International Agency for Research on Cancer

World Health Organization

IARC Monographs

Volume 105 – Diesel and gasoline engine exhausts and some nitroarenes

5-12 June 2012

Preliminary list of agents to be reviewed
WHO Declaration of Interests for this volume

In 1989, the International Agency for Research on Cancer (IARC) classified diesel exhaust as *probably carcinogenic to humans (Group 2A)*. However, an Advisory Group which reviews and recommends future priorities for evaluation or re-evaluation by the IARC Monographs Program has recommended diesel engine exhaust as a high priority for re-evaluation since 1998.

IARC Monographs procedures

The *IARC Monographs* Program identifies environmental factors that can increase the risk of human cancer. These include chemicals, complex mixtures, occupational exposures, physical agents, biological agents, and personal habits. An *IARC Monograph* is not "a new study" but the comprehensive and critical review and evaluation of the published scientific evidence on the carcinogenicity of human exposures; this includes data on cancer in humans, cancer bioassays and data on the mechanisms of carcinogenesis. National health agencies can use this information as scientific support for their actions to prevent exposure to potential carcinogens.

A well defined classification

The evaluation results in the classification of environmental factors in 5 groups.

- 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*

Since 1971, more than 900 agents have been evaluated, of which more than 100 have been identified as *carcinogenic* to humans (Group 1), and more than 300 as *probably carcinogenic*, or *possibly carcinogenic* to humans (Groups 2A, 2B).

A meeting to decide

Interdisciplinary working groups of expert scientists meet to review the published studies and evaluate the weight of the evidence that an agent can increase the risk of cancer. The Working Group meets at IARC for eight days to discuss and finalize the critical review and to formulate the evaluations. The experts meet mostly in subgroups according to type of expertise during the first part of the meeting and in plenary during the second part of the meeting. The objectives of the meeting are peer review and consensus. As a result, the agent is classified into one of the 5 categories shown previously.

Data sources

About one year before the meeting, relevant biological and epidemiological data are collected by IARC from recognized sources of information, including data storage and

retrieval systems such as PubMed. Meeting participants who are asked to prepare preliminary working papers for specific sections are expected to supplement the IARC literature searches with their own searches.

Several months before the meeting, the material obtained is sent to meeting participants to prepare preliminary working papers. The latter are compiled by IARC staff and sent, prior to the meeting, to Working Group Members and Invited Specialists for review. All eligible literature published prior to the meeting is considered.

Participants

Five categories of participants can be present at *Monograph* meetings.

- **The Working Group** is responsible for the critical reviews and evaluations that are developed during the meeting. Working Group Members are selected on the basis of knowledge and experience, and absence of real or apparent conflicts of interests. They serve as individual scientists and not as representatives of any organization, government or industry.
- **Invited Specialists** are experts who also have critical knowledge and experience but have a real or apparent conflict of interests. These experts are invited when necessary to assist in the Working Group by contributing their unique knowledge and experience during subgroup and plenary discussions. Invited Specialists do not serve as meeting chair or subgroup chair, draft text that pertains to the description or interpretation of cancer data, or participate in the evaluations.
- **Representatives of national and international health agencies** often attend meetings because their agencies sponsor the program or are interested in the subject of a meeting. Representatives do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations.
- **Observers** with relevant scientific credentials may be admitted to a meeting by IARC in limited numbers. Observers do not serve as meeting chair or subgroup chair, draft any part of a *Monograph*, or participate in the evaluations. At the meeting, the meeting chair and subgroup chairs may grant Observers an opportunity to speak, generally after they have observed a discussion.
- **The IARC Secretariat** consists of scientists who are designated by IARC and who have relevant expertise. They serve as *rapporteurs* and participate in all discussions. When requested by the meeting chair or subgroup chair, they may also draft text or prepare tables and analyses.
  More details from IARC Monographs Preamble

Conflicts of interest

Before an invitation is extended, each potential participant, including the IARC Secretariat, completes the WHO Declaration of Interests to report financial interests, employment and consulting, and individual and institutional research support related to the subject of the meeting. IARC assesses these interests to determine whether there is a conflict that warrants some limitation on participation. The declarations are updated and reviewed again at the opening of the meeting. Interests related to the subject of the meeting are disclosed to the meeting participants and in the published volume (Cogliano *et al.*, 2004).

The names and principal affiliations of participants are available on the Monographs program website approximately two months before each meeting. It is not acceptable for Observers or third parties to contact other participants before a meeting or to lobby them at any time. Meeting participants are asked to report all such contacts to IARC. (Cogliano *et al.*, 2005).

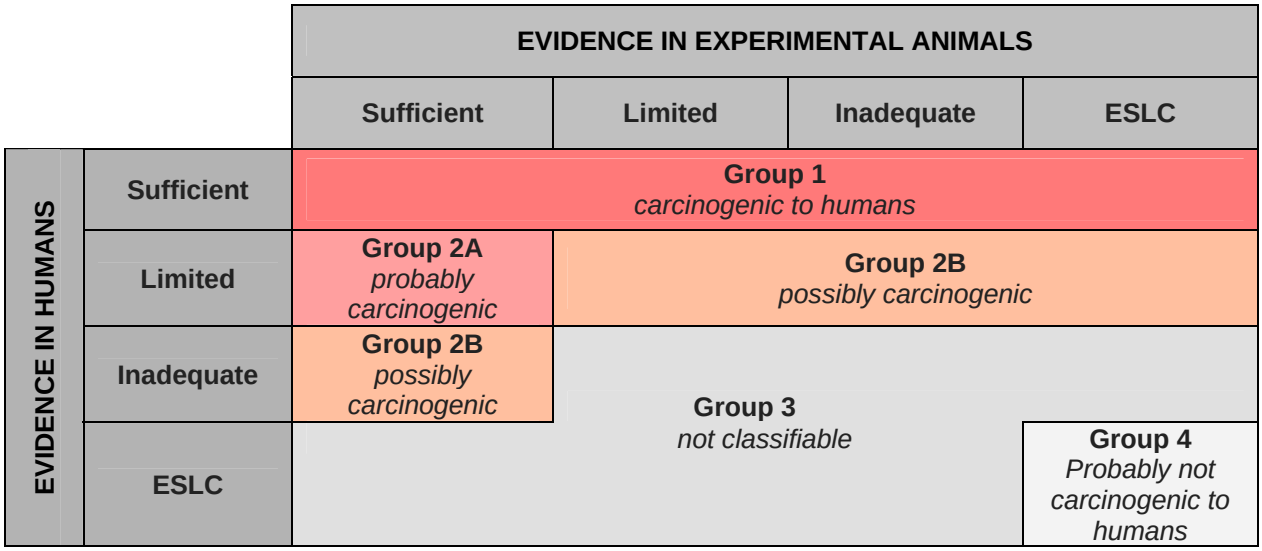
The evaluation

The categorization of an agent is a matter of scientific judgment. The strength of the evidence for carcinogenicity arising from human and experimental animal data is evaluated using standard terms. The strength of the mechanistic data is characterized and complements this first judgment.

The evidence relevant to carcinogenicity from studies in humans and experimental animals is classified into one of the following categories:

- **Sufficient :** A causal relationship has been established.
- **Limited :** A positive association has been observed but chance, bias or confounding could not be ruled out with reasonable confidence.
- **Inadequate :** The studies cannot be interpreted as showing either the presence or absence of a carcinogenic effect.
- **Evidence suggesting lack of carcinogenicity (ESLC) :** Several adequate studies show that the agent is not carcinogenic. A conclusion of *ESLC* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies.

In plenary session, the Working group combine the human and experimental evaluations to evaluate the carcinogenicity of the agent as it describes below.



Mechanistic data can be pivotal when the human data are inconclusive. For example, if an agent shows inadequate evidence in humans and experimental animals, this agent is classified in the Group 3 (not classifiable). Now, if the same agent presents strong evidence from mechanistic and other relevant data, it can be classified in Group 2B (possibly carcinogenic).

Finally, the body of evidence is considered as a whole, in order to reach an overall evaluation of the carcinogenicity of the agent to humans.

The principles, procedures, and scientific criteria that guide the evaluations are described in the Preamble to the IARC Monographs.

Annexes

Evaluation groups - Definitions

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.

Group 2.
This category includes agents for which, at one extreme, the degree of evidence of carcinogenicity in humans is almost *sufficient*, as well as those for which, at the other extreme, there are no human data but for which there is evidence of carcinogenicity in experimental animals. Agents are assigned to either Group 2A (*probably carcinogenic to humans*) or Group 2B (*possibly carcinogenic to humans*) on the basis of epidemiological and experimental evidence of carcinogenicity and mechanistic and other relevant data. The terms *probably carcinogenic* and *possibly carcinogenic* have no quantitative significance and are used simply as descriptors of different levels of evidence of human carcinogenicity, with *probably carcinogenic* signifying a higher level of evidence than *possibly carcinogenic*.

- **Group 2A:** The agent is *probably carcinogenic to humans*.
  This category is used when there is *limited evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals. In some cases, an agent may be classified in this category when there is *inadequate evidence of carcinogenicity* in humans and *sufficient evidence of carcinogenicity* in experimental animals and strong evidence that the carcinogenesis is mediated by a mechanism that also operates in humans. Exceptionally, an agent may be classified in this category solely on the basis of *limited evidence of carcinogenicity* in humans. An agent may be assigned to this category if it clearly belongs, based on mechanistic considerations, to a class of agents for which one or more members have been classified in Group 1 or Group 2A.

- **Group 2B:** The agent is *possibly carcinogenic to humans*.
  This category is used for agents for which there is *limited evidence of carcinogenicity* in humans and less than *sufficient evidence of carcinogenicity* in experimental animals. It may also be used when there is *inadequate evidence of carcinogenicity* in humans but there is *sufficient evidence of carcinogenicity* in experimental animals. 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. An agent may be classified in this category solely on the basis of strong evidence from mechanistic and other relevant data.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.
This category is used most commonly for agents for which the evidence of carcinogenicity is *inadequate* in humans and *inadequate* or *limited* in experimental animals.
Exceptionally, agents for which the evidence of carcinogenicity is *inadequate* in humans but *sufficient* in experimental animals may be placed in this category when there is strong evidence that the mechanism of carcinogenicity in experimental animals does not operate in humans.

Agents that do not fall into any other group are also placed in this category.
An evaluation in Group 3 is not a determination of non-carcinogenicity or overall safety. It often means that further research is needed, especially when exposures are widespread or the cancer data are consistent with differing interpretations.

Group 4: The agent is *probably not carcinogenic to humans*.
This category is used for agents for which there is *evidence suggesting lack of carcinogenicity* in humans and in experimental animals. In some instances, agents for which there is *inadequate evidence of carcinogenicity* in humans but *evidence suggesting lack of carcinogenicity* in experimental animals, consistently and strongly supported by a broad range of mechanistic and other relevant data, may be classified in this group.

Evidence for studies in humans - Definition

As shown previously, the evidence relevant to carcinogenicity is evaluated using standard terms. For studies in humans, evidence is defined into one of the following categories:

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 the exposure and cancer in studies in which chance, bias and confounding could be ruled out with reasonable confidence. A statement that there is *sufficient evidence* is followed by a separate sentence that identifies the target organ(s) or tissue(s) where an increased risk of cancer was observed in humans. Identification of a specific target organ or tissue does not preclude the possibility that the agent may cause cancer at other sites.

Limited evidence of carcinogenicity: A positive association has been observed between exposure to the agent and cancer for which a causal interpretation is considered by the Working Group to be credible, but chance, bias or confounding could not be ruled out with reasonable confidence.

Inadequate evidence of carcinogenicity: The available studies are of insufficient quality, consistency or statistical power to permit a conclusion regarding the presence or absence of a causal association between exposure and cancer, or no data on cancer in humans are available.

Evidence suggesting lack of carcinogenicity: There are several adequate studies covering the full range of levels of exposure that humans are known to encounter, which are mutually consistent in not showing a positive association between exposure to the agent and any studied cancer at any observed level of exposure. The results from these studies alone or combined should have narrow confidence intervals with an upper limit close to the null value (e.g. a relative risk of 1.0). Bias and confounding should be ruled out with reasonable confidence, and the studies should have an adequate length of follow-up. A conclusion of *evidence suggesting lack of carcinogenicity* is inevitably limited to the cancer sites, conditions and levels of exposure, and length of observation covered by the available studies. In addition, the possibility of a very small risk at the levels of exposure studied can never be excluded.

In some instances, the above categories may be used to classify the degree of evidence related to carcinogenicity in specific organs or tissues.