International Agency for Research on Cancer

World Health Organization

26 June 2023 (updated 27 June 2023)

Aspartame
Questions and Answers (Q&A)

IARC has assessed the potential carcinogenic effect of aspartame (hazard identification). Following this, the Joint FAO/WHO Expert Committee on Food Additives (JECFA) will update its risk assessment exercise on aspartame, including the reviewing of the acceptable daily intake and dietary exposure assessment for aspartame.

The results of both evaluations will be made available together, on 14 July 2023.

Background

Aspartame is a non-nutritive sweetener widely used since the 1980s as a table-top sweetener, in low-calorie beverages such as diet soda, in prepared food, and in chewing gum, gelatin, ice cream, and breakfast cereals, as well as in medications, such as cough drops, and other products such as toothpaste.

The safety of aspartame was evaluated in 1981 by the Joint FAO/WHO Expert Committee on Food Additives (JECFA), a programme of risk assessment for additives and contaminants in food, and an acceptable daily intake (ADI) was established at 40 mg/kg body weight per day.

Given the availability of new research results, the Advisory Group to Recommend Priorities for the *IARC Monographs* recommended that aspartame be evaluated with high priority during 2020–2024 (for cancer hazard identification). Aspartame was also recommended for evaluation by the WHO/JECFA committee (for risk assessment).

The two evaluations are complementary. An *IARC Monographs* Working Group assessed the potential carcinogenic hazard of aspartame on 6–13 June 2023, while JECFA is conducting a risk assessment between 27 June and 6 July 2023, including a review of the acceptable daily intake and dietary exposure assessment for aspartame.

The sequence of these evaluations and the close collaboration between the *IARC Monographs* programme Secretariat and the WHO/JECFA Secretariat has permitted a comprehensive evaluation of the health effects of aspartame consumption based on the latest available evidence.

The aim of hazard identification is to identify something that has the potential to harm people, whereas the aim of a risk assessment is to assess the likelihood of a hazard causing harm. This is why

it is important to look at both findings together. These complementary results will be announced jointly by IARC and JECFA on 14 July 2023.

What is the relationship between IARC and WHO?

The International Agency for Research on Cancer (IARC) is the specialized cancer research agency of WHO, established in May 1965 by a resolution of the World Health Assembly. IARC is governed by its Governing Council and Scientific Council; the former comprises representatives from each Participating State, plus the WHO Director-General. IARC has its own defined scientific methods as set by the Preamble to the *IARC Monographs*. More information about IARC governance can be found here: https://www.iarc.who.int/cards_page/organization-and-management/.

IARC has a unique dual position as an independent international cancer research institute, and as the specialized cancer research agency of the World Health Organization (WHO) within the United Nations system.

How is the IARC evaluation carried out?

An *IARC Monographs* 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.who.int/iarc-monographs-preamble-preamble-to-the-iarc-monographs/.

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 four different categories into which agents are classified by IARC?

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.

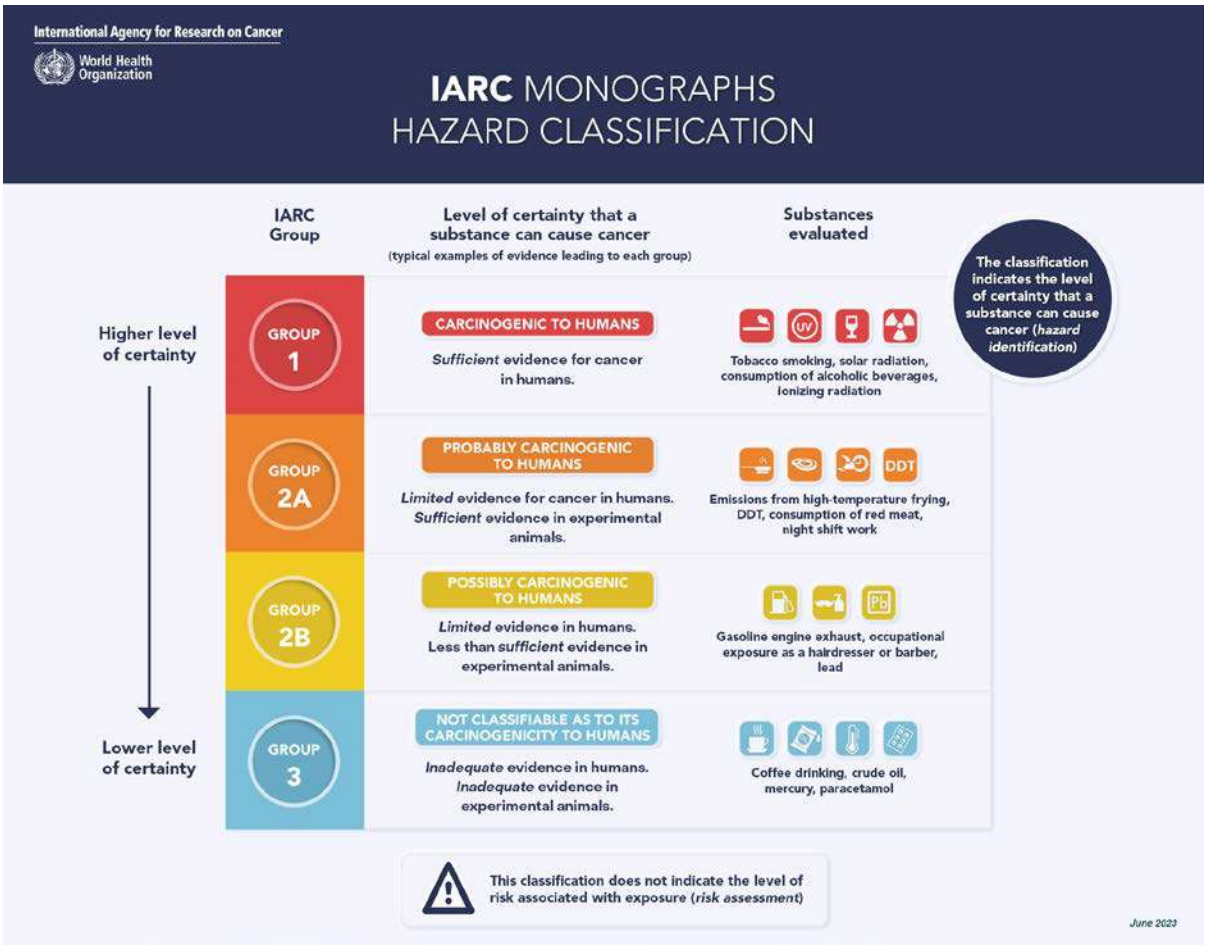
Group 2: This category includes agents with a range of evidence for carcinogenicity in humans and in experimental animals. At one extreme of the range are agents with positive but not conclusive evidence in humans. At the other extreme are agents for which evidence in humans is not available but for which there is *sufficient* evidence of carcinogenicity in experimental animals. There are two subcategories, which indicate different levels of evidence.

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 in experimental animals.



What does the IARC classification indicate?

The *IARC Monographs* classifications reflect the strength of the scientific evidence as to whether an agent can cause cancer in humans, but they do not indicate the degree of risk of developing cancer at a given exposure level or with a given route of exposure. The types of exposure, 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.

Since the IARC Group indicates the strength of the evidence regarding a cancer hazard and not the cancer risk at a given level of exposure, the cancer risk (at typical exposure levels) associated with two agents classified in the same IARC Group may be very different.

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

IARC is a research organization that evaluates evidence on the causes of cancer but does not make health recommendations. Health and regulatory agencies may include *IARC Monographs* 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.

How many studies were evaluated in the IARC assessment of aspartame?

More than 7000 references were collected and screened. Approximately 1300 studies were included in the review and made available to the Working Group.

Has the *IARC Monographs* programme previously evaluated food additives?

Over the course of its 51-year history, the *IARC Monographs* programme has evaluated over 70 different substances that have been or are used as food additives. Examples include the first sweetener dulcin, evaluated in 1968, as well as cyclamates, d-limonene, coumarin, the artificial sweetener saccharin, quinoline, mineral oils, and many others.

Why has IARC decided to evaluate aspartame?

Following 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 that may lead to a determination of carcinogenicity (or probable or possible carcinogenicity).

In 2019, the Advisory Group to Recommend Priorities for the *IARC Monographs* recommended a wide variety of agents or substances for a new or updated evaluation by the *IARC Monographs* programme during 2020–2024. These agents may have different impacts on public health. The food additive aspartame was accorded high priority for evaluation by the *IARC Monographs* programme based on emerging cancer evidence in humans and in laboratory animals.

A Working Group evaluated the carcinogenicity of aspartame for the first time at *IARC Monographs* Meeting 134, which took place on 6–13 June 2023 in Lyon, France.

What are the differences between JECFA's and IARC's evaluations?

In the *IARC Monographs* programme, IARC undertakes hazard identification, which is the first fundamental step to understanding carcinogenicity. Hazard identification aims to identify the specific properties of the agent and its potential to cause harm, i.e. the potential for an agent to cause cancer.

The JECFA programme undertakes risk assessment, which determines the probability that a specific type of harm (e.g. cancer, reproductive toxicity, genotoxicity) will occur under certain conditions and levels of exposure. As such, it is based on the identified hazard properties of an agent and the

anticipated exposures in specific scenarios, thus considering the routes, conditions, frequency, and levels of exposure. JECFA specifically performs a risk assessment for the dietary exposure scenario since it evaluates food additives.

Did IARC work with JECFA on these hazard and risk evaluations?

The two evaluations are independent. The *IARC Monographs* programme and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) have distinct roles, Working Group members, and rules and principles governing the evaluations of hazard and risk. However, in the case of aspartame the two secretariats followed side-by-side the progress of the evaluation, informed each other about the data available, and shared members of the Secretariat.