International Agency for Research on Cancer

World Health Organization

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IARC Monographs evaluate the carcinogenicity of automotive gasoline and some oxygenated gasoline additives

IARC Monographs Volume 138

Questions and Answers (Q&A)

The meeting for *IARC Monographs* Volume 138: Automotive Gasoline and Some Oxygenated Gasoline Additives, convened by the International Agency for Research on Cancer (IARC) in Lyon, France, took place between 25 February and 4 March 2025.

The Working Group of 20 international experts from 16 countries evaluated the carcinogenicity of automotive gasoline and some oxygenated gasoline additives, specifically: methyl *tert*-butyl ether (MTBE), ethyl *tert*-butyl ether (ETBE), *tert*-butyl alcohol (TBA), diisopropyl ether (DIPE), and *tert*-amyl methyl ether (TAME).

More information about the meeting is available on the *IARC Monographs* website: https://monographs.iarc.who.int/iarc-monographs-volume-138/.

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 138 of the *IARC Monographs*, to be published in 2026.

1. What was evaluated in *IARC Monographs* Meeting 138?

The Working Group for *IARC Monographs* Volume 138 evaluated automotive gasoline and five oxygenated gasoline additives (MTBE, ETBE, TBA, DIPE, and TAME). Studies associated with gasoline fuel and vapours were evaluated. Gasoline exhaust and diesel exhaust were not evaluated at the present meeting. Gasoline exhaust and diesel exhaust were previously evaluated by the *IARC Monographs* programme in 2012, in Volume 105.[2] Diesel engine exhaust is classified as *carcinogenic to humans* (Group 1). Gasoline engine exhaust is classified as *possibly carcinogenic to humans* (Group 2B).

2. What is automotive gasoline?

[1] Turner MC, Godderis L, Guénel P, Hopf N, Quintanilla-Vega B, Soares-Lima SC, et al. (2025). Carcinogenicity of automotive gasoline and some oxygenated gasoline additives. *Lancet Oncol*. Published online 21 March 2025; https://doi.org/10.1016/S1470-2045(25)00165-2

[2] IARC (2013). Diesel and gasoline engine exhausts and some nitroarenes. *IARC Monogr Eval Carcinog Risks Hum*. 105:1–703. PMID:26442290. Available from: https://publications.iarc.who.int/129.

Automotive gasoline is a commercial product and a complex mixture, primarily used in internal combustion engines. The typical components of gasoline are volatile, petroleum-derived hydrocarbons, including alkanes, alkenes, and aromatics (primarily C5–C10), which are blended with various additives. Among these volatile additives, benzene is classified by the *IARC Monographs* programme as *carcinogenic to humans* (Group 1).[3] The concentration of benzene in gasoline is highly regulated in most countries. Various other components of gasoline have also been previously evaluated by the *IARC Monographs* programme. Automotive gasoline as a complex mixture was previously evaluated as *possibly carcinogenic to humans* (Group 2B) in 1988, in Volume 45.[4]

3. Who is exposed to automotive gasoline, and how?

Occupational and general population exposure occurs primarily through inhalation of gasoline vapours. Occupational exposure is expected mainly during the production and transport of gasoline and during vehicle refuelling. Service station attendants are exposed to higher levels of gasoline than is the general population.

4. What are oxygenated gasoline additives?

Oxygenated gasoline additives are used to enhance octane rating and to increase combustion efficiency, as well as minimize atmospheric pollution. There are several oxygenated additives in use, especially since the phase-out of leaded gasoline. Their use in gasoline varies among different regions and over time. For example, the use of MTBE and ETBE has been discontinued in the USA and largely replaced with ethanol, whereas these oxygenated additives are still used in Europe, in some Asian countries, and elsewhere.

5. Who is exposed to oxygenated gasoline additives, and how?

Workers may be exposed during the production of these agents and via gasoline vapours when present as additives. Occupational exposure has been measured among ship and railroad tanker workers, gasoline pump repairers and inspectors, service station attendants, and automobile mechanics. The general population is mainly exposed via gasoline vapours at service stations, in air pollution, or via contaminated water and soil in the context of gasoline spills.

6. What are the results of the evaluation?

The results of the evaluation are summarized in Table 1.

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[3] IARC (2018). Benzene. *IARC Monogr Eval Carcinog Risks Hum*. 120:1–301. PMID:31769947. Available from: https://publications.iarc.who.int/576.

[4] IARC (1989). Occupational exposures in petroleum refining; crude oil and major petroleum fuels. *IARC Monogr Eval Carcinog Risks Hum*. 45:1–322. PMID:2664246. Available from: https://publications.iarc.who.int/63.

Table 1. Summary of classifications in *IARC Monographs* Volume 138

Agent	Evidence stream			Overall evaluation
	Cancer in humans	Cancer in experimental animals	Mechanistic evidence	
Automotive gasoline	*Sufficient* (bladder cancer and acute myeloid leukaemia, AML)	*Sufficient*	*Strong* in exposed humans and in experimental systems	**Group 1**
Methyl *tert*-butyl ether (MTBE)	*Inadequate*	*Sufficient*	*Limited*	**Group 2B**
Ethyl *tert*-butyl ether (ETBE)	*Inadequate*	*Sufficient*	*Strong* in experimental systems	**Group 2B**
***tert*-Butyl alcohol (TBA)**	*Inadequate*	*Limited*	*Limited*	**Group 3**
Diisopropyl ether (DIPE)	*Inadequate*	*Limited*	*Inadequate*	**Group 3**
***tert*-Amyl methyl ether (TAME)**	*Inadequate*	*Inadequate*	*Inadequate*	**Group 3**

7. How did the Working Group arrive at these classifications?

Automotive gasoline: The Group 1 evaluation for automotive gasoline is based on *sufficient* evidence for cancer in humans and also on the combination of *sufficient* evidence for cancer in experimental animals and *strong* mechanistic evidence for the key characteristics of carcinogens in exposed humans. There was *sufficient* evidence in humans that gasoline exposure causes urinary bladder cancer and acute myeloid leukaemia in adults. There was also *limited* evidence in humans for non-Hodgkin lymphoma (including chronic lymphocytic leukaemia), multiple myeloma, myelodysplastic syndromes, and cancers of the stomach and kidney, based largely on the same types of studies. There was also *limited* evidence for acute lymphoblastic leukaemia in children.

In addition, there was *sufficient* evidence for cancer in experimental animals on the basis of an increase in the incidence of malignant neoplasms in both sexes of two species (mouse and rat) in multiple studies, including one conducted under Good Laboratory Practice (GLP), and *strong* mechanistic evidence, based on consistent

and coherent evidence for the key characteristics of carcinogens showing that automotive gasoline is genotoxic, induces oxidative stress, and induces chronic inflammation in exposed humans, mainly service station attendants.

Methyl *tert*-butyl ether (MTBE): The Group 2B evaluation for MTBE is based on *sufficient* evidence for cancer in experimental animals. Treatment with MTBE caused an increase in the incidence of malignant neoplasms and a combination of benign and malignant neoplasms in both sexes of two species (mouse and rat) in three studies conducted under GLP.

Ethyl *tert*-butyl ether (ETBE): The Group 2B evaluation for ETBE is based on *sufficient* evidence for cancer in experimental animals and on *strong* mechanistic evidence in experimental systems. The *sufficient* evidence for cancer in experimental animals is based on an increase in the incidence of benign and malignant neoplasms in both sexes of a single species (rat) in two studies carried out under GLP. The mechanistic evidence is *strong* because there is consistent and coherent evidence that ETBE alters cell proliferation, cell death, or nutrient supply in experimental systems.

***tert*-Butyl alcohol (TBA):** The Group 3 evaluation for TBA is based on *limited* evidence for cancer in experimental animals, *limited* mechanistic evidence, and *inadequate* evidence regarding cancer in humans.

Diisopropyl ether (DIPE): The Group 3 evaluation for DIPE is based on *limited* evidence for cancer in experimental animals, *inadequate* evidence regarding cancer in humans, and *inadequate* mechanistic evidence.

***tert*-Amyl methyl ether (TAME):** The Group 3 evaluation for TAME is based on *inadequate* evidence regarding cancer in humans and in experimental animals, and *inadequate* mechanistic evidence.

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

Automotive gasoline was evaluated by the *IARC Monographs* programme in 1988 (Volume 45)[4] and classified as *possibly carcinogenic to humans* (Group 2B). MTBE was evaluated in 1999 (Volume 73)[5] and was evaluated as *not classifiable as to its carcinogenicity to humans* (Group 3). ETBE, TBA, DIPE, and TAME have not been previously evaluated by the *IARC Monographs* programme.

9. Why was automotive gasoline re-evaluated?

[5] IARC (1999). Some chemicals that cause tumours of the kidney or urinary bladder in rodents and some other substances. *IARC Monogr Eval Carcinog Risks Hum*. 73:1–674. Available from: https://publications.iarc.who.int/91.

The Advisory Group to Recommend Priorities for the *IARC Monographs* during 2020–2024[6] recommended that automotive gasoline should be re-evaluated with high priority by the *IARC Monographs* programme. This recommendation was based on the publication of new evidence coming from several studies on cancer in humans, cancer in experimental animals, and a large volume of scientific literature on mechanistic data.

10. Why were oxygenated gasoline additives evaluated?

The Advisory Group to Recommend Priorities for the IARC Monographs during 2020–2024[6] recommended that MTBE should be re-evaluated with high priority by the *IARC Monographs* programme. In addition, the Advisory Group recommended that ETBE, TBA, DIPE, and TAME should be evaluated for the first time by the *IARC Monographs*. These recommendations were based on the publication of relevant evidence of cancer in experimental animals and mechanistic evidence.

11. On the basis of this evaluation, what recommendations does IARC make?

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 minimize cancer risks.

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.

12. 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 agents with 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.

13. What are the different strength-of-evidence evaluation groups used by the *IARC Monographs*?

The strength-of-evidence groups that contribute to each evaluation are summarized in Table 2.

[6] 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.

Table 2. Strength-of-evidence groups used by the *IARC Monographs*

Evidence of Cancer in Humans	Evidence of Cancer in Experimental Animals	Mechanistic Evidence	Evaluation
Sufficient			Carcinogenic (Group 1)
	Sufficient	Strong (exposed humans)	
Limited	Sufficient		Probably carcinogenic (Group 2A)
Limited		Strong	
	Sufficient	Strong (human cells or tissues)	
		Strong (mechanistic class)	
Limited			Possibly carcinogenic (Group 2B)
	Sufficient		
		Strong	
	Sufficient	Strong (does not operate in humans)	Not classifiable (Group 3)
All other situations not listed above			

14. What are the four different categories into which agents are classified by the *IARC Monographs*?

Group 1: The agent is *carcinogenic to humans*.

This category is used when there is *sufficient* evidence for cancer 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 the development of cancer in exposed humans. Agents can also be classified in Group 1 on the basis of *sufficient* evidence for cancer in experimental animals supported by *strong* evidence in exposed humans that the agent has mechanistic effects that are important for cancer development. Automotive gasoline reached Group 1 in both of these ways.

Group 2:

This category includes agents with a range of evidence regarding cancer in humans and 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 four 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;
4. When, based on mechanistic considerations, the agent belongs to a class of agents of which one or more is *probably carcinogenic to humans* (Group 2A) or *carcinogenic to humans* (Group 1).

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. It can also be used when there is *strong* mechanistic evidence.

Group 3: The agent is *not classifiable as to its carcinogenicity to humans*.
This category is used most commonly when the evidence is *inadequate* regarding cancer in humans and *inadequate* or *limited* for cancer in experimental animals, and mechanistic evidence is less than *strong*. "*Limited* evidence for cancer in experimental animals" means that the available information suggests a carcinogenic effect but is not conclusive.

15. How was the evidence reviewed in the *IARC Monographs* evaluation?

During an *IARC Monographs* evaluation, experts critically review the scientific evidence according to strict criteria, which focus on determining the strength of the available evidence that the agent causes cancer. These criteria are described in the Preamble to the *IARC Monographs*, which is available on the *IARC Monographs* website: https://monographs.iarc.who.int/wp-content/uploads/2019/07/Preamble-2019.pdf.

The experts critically review four types of data:

- the situations in which people are exposed to the agent;
- epidemiological studies on cancer in humans exposed to the agent (scientific evidence regarding cancer in humans);
- experimental studies of cancer in laboratory animals treated with the agent (scientific evidence regarding cancer in experimental animals); and
- studies on how cancer develops in response to the agent (scientific evidence on carcinogen mechanisms).

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For more information, please contact:

Véronique Terrasse, Communications Team, at +33 (0)6 45 28 49 52 or terrassev@iarc.who.int
or IARC Communications, at com@iarc.who.int

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