 1933 Cook | Identification of benzo[a]pyrene in coal tar |
| 1947 Kennaway & Kennaway | Lung cancer in coal gas & tar workers |
| 1964 Berenblum | 2-Stage theory of carcinogenesis (benzo[a]pyrene & croton oil) |



# IARC: Cancer Research for Cancer Prevention

- Rising burden of cancer: estimates by 2040 29.5 million new cases/a compared to 18.1 million in 2018
- Majority of the increase in cancer burden expected in low- and middle-income countries (LMIC)

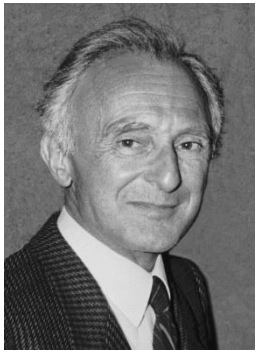



- No country can treat its way out of the cancer problem
- Prevention probably the single most effective response to these challenges,
- The first step in cancer prevention is to identify the causes of human cancer (Monographs)

# "The encyclopaedia of carcinogens"

The *IARC Monographs* evaluate

- Chemicals
- Complex mixtures
- Occupational exposures
- Physical and biological agents
- Personal habits



Lorenzo Tomatis
1929-2007

More than 1000 agents have been evaluated

- 120 are *carcinogenic to humans* (Group 1)
- 83 are *probably carcinogenic to humans* (Group 2A)
- 314 are *possibly carcinogenic to humans* (Group 2B)

National and international health agencies use the *Monographs*

- As a source of scientific information on known or suspected carcinogens
- As scientific support for their actions to prevent exposure to known or suspected carcinogens

# How Are Agents Selected?

- Agents with evidence of human exposure and suspicion of carcinogenicity are evaluated
- Public call for nominations
  http://monographs.iarc.fr/ENG/Meetings/index.php
  - Scientists, governments, NGOs, industry and individuals can nominate agents
- International expert Advisory Group on Priorities (ongoing)
  - Scientists and representatives of governments and health agencies
  - Advises IARC on priority of nominated agents

**Call for nominations of agents for review in future *IARC Monographs***

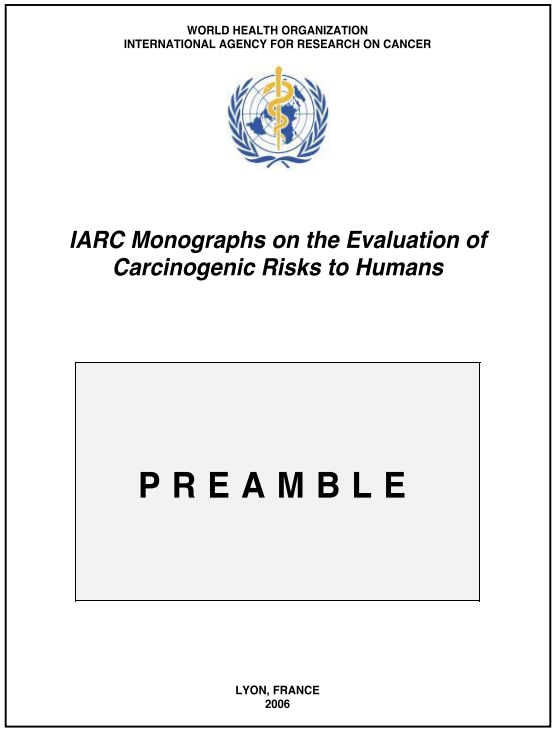
IARC encourages the general public, the scientific community, national health agencies, and other organizations, to nominate agents for review in future *IARC Monographs*. For details, please see:

Information on nominations

Nomination form

WHO Declaration of Interests (to be submitted with each nomination)

# How are Evaluations Conducted?


- Published guidelines for participant selection, conflict of interest & stakeholder involvement
- Criteria for data eligibility
- Guidelines for review of human, animal and mechanistic evidence
- Decision process for overall evaluations

http://monographs.iarc.fr/ENG/Preamble/index.php

# Conflicts of interest: management and disclosure

- Independent evaluations by the world's leading experts world's leading experts free from conflicts of interests
- Only these experts draft text and perform evaluations, BUT other scientists can participate in defined roles:
  - Invited Specialists
  - Representatives of national and international health agencies
  - Observers
  - IARC Secretariat
- Real or apparent conflicts of interest publicly announced:
  - In advance (2 months before the in-person meeting)
  - In the published *The Lancet Oncology* summaries
  - In the published volume of *Monographs*

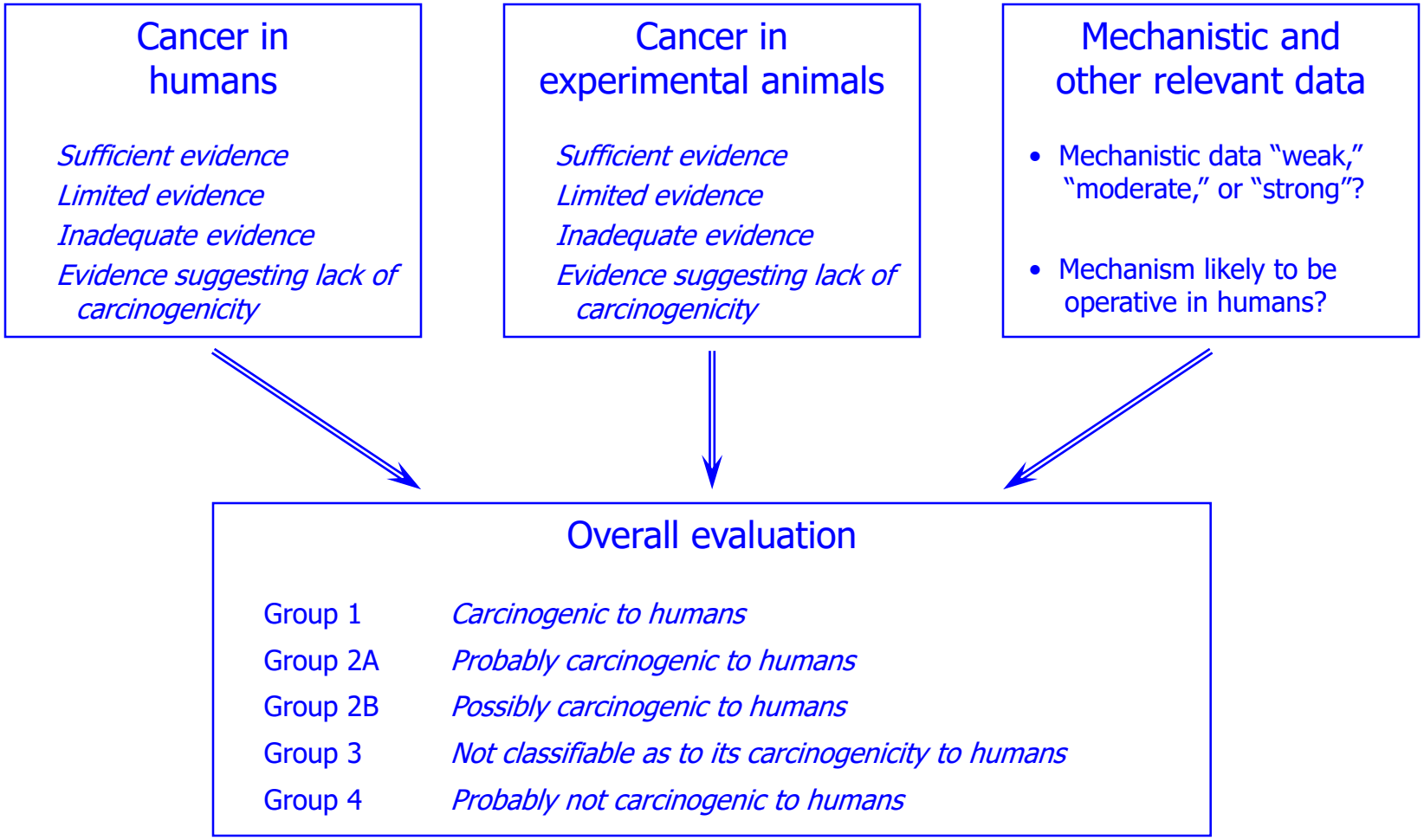
# How is transparency assured before, during and after the evaluation?

- Public announcements:
  - Methods (published online, in advance)
  - Topic and timing (1 year in advance)
  - Working Group and all other participants (2 months in advance)
  - Results (*The Lancet Oncology*, full *Monograph*)
- Public process open to scientific observers
- Fully referenced *Monograph* is published online for free download
  - Cites only peer-reviewed and published, publicly available data (available for independent scientific scrutiny)
  - All studies (positive and negative) are described
  - Rationale for conclusions is given

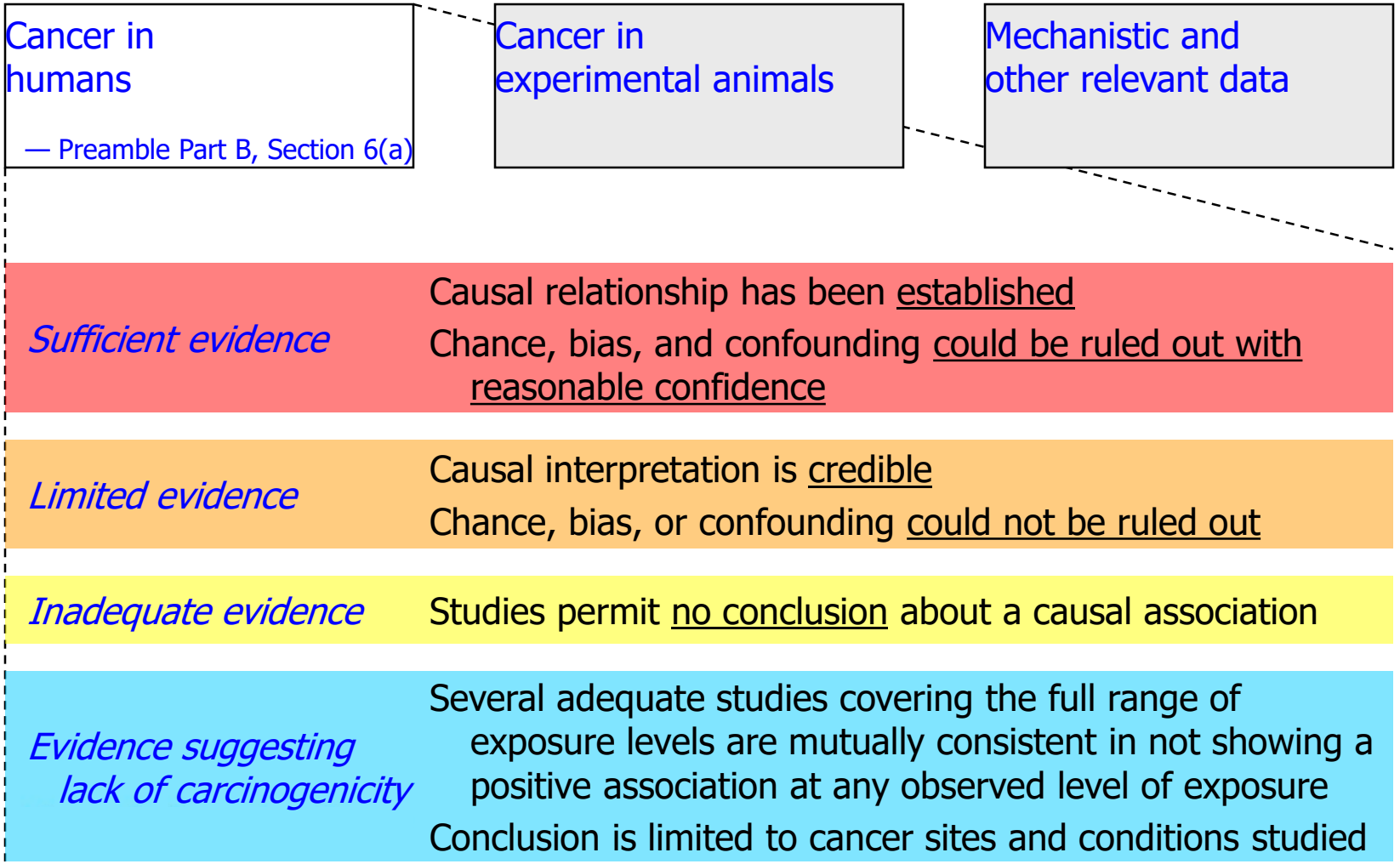
# Systematic scientific evaluation

- Systematic gathering and evaluation of original research that is available in the public domain for independent scientific review
  - Published methods based on international guidance
  - Conclusions described using internationally defined terms
  - Uniform, hierarchic evaluation structure
    - Same criteria applied in all evaluations
    - Same criteria applied to all studies
    - Working Group comments [in square brackets]
- Fully referenced *Monograph* is published online for free download
  - All studies (positive and negative) are described
  - Rationale for conclusions is given

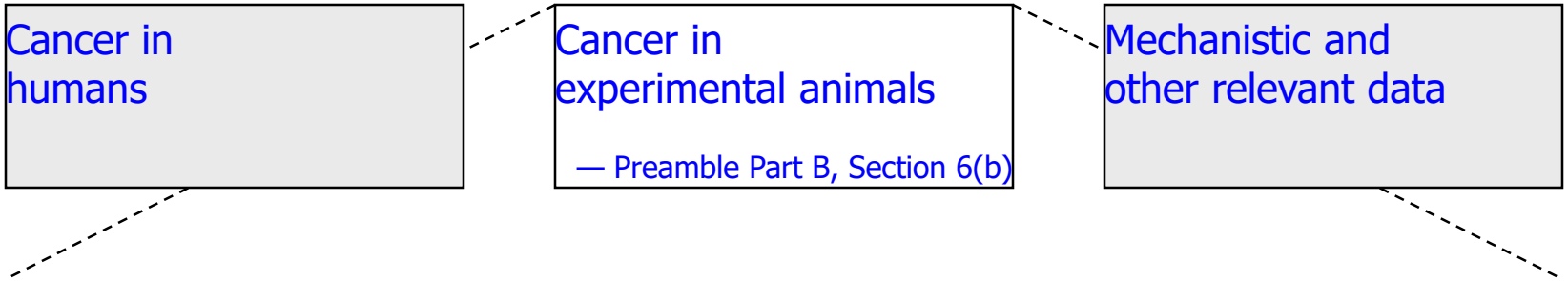
# The IARC Monographs Evaluations



# Evaluating human data (Subgroup 2)



# Evaluating experimental animal data (Subgroup 3)




| | |
|---|---|
| *Sufficient evidence* | Causal relationship has been <u>established</u> through either:<br>- <u>Multiple positive results</u> (2 species, studies, sexes of GLP)<br>- <u>Single unusual result</u> (incidence, site/type, age, multi-site) |
| *Limited evidence* | Data <u>suggest</u> a carcinogenic effect but: (*e.g.*) single study, benign tumours only, promoting activity only |
| *Inadequate evidence* | Studies permit <u>no conclusion</u> about a carcinogenic effect |
| *Evidence suggesting lack of carcinogenicity* | Adequate studies in at least two species show that the agent is not carcinogenic<br>Conclusion is limited to the species, tumour sites, age at exposure, and conditions and levels of exposure studied |

# IARC Monographs, Volume 100
# *A Review of Human Carcinogens*

- Scope of volume 100
  - Update the critical review for each carcinogen in Group 1
  - Identify tumour sites and plausible mechanisms
  - Compile information for subsequent scientific publications
- The volume was developed over the course of 6 meetings
  A. Pharmaceuticals (23 agents, Oct 2008)
  B. Biological agents (11 agents, Feb 2009)
  C. Metals, particles and fibres (14 agents, Mar 2009)
  D. Radiation (14 agents, June 2009)
  E. Lifestyle factors (11 agents, Sept 2009)
  F. Chemicals and related occupations (34 agents, Oct 2009)


## Preventable Exposures Associated With Human Cancers

Vincent James Cogliano, Robert Baan, Kurt Straif, Yann Grosse, Béatrice Lauby-Secretan, Fatiha El Ghissassi, Véronique Bouvard, Lamia Benbrahim-Tallaa, Neela Guha, Crystal Freeman, Laurent Galichet, Christopher P. Wild

# Known and suspected causes of cancer

**List of Classifications by cancer sites with *sufficient* or *limited evidence* in humans, Volumes 1 to 114***

| Cancer site | Carcinogenic agents with *sufficient evidence* in humans | Agents with *limited evidence* in humans |
|---|---|---|
| Lung | Acheson process, occupational exposures associated with<br>Aluminum production<br>Arsenic and inorganic arsenic compounds<br>Asbestos (all forms)<br>Beryllium and beryllium compounds<br>Bis(chloromethyl)ether; chloromethyl methyl ether (technical grade)<br>Cadmium and cadmium compounds<br>Chromium(VI) compounds<br>Coal, indoor emissions from household combustion<br>Coal gasification<br>Coal-tar pitch<br>Coke production | Acid mists, strong inorganic<br>Art glass, glass containers and pressed ware (manufacture of)<br>Biomass fuel (primarily wood), indoor emissions from household combustion of<br>Bitumens, occupational exposure to oxidized bitumens and their emissions during roofing<br>Bitumens, occupational exposure to hard bitumens and their emissions during mastic asphalt work<br>Carbon electrode manufacture<br>*alpha*-Chlorinated toluenes and |

# 10 Key Characteristics of Human Carcinogens

| Key characteristic: |
| --- |
| 1. Is electrophilic or can be metabolically activated |
| 2. Is genotoxic |
| 3. Alters DNA repair or causes genomic instability |
| 4. Induces epigenetic alterations |
| 5. Induces oxidative stress |
| 6. Induces chronic inflammation |
| 7. Is immunosuppressive |
| 8. Modulates receptor-mediated effects |
| 9. Causes immortalization |
| 10. Alters cell proliferation, cell death, or nutrient supply |

- Established human carcinogens commonly exhibit one or more characteristics
- Data on these characteristics can provide evidence of carcinogenicity
- They can also help in interpreting the relevance and importance of findings of cancer in animals and in humans.

Smith MT, et al.. *Env Health Persp.*, *124(6):713-21*

# High-Throughput Screening Data

**ToxCast iCSS dashboard**
(http://actor.epa.gov/dashboard/)

- 821 assays
- 1860 chemicals

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| 10 Key Characeristics of Human Carcinogens: |
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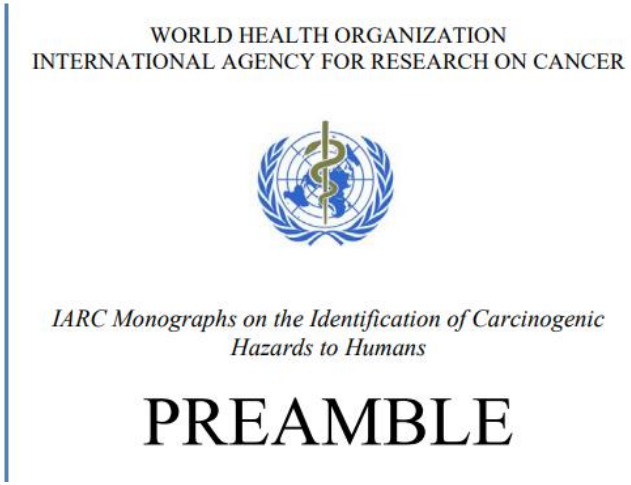
**At most, 274 ToxCast/Tox21 assays could be mapped to a "key characteristic":**

| Key characteristic | 1. Is electrophilic or can be metabolically activated | 4. Induces epigenetic alterations | 5. Induces oxidative stress | 6. Induces chronic inflammation | 8. Modulates receptor-mediated effects | 10. Alters cell proliferation, cell death and nutrient supply |
|---|---|---|---|---|---|---|
| Assay Endpoints | 31 assays:<br>•CYP inhibition (29)<br>•Aromatase inhib. (2) | 11 assays:<br>•DNA binding (4)<br>•Transformation (7) | 18 assays:<br>•Metalloproteinase (5)<br>•Oxidative stress (7)<br>•Oxidative stress marker (6) | 45 assays:<br>•Cell adhesion (14)<br>•Cytokines (29)<br>•NFkB (2) | 81 assays:<br>•AhR (2)<br>•AR (11)<br>•ER (18)<br>•FXR (7)<br>• Others (18)<br>• PPAR (12)<br>• PXR_VDR (7)<br>• RAR (6) | 68 assays:<br>• Cell cycle (16)<br>• Cytotoxicity (41)<br>• Mitochondrial toxicity (7)<br>• Proliferation (4) |

# *Monographs* Preamble Update, 2019


Key features:

- Strong procedures for conflict of interest management, public engagement and stakeholder involvement
- Robust systematic review methodology
- New section on critical review of exposure methods in epidemiologic studies of cancer and mechanisms
- Refined evaluation criteria for mechanistic evidence
- Rigorous and transparent integration of human cancer, animal bioassay and mechanistic evidence streams

Highlights:

- Enhanced transparency
- Increased rigor
- Modernized methods

Preamble to the IARC Monographs (amended January 2019):
https://monographs.iarc.fr/wp-content/uploads/2019/01/Preamble-2019.pdf

# How Are Overall Evaluations Determined?

| Evidence of Cancer in Humans | Evidence of Cancer in Experimental Animals | Mechanistic Evidence | Evaluation |
|---|---|---|---|
| Sufficient | | | Carcinogenic (Group 1) |
| | Sufficient | Strong (exposed humans) | |
| Limited | Sufficient | | Probably carcinogenic (Group 2A) |
| Limited | | Strong | |
| | Sufficient | Strong (human cells or tissues) | |
| | | Strong (mechanistic class) | |
| Limited | | | Possibly carcinogenic (Group 2B) |
| | Sufficient | | |
| | | Strong (experimental systems) | |
| | Sufficient | Strong (does not operate in humans) | Not classifiable (Group 3) |
| All other situations not listed above | | | |

# Vol. 105: Diesel engine exhaust: exposure

- Diesel engines are used for on-road and non-road transport (eg, trains, ships) and (heavy) equipment in various industrial sectors (eg, mining, construction), and in electricity generators, particularly in developing countries.
- Emissions from these engines are complex, with varying composition.
- The gas phase consists of carbon monoxide, nitrogen oxides, and volatile organic compounds such as benzene and formaldehyde.
- Particles consist of elemental and organic carbon, ash, sulfate, and metals.
- Polycyclic aromatic hydrocarbons and nitroarenes are distributed over the gas and the particle phase.

# Diesel engine exhaust and lung cancer

- In a large US miners study diesel engine exhaust was quantified via estimated elemental carbon as a proxy of exposure
- Cohort and nested case–control analyses adjusted for tobacco smoking showed positive trends in lung cancer risk with increasing exposure to diesel exhaust, with 2–3-fold increased risk in the highest categories of cumulative or average exposure. (Attfield et al 2012, Silverman et al 2012).
- In US railroad workers exposed to diesel exhaust a 40% increased risk for lung cancer was observed.
- A large cohort study in the US trucking industry reported a 15–40% increased lung cancer risk
- Findings of above cohort studies were supported by those in other occupational groups and by case–control studies including various occupations involving exposure to diesel-engine exhaust.

# SYNERGY: Diesel engine exhaust

## Cumulative DME exposure and lung cancer risk

| **Cumulative DME exposure** $\sum(\text{level}^2 * \text{duration})$ | **Cases** | **Controls** | **OR1** | **95% CI** | **OR2** | **95% CI** |
|---|---|---|---|---|---|---|
| Never | 7676 | 10320 | 1.00 | Reference cat. | 1.00 | Reference cat. |
| <6 | 1270 | 1514 | 0.92 | 0.78 – 1.08 | 0.88 | 0.74 – 1.03 |
| 6-17.33 | 1325 | 1499 | 1.00 | 0.88 – 1.12 | 0.92 | 0.82 – 1.04 |
| 17.34-34.5 | 1441 | 1502 | 0.99 | 0.85 – 1.15 | 0.91 | 0.79 – 1.05 |
| >34.5 | 1594 | 1450 | 1.27 | 1.14 – 1.41 | 1.14 | 1.03 – 1.26 |
| *Test for trend, p-value* | | | *0.001* | | *0.070* | |
| *Trend among exposed, p-value* | | | *0.000* | | *0.002* | |
| *>34.5, never smokers* | *47* | *314* | *1,27* | *0.90 - 1.79* | *1.14* | *0.81 - 1.62* |
| *>34.5, never List A job* | *1449* | *1337* | *1.35* | *1.23 - 1.48* | *1.21* | *1.10 - 1.33* |
| *>34.5, women* | *35* | *45* | *1.61* | *0.98 - 2.65* | *1.41* | *0.86 - 2.32* |

Random effect model based on study specific results OR1 adjusted for age, sex, smoking pack years, time since quitting smoking, ever employed in "List A" job OR2 in addition adjusted for education

# Diesel engine exhaust, cancer bioassays Evaluation

- The Working Group concluded that there was "sufficient evidence" in experimental animals for the carcinogenicity of whole diesel-engine exhaust, of diesel-engine exhaust particles and of extracts of diesel-engine exhaust particles.

# DEE, mechanisms of carcinogenicity

- DEE, DEE particles, DEE condensates, and organic solvent extracts of DEE particles induced in vitro and in vivo, various forms of DNA damage
- Increased expression of genes involved in xenobiotic metabolism, oxidative stress, inflammation, antioxidant response, apoptosis, and cell cycle regulation in mammalian cells was observed.
- Positive genotoxicity biomarkers of exposure and effect were also observed in humans exposed to diesel engine exhaust.

The Working Group concluded that there is "strong evidence" for the ability of whole diesel-engine exhaust to induce cancer in humans through genotoxicity.

# Diesel engine exhaust
# Overall Evaluation

- There is sufficient evidence for the carcinogenicity in humans of diesel engine exhaust. Diesel engine exhaust causes lung cancer. Also, a positive association between diesel engine exhaust and bladder cancer has been observed.
- There is sufficient evidence for the carcinogenicity in experimental animals of whole diesel engine exhaust.

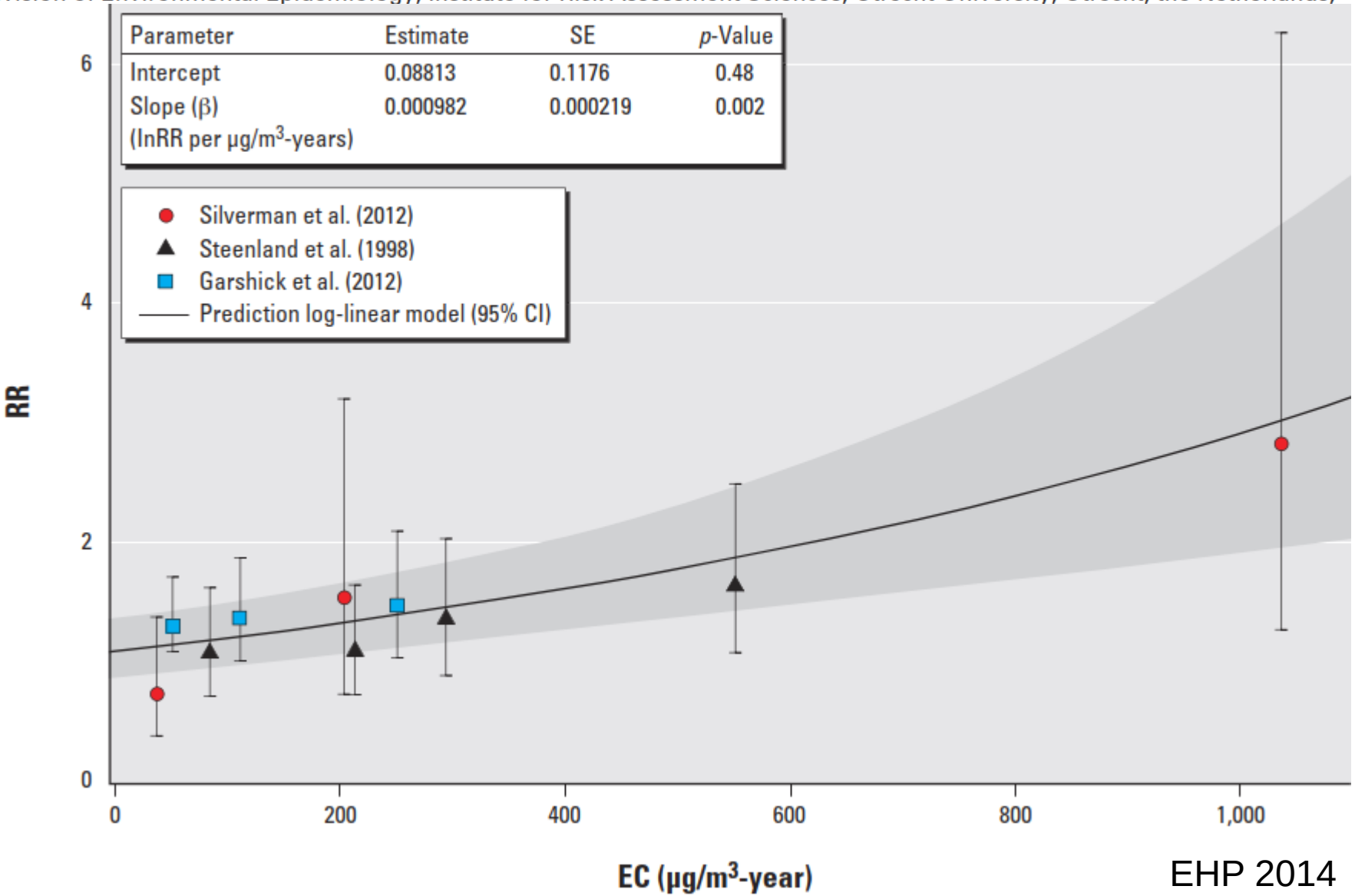
Overall evaluation

- Diesel engine exhaust is carcinogenic to humans (Group 1).

# Exposure-Response Estimates for Diesel Engine Exhaust and Lung Cancer Mortality Based on Data from Three Occupational Cohorts

*Roel Vermeulen,[1] Debra T. Silverman,[2] Eric Garshick,[3] Jelle Vlaanderen,[1,4] Lützen Portengen,[1] and Kyle Steenland[5]*

[1]Division of Environmental Epidemiology, Institute for Risk Assessment Sciences, Utrecht University, Utrecht, the Netherlands;




EHP 2014

# IARC Monographs Vol. 111, CNT

- MWCNT-7 caused peritoneal mesotheliomas in rats & mice
- 2 other types of MWCNTs with physical dimensions similar to those of MWCNT-7 caused mesotheliomas in male and female rats in one intraperitoneal study, (Nagai et al., 2011).
- Two studies with SWCNTs in rats were inconclusive.

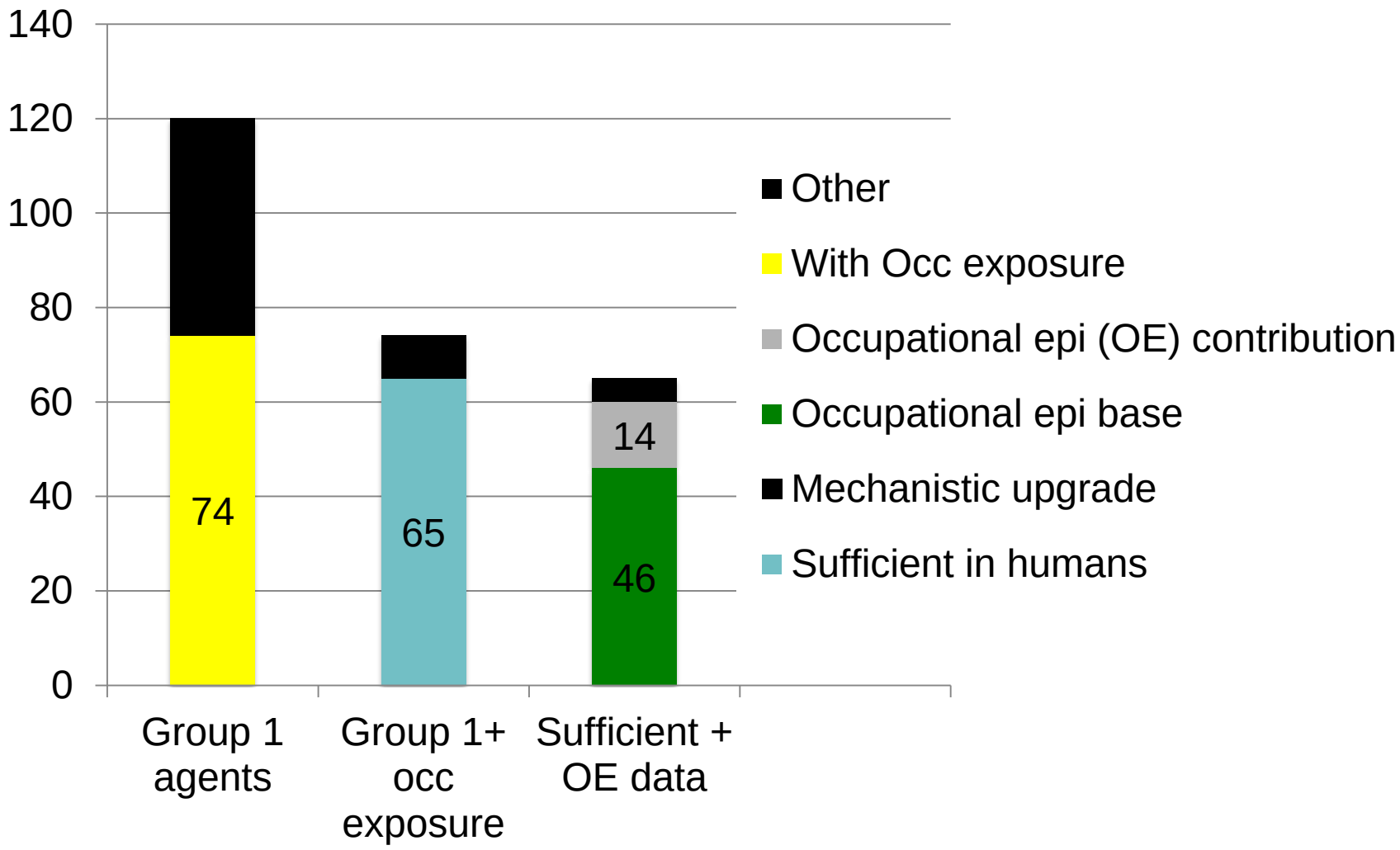
## Carcinogenicity in experimental animals

- *sufficient evidence* for MWCNT-7,
- *limited evidence* for the two other types of MWCNTs with dimensions similar to MWCNT-7,
- *inadequate evidence* for SWCNTs.

## Overall evaluation

- MWCNT-7 is *possibly carcinogenic to humans* (Group 2B);
- SWCNTs and MWCNTs excluding MWCNT-7 are *not classifiable as to their carcinogenicity to humans* (Group 3)

# Identifying occupational carcinogens



# Future Priorities for the IARC Monographs

| | Rationale |
|---|---|
| **Agents not previously evaluated by IARC Monographs** | |
| Haloacetic acids (and other disinfection byproducts) | Relevant human cancer, bioassay, and mechanistic evidence |
| Metalworking fluids | Relevant human cancer and bioassay evidence |
| Cannabis smoking, fertility treatment, glucocorticoids, *Salmonella typhi*, sedentary behaviour*, tetracyclines and other photosensitising drugs | Relevant human cancer and mechanistic evidence |
| Cupferron, gasoline oxygenated additives, gentian violet, glycidamide, malachite green and leucomalachite green, oxymetholone, pentabromodiphenyl ethers, vinclozolin | Relevant bioassay and mechanistic evidence |
| Breast implants, dietary salt intake*, neonatal phototherapy*, poor oral hygiene* | Relevant human cancer evidence |
| Aspartame | Relevant bioassay evidence |
| Arecoline, carbon disulphide, electronic nicotine delivery systems and nicotine*, human cytomegalovirus, parabens | Relevant mechanistic evidence |
| **Agents previously evaluated by IARC Monographs†** | |
| Automotive gasoline (leaded and unleaded), carbaryl, malaria | New human cancer, bioassay, and mechanistic evidence to warrant re-evaluation of the classification |
| Acrylamide*, acrylonitrile, some anthracyclines, coal dust, combustion of biomass, domestic talc products, firefighting exposure, metallic nickel, some pyrethroids (ie, permethrin, cypermethrin, deltamethrin) | New human cancer and mechanistic evidence to warrant re-evaluation of the classification |
| Aniline, acrolein, methyl eugenol and isoeugenol*, multi-walled carbon nanotubes*, non-ionising radiation (radiofrequency)*, some perfluorinated compounds (eg, perfluorooctanoic acid) | New bioassay and mechanistic evidence to warrant re-evaluation of the classification |
| Ostrogen:oestradiol and oestrogen-progestogens‡, hydrochlorothiazide, Merkel cell polyomavirus, perchloroethylene, very hot foods and beverages | New human cancer evidence to warrant re-evaluation of the classification |
| 1,1,1-trichloroethane, weapons-grade alloy (tungsten, nickel, and cobalt) | New bioassay evidence to warrant re-evaluation of the classification |
| Acetaldehyde, bisphenol A*, cobalt and cobalt compounds, crotonaldehyde, cyclopeptide cyanotoxins, fumonisin $B_1$, inorganic lead compounds, isoprene, o-anisidine | New mechanistic evidence to warrant re-evaluation of the classification |

# Global, regional, and national comparative risk assessment of 84 behavioural, environmental and occupational, and metabolic risks or clusters of risks for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017

| | Risk factors and outcomes | 2007 deaths (thousands) | 2017 deaths (thousands) | Percentage change in deaths, 2007–17 | Percentage change in age-standardised death rate, 2007–17 | 2007 DALYs (thousands) | 2017 DALYs (thousands) | Percentage change in DALYs, 2007–17 | Percentage change in age-standardised DALY rate, 2007–17 |
|---|---|---|---|---|---|---|---|---|---|
| 3 | Occupational carcinogens: all causes | 271 (220 to 322) | 334 (271 to 397) | 23·3% (19·1 to 27·1)* | −7·4% (−10·5 to −4·5)* | 5600 (4560 to 6710) | 6750 (5490 to 8120) | 20·6% (16·5 to 24·5)* | −8·0% (−11·3 to −5·0)* |
| 4 | Occupational exposure to asbestos: all causes | 194 (148 to 243) | 232 (177 to 289) | 19·6% (14·6 to 23·6)* | −10·5% (−14·2 to −7·5)* | 3410 (2570 to 4310) | 3930 (2980 to 4950) | 15·3% (9·9 to 19·8)* | −12·7% (−16·7 to −9·4)* |
| 4 | Occupational exposure to diesel engine exhaust: all causes | 12 (11 to 13) | 18 (16 to 20) | 48·9% (41·6 to 55·4)* | 13·5% (8·5 to 18·1)* | 344 (304 to 386) | 494 (434 to 559) | 43·9% (36·8 to 50·5)* | 10·8% (5·7 to 15·3)* |

***GBD 2017 Risk Factor Collaborators, Lancet* 2018**

# Occupational cancer: AF

‘‘Occupational cancer, moreover, tends to be concentrated among relatively small groups of people among whom the risk of developing the disease may be quite large, and

such risks can usually be reduced or even eliminated, once they have been identified.

The detection of occupational hazards should therefore have a higher priority in any program of cancer prevention than their proportional importance might suggest.’’

Doll & Peto, 1981

# CANCER ET TRAVAIL

Cancer@Work

**Merci!**

Questions?

SYMPOSIUM

INMA – IMTVL - SMTVL

INMA
Santé Sécurité Agriculture

IMT
INSTITUT DE MEDECINE DU TRAVAIL
DU VAL DE LOIRE

((S)).((M)).((T))
Val de Loire

# Declaration of Interests

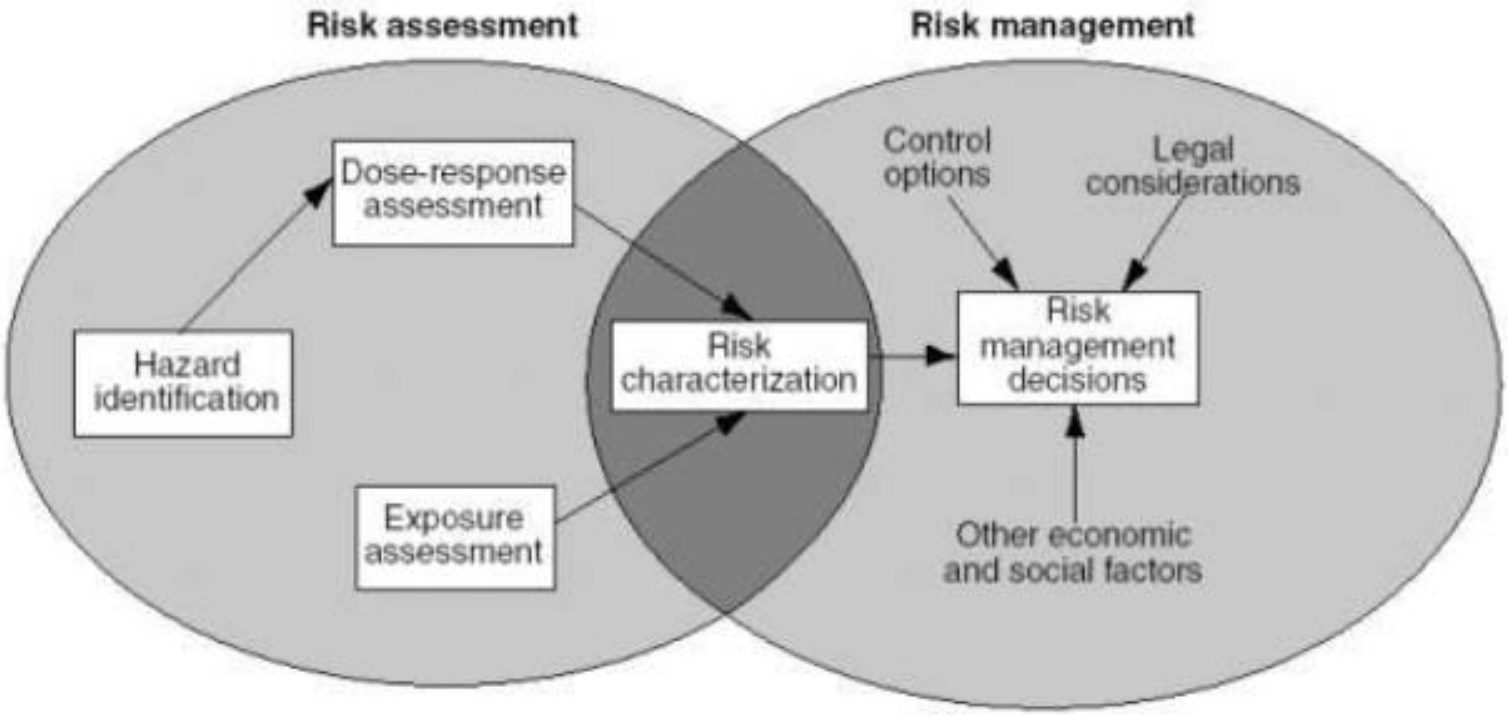
2001 – 11/2018, Senior Epidemiologist and **Head of the IARC Monographs programme**, Head of Section of Evidence Synthesis and Classification (WHO Classification of Tumours, IARC Monographs, IARC Handbooks of Cancer Prevention)

12/2018 – 04/2019, Consultant to IARC, Section of Evidence Synthesis and Classification

The **IARC Monographs are supported by grants** from

U.S. National Cancer Institute (since 1982)
European Commission, Employment and Social Affairs (since 1986)
U.S. National Institute of Environmental Health Sciences (since 1992)

# Hazard Identification, Risk Assessment and Risk Management




Source: EPA Office of Research and Development.

# Dose-response analyses of occupational and residential radon exposure and lung cancer

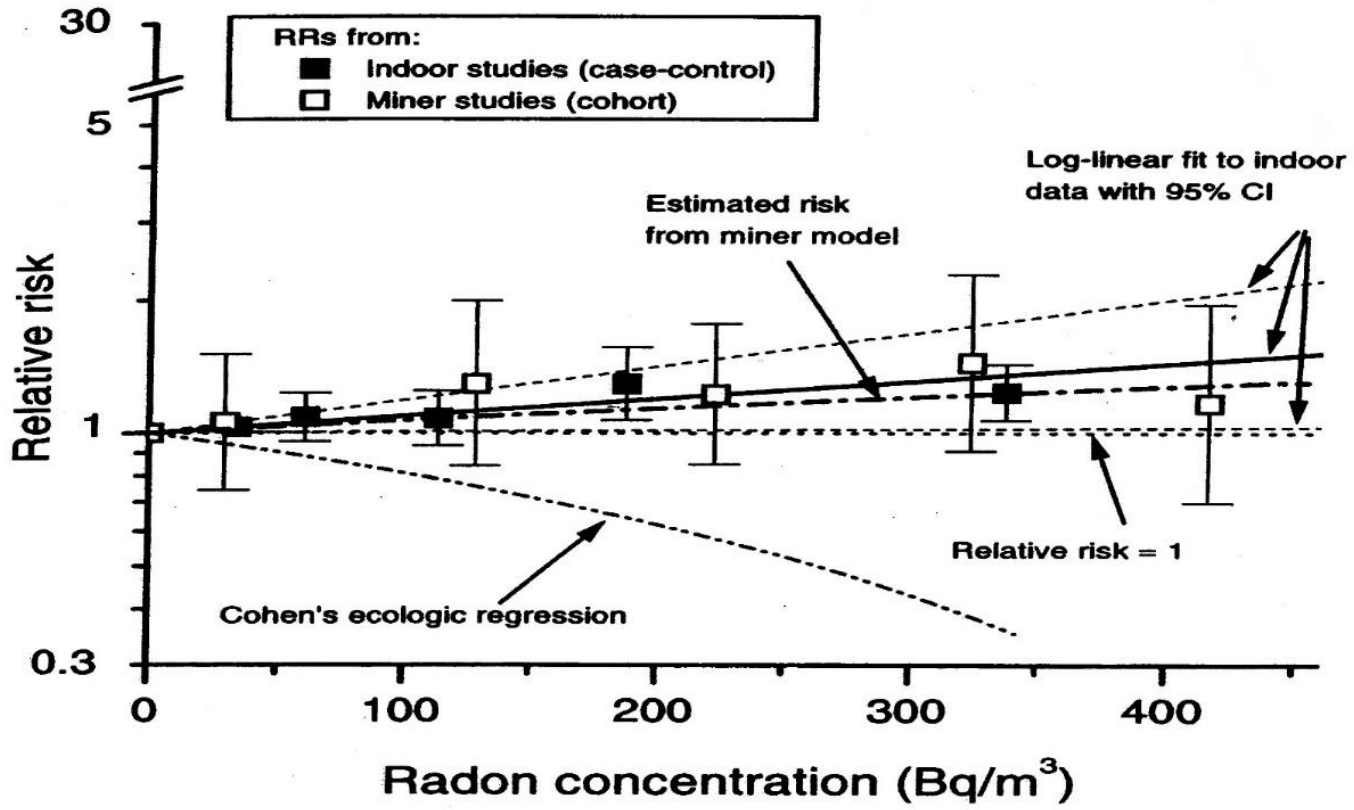
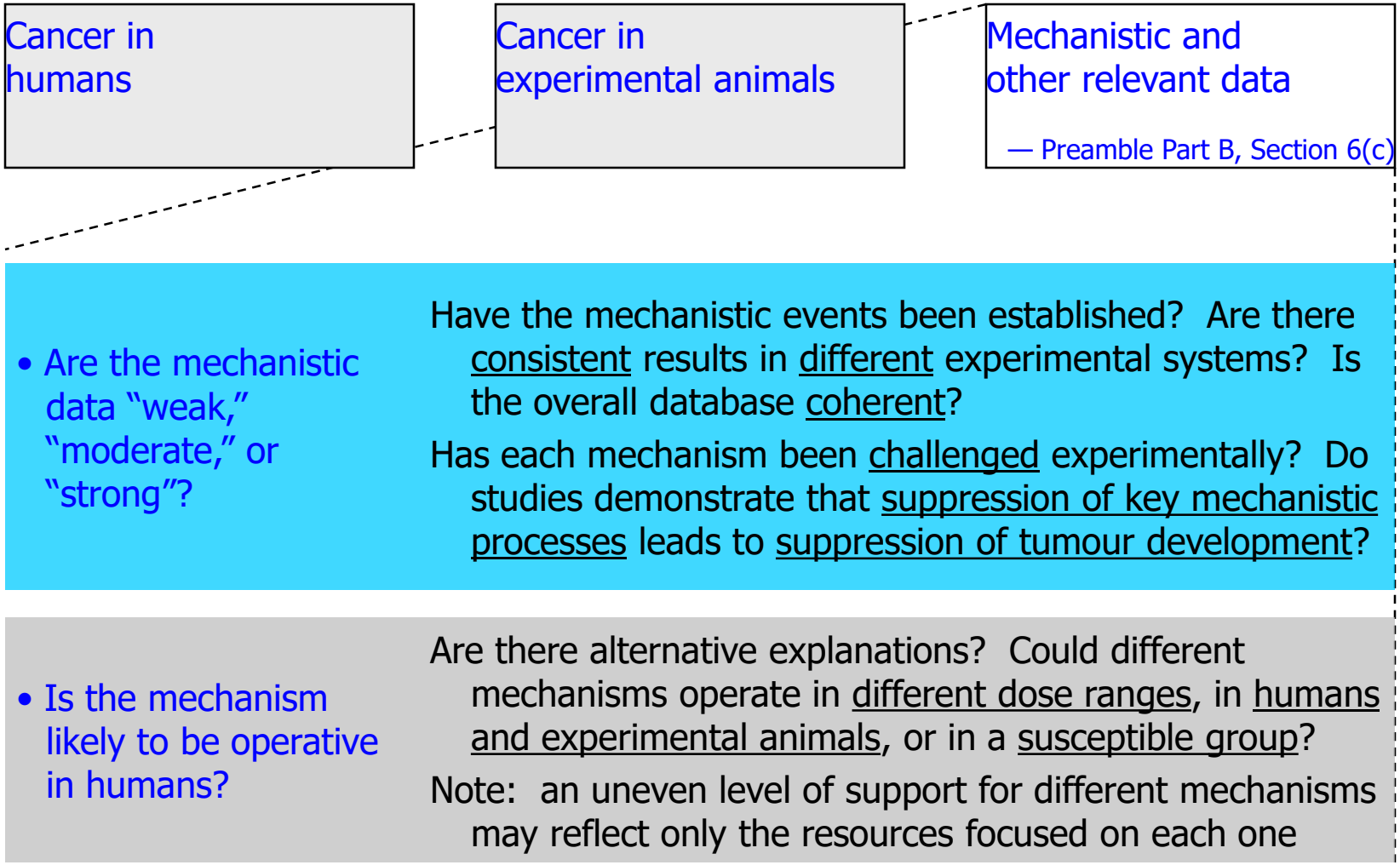


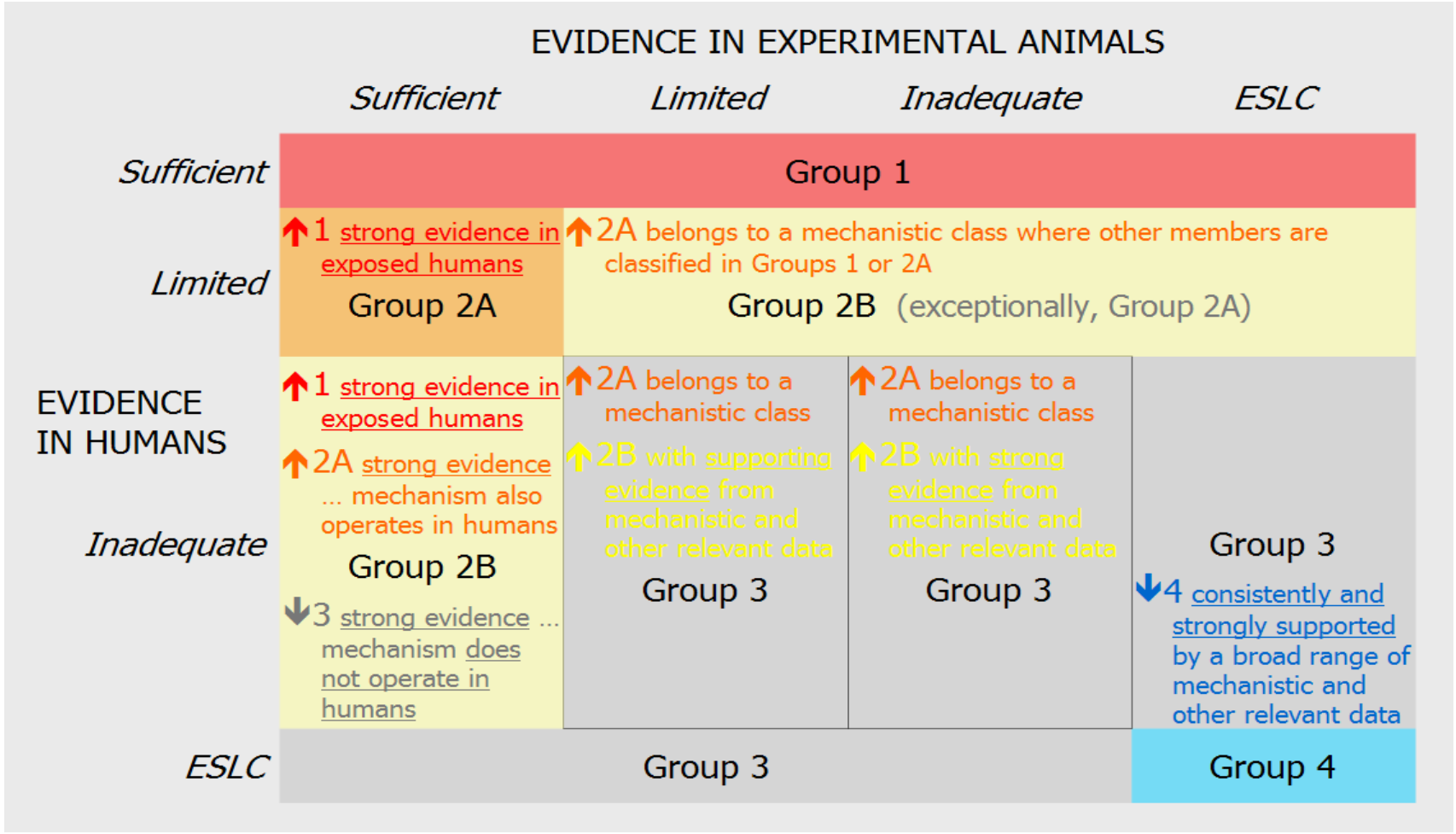

FIGURE 3-2 Summary relative risks (RR) from meta-analysis of indoor-radon studies and RRs from pooled analysis of underground-miner studies, restricted to exposures under 0.175 $Jhm^{-3}$ (50 WLM). Included are RR of 1, fitted exposure-response and its 95% confidence interval from indoor-radon studies, and estimated linear RR based on ecologic analysis by Cohen (1995).

BEIR VI, 1999

# Evaluating mechanistic and other data (Subgroup 4)



# Overall carcinogenicity evaluation



# Systematic Approach
# Using Key Characteristics of Carcinogens

**Targeted searches for each key characteristic**

### Is Genotoxic (#2)

Actions

| | |
|---|---|
| Description | First three characteristics |
| Search type | Search |
| Search database | PubMed |
| Search text | Benzene[Mesh] AND ("Mutation"[Mesh] OR "Cytogenetic Analysis"[Mesh] OR "Mutagens"[Mesh] OR "Oncogenes"[Mesh] OR "Genetic Processes"[Mesh] OR "genomic instability"[MeSH] OR chromosom* OR clastogen* OR "genetic toxicology" OR "strand break" OR "unscheduled DNA synthesis" OR "DNA damage" OR "DNA adducts" OR "SCE" OR "chromatid" OR micronucle* OR mutagen* OR "DNA repair" OR "UDS" OR "DNA fragmentation" OR "DNA cleavage") |

### Induces Epigenetic Alterations (#4)

Actions

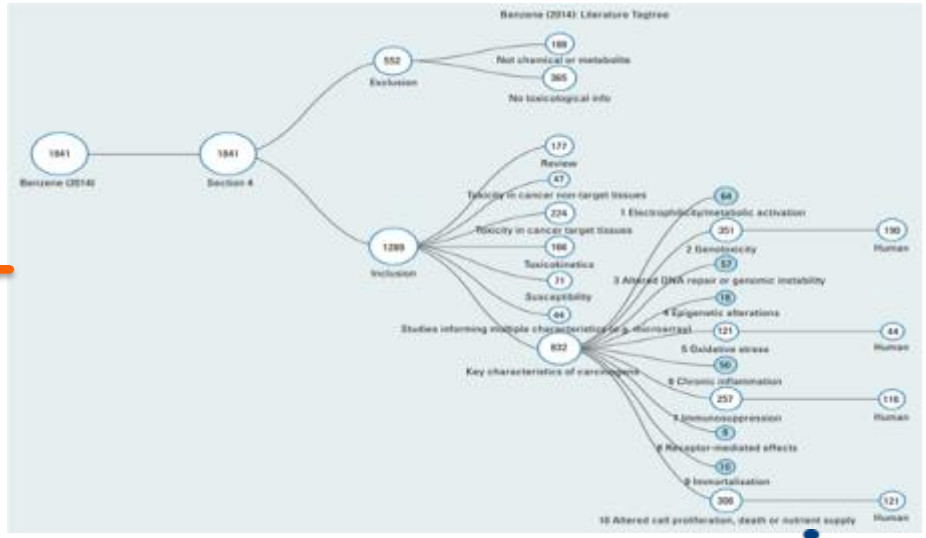
| | |
|---|---|
| Description | Epigenetics |
| Search type | Search |
| Search database | PubMed |
| Search text | Benzene[Mesh] AND ("rna"[MeSH] OR "epigenesis, genetic"[Mesh] OR rna OR "rna, messenger"[MeSH] OR "rna" OR "messenger rna" OR mrna OR "histones"[MeSH] OR histones OR epigenetic OR miRNA OR methylation) |

### Induces oxidative stress (#5)

Actions

| | |
|---|---|
| Description | Oxidative stress |
| Search type | Search |
| Search database | PubMed |
| Search text | Benzene[Mesh] AND ("reactive oxygen species"[MeSH] OR "reactive nitrogen species"[MeSH] OR "reactive oxygen species" OR "oxygen radicals" OR "oxidative stress"[MeSH] OR oxidative OR "oxidative stress" OR "free radicals") |

**Organize results by key characteristics, species, etc**



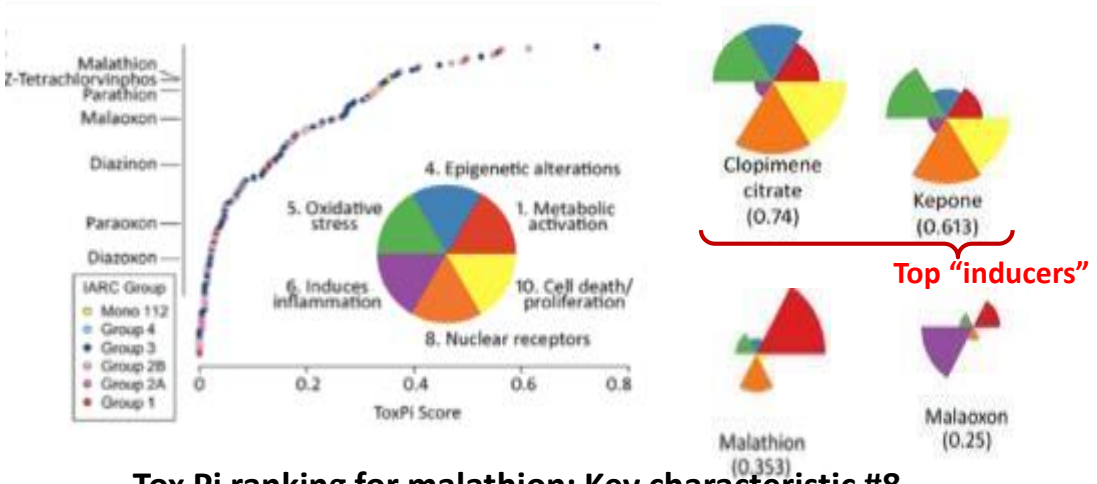

HAWC
HEALTH ASSESSMENT WORKSPACE COLLABORATIVE

Smith MT, Guyton KZ, Gibbons CF, Fritz JM et al.. *Env Health Persp.*, *124(6):713-21*

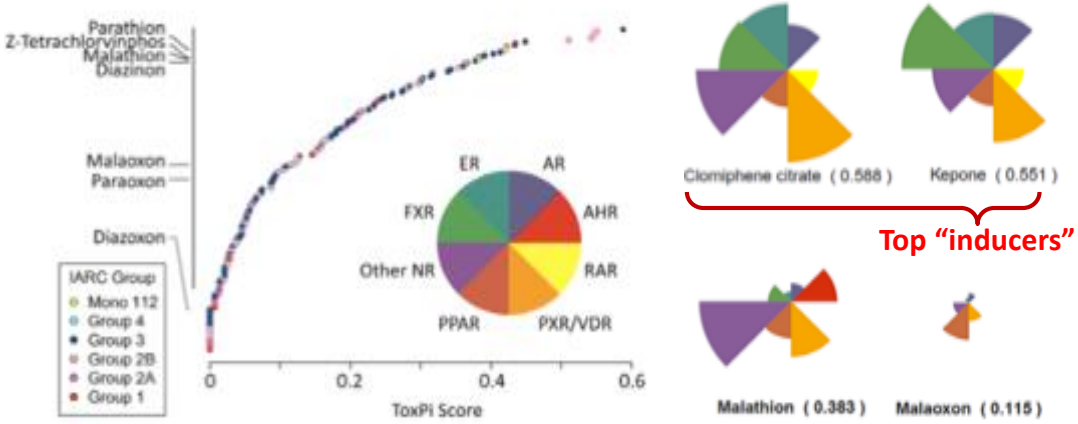
# High Throughput Screening Data: *Questions*

- How does activity compare across– and within– key characteristics, and across all Tox21 compounds evaluated by IARC?
- Is activity more closely associated with the parent compound or metabolite(s)?

**Tox Pi ranking for malathion: <u>All key characteristics</u>**




**Tox Pi ranking for malathion: <u>Key characteristic #8</u>**




http://monographs.iarc.fr ; Chiu WA, Guyton KZ, Martin MT, Reif DM, Rusyn I. *Reg Tox Pharm., submitted.*

# Group-1 agents with less than *sufficient evidence* in humans

- Ethylene oxide (vol 60, 1994, Vol 97, 2007)
- 2,3,7,8-Tetrachlorodibenzo-para-dioxin (vol 69, 1997)
- Neutron radiation (vol 75, 2000)
- Areca nut (Vol 85)
- Gallium Arsenide (Vol 86, 2003)
- Tobacco-specific nitrosamines NNN and NNK (Vol 85)
- Benzo[a]pyrene (vol 92, 2005)
- Ethanol in alcoholic beverages
- Dyes metabolized to benzidine (Vol 99, 2007)
- MOCA (Vol 99, 2007)
- Aristolochic acid (Vol 100A)
- Acetaldehyde associated with consumption of alcoholic beverages (Vol 100E)
- pentachloro-dibenzofuran and pentachloro-biphenyl (Vol 100F, 2009), Dioxin-like PCBs (Vol 107)

# IARC Monographs Vol. 111, CNT

- The Working Group acknowledged that the above mechanisms are all relevant to humans.
- However, a majority did not consider the mechanistic evidence for carcinogenicity - especially concerning chronic endpoints – to be strong for any specific CNT.
- Furthermore, the lack of coherent evidence across the various distinct CNTs precluded generalisation to other types of CNTs.

## Overall evaluation

- MWCNT-7 is *possibly carcinogenic to humans* (Group 2B);
- SWCNTs and MWCNTs excluding MWCNT-7 are *not classifiable as to their carcinogenicity to humans* (Group 3).

# Epidemiologic data for occupational carcinogen risk assessment