

14 July 2023

IARC Monographs evaluate the carcinogenicity of aspartame, methyleugenol, and isoeugenol

Questions and Answers (Q&A) for Methyleugenol and Isoeugenol

The meeting for *IARC Monographs* Volume 134: Aspartame, Methyleugenol, and Isoeugenol, convened by the International Agency for Research on Cancer (IARC) in Lyon, France, took place on 6–13 June 2023.

The Working Group of 25 [independent experts](#) (including one Invited Specialist) from 12 countries evaluated the carcinogenicity of aspartame, methyleugenol, and isoeugenol.

More information about the meeting is available on the *IARC Monographs* website: <https://monographs.iarc.who.int/iarc-monographs-volume-134/>.

The outcome of the assessment has been published in a summary article in *The Lancet Oncology*¹ and will be described in detail in Volume 134 of the *IARC Monographs*, to be published in 2024.

The Questions and Answers (Q&As) below focus exclusively on the results of the evaluation for methyleugenol and isoeugenol.

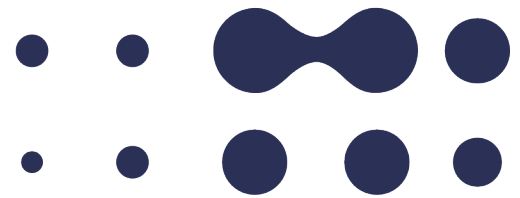
Regarding aspartame, the results for the hazard identification by IARC and the risk assessment carried out subsequently by the Joint Food and Agriculture Organization/World Health Organization (FAO/WHO) Expert Committee on Food Additives (JECFA) have been made available in a joint communication. For more information, see the corresponding [IARC News item](#) and the IARC [Featured News](#) page on aspartame.

What are the results of the evaluation for methyleugenol?

Methyleugenol was classified as *probably carcinogenic to humans* (Group 2A) on the basis of:

- *inadequate* evidence regarding cancer in humans (no studies were available);
- *sufficient* evidence for cancer in experimental animals (based on an increased incidence either of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in two species); and
- *strong* mechanistic evidence in experimental systems, including humanized mice, and supported by studies in humans.

¹ Riboli E, Beland FA, Lachenmeier DW, Marques MMSD, Phillips D, Schernhammer E, et al. (2023). Carcinogenicity of aspartame, isoeugenol, and methyleugenol. *Lancet Oncol*, Published online 13 July 2023; [https://doi.org/10.1016/S1470-2045\(23\)00341-8](https://doi.org/10.1016/S1470-2045(23)00341-8)



What are the results of the evaluation for isoeugenol?

Isoeugenol was classified as *possibly carcinogenic to humans* (Group 2B) on the basis of:

- *inadequate* evidence regarding cancer in humans (no studies were available);
- *sufficient* evidence for cancer in experimental animals (based on an increased incidence either of malignant neoplasms or of an appropriate combination of benign and malignant neoplasms in two species); and
- *inadequate* mechanistic evidence in experimental systems.

Table 1. Summary of classifications of methyleugenol and isoeugenol in IARC Monographs Volume 134

Agent	Evidence stream			Overall evaluation
	Cancer in humans	Cancer in experimental animals	Mechanistic evidence (key characteristics of carcinogens)	
Methyleugenol	<i>Inadequate</i>	<i>Sufficient</i>	<i>Strong</i>	Group 2A
Isoeugenol	<i>Inadequate</i>	<i>Sufficient</i>	<i>Inadequate</i>	Group 2B

What does classification in Group 2A or Group 2B mean?

Group 2:

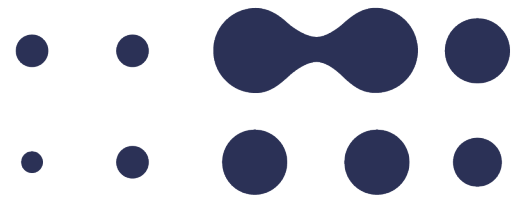
This category includes agents with a range of evidence regarding cancer in humans and in experimental animals. At one extreme of the range are agents with positive but not conclusive evidence regarding cancer in humans. At the other extreme are agents for which evidence in humans is not available but for which there is *sufficient* evidence for cancer 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 in three different scenarios:

1. When there is *limited* evidence for cancer in humans and *sufficient* evidence for cancer in experimental animals (*“limited”* evidence for cancer in humans” 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);
2. When there is *limited* evidence for cancer in humans and *strong* mechanistic evidence;
3. When there is *sufficient* evidence for cancer in experimental animals and *strong* mechanistic evidence in human primary cells or tissues.

These scenarios may also occur simultaneously within a Group 2A classification.



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

This category is used when there is *limited* evidence for cancer in humans and less-than-sufficient evidence for cancer in experimental animals. It may also be used when the evidence regarding cancer in humans does not permit a conclusion to be drawn (referred to as *inadequate* evidence) but there is *sufficient* evidence for cancer in experimental animals or *strong* mechanistic evidence.

Have these agents previously been evaluated by the *IARC Monographs* programme?

Methyleugenol was previously evaluated by the *IARC Monographs* programme in 2013 as *possibly carcinogenic to humans* (Group 2B)² on the basis of *inadequate* evidence regarding cancer in humans and *sufficient* evidence for cancer in experimental animals. JECFA has conducted a risk assessment of methyleugenol and listed it as a flavouring agent (in 1981). No acceptable daily intake (ADI) has been established.

Isoeugenol was evaluated for the first time by the *IARC Monographs* programme. The agent has been listed as a flavouring agent by JECFA (in 2003), with “no safety concerns at current levels of intake”. No acceptable daily intake (ADI) has been established.

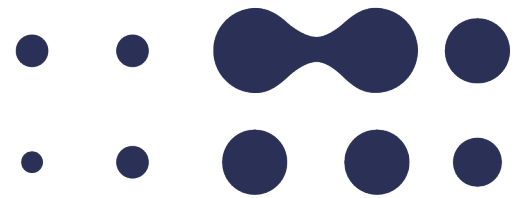
Why were methyleugenol and isoeugenol evaluated?

The Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024³ recommended that both methyleugenol and isoeugenol should be evaluated with high priority by the *IARC Monographs* programme.

The recommendation was based on the availability of new mechanistic data and additional evidence on cancer in rodents since the previous *IARC Monographs* evaluation (in 2013) for methyleugenol, and on new data on cancer in rodents for isoeugenol.

² IARC (2013). Some chemicals present in industrial and consumer products, food, and drinking-water. *IARC Monogr Eval Carcinog Risks Hum.* 101:1–553. Available from: <https://publications.iarc.fr/125>.

³ IARC (2019). Report of the Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024. Lyon, France: International Agency for Research on Cancer. Available from: https://monographs.iarc.who.int/wp-content/uploads/2019/10/IARCMonographs-AGReport-Priorities_2020-2024.pdf.



Was there a key new study or evidence that was used in the re-evaluation of methyleugenol?

A two-year bioassay performed by the United States National Toxicology Program (NTP)⁴ was re-evaluated using the most recent criteria described in the updated Preamble to the *IARC Monographs*⁵. In addition, robust mechanistic evidence had become available showing that methyleugenol induces DNA adducts and genotoxicity in experimental animals, and supported by studies in humans⁶.

Was there a key new study or evidence that was used in the evaluation of isoeugenol?

A key study used in the evaluation of isoeugenol was a two-year bioassay⁷ performed by the NTP showing that isoeugenol induces liver tumours in mice.

Who is exposed to methyleugenol and isoeugenol, and how?

Methyleugenol belongs to a class of plant-derived volatile chemicals called phenylpropenes, and it is a flavour and fragrance compound that occurs naturally in essential oils of various plants. The general population is exposed, mostly to low levels, through the ingestion of food or dermally while using personal-care products. Methyleugenol is used in cosmetics and personal-care products and as an insect attractant. Its use as a flavouring agent has recently been prohibited in the European Union (EU) and the USA. It is still present in various foods and consumer products because of its natural occurrence in herbs and spices.

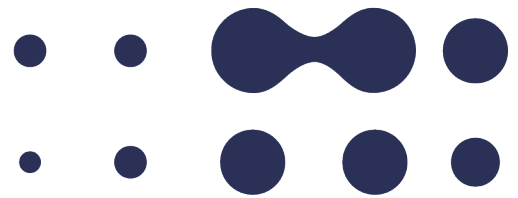
Isoeugenol belongs to same class of plant-derived volatile chemicals as methyleugenol, but it is used mainly as a fragrant essential oil. It is found in various spices and herbs and occurs in wood smoke. Isoeugenol is added to food, cosmetics, household products, animal feed, and veterinary medicines. Workers involved in the synthesis of isoeugenol or the handling of isoeugenol-containing products and firefighters may be exposed via dermal and/or inhalation routes. Isoeugenol is “generally recognized as safe (GRAS)” by the United States Food and Drug Administration for use in foods. In the EU (2003/15/EC), the maximum authorized concentration in a finished cosmetic product is 0.02%, except for oral products.

⁴ National Toxicology Program (2000). NTP toxicology and carcinogenesis studies of methyleugenol (CAS No. 93-15-2) in F344/N rats and B6C3F₁ mice (gavage studies). *Natl Toxicol Program Tech Rep Ser.* 491:1–412.

⁵ IARC (2019). Preamble to the *IARC Monographs*. Lyon, France: International Agency for Research on Cancer. Available from: <https://monographs.iarc.who.int/wpcontent/uploads/2019/07/Preamble-2019.pdf>.

⁶ Tremmel R, Herrmann K, Engst W, Meinel W, Klein K, Glatt H, et al. (2017). Methyleugenol DNA adducts in human liver are associated with *SULT1A1* copy number variations and expression levels. *Arch Toxicol.* 91:3329–39.

⁷ National Toxicology Program (2010). Toxicology and carcinogenesis studies of isoeugenol (CAS No. 97-54-1) in F344/N rats and B6C3F₁ mice (gavage studies). *Natl Toxicol Program Tech Rep Ser.* 551:1–178.



What cancer sites were associated with exposure to methyleugenol?

In experimental animals, both methyleugenol exposure and isoeugenol exposure are associated mainly with liver tumours.

What about the risk to consumers exposed through fragrance? Should they be concerned?

IARC is a research organization that generates and evaluates evidence related to the causes of cancer but does not make health recommendations. However, the evaluations made by the *IARC Monographs* programme are often used as a basis for national and international policies, guidelines, and recommendations to reduce exposures in order to minimize cancer risks.

What does the *IARC Monographs* classification mean in terms of risk?

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

On the basis of these evaluations, what recommendations does IARC make?

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You can find more information on the *IARC Monographs* evaluation process here: https://monographs.iarc.who.int/wp-content/uploads/2018/07/QA_ENG.pdf.

For more information, please contact:

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The International Agency for Research on Cancer (IARC) is part of the World Health Organization. Its mission is to coordinate and conduct research on the causes of human cancer, the mechanisms of carcinogenesis, and to develop scientific strategies for cancer control. The Agency is involved in both epidemiological and laboratory research and disseminates scientific information through publications, meetings, courses, and fellowships. If you wish your name to be removed from our press release emailing list, please write to com@iarc.who.int.