

WORLD HEALTH ORGANIZATION
INTERNATIONAL AGENCY FOR RESEARCH ON CANCER



IARC Monographs on the Evaluation of Carcinogenic Risks to Humans



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Outline

Background on the *IARC Monographs*

How *Monographs* are developed

Types of data considered

Identifying carcinogens at IARC and other health agencies

Some recent examples





Background

The first step in cancer prevention is to identify the causes of human cancer

The *IARC Monographs* are a series of scientific reviews that identify environmental factors that can increase the risk of human cancer

Each *Monograph* includes

- Critical review of the pertinent scientific literature
- Evaluation of the weight of the evidence that the agent can alter the risk of cancer in humans

The *IARC Monographs* are unique in that the critical reviews and evaluations are developed by the experts who did the original research





The *Monographs* are a worldwide endeavour that since 1971 has involved over 1000 scientists from 51 countries





“The encyclopaedia of carcinogens”

The *IARC Monographs* evaluate

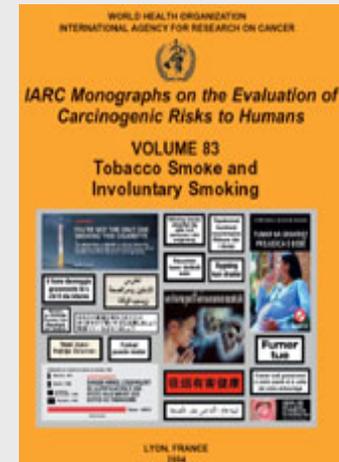
- Chemicals
- Complex mixtures
- Occupational exposures
- Physical and biological agents
- Lifestyle factors

More than 900 agents have been evaluated since 1971

- 100 are *carcinogenic to humans*
- 68 are *probably carcinogenic to humans*
- 246 are *possibly carcinogenic to humans*

National and international health agencies use the *Monographs*

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





Monograph meeting preparations

Agents are selected for review on the basis of

- Evidence of human exposure
- Some evidence or suspicion of carcinogenicity
- Advisory Groups meet every 5 years to recommend agents for future review

Working Group Members are selected on the basis of

- Knowledge and experience
- Absence of real or apparent conflicts of interests
- Consideration is also given to demographic diversity and balance of scientific findings and views

Working Group Members search the scientific literature and prepare preliminary working papers for the critical review





Monograph meetings are about peer review and consensus

The first 3-4 days are for work in discipline-specific subgroups

- Review the working papers, develop a joint subgroup draft (sections 1–4)
- Write a summary of the database as a whole (sections 5.1–5.4)
- Propose an evaluation of the human evidence, animal evidence, or mechanistic data (section 6)

The last 3-4 days are for work in plenary session

- Peer-review the subgroup drafts and reach consensus
- Discuss the subgroup evaluations and reach consensus
- Develop an overall evaluation and reach consensus

The entire volume is the joint product of the Working Group, and there are no individually authored sections

After the meeting, IARC scientists review the final text and tables for accuracy and clarity





Evaluating the weight of the evidence



Cancer in humans

Sufficient evidence
Limited evidence
Inadequate evidence
Evidence suggesting lack of carcinogenicity

Cancer in experimental animals

Sufficient evidence
Limited evidence
Inadequate evidence
Evidence suggesting lack of carcinogenicity

Mechanistic and other relevant data

- Mechanistic data “weak,” “moderate,” or “strong”?
- Mechanism likely to be operative in humans?

Overall evaluation

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*
Group 4 *Probably not carcinogenic to humans*



The Preamble: IARC's guidelines

During 2005 the Preamble was amended with the participation of the scientific community

- March-April 2005 Gather suggestions from recent meeting chairs and subgroup chairs
- May Convene an Advisory Group to recommend updates to the Preamble
- May-August Develop a draft Preamble
- Sept-October Make the draft Preamble available for public comment
- December Convene an Advisory Group to review the amended Preamble
- January 2006 Publish the final Preamble

— <http://monographs.iarc.fr/>





Key features of the amended Preamble

Background and scope

- Opens the possibility of quantitative dose-response analyses

Principles and procedures

- Clarifies the roles of all participants
- Describes the use of WHO's Declaration of Interests

Types of evidence considered

- Discusses meta-analysis and joint analysis
- Updates the guidance for considering molecular and mechanistic data
- Restructures *Monographs* to emphasize mechanistic and other relevant data

Evaluations

- Updates criteria emphasize importance of GLP studies and mechanistic data
- Introduces a new *Monograph* section to discuss the rationale for an evaluation





Types of data: epidemiologic studies



Sufficient evidence generally means that a causal relationship has been established and that chance, bias, and confounding could be ruled out with reasonable confidence

The relevance of epidemiology is clear, but it can be difficult to assess causality

- Humans do not live in controlled environments, as do experimental animals
- Assessing human exposures can be difficult, especially in retrospective studies
- There are often confounding exposures, particularly for the more prevalent cancers
- Many occupations involve mixed exposures that change over time
- Some agents cannot be isolated as an agent for study (eg, benzo[*a*]pyrene)
- Studies of several hundred or several thousand people can detect only large risks
- Cancer can take more than 20-30 years to develop, during which time exposure can become widespread

➔ Epidemiology finds associations, the question is causality



Types of data: animal studies

Sufficient evidence generally means that positive results have been replicated in independent studies

The strengths and limitations of animal studies complement those of epidemiology

- Exposure is clearly defined
- Confounding factors can be controlled, so causality can be attributed to a specific agent
- Small risks can be investigated through high-dose testing
- Results are available in about 3 years

There is sometimes the question of whether the experimental results are relevant to humans

➔ Bioassays demonstrate causality, the question is relevance





Types of data: mechanistic studies



Mechanistic studies seek to “fill in the blanks” between exposure and the occurrence of tumours

Knowledge of intermediate steps can provide information about relevance

- Is the mechanism in experimental animals likely to be operating in humans?
- Is the mechanistic evidence weak, moderate, or strong?

Knowledge of intermediate steps allows epidemiologic and experimental studies to focus on target cells and tumour precursors





What makes a human carcinogen?

Before 1991, a human carcinogen was defined as an agent with *sufficient evidence* in humans

Group 1: The agent is *carcinogenic to humans*

- “This category is used only when there is *sufficient evidence of carcinogenicity* in humans.”

Sufficient evidence of carcinogenicity

- “The Working Group considers that a causal relationship has been established between exposure to the agent and human cancer. That is, a positive relationship has been observed between exposure to the agent and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence.”

— Preamble to the *IARC Monographs*, 1987





What makes a human carcinogen?

A series of scientific workshops reached a consensus that mechanistic evidence in humans could substitute for epidemiologic studies

Group 1: The agent is *carcinogenic to humans*

- “This category is used when there is *sufficient evidence of carcinogenicity* in humans.
- “Exceptionally, an agent may be placed in this category when evidence of carcinogenicity in humans is less than *sufficient* but there is *sufficient evidence of carcinogenicity* in experimental animals and strong evidence in exposed humans that the agent acts through a relevant mechanism of carcinogenicity.”

— Preamble to the *IARC Monographs*, 1991





Why is it important to consider more than traditional human cancer studies?

Although they are the most definitive source of risk information, epidemiologic studies have practical limitations (mentioned earlier)

- Exposure can be difficult to assess
- Confounding exposures can make it difficult to attribute risk to a specific agent
- Studies can generally detect only large risks
- Cancer can have a long latent period

Biomarker information from molecular epidemiology can sometimes address these limitations

- It is not necessary to wait decades for a cancer risk to become manifest
- Biomarkers can provide evidence of early effects at the cell, tissue, or organism level
- They can sometimes provide a “fingerprint” to distinguish among confounding exposures
 - Buffler et al (2004) IARC Scientific Publication 157
 - Vineis et al (1999) IARC Scientific Publication 148





Overview of IARC's classifications

		EVIDENCE IN EXPERIMENTAL ANIMALS			
		<i>Sufficient</i>	<i>Limited</i>	<i>Inadequate</i>	<i>ESLC</i>
EVIDENCE IN HUMANS	<i>Sufficient</i>	Group 1			
	<i>Limited</i>	Group 2A	Group 2B (exceptionally, Group 2A)		
	<i>Inadequate</i>	Group 2B	Group 3		
	<i>ESLC</i>				Group 4





Biomarker data can be part of an evaluation in Group 1

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Example: ethylene oxide (volume 60)

Cancer evidence

- Cancer in humans: *limited evidence*
- Cancer in experimental animals: *sufficient evidence* (strong evidence at multiple sites)
- Mechanistic evidence: "Ethylene oxide is a directly acting alkylating agent that:
 - "(i) induces a sensitive, persistent dose-related increase in the frequency of chromosomal aberrations and sister chromatid exchange in peripheral lymphocytes and micronuclei in bone-marrow cells of exposed workers;
 - "(ii) has been associated with malignancies of the lymphatic and haematopoietic system in both humans and experimental animals;
 - "(iii) induces a dose-related increase in the frequency of haemoglobin adducts in exposed humans and dose-related increases in the numbers of adducts in both DNA and haemoglobin in exposed rodents;
 - "(iv) induces gene mutations and heritable translocations in germ cells of exposed rodents; and
 - "(v) is a powerful mutagen and clastogen at all phylogenetic levels."

Evaluation

- Ethylene oxide is *carcinogenic to humans* (Group 1)
- Without mechanistic evidence, would have been *probably carcinogenic* (Group 2A)
 - IARC Monographs volume 60 (1994)





Example: benzo[*a*]pyrene (volume 92)

Benzo[*a*]pyrene is an indicator compound found in all PAH mixtures

Cancer evidence

- Cancer in humans: *inadequate evidence* (cannot attribute risk to B[*a*]P, occurs in mixtures)
- Cancer in experimental animals: *sufficient evidence* (used as a positive control)
- Mechanisms: diol-epoxide for lung and skin tumours, radical-cation for skin tumours
- Diol-epoxide mechanism: PAHs → oxides and dihydrodiols → diol epoxides; these form stable or depurinating adducts with guanines and adenines, which can induce mutations (eg, in *ras* proto-oncogenes) strongly associated with tumorigenesis
- Radical-cation mechanism: one-electron oxidation creates radical cations; these result in depurinating DNA adducts with guanines and adenines, which generate apurinic sites that can induce mutations in *ras* proto-oncogenes

Evaluation

- Complete sequence of steps in the metabolic activation to mutagenic diol epoxides has been demonstrated in animals, in human tissues, and in humans
- Benzo[*a*]pyrene is *carcinogenic to humans* (Group 1)
- Without mechanistic evidence, would have been *possibly carcinogenic* (Group 2B)
 - Straif et al (2006) *Lancet Oncology* 6(12): 931-932





Similar principles have been adopted by other health agencies

U.S. Environmental Protection Agency

Carcinogenic to humans

- “This descriptor is appropriate when there is convincing epidemiologic evidence of a causal association between human exposure and cancer.
- “Exceptionally, this descriptor may be equally appropriate with a lesser weight of epidemiologic evidence that is strengthened by other lines of evidence. It can be used when all of the following conditions are met:
 - (a) there is strong evidence of an association between human exposure and either cancer or the key precursor events of the agent’s mode of action but not enough for a causal association, and
 - (b) there is extensive evidence of carcinogenicity in animals, and
 - (c) the mode(s) of carcinogenic action and associated key precursor events have been identified in animals, and
 - (d) there is strong evidence that the key precursor events that precede the cancer response in animals are anticipated to occur in humans and progress to tumors, based on available biological information.”

— Guidelines for carcinogen risk assessment (2005)





Similar principles have been adopted by other health agencies

National Toxicology Program

Known to be a human carcinogen

- “There is sufficient evidence of carcinogenicity from studies in humans,* which indicates a causal relationship between exposure to the agent, substance, or mixture, and human cancer.”
- * “This evidence can include traditional cancer epidemiology studies, data from clinical studies, and/or data derived from the study of tissues or cells from humans exposed to the substance in question that can be useful for evaluating whether a relevant cancer mechanism is operating in people.”

— *Report on Carcinogens*, eleventh edition (2004)





Example: 1,3-butadiene

National Toxicology Program

"1,3-Butadiene is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans, including epidemiological and mechanistic information, which indicate a causal relationship between occupational exposure to 1,3-butadiene and excess mortality from lymphatic and/or hematopoietic cancers."

- Mouse, rat, and human liver microsomes were shown to oxidize 1,3-butadiene
- Metabolites form *N*'-alkylguanine adducts, detected in mouse liver DNA and in human urine
- Activated *K-ras* genes and inactivated tumor suppressor genes in mice are analogous to genetic alterations frequently observed in a wide variety of human cancers
- Dose-related increases in *hprt* mutations were seen in lymphocytes in mice and in workers
- Mechanism appears to be due to its metabolism to DNA-reactive intermediates resulting in genetic alterations in proto-oncogenes and/or tumor suppressor genes

— *Report on Carcinogens*, ninth edition (2000)





Example: 2,3,7,8-tetrachlorodibenzo-*p*-dioxin

National Toxicology Program

"2,3,7,8-Tetrachlorodibenzo-*p*-dioxin is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity from studies in humans involving a combination of epidemiological and mechanistic information that indicates a causal relationship between exposure to TCDD and human cancer."

- There is scientific consensus for a common mode of action of TCDD and other chlorinated dibenzodioxins, dibenzofurans, and planar polychlorinated biphenyls (PCBs)
- In humans and rodents, this involves initial binding to the aryl hydrocarbon (Ah) receptor
- Through activation of the Ah receptor, TCDD induces a wide spectrum of biological responses considered important to the carcinogenic process, including changes in gene expression, altered metabolism, altered cell growth and differentiation, and disruption of steroid-hormone and growth-factor signal transduction pathways

— *Report on Carcinogens*, ninth edition (2000)





Experimental studies: What are the hallmarks of a carcinogen?

Six essential alterations in cell physiology that collectively dictate malignant growth

- self-sufficiency in growth signals
- insensitivity to growth-inhibitory (antigrowth) signals
- evasion of programmed cell death (apoptosis)
- limitless replicative potential
- sustained angiogenesis
- tissue invasion and metastasis

An enabling characteristic: genome instability

- loss of p53 function (elicits cell cycle arrest or apoptosis)
- loss of other tumor suppressor genes (involved in DNA repair and mitosis)

— Hanrahan and Weinberg (2000) *Cell* 100: 57-70





Scientific consensus: mechanistic data can be used to identify carcinogens

“In the absence of data from conventional long-term bioassays of carcinogenesis or from assays with neoplasia as the end-point, consistently positive results in several models addressing several stages in the multistage process of carcinogenesis should be considered in evaluating the degree of evidence of carcinogenicity in experimental animals.”

- McGregor et al (1999) IARC Scientific Publication 146
- (represents the consensus of 19 scientists from 8 countries)





Scientific consensus: mechanistic data can be used to identify carcinogens

“The Advisory Group supported [the proposed change to allow a classification of *possibly carcinogenic to humans* (Group 2B) solely on the basis of mechanistic and other relevant data] and noted that there is increasing confidence in our understanding of mechanisms which is supported by the science.”

- Advisory Group to Review the Amended Preamble to the *IARC Monographs* (2006)
- (represents the recommendation of 19 scientists from 14 countries)

This consensus has been incorporated into IARC’s guidelines

- Group 2B: The agent is *possibly carcinogenic to humans*
- “. . . In some instances, an agent for which there is *inadequate evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals together with supporting evidence from mechanistic and other relevant data may be placed in this group [Group 2B]. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.”

— Preamble to the *IARC Monographs* (2006)





Why is it important to consider more than traditional animal bioassays?

The field is moving away from 2-year carcinogenicity studies to more mechanistic studies

- Studies by the National Toxicology Program are unlikely to be replicated
- NTP is shifting resources from 2-year cancer bioassays to more mechanistic studies
- Mechanistic studies are much more numerous
- There is pressure to reduce the use of animal testing

Mechanistic studies can help address the question of relevance of animal studies

- IARC's evaluation criteria consider whether the mechanisms of carcinogenesis in experimental animals are likely to be operative in humans





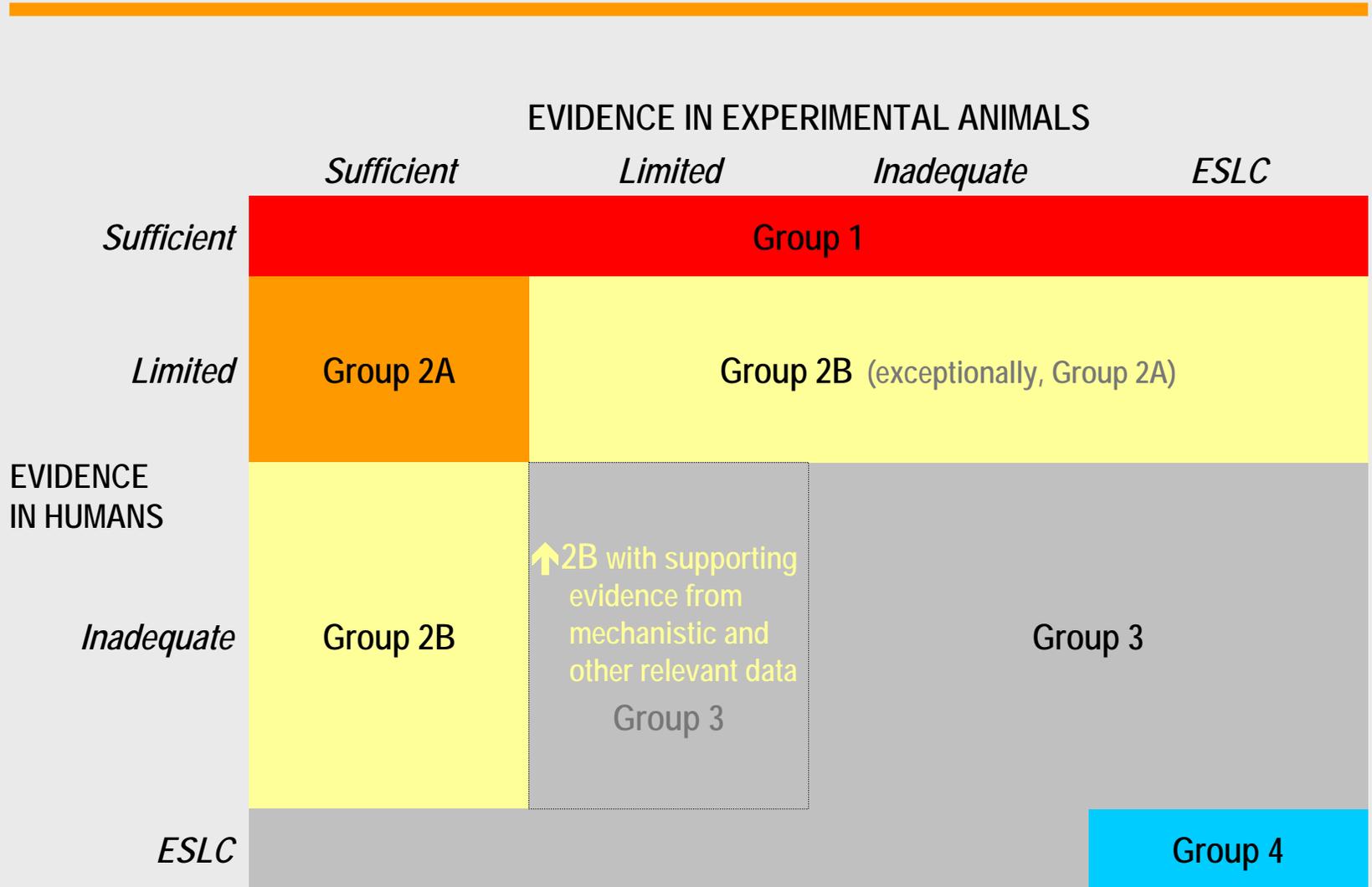
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Mechanistic data can substitute for cancer bioassays





Mechanistic data can substitute for cancer bioassays

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EVIDENCE IN HUMANS	<i>Sufficient</i>	Group 1			
	<i>Limited</i>	Group 2A	Group 2B (exceptionally, Group 2A)		
	<i>Inadequate</i>	Group 2B	↑2B with <u>supporting evidence from mechanistic and other relevant data</u> Group 3	<u>evidence from mechanistic and other relevant data</u> Group 3	Group 3
	<i>ESLC</i>		Group 3		Group 4





Example: benz[*a*]aceanthrylene (volume 92)

Cancer evidence

- Cancer in humans: *inadequate evidence* (occurs in PAH mixtures)
- Cancer in experimental animals: *limited evidence* (highly significant results after intraperitoneal injection in mice and initiation-promotion study in mouse skin)
- Mechanistic evidence
 - Strong evidence of cyclopenta-ring oxidation and formation of diol epoxide
 - Mutagenic in bacteria and mammalian cells, causes morphological cell transformation in mouse embryonic fibroblasts
 - Diol epoxide metabolites are mutagenic in bacteria, cause malignant cell transformation in mouse embryonic fibroblasts, form DNA adducts in these cells

Evaluation

- Benz[*a*]aceanthrylene is *possibly carcinogenic to humans* (Group 2B)
- Without mechanistic evidence, would have been *not classifiable* (Group 3)
 - *IARC Monographs* volume 92





Example: microcystin-LR (volume 94)

Microcystin-LR is a toxin produced by cyanobacteria

- Cyanobacteria are found in water and soil, eutrophication can cause microcystin-LR and related toxins to occur at high concentrations, these toxins accumulate in fish and shellfish
- Exposure via contaminated water, fish, and shellfish, and blue-green algae supplements

Cancer evidence

- Cancer in humans: *inadequate evidence*
- Cancer in experimental animals: *inadequate evidence* (no cancer bioassays)
- Mechanistic evidence is strong, supporting a plausible tumour-promoter mechanism
- Mechanism is mediated through inhibition of protein phosphatases 1 and 2A; hyperphosphorylation of intracellular proteins; modulation of expression of oncogenes, early-response genes, and tumour necrosis factor alpha; affecting cell division, cell survival, and apoptosis

Evaluation

- Microcystin-LR is *possibly carcinogenic to humans* (Group 2B)
- Without mechanistic evidence, would have been *not classifiable* (Group 3)

— Grosse et al (2006) *Lancet Oncology* 7(8): 628-629





Many other evaluations have been based on mechanistic data

Upgrades to Group 1 (5)

- Benzo[*a*]pyrene
- Ethylene oxide
- Neutrons
- NNN and NNK
- 2,3,7,8-Tetrachlorodibenzo-*para*-dioxin

Upgrades to Group 2A (39)

- Acrylamide, adriamycin, azacitidine, benzidine-based dyes, captafol, chloramphenicol, CCNU, chlorozotocin, cisplatin, *Clonorchis sinensis*, cyclopenta[*cd*]pyrene, dibenz[*a,h*]anthracene, dibenzo[*a,l*]pyrene, diethyl sulfate, dimethylcarbamoyl chloride, 1,2-dimethylhydrazine, dimethyl sulfate, epichlorohydrin, ethylene dibromide, *N*-ethyl-*N*-nitrosourea, etoposide, glycidol, indoor emissions from household combustion of biomass fuel (mainly wood), IQ, 5-methoxypsoralen, MOCA, methyl methanesulfonate, MNNG, *N*-methyl-*N*-nitrosourea, *N*-nitrosodiethylamine, *N*-nitrosodimethylamine, procarbazine hydrochloride, styrene-7,8-oxide, tenopside, tris(2,3-dibromopropyl) phosphate, UVA, UVB, UVC, vinyl bromide

Upgrades to Group 2B (8)

- Aziridine, benz[*j*]aceanthrylene, benzo[*c*]phenanthrene, bleomycins, 1,2-epoxybutane, gasoline, marine diesel fuel, microcystin-LR

Downgrades to Group 3 (8)

- Amitrole
- Atrazine
- Di(2-ethylhexyl) phthalate
- Ethylenethiourea
- *d*-Limonene
- Melamine
- Saccharin
- Sulfamethazine





A few words about conflicts of interests

It is important to ensure public confidence that interested parties do not have links to the Working Group and that special interests cannot influence a meeting

- Experts declare employment, research, and financial interests before invitations are sent
- Experts update their declarations at the opening of the meeting

IARC posts each list of participants on our website 2 months in advance, and we ask

- “IARC requests that you do not contact or lobby meeting participants, send them written materials, or offer favours that could appear to be linked to their participation . . . IARC will ask participants to report all such contacts and will publicly reveal any attempt to influence the meeting.”

Conflicts are independently assessed and reported by *Lancet Oncology*

— Cogliano et al (2005) *Lancet Oncology* 6(10): 747





Summary

The *IARC Monographs* use an international, interdisciplinary, expert-consensus approach that has been refined over a 35-year history

IARC invites knowledgeable expert scientists, who develop consensus evaluations during the course of an 8-day review meeting

The science of carcinogen identification has evolved over recent years

Biomarker and mechanistic studies are increasingly able to identify carcinogens with the same level of confidence as traditional epidemiologic studies and cancer bioassays

IARC has been using biomarker and mechanistic evidence in its evaluations for many years





Acknowledgements

IARC Monographs programme staff



Robert
Baan



Sandrine
Égraz



Martine
Lézère



Béatrice
Secretan



Véronique
Bouvard



Fatiha
El Ghissassi



Helene
Lorenzen-Augros



Kurt
Straif



Yann
Grosse



Jane
Mitchell

Many other IARC scientists and staff also contribute to the *Monographs*

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)
- U.S. Environmental Protection Agency (since 2001)
- German Federal Ministry of Health and Social Security (2005)







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Mechanistic data can be pivotal when the human data are not conclusive

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	<i>Limited</i>	↑1 <u>strong evidence in exposed humans ... agent acts through a relevant mechanism</u> Group 2A	↑2A belongs to a mechanistic class where other members are classified in Groups 1 or 2A Group 2B (exceptionally, Group 2A)		
	<i>Inadequate</i>	↑1 <u>strong evidence in exposed humans ...</u> ↑2A <u>strong evidence ... mechanism also operates in humans</u> Group 2B	↑2A belongs to a mechanistic class ↑2B with <u>supporting evidence from mechanistic and other relevant data</u> Group 3	↑2A belongs to a mechanistic class ↑2B with <u>strong evidence from mechanistic and other relevant data</u> Group 3	Group 3 ↓4 <u>consistently and strongly supported by a broad range of mechanistic and other relevant data</u>
	<i>ESLC</i>	↓3 <u>strong evidence ... mechanism does not operate in humans</u>	Group 3		Group 4

