Carcinogenicity of automotive gasoline and some oxygenated gasoline additives

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Declaration of interests
JK is a collaborator on a project that receives funding from the Research Council of Norway (a governmental agency) in the form of an industry-collaborative grant requiring 20% of the sum to be covered by industry for common interests of occupational health among petroleum workers; the Research Council of Norway governed the application process independently and the grant did not cover salaries of the principal investigators or any of the collaborators. AT has acted as a pathology consultant, with fees received, for contract research organisations (Evotec and Accelera) for topics unrelated to the agents evaluated at this meeting. All other Working Group Members declare no competing interests

Invited Specialists
None

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Declaration of interests
All Representatives declare no competing interests.

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In February–March, 2025, a Working Group of 20 scientists from 16 countries met at the International Agency for Research on Cancer (IARC) in Lyon, France, to finalise their evaluation of the carcinogenicity of automotive gasoline and some oxygenated gasoline additives.

Automotive gasoline (hereafter, referred to as gasoline) was classified as "carcinogenic to humans" (Group 1) based on "sufficient" evidence for cancer in humans, and the combination of "sufficient" evidence for cancer in experimental animals and "strong" mechanistic evidence in exposed humans. Methyl *tert*-butyl ether (MTBE) and ethyl *tert*-butyl ether (ETBE) were each classified as "possibly carcinogenic to humans" (Group 2B) based on "sufficient" evidence for cancer in experimental animals and also (for ETBE) "strong" mechanistic evidence in experimental systems. *tert*-Butyl alcohol (TBA), diisopropyl ether (DIPE), and *tert*-amyl methyl ether (TAME) were each evaluated as "not classifiable as to its carcinogenicity to humans" (Group 3). These assessments will be published in Volume 138 of the *IARC Monographs*.[1]

Gasoline, a commercial product, is 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. The composition of gasoline has changed over time. Exposure to gasoline is assessed by measuring components (eg, benzene) and their metabolites in air, blood, and urine. Occupational and general population exposure occurs primarily through inhalation of gasoline vapour. Occupational exposure is expected mainly during the production and transport of gasoline and during vehicle refuelling, and includes occupations such as refinery workers, tanker drivers, mechanics, and service station attendants. This evaluation does not include engine exhaust; however, co-exposure to diesel and gasoline engine exhaust can occur in some of these work environments. Compared with the general population, service station attendants are exposed to higher levels of gasoline and similar levels of engine exhaust. Few data on the absorption, distribution, and excretion of gasoline are available, but most individual components of gasoline are absorbed via inhalation and dermally, redistributed to various organs, and mainly exhaled or excreted via urine.

Since the previous classification of gasoline as "possibly carcinogenic to humans" in 1988 (Volume 45), many studies have investigated the association between gasoline exposure and cancer in humans and experimental animals, and the underlying mechanistic evidence.

There is "sufficient" evidence in humans that gasoline causes urinary bladder cancer and acute myeloid leukaemia (AML) in adults. Consistent increases in the incidence of bladder cancer and AML were noted across occupational cohort and case–control studies of service station attendants, gasoline distribution workers,[2] and studies specifically assessing gasoline exposure.[3] Working Group meta-analyses combining these studies found elevated rates of bladder cancer incidence (n=16, meta-rate ratio [RR] 1·31; 95% CI 1·14–1·51) and of adult AML incidence or mortality (n=5, meta-RR 1·51; 95% CI 1·06–2·16). Studies indicating an increased incidence of myelodysplastic syndromes (MDS) were deemed to support the evaluation of AML, as MDS often progresses to AML, but there was "limited" evidence for a causal role of gasoline with MDS itself. Concerns about confounding by smoking or engine exhausts were allayed because lung cancer incidence or mortality was generally not elevated in the available studies. There was also "limited" evidence that gasoline causes non-Hodgkin lymphoma (including chronic lymphocytic leukaemia), multiple myeloma, and cancers of the stomach and kidney; for these cancer types, chance and bias could not be ruled out. There was "limited" evidence that gasoline causes acute lymphoblastic leukaemia (ALL) in children. Studies of parental exposure to gasoline indicated an increased incidence of childhood ALL, although recall bias and chance could not be ruled out. Studies using residential address records indicated an increased incidence of leukaemia in children living within 150 m of service stations, but too few differentiated by leukaemia subtype.

The "sufficient" evidence of cancer in experimental animals after gasoline administration was based on an increase in the incidence of renal tubular cell adenoma or carcinoma (combined) in male Fischer 344 rats;[4] hepatocellular adenoma or carcinoma (combined) in female B6C3F$_1$ mice;[5] renal carcinoma, and renal carcinoma, adenoma, or sarcoma (combined) in male Fischer 344 rats;[5] and total malignant tumours of the nasal cavity in Sprague-Dawley male rats. Numerous studies in service station attendants showed consistent and coherent evidence that gasoline is genotoxic,[6] and induces oxidative stress[6,7] and chronic inflammation.[6,7] Significant increases in micronuclei formation in peripheral blood lymphocytes and buccal exfoliated cells were observed in service station attendants, correlating with exposure to some components of gasoline and exposure duration. Service station attendants also had elevated levels

of oxidative DNA damage endpoints, and compromised antioxidant defence systems. The same studies also showed that chronic exposure to gasoline induced a systemic inflammatory response that correlated with the duration of exposure. There was also suggestive evidence that gasoline induces epigenetic alterations, immunosuppression, and hormonal alterations in service station attendants. In experimental systems, gasoline induced oxidative stress (associated with inflammatory reactions) and altered cell proliferation in the liver of female mice and the kidney of male rats.

MTBE, ETBE, TBA, TAME, and DIPE are volatile compounds used as oxygenated additives in gasoline to increase combustion efficiency, especially since the elimination of lead. All except TAME are listed as high-production-volume chemicals. MTBE and ETBE have been used most widely as gasoline additives, at concentrations up to 15% and 22%, respectively. Although no longer added to gasoline in the USA, MTBE and ETBE are currently used in Europe, Asia, and elsewhere. Workers can be exposed during additive production or via gasoline vapours containing these additives. Occupational exposure has been measured in 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, via air pollution, or via water and soil contaminated by gasoline spills.

MTBE, ETBE, and TBA are readily absorbed, partially exhaled, and distributed through the body. MTBE and ETBE are metabolised to TBA, which is either conjugated or further metabolised, and finally excreted in urine. The "sufficient" evidence of cancer in experimental animals after MTBE administration was based on an increase in the incidence of hepatocellular adenomas, and hepatocellular adenomas or carcinomas (combined) in female CD-1 mice,[8] renal tubular cell adenoma or carcinoma (combined) in male Fischer 344 rats,[8] and brain astrocytoma in male Wistar rats.[9] The mechanistic evidence was "limited" in different experimental systems.

The "sufficient" evidence of cancer in experimental animals after ETBE administration was based on an increase in the incidence of uterine schwannoma in Sprague-Dawley rats by gavage[10] and hepatocellular adenoma with a single instance of hepatocellular carcinoma at the highest tested dose in male Fischer rats by inhalation.[11] In addition, there was consistent and coherent evidence that ETBE induces cell proliferation in the liver of mice and rats and urothelial hyperplasia in rats.

The "limited" evidence in experimental animals for the carcinogenicity of TBA was based on an increase in the incidence of malignant neoplasms and a combination of benign or malignant neoplasms in one sex (male) of a single species (rat). For DIPE, the "limited" evidence for cancer in experimental animals was based on an increase in the incidence of malignant neoplasms in one sex (male) of a single species (rat). For TAME, both animal cancer and mechanistic evidence were "inadequate". For all the gasoline additives, the evidence for cancer in humans was "inadequate" because no studies were available.

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Declaration of interests
DH received travel costs to attend the meeting, paid for by Exxon-Mobil, which is a US multinational oil and gas corporation. GP is a full-time employee of Eni. ER is employed as a toxicologist for a company that produces MTBE, ETBE, and TBA. He receives a salary and owns stock in the company and received funding to travel to the meeting. AS's travel costs to attend the meeting were covered by American Petroleum Institute and American Fuel & Petrochemical Manufacturers.

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All Secretariat declare no competing interests.

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28 October–4 November 2025: Volume 140: Atrazine, alachlor, and vinclozolin

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