International Agency for Research on Cancer

World Health Organization

IARC Monographs on the Identification of Carcinogenic Hazards to Humans

Questions and Answers

What does the *IARC Monographs* Programme do?

The *IARC Monographs* Programme identifies and evaluates the preventable causes of cancer in humans. Since 1971, more than 1000 agents have been evaluated.

What types of agents or substances are evaluated?

The *IARC Monographs* Programme evaluates chemicals (e.g. formaldehyde), complex mixtures (e.g. air pollution), occupational exposures (e.g. work in coke production), physical agents (e.g. solar radiation), biological agents (e.g. hepatitis B virus), pharmaceuticals (e.g. diethylstilbestrol), and other important factors (e.g. tobacco smoking).

How does the *IARC Monographs* Programme choose which agents to evaluate?

On the basis of the recommendations of an independent Advisory Group of international experts, the *IARC Monographs* Programme evaluates agents that are suspected to cause cancer. Agents are recommended for evaluation when there is evidence that people may be exposed, and when there is also scientific evidence available to evaluate carcinogenicity. In 2019, an Advisory Group recommended a wide variety of agents or substances for a new or updated evaluation by the *IARC Monographs* Programme. These agents may have different impacts on public health. For example, air pollution has a high impact because everyone is exposed to air pollution at some level, even if exposure levels are generally low. In contrast, occupational exposures, such as those involved in firefighting, may be very high and can therefore have a marked public health impact even if fewer people are exposed through their work.

How is the evaluation carried out?

A Working Group of independent international experts carries out the evaluation. The independent experts assemble and critically review the scientific evidence according to strict criteria. These criteria focus on determining the strength of the available evidence that the agent causes cancer, as described in the Preamble to the *IARC Monographs*, which is available here: https://monographs.iarc.fr/wp-content/uploads/2019/07/Preamble-2019.pdf.

IARC Monographs on the
Identification of Carcinogenic Hazards to Humans

Questions and Answers

The experts review the data available globally on situations in which people are exposed to the agent. They also critically review three different types of data:

1. Epidemiological studies on cancer in humans exposed to the agent (scientific evidence of carcinogenicity in humans)

2. Experimental studies on cancer in laboratory animals treated with the agent (scientific evidence of carcinogenicity in experimental animals)

3. Studies on whether the agent has any of the recognized key characteristics of human carcinogens (scientific evidence on carcinogen mechanisms).

During the in-person meeting in Lyon, France, the Working Group finalizes the scientific review and evaluation of these three streams of evidence. The Working Group also combines its conclusions into a consensus overall evaluation of the strength of the evidence of the carcinogenicity of the agent to humans. The Working Group classifies the agent into one of four categories.

What are the classification categories?

The Working Group classifies an agent into one of four categories, ranging from *carcinogenic to humans* (Group 1) to *not classifiable as to its carcinogenicity to humans* (Group 3). The categories of the classification indicate the strength of the evidence as to whether an agent is capable of causing cancer (technically called "hazard"), **but it does not measure the likelihood that cancer will occur (technically called "risk") at a particular level of exposure to the agent.**

What are the four different categories into which agents are classified?

Group 1: The agent is *carcinogenic to humans*

This category is used when there is *sufficient evidence of carcinogenicity* in humans. In other words, there is convincing evidence that the agent causes cancer in humans. The evaluation is usually based on the results of epidemiological studies showing development of cancer in exposed humans. Agents can also be classified in Group 1 on the basis of *sufficient evidence of carcinogenicity* in experimental animals supported by *strong* evidence in exposed humans that the agent exhibits one or more of the recognized key characteristics of human carcinogens.

Group 2

This category includes agents with a range of evidence for carcinogenicity in humans and in experimental animals. At one extreme of the range are agents with positive but not conclusive evidence in humans. At the other extreme are agents for which evidence in humans is not available but for which there is *sufficient evidence of carcinogenicity* in experimental animals. There are two subcategories, which indicate different levels of evidence.

IARC Monographs on the
Identification of Carcinogenic Hazards to Humans

Questions and Answers

Group 2A: The agent is *probably carcinogenic to humans*

This category is used when there is *limited evidence of carcinogenicity* in humans and either *sufficient evidence of carcinogenicity* in experimental animals or *strong* mechanistic evidence, showing that the agent exhibits key characteristics of human carcinogens. *Limited evidence of carcinogenicity* means that a positive association has been observed between exposure to the agent and cancer but that other explanations for the observations (technically termed "chance", "bias", or "confounding") could not be ruled out with reasonable confidence. This category may also be used when there is *inadequate evidence regarding carcinogenicity* in humans but both *sufficient evidence of carcinogenicity* in experimental animals and *strong* mechanistic evidence in human cells or tissues.

Group 2B: The agent is *possibly carcinogenic to humans*

This category is generally used when only one of the following evaluations has been made by the Working Group:

- *limited evidence of carcinogenicity* in humans
- *sufficient evidence of carcinogenicity* in experimental animals
- *strong* mechanistic evidence, showing that the agent exhibits key characteristics of human carcinogens.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans*

This category is used most commonly when the evidence of carcinogenicity in humans is *inadequate*, the evidence of carcinogenicity in experimental animals is *limited* (or *inadequate*), and the mechanistic evidence is *limited* (or *inadequate*). *Limited evidence of carcinogenicity* in experimental animals means that the available information suggests a carcinogenic effect but is not conclusive.

How are these classifications used? Can IARC enforce regulations based on these classifications?

IARC is a research organization that evaluates the evidence on the causes of cancer but does not make health recommendations. Health and regulatory agencies include IARC evaluations in their consideration of actions to prevent exposure to potential carcinogens. IARC does not recommend regulations, legislation, or public health interventions, which remain the responsibility of individual governments and other international organizations.

What does the classification mean in terms of risk?

The classification indicates the strength of the evidence that a substance or agent can cause cancer. The *IARC Monographs* Programme seeks to identify agents that are cancer hazards, meaning they pose the potential for the exposure to cause cancer. However, the classification does not indicate the level of risk associated with a given level or circumstance of exposure. The cancer risk associated with substances or agents assigned the same classification may be very different, depending on factors such as the type and extent of exposure and the degree of the effect of the agent at a given level of exposure.

IARC Monographs on the
Identification of Carcinogenic Hazards to Humans

Questions and Answers

What is the difference between risk and hazard?

The *IARC Monographs* Programme **identifies cancer hazards but does not evaluate the risks associated with specific levels or circumstances of exposure**.

The distinction between *hazard* and *risk* is important. An agent is considered a cancer *hazard* if it is capable of causing cancer under some circumstances. *Risk* measures the probability that cancer will occur, taking into account the level of exposure to the agent. The *IARC Monographs* Programme may identify cancer hazards even when risks are very low with known patterns of use or exposure. Recognition of such carcinogenic hazards is important because new uses or unforeseen exposures could lead to risks that are much higher than those currently seen.

What do classifications in Groups 2A and 2B mean?

Group 2A means that the agent is **probably** carcinogenic to humans. For agents in this category, there is usually convincing evidence that the agent causes cancer in laboratory animals and some evidence that it could cause cancer in humans, but the evidence in humans is not conclusive. There could also be consistent mechanistic evidence, showing that the agent exhibits one or more of the recognized key characteristics of human carcinogens, or that it belongs (based on mechanistic considerations) to a class of agents for which one or more members have been classified as *carcinogenic to humans* or *probably carcinogenic to humans*.

Group 2B means that the agent is **possibly** carcinogenic to humans. Agents can be classified in Group 2B in several different ways. Usually a classification of Group 2B means that there is convincing evidence that the agent causes cancer in experimental animals but little or no information about whether it causes cancer in humans. This category can also be used when there is some evidence that the agent could cause cancer in humans and in experimental animals but neither the evidence in humans nor the evidence in experimental animals is convincing enough to permit a definite conclusion to be drawn. There may also be consistent mechanistic evidence, showing that the agent exhibits one or more of the recognized key characteristics of human carcinogens.

For example, radiofrequency electromagnetic fields are classified in Group 2B because there is evidence that falls short of being conclusive that exposure may cause cancer in humans and in experimental animals. Whole leaf extract of aloe vera is also classified in Group 2B, on the basis of studies showing that it causes cancer in rats, but it has not been studied in humans.

Why should two substances or agents classified in the same Group not be compared?

The classifications reflect the strength of the scientific evidence as to whether an agent can cause cancer in humans, but they do not reflect how high the risk of developing cancer is at a given exposure level. The types of exposures, the extent of risk, the people who may be at risk, and the cancer types linked with the agent can be very different across agents. Therefore, comparisons within a category can be misleading.

IARC Monographs on the
Identification of Carcinogenic Hazards to Humans

Questions and Answers

First, exposures may vary widely. For example, there is widespread exposure to the Group 1 agent air pollution, whereas far fewer people would be exposed to certain Group 1 chemicals, such as 1,2-dichloropropane. Second, the magnitude of risk associated with exposure to two agents may be very different. Active smoking carries a much higher risk of lung cancer than do second-hand smoke or air pollution, although all three are classified in Group 1. Third, the number of resulting cancers can be different; for example, tobacco smoking causes some common cancer types, whereas 1,2-dichloropropane causes a rare cancer of the bile duct. This also applies to Group 2 agents. For example, radiofrequency electromagnetic fields and the prescription drug digoxin are both classified in Group 2B.

In summary, because the Groups indicate the strength of the evidence regarding a cancer *hazard* and not the cancer *risk* at a given level of exposure, the cancer risk associated with two agents classified in the same Group may be very different.

What is the impact of the revised Preamble on the current classifications?

The Preamble to the *IARC Monographs* was revised in January 2019. IARC maintains a list of current classifications on its website (see https://monographs.iarc.fr/agents-classified-by-the-iarc/). Although the revised Preamble provides clarifications on how evidence is evaluated and synthesized in overall evaluations, all current classifications remain in effect.

Agents may be re-evaluated according to the most recent Preamble when significant additional scientific evidence becomes available. In 2019, an Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020-2024 considered a broad set of more than 170 agents (many with existing evaluations) received in response to a public call for nominations. The Advisory Group recommended a number of currently classified agents for re-evaluation with high or medium priority in the forthcoming 5-year period. A full list of the recommended priorities is available in the published summary of the Advisory Group meeting (see https://www.thelancet.com/journals/lanonc/article/PIIS1470-2045(19)30246-3/fulltext), and more information is provided in the full Advisory Group report (https://monographs.iarc.fr/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf).

Where can I find the list of agents evaluated and their categories?

The list of agents classified by the *IARC Monographs* Programme can be found at:
https://monographs.iarc.fr/agents-classified-by-the-iarc/.

More information about the *IARC Monographs* Programme is available at:
https://monographs.iarc.fr/.