

Impact of nitrogen-containing octane boosters used as fuel blending components on health, the environment, air quality, and engines

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Abstract

- Automotive fuels are derived from crude-oil and renewable feedstocks, then undergo modifications of the physical and chemical properties to obtain final formulations with desired specifications. The formulations are usually enriched with various types of additives and blending components to improve, maintain, or impart new beneficial characteristics to the fuels.
- Vehicle manufacturers and refiners have always paid particular attention to research on engine knocking, an undesired phenomenon threatening both petrol and diesel engines which can cause severe engine damage, up to total disruption. One method to prevent knocking and increase the octane rating of fuels is to enrich them with high-octane chemicals, also called 'octane boosters'. Examples include organometallic and nitrogen-containing octane boosters.
- Today, vehicle manufacturers are strongly opposing the inclusion of currently marketed nitrogen-containing compounds in fuels for efficiency and safety reasons, as well as issues with increased greenhouse gas emissions. Some countries have limited their use or banned them, while research is ongoing to find more sustainable alternatives.
- The present literature review was conducted to evaluate the impact of commonly used aniline derivatives, specifically N-methylaniline (NMA), N,N-dimethylaniline, xylidines, and toluidines, on human health, the environment, and engines.
- The information collected confirms that they have unfavourable human health and environment profiles, and may be detrimental to air quality and car engines. Existing and future nitrogen-containing octane boosters should only be allowed in fuels if they successfully pass properly designed screens that consider both efficiency and safety for man and the environment.

Keywords

Fuel additive; nitrogen-containing octane boosters; human health impact; environmental impact; engine impact.

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EU Transparency Register n° 64879142323-90

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1. INTRODUCTION

Combustion of fossil fuels is regarded as the main contributing activity to air quality deterioration and greenhouse gas emissions. One of the most energy-intensive sectors is road transport, which plays a key role in the production of hazardous pollutants such as nitrogen oxides (NO_x), particulate matter (PM), unburned hydrocarbons (HC), and carbon dioxide (CO₂). It is therefore imperative to find alternatives allowing to reduce the local and global environmental impact of transport. Automotive emission reduction may be achieved by acting at the different levels: 1) improvement of exhaust gas systems (e.g., use of PM filters), 2) engine refinement (e.g., engines equipped with three-way catalytic converters), and 3) engine fuel optimization (e.g., use of renewable fuels). Besides a number of promising alternatives that still face significant barriers to unlimited expansion, the development of currently used fuels is still ongoing.



This paper focuses on fuel additives or blending components (blend stocks) that are chemical substances added to automotive fuels such as gasoline, diesel, or race fuel to improve performance, stability and many other properties (Dabelstein et al. 2017). Performance additives, alone or in combination, are today present in over 95% of European road fuels (ATC 2020).

Vehicle manufacturers and refiners have always paid particular attention to research on engine knocking, a mild explosive sound and vibration occurring in internal combustion engines (ICE) due to the premature ignition of the fuel-air mixture (see Figure 1). Engine knocking is an undesired phenomenon which can cause severe engine damage, up to total disruption. One method to prevent knocking and increase the

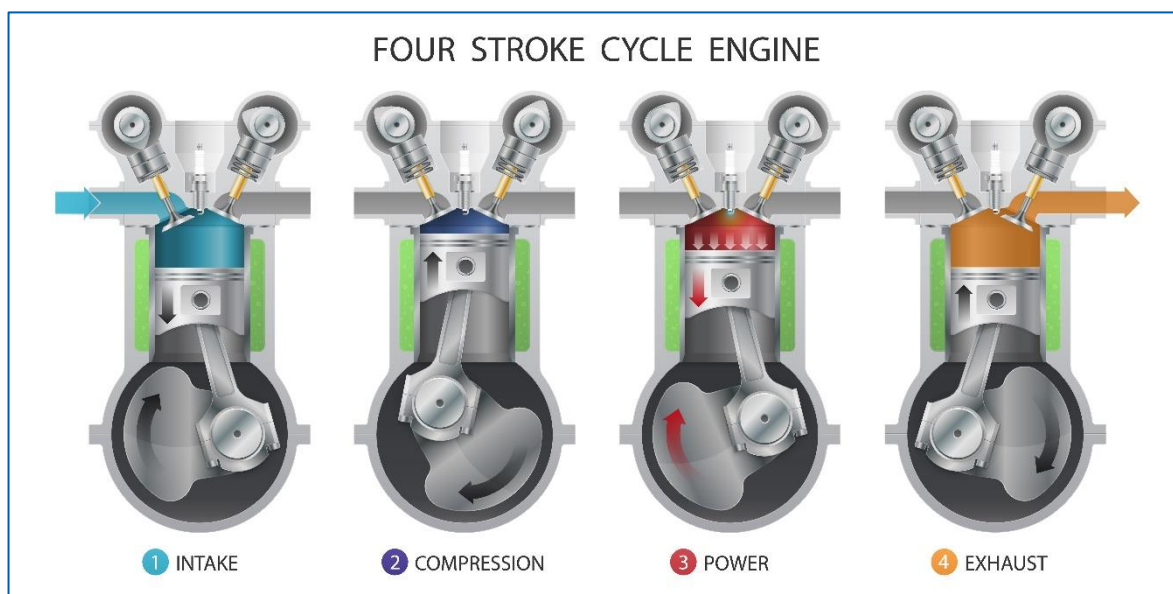


Figure 1: pre-ignition occurs when the fuel combusts prematurely as the piston moves up (phase 2). This creates resistance and consumes fuel, reducing the downward force on the piston (phase 3).



octane rating of fuels is to enrich them with so-called antiknock ‘additives’ or ‘blending components’ (Ure et al. 2020).



‘Additives’ can be defined as chemicals or packages that are blended at part per million (ppm) dosages. These include for example metal-based octane boosters such as tetraethyllead (TEL), methylcyclopentadienyl manganese tricarbonyl (MMT), ferrocene (iron), and other performance improver packages (e.g., friction modifiers, rust preventers, anti-foaming agents, etc.). ‘Blending components’, also referred to as ‘blend stocks’ (e.g., methanol, ethanol, methyl tert-butyl ether (MTBE), ethyl tert-butyl ether (ETBE), as well as

aromatic amines) are added to fuels at percentage levels.

The risk for health and the environment of metal-based octane boosters was reviewed in 2013 by the European Commission (BIO Intelligence Service 2013) and in a 2018 paper by Benjamin Afotey (Afotey 2018). The present paper focuses on those N-containing octane boosters that are most widely used in today’s petrol market (e.g., aniline and its derivatives such as NMA) and which have not been subject to such reviews as a group. The paper is based on a screening of the literature and presents, in a single structured document and in layman terms, the key information relating to the effect of these substances on human health, the environment, and the engine itself.

2. HUMAN HEALTH AND ENVIRONMENTAL EFFECTS OF COMMON NITROGEN-CONTAINING OCTANE BOOSTERS

The antiknock characteristics of amines were known as early as 1919 when Midgley and Boyd added a few drops of aniline to test engines at General Motors and found that it considerably reduced knocking (Leslie 1980). Aniline compounds were initially rejected for their toxicity, poor organoleptic properties, and resinifying nature but regained attention as antiknock agents after the use of tetraethyllead was discouraged by the United States Environmental Protection Agency (US EPA) in 1972. Aniline was then progressively replaced by a number of derivatives (Branstetter 1944; Bull et al. 1946; Jin and Yu 2011; Stytsenko et al. 2005). The anti-knock mechanism of action and comparative efficiency of selected aniline-type aromatic amines were reviewed in Brown et al. (1955) and more recently in Badia et al. (2021). The present evaluation focuses on commonly used substances, specifically N-methylaniline (NMA), N,N-dimethylaniline, various xylidines (dimethylanilines), and toluidines (see Table 1). The main physical and chemical characteristics of these nitrogen-containing octane boosters and their safety profile are presented. Subsequent sections discuss their impact on air quality and effects on engines.



2.1. N-Methylaniline (NMA)

NMA (see Table 1 for the structure) is a colourless or slightly yellow viscous liquid characterised by a strong fish odour. It is soluble in water and in organic solvents, but less so in oily liquids such as octanol. For this



reason, it is not expected to bioaccumulate in the fatty tissues of living organisms. NMA has a low vapour pressure, which makes it less prone to evaporate into air under environmental conditions. It is however flammable (ECHA 2021a).

Extensive information on the toxicity of NMA to man and the environment can be found on the publicly available website of the agency which regulates the use of chemicals in the European Union (EU), the European Chemicals Agency (ECHA), in the frame of Regulation (EC) 1109/2006 (also called the 'REACH' Regulation) (ECHA 2021a). Based on available data, NMA was attributed a classification and labelling¹ according to the Globally Harmonised System (GHS – ST/SG/AC.10/30/Rev.8). The substance also has a harmonised classification specific for the EU, as laid out in Annex VI of the classification and labelling regulation (CLP, Regulation (EC) 1272/2008). In addition, NMA has a slightly more stringent 'self-classification' proposed by its manufacturers or importers in the frame of its registration under the REACH regulation. The latter stricter classification is laid out in Table 2.

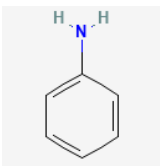
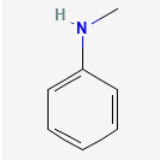
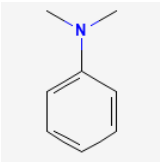
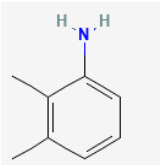
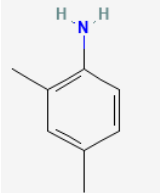
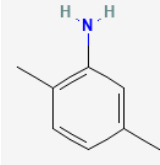


NMA was originally included in the EU's Community Rolling Action Plan (CoRAP) covering the years 2021 to 2023 (ECHA 2021b) and in the plan covering years 2023-2025, for being evaluated in 2023 by Poland as leading member state. The CoRAP list contains substances suspected of posing a risk to human health or the environment and identified for further evaluation. Initial grounds of concerns for NMA included suspected carcinogenicity and mutagenicity combined with wide dispersive use. Also, it was flagged that its various applications could result in cumulative exposure for workers at industrial sites and for consumers.

¹ Classification and labelling identify hazardous chemicals and inform users about their hazards through standard symbols and phrases. They are harmonised to ensure good worldwide understanding and facilitate the free flow of goods.



Table 1: Structure of the aniline-type N-containing octane boosters

Substance	Chemical Abstracts Service (CAS) number	European Community (EC) number	Structure
Aniline			
Aniline	62-53-3	200-539-3	
NMA			
N-Methylaniline	100-61-8	202-870-9	
N,N-Dimethylaniline			
N,N-Dimethylaniline	121-69-7	204-493-5	
Xylidines			
2,3-Dimethyl aniline	201-755-0	87-59-2	
2,4-Dimethyl aniline	202-440-0	95-68-1	
2,5-Dimethyl aniline	202-451-0	95-78-3	

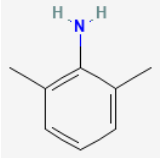
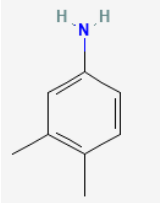
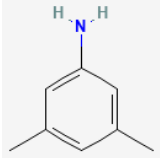
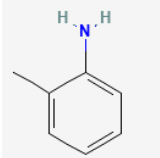
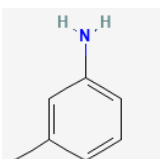
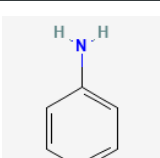
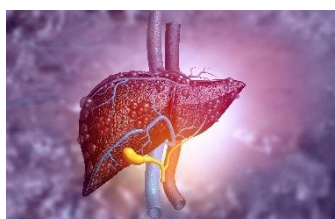
Substance	Chemical Abstracts Service (CAS) number	European Community (EC) number	Structure
2,6-Dimethyl aniline	201-758-7	87-62-7	
3,4-Dimethyl aniline	202-437-4	95-64-7	
3,5-Dimethyl aniline	203-607-0	108-69-0	
Toluidines			
<i>o</i> -Toluidine	95-53-4	202-429-0	
<i>m</i> -Toluidine	108-44-1	203-583-1	
<i>p</i> -Toluidine	106-49-0	203-403-1	

Table 2: Hazard classification and labelling for N-methylaniline (NMA): ‘Self-classification’ proposed by its manufacturers or importers in the frame of its registration under the European Chemicals legislation (REACH Regulation, (EC) 1907/2006)

Hazard Class and Category Code(s)	Hazard Statement Code
Acute Tox. 3	H301 – Toxic if swallowed
Acute Tox. 3	H311 – Toxic in contact with skin
Acute Tox. 3	H331 – Toxic if inhaled
Eye Irrit. 2 A	H319 – Causes serious eye irritation
STOT RE 2	H373 - May cause damage to organs through prolonged or repeated exposure*
Aquatic Acute 1	H400 – Very toxic to aquatic life
Aquatic Chronic 1	H410 – Very toxic to aquatic life with long-lasting effects

* Affected organs: target: spleen, liver, and bone marrow; route of exposure: oral and inhalation.

2.1.1. Human health effects



One key piece of information is how NMA enters the body after exposure through ingestion, skin contact, or inhalation. The available studies show that NMA is well absorbed from all three routes and is then distributed in the body to the liver, kidneys, lungs, small intestine, brain, and bladder. The substance is broken down (‘metabolised’) in the liver to aniline by removal of a methyl (‘-CH₃’) group. It can also be broken down to *o*- and *p*-methylaminophenols by the addition of a hydroxyl group (‘-OH’) onto the ring structure. NMA does not bioaccumulate in tissues and is readily excreted in urine.

After exposure periods of short duration via ingestion or skin contact, NMA shows a moderate level of toxicity. There is no data for short-term inhalation toxicity but effects are expected to occur since the substance is well absorbed also via this route. NMA is not irritating to skin but is slightly irritating to eyes. It is not a skin sensitiser, meaning that it does not induce an allergic response following skin contact.

In studies where test animals are repeatedly exposed to NMA over a period of several weeks through ingestion or inhalation, toxicity is observed. The substance primarily targets red blood cells and the spleen. The effects occur at sufficiently low doses for the substance to be attributed a hazard classification according to EU (CLP) and worldwide (GHS) classification and labelling rules. No data on repeated dose dermal toxicity are available.

Laboratory testing shows that NMA does not induce changes ('mutations') in the genetic material of bacteria but it is suspected of potentially causing breaks in the chromosomes (the long DNA molecules carrying part or all of the genetic material of the organism) of mammalian cells. The available information does not allow a clear conclusion to be drawn on whether NMA is a genetic toxicant or not.



There is also not enough scientific data to support that NMA has a potential to cause cancer, although studies exist for aniline, which is one of the breakdown products of NMA in the body. Aniline is known to induce spleen tumours in rats but not in mice. The suspected carcinogenic mode of action involves the formation of tumours resulting from toxicity to red blood cells and perturbations in iron metabolism in the spleen. Based on these data for aniline, the German committee for the determination of occupational exposure limits ('MAK-Commission') classified NMA as a suspected carcinogen, but the information is currently considered insufficient to conclude on the carcinogenic potential of NMA at the EU or worldwide level.

The possible effects of NMA on reproduction and development may be assessed based on data for the substance itself or for aniline. In various animal studies involving pregnant rats, NMA given at high doses caused anaemia and changes in thyroid hormone levels in the dams and toxicity to the embryos. Aniline is also known to cross the placenta and induce methaemoglobinaemia in the foetus, a condition of elevated methemoglobin² in the blood. However, the evidence is not sufficient to classify NMA as a reproductive toxicant according to EU or worldwide legislation.

- **2.1.2. Environmental properties**

When released to water or soil, NMA is rapidly broken down by microorganisms and is therefore not persistent in the environment. It biodegrades well in soils with high organic content and sufficient microbial activity. Also, NMA does not bioaccumulate in the tissues of fish and does not meet the criteria for being a 'persistent, bioaccumulative and toxic (PBT)' substance, or a 'persistent organic pollutant (POP)'.



NMA is very toxic to aquatic life (fish, invertebrates, and algae), with long-lasting effects, but no information is available on its impact on soil organisms.

² Hemoglobin in the form of metalloprotein, in which the iron in the heme group is in the Fe (ferric) state, not the Fe (ferrous) of normal hemoglobin.



2.2. N,N-Dimethylaniline

N,N-dimethylaniline (see Table 1) is an oily liquid. It is colourless when pure, but commercial samples are often yellow with a fishlike odour. N,N-dimethylaniline is soluble in water, highly soluble in organic solvents but poorly soluble in oily liquids. As for NMA, these properties explain that N,N-dimethylaniline does not preferentially bioaccumulate in the fatty tissues of living organisms. The substance is also not volatile and non-flammable (ECHA 2021c).


 Information on the toxicity of N,N-dimethylaniline to man and the environment can be found on the publicly available website of the European Chemicals Agency (ECHA 2021c) as well as in reports from the German committee for the determination of occupational exposure limits (Hartwig 2012), the United States National Toxicology Program (US NTP 1989), and the Australian National Industrial Chemicals Notification and Assessment Scheme (NICNAS 2016). According to GHS rules, the substance is not classified. The 'self-classification' proposed in the frame of the substance's registration in the EU under the REACH regulation is currently in line with its harmonised classification as per Annex VI of the CLP regulation (see Table 3).

Table 3: Hazard classification and labelling for N,N-dimethylaniline: EU harmonised classification, as per Annex VI of the CLP regulation ((EC) 1272/2008)

Hazard Class and Category Code(s)	Hazard Statement Code
Acute Tox. 3	H301 – Toxic if swallowed
Acute Tox. 3	H311 – Toxic in contact with skin
Acute Tox. 3	H331 – Toxic if inhaled
Carc. 2	H351 – Suspected of causing cancer
Aquatic Chronic 2	H411 – Toxic to aquatic life with long-lasting effects

- **2.2.1. Human health effects**

N,N-Dimethylaniline is well taken up into the body after exposure via ingestion, skin contact, or inhalation. It is broken down to a series of metabolites which include 4-methylaminophenol, 2-aminophenol, and aniline, then excreted. N,N-dimethylaniline does not bioaccumulate in the body after exposure to low doses.

Following exposure periods of short duration via ingestion, skin, or inhalation, N,N-dimethylaniline shows a moderate level of toxicity. It is non-irritating to skin, slightly irritating to eyes, and does not induce an allergic response upon skin contact.



In studies where test animals are repeatedly exposed over a period of several weeks through ingestion, N,N-dimethylaniline causes harmful effects in blood and the spleen. In rats, extramedullary haematopoiesis (non-bone marrow red blood cell production) and haemosiderosis (iron overload disorder resulting in the



accumulation of hemosiderin) in the spleen were observed at all exposure doses of NMA. The increased number of haematopoietic cells led to spleen enlargement in some of the animals. Limited information is available for repeated dose toxicity via the dermal and inhalation routes.



Like NMA, N,N-dimethylaniline does not induce changes ('mutations') in the genetic material of bacteria but may cause clastogenic effects (disruption or breakage of chromosomes) in mammalian cells, as shown in testing with cell cultures in the laboratory or in studies with rats and mice. The available data are overall not sufficient to classify N,N-dimethylaniline as a genetic toxicant according to EU (CLP) or worldwide (GHS) classification and labelling rules.

N,N-Dimethylaniline showed evidence of carcinogenic activity in testing with male rats (but not in females), as indicated by an increased incidence of sarcomas (malignant connective tissue tumours) of the spleen and the bone (osteosarcomas). In another study, there was equivocal evidence of carcinogenicity in female (but not male) mice, as indicated by an increased incidence of benign forestomach lesions (squamous cell papillomas).

Based on the limited information available, N,N-dimethylaniline is not thought to have effects on reproduction or development.

• 2.2.2. *Environmental properties*



When released to the environment, N,N-dimethylaniline rapidly degrades in water but may be persistent in soil. Its potential to bioaccumulate in the tissues of aquatic or terrestrial organisms is low. N,N-Dimethylaniline does not meet the criteria for being a 'persistent, bioaccumulative, and toxic (PBT)' substance or a 'persistent organic pollutant (POP)'.

N,N-Dimethylaniline is toxic to aquatic organisms (fish, invertebrates, and algae) when exposed to concentrations up to its limit of solubility in water. Adverse effects have also been noted in testing with terrestrial organisms (earthworms, terrestrial plants, and soil microorganisms).

2.3. Xylidines

Xylidines fall into the dimethylaniline category and consist of six different xylene amines with an identical number of atoms but distinct arrangements of the atoms in space (called 'isomers') (see Table 1). Xylidines are all liquids, except for 3,4-dimethyl aniline which is a solid. They have low to moderate solubility in water and low solubility in oily liquids, rendering their bioaccumulation in the fatty tissues of living organisms unlikely. Xylidines have low vapour pressures and therefore do not easily volatilise at room temperature. They are non-flammable (ECHA 2021d; 2021e; 2021f; 2021g; 2021h; 2021i; OECD 2012).

Information on the toxicity of xylidines to man and the environment was gathered from the publicly available website of the European Chemicals Agency (ECHA 2021d; 2021e; 2021f; 2021g; 2021h), as well as from a report of the Organisation for Economic Cooperation and Development (OECD 2012). Xylidines are classified and labelled according to the GHS and selected substances also have a harmonised classification



specific for the EU. Xylidines have a slightly more differentiated 'self-classification' proposed in the frame of their registration under the European Chemicals legislation (REACH regulation), as reported in Table 4.

Table 4: Hazard classification and labelling for xylidines: 'Self-classification' proposed in the frame of their registration under the European Chemicals legislation (REACH regulation, (EC) 1907/2006)

Hazard Class and Category Code(s)	Hazard Statement Code
2,4-Dimethyl aniline	
Acute Tox. 3	H301 – Toxic if swallowed
Acute Tox. 3	H311 – Toxic in contact with skin
Acute Tox. 2	H330 – Fatal if inhaled
Eye Irrit. 2	H319 – Causes serious eye irritation
STOT RE 2	H373 – May cause damage to organs through prolonged or repeated exposure
Aquatic Chronic 2	H411 – Toxic to aquatic life with long-lasting effects
2,5-Dimethyl aniline	
Acute Tox. 4	H302 – Harmful if swallowed
STOT RE 2	H373 – May cause damage to organs through prolonged or repeated exposure
Aquatic Chronic 3	H412 – Harmful to aquatic life with long-lasting effects
2,6-Dimethyl aniline	
Acute Tox. 4	H302 – Harmful if swallowed
Acute Tox. 4	H312 – Harmful in contact with skin
Acute Tox. 4	H332 – Harmful if inhaled
Eye Irrit. 2	H319 – Causes serious eye irritation
Skin Irrit. 2	H315 – Causes skin irritation
STOT SE 3	H335 – May cause respiratory irritation
Carc. 2	H351 – Suspected of causing cancer
Aquatic Chronic 2	H411 – Toxic to aquatic life with long-lasting effects

Hazard Class and Category Code(s)	Hazard Statement Code
3,4-Dimethyl aniline	
Acute Tox. 4	H302 – Harmful if swallowed
Acute Tox. 3	H311 – Toxic in contact with skin
Acute Tox. 3	H331 – Toxic if inhaled
STOT RE 2	H373 – May cause damage to organs through prolonged or repeated exposure
Aquatic Chronic 2	H411 – Toxic to aquatic life with long-lasting effects

- **2.3.1. Human health effects**

The ability to enter the body after exposure through ingestion, skin contact, or inhalation has been studied for several of the xylidines. In animal testing, 2,4-dimethyl aniline was shown to be well absorbed after ingestion. The substance and its breakdown products (N-acetyl-4-amino-3-methylbenzoic acid and N-2,4-trimethylaniline) were then eliminated via urine. Similarly, after oral exposure in rats, 2,6-dimethyl aniline was readily absorbed and distributed throughout the body. It is suggested that 2,6-dimethyl aniline or its metabolites bind to blood and/or tissues.

After exposure periods of short duration via ingestion, skin contact, or inhalation, xylidines show a moderate level of toxicity. 2,4-Dimethyl aniline has a weak irritating effect on skin and is irritating to the eyes of rabbits. 2,6-Dimethyl aniline has an irritant effect on skin and a weak irritant effect on eyes. 3,5-Dimethyl aniline has no irritant effect on skin and is a weak irritant for eyes. Apart from 2,6-dimethyl aniline, xylidines are not considered as irritating or corrosive to skin. None of xylidines induce an allergic response following skin contact.

In studies where test animals were repeatedly exposed to xylidines over a period of several weeks, adverse effects on blood were consistently observed. These included increased methaemoglobin (hemoglobin in the form of metalloprotein) concentrations, resulting in haemolysis (rupturing of red blood cells). The target organs were blood, spleen, liver, and kidneys. These effects lead to a hazard classification for most of the xylidines according to EU (CLP) and worldwide (GHS) classification and labelling rules.



Xylidines are suspected of being potentially genotoxic. There is a lack of data for individual members of the group but haemolysis and methaemoglobinaemia are markers of transformations that can lead to a genotoxic outcome. The data is currently not sufficient to classify the substances as genetic toxicants under EU or worldwide legislation.

In a two-year carcinogenicity study, rats were given 2,6-dimethyl aniline in their diet. Increased incidences of carcinomas (malignant epithelial cell tumor) of the nasal cavity and papillary adenomas (benign

epithelium cell tumor) were observed at the highest exposure dose. In addition, rare tumors of the nasal cavity and rhabdomyosarcomas (a rare type of cancer that forms in soft tissue) were seen. Increased incidences of adenocarcinomas (malignant mesenchymal tissue tumors) were observed in high dose males and sarcomas were present in high dose females. In line with these findings, 2,6-dimethyl aniline is considered to be carcinogenic. While data on other members of the group are not available, these may also be treated as potential carcinogens given the uniform observation of metabolite pathways leading to methaemoglobinaemia (which is related to the formation of carcinogenic metabolites) and the evidence of potential genotoxic activity.

Based on the limited information available, xylidines do not show specific reproductive or developmental toxicity.

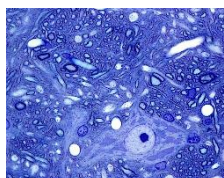
- **2.3.2. Environmental properties**

In the environment, xylidines do not break down rapidly and have a high affinity for soil organic matter. They are therefore potentially persistent in both water and soil. They do not however tend to bioaccumulate in the tissues of aquatic or terrestrial organisms.

Overall, xylidines are toxic to aquatic organisms (fish, invertebrates, and algae) but little data is currently available on their effects in the terrestrial environment.

2.4. Toluidines

Toluidines are derivatives of aniline in which an aromatic hydrogen (a hydrogen of the unsaturated ring structure) is replaced by a methyl ('-CH₃') group (see Table 1). There are three toluidines with an identical number of atoms but distinct arrangements of the atoms in space ('isomers'), called *o*-toluidine, *m*-toluidine, and *p*-toluidine. The '*o*', '*m*' and '*p*' prefixes are abbreviations for *ortho*, *meta*, and *para*, indicating the position of the -CH₃ group on the ring. *O*-toluidine is a light-yellow liquid that rapidly darkens upon exposure to air and light, whereas *m*-toluidine is a clear colourless liquid and *p*-toluidine forms white, lustrous plates or leaflets, which turn dark upon exposure to air and have a wine-like odor. The three toluidine isomers are soluble in water and organic solvents, but less soluble in oily liquids. They are therefore not prone to bioaccumulating in the fatty tissues of living organisms. Also, they are not volatile and non-flammable (ECHA 2021j; 2021k; 2021l; WHO 1998).



Information on the toxicity of toluidines to man and the environment is available on the website of the European Chemicals Agency (ECHA) (ECHA 2021j; 2021k; 2021l) and has also been published by the Organisation for Economic Cooperation and Development, and the World Health Organisation (Cheever et al. 1980; OECD 2001; 2004; 2005; WHO 1998). Toluidines are classified and labelled according to GHS and also have a harmonised classification specific for the EU. Toluidines have a slightly more differentiated 'self-classification' proposed in the frame of their registration under the European Chemicals legislation (REACH regulation), as reported in Table 5.

Table 5: Hazard classification and labelling for toluidines: ‘Self-classification’ proposed in the frame of their registration under the European Chemicals legislation (REACH regulation, (EC) 1907/2006)

Hazard Class and Category Code(s)	Hazard Statement Code
<i>o</i>-Toluidine	
Acute Tox. 3	H301 – Toxic if swallowed
Acute Tox. 4	H312 – Harmful in contact with skin
Acute Tox. 3	H331 – Toxic if inhaled
Skin Irrit. 2	H315 – Causes skin irritation
Eye Dam. 1	H318 – Causes serious eye damage
Muta. 2	H341 – Suspected of causing genetic defects
Carc. 1B	H350 – May cause cancer
Aquatic Acute 1	H400 – Very toxic to aquatic life
Aquatic Chronic 2	H411 – Toxic to aquatic life with long-lasting effects
<i>m</i>-Toluidine	
Acute Tox. 3	H301 – Toxic if swallowed
Acute Tox. 3	H311 – Toxic in contact with skin
Acute Tox. 3	H331 – Toxic if inhaled
STOT RE 2	H373 – May cause damage to organs through prolonged or repeated exposure
Aquatic Acute 1	H400 – Very toxic to aquatic life
Aquatic Chronic 1	H411 – Toxic to aquatic life with long-lasting effects
<i>p</i>-Toluidine	
Acute Tox. 3	H301 – Toxic if swallowed
Acute Tox. 3	H311 – Toxic in contact with skin
Acute Tox. 3	H331 – Toxic if inhaled
Eye Irrit. 2	H319 – Causes serious eye irritation

Hazard Class and Category Code(s)	Hazard Statement Code
Skin Sens. 1, 1A	H317 – May cause an allergic skin reaction
Carc. 2	H351 – Suspected of causing cancer
Aquatic Acute 1	H400 – Very toxic to aquatic life
Aquatic Chronic 2	H411 – Toxic to aquatic life with long-lasting effects

- **2.4.1. Human health effects**

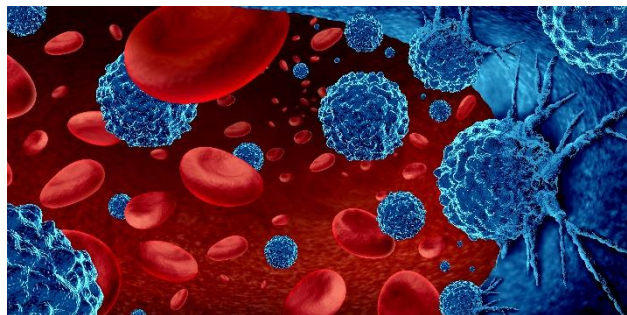
O-toluidine is well absorbed into the body when exposure occurs through ingestion, the skin, or inhalation. It is then rapidly distributed, broken down, and excreted mainly via urine. *m*-Toluidine is equally rapidly absorbed from the gastrointestinal tract and skin, followed by breakdown and excretion. No information is available on this substance for the inhalation exposure pathway. *p*-Toluidine is absorbed via the gastrointestinal tract and is distributed, broken down, and excreted via urine and faeces. There are no specific data on its absorption via skin or inhalation.

All toluidines show a moderate level of toxicity after exposure periods of short duration via ingestion, skin contact, and inhalation. In concentrated form, *o*-toluidine is irritating to skin and severely irritating to eyes. *m*-Toluidine is slightly irritating to skin and moderately irritating to eyes, and *p*-toluidine causes reversible irritation to the eyes of rabbits but no skin irritation. *O*-toluidine and *m*-toluidine do not induce an allergic response following skin contact, but *p*-toluidine is a strong skin sensitiser.

After repeated oral exposure over several weeks, *o*-toluidine is toxic to red blood cells and is a methaemoglobin-forming chemical. Its target organs are liver and kidney (haemosiderin deposition), as well as urinary bladder (enlargement). *m*-Toluidine causes harmful effects in the spleen, kidney, and blood. In a study in rats, the critical effects were haemolytic anaemia, revealed by reduction of red blood cells counts and haemoglobin concentration, and histological changes such as pigment deposit and extramedullary hematopoiesis in liver and spleen. There are no adequate repeated dose toxicity studies available for *p*-toluidine but the limited information suggests low toxicity, with liver and blood as target organs.

Based on data from laboratory cell cultures and evidence from animal studies, *o*-toluidine is suspected to act as a genotoxic carcinogen. *M*-toluidine is not considered to be genotoxic and there is only inconclusive evidence relating to the genetic toxicity potential of *p*-toluidine.

In several carcinogenicity studies conducted with rodents exposed to toluidines via the oral route, there was a significant increase in the incidence of benign and malignant tumours (for example sarcomas) in various tissues. Tumours were not observed in a dietary study in rats after exposure to *m*-toluidine. However, a definite conclusion could not be drawn because the experimental conditions were insufficient compared to current standard testing protocols. There are no adequate studies with *p*-toluidine to evaluate carcinogenicity.



Information relevant to assessing the risks of reproductive or developmental effects of *o*-toluidine was not identified. In a study conducted in rats, *m*-toluidine induced implantation loss but no developmental toxicity. There are no specific data on the toxicity for reproduction of *p*-toluidine. Data from repeated dose toxicity studies provide no evidence for possible effects of *p*-toluidine on reproductive organs.

- **2.4.2. Environmental properties**

The three toluidines are rapidly biodegradable in the environment and are therefore not considered to be persistent. They have a low potential to bioaccumulate in the tissues of aquatic organisms and do not meet the criteria for being for being 'persistent, bioaccumulative, and toxic (PBT)' substances or 'persistent organic pollutants (POP)'.

The toxicity of toluidines to aquatic organisms, especially to aquatic invertebrates, is high. No information is currently available on their effects on the terrestrial environment.

3. IMPACT OF NITROGEN-CONTAINING OCTANE BOOSTERS ON AIR QUALITY

During fuel combustion, the nitrogen and oxygen present in the fuel-air mixture react under the heat and pressure conditions of the vehicle combustion chamber to form **nitrogen oxide** (NO_x) gases, mainly nitric oxide (NO) and nitrogen dioxide (NO₂), as shown in Figure 2. NO_x formation is governed by several factors, including the amount of nitrogen (N) available (Kemp et al. 2013).

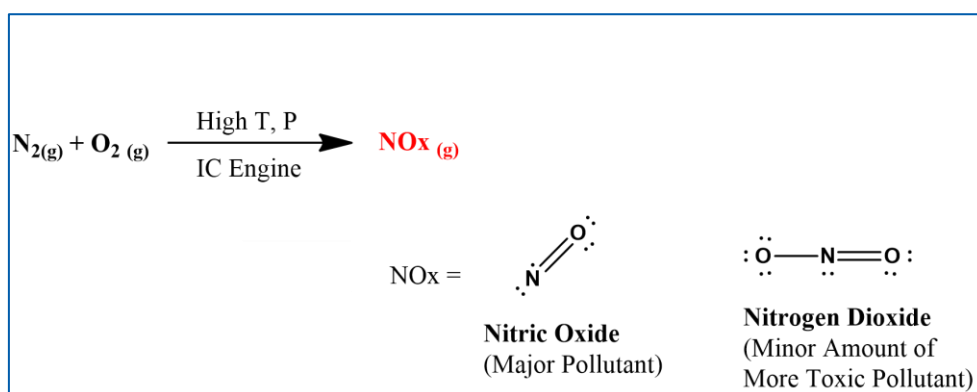


Figure 2: Reaction mechanism between the nitrogen and oxygen present in the fuel-air mixture during fuel combustion to form nitrogen oxide (NO_x) gases.

NO_x formation can be attributed to four distinct reaction schemes: 1) thermal NO_x formation, based on the oxidation of nitrogen from air and dominant at high temperatures, 2) prompt NO_x formation from high velocity reactions in the presence of hydrocarbons, 3) combustible NO_x formation, from the oxidation of nitrogen in the fuel by oxygen from air, and 4) NO_x formation via N₂O, in oxygen-rich zones and at high pressure. In conventional combustion regimes, the thermal and fuel-N routes, when nitrogen is present in the fuel, are the relevant pathways of NO_x formation.



Due to their chemical composition, the use of nitrogen-containing octane boosters can be expected to result in an increased release of nitrogen during fuel combustion, leading to higher end levels of NO_x gases. Increased NO_x emissions from cars exhaust systems were detected for the first time when pyridine was added to petrol or diesel. Otto and Roby showed that the presence of 5 vol% of nitrogenous compounds such as aniline, pyrrole, cyclohexylamine, piperidine, pyridine, pyrrolidine, and n-hexylamine substantially elevated NO_x concentrations as compared to emissions from iso-

octane (Otto and Roby 1984). In another study, an aniline content of 3% in gasoline resulted in an NO_x emission increase of 5% (Tang et al. 2015). This is in line with a technical report of the Italian Fuel Standardization body showing that 1% of NMA can increase the level of NO_x emissions by 9.86% (CUNA 2017).

NOx are significant [greenhouse gases](#) playing a role in [global climate change](#). Like CO₂, NOx gases trap the infrared radiation reflected from the Earth's surface, warming up the troposphere. Its global warming potential is approximately 300 times higher than that of carbon dioxide (CO₂) per unit mass (Chao 2012).

NOx gases are also known to participate to the formation of smog, producing the brown haze often observed over cities, particularly during the summer. During exposure to UV rays in sunlight and heat, NOx molecules interact with volatile organic compounds (VOC) and form ground-level (or tropospheric) ozone (O₃). Ozone at the ground level is a serious pollutant, unlike [the protective ozone layer](#) much higher up in the stratosphere.

In the presence of rain, nitrogen oxides form nitric acid, contributing to the problem of acid rain. Acid rain significantly damages crops, forests, buildings, water resources, and aquatic organisms. Additionally, NOx deposition in the oceans [provides phytoplankton with nutrients](#), worsening the issue of [red tides and other harmful algal blooms](#).

In addition to their impact on the ecosystem, the release of NOx gases into the atmosphere can adversely affect human health (US EPA 2010). NOx, nitric acid, and ozone all readily enter the lungs, where they induce serious pulmonary damage such as emphysema and bronchitis. Even short-term exposure can irritate the lungs of healthy people (Thaller et al. 2008). For those with medical conditions such as asthma, just a short time spent breathing these pollutants has been shown to increase the risks of an emergency room visit or hospital stay (US EPA 2012). Indeed, it was shown that NOx pollution can exacerbate asthma and heart disease, and is tied to elevated risks of premature death (Jiang et al. 2016). According to the European Environment Agency (EEA 2014), ground-level ozone leads to about 16,000 premature deaths across Europe each year, assuming a threshold of 35 ppb.



4. ENGINE EFFECTS OF NITROGEN-CONTAINING OCTANE BOOSTERS

Nitrogen-containing octane boosters are significantly less effective in reducing engine knocking than their organometallic counterparts and must therefore be used at higher concentrations. A number of studies indicate deleterious effects of this type of octane boosters on internal combustion vehicle engines.

Despite their antiknock properties, aniline and monomethyl aniline have been shown to favour pre-ignition of gasoline, an uncontrolled ignition of the fuel-air mixture occurring at the hot surface of internal combustion engines, usually followed by knocking (Downs and Pignegy 1950).

Jingdong (2012; cited in ACFA, 2014) showed that adding aniline type components drastically shortened the induction period in internal combustion engines. Shorter induction times can cause gasoline stability to decline and increase engine knocking. NMA also causes shorter induction time and negatively affects engine performance (Caltex 2016).

Investigations by the researchers of Toyota Motors (Nagano et al. 2017) and the experimental results of Albright and co-workers (Albright et al. 1949) and Shatalov and co-workers (Bol'shakov and Stekhun 1972; Yakovlev et al. 2015) indicate that the use of amine additives increases carbon deposits, lowering engine



efficiency. Among the commercial gasolines, monomethylaniline-blended gasoline caused a large increase in engine deposits.

The impacts of NMA on lubricating oils were studied due to the heavy sludge formation and engine malfunctions encountered in some regions of the world where aniline-based octane boosters are used. Test results confirmed that 3.5 wt.% NMA increased sludge formation considerably (Marie et al. 2016).



While analysing the decomposition of anilines by an electric spark, Fowler and Mardles observed that the reactive amino or phenyl free radicals underwent further chain reactions to form complex oxidised and polymerized high molecular weight products known as tar or gum (Fowler and Mardles 1927). Gum deposited on engine components causes choking of intake valves and engine stalling, upsetting of the air-fuel ratio resulting in power loss and poor fuel economy, and plugging of fuel filters. Bol'shakov *et al.* similarly demonstrated that amines present in diesel resulted in the formation of gums and decreased the stability of the fuel (Bol'shakov and Stekhun 1972). Sharifullin and co-workers studied the gum formation tendency of a straight-run gasoline containing binary component based on tert-butyl alcohol and substituted alkylamines, and ternary blends based on tert-butyl alcohol, isopropyl alcohol and substituted alkylamines. The use of binary and ternary components led to substantial increase in gum formation tendency for straight-run gasolines (Sharifullin *et al.* 2016).

A report from Stellantis (formerly FIAT Chrysler Automobiles - FCA) describes harmful effects of nitrogen-containing compounds used as fuel blendstock (CEN 2021). The report was presented at the CEN TC19 WG21 meeting in Belgrade on 6th November 2018 and focuses on aniline derivatives such as NMA, dimethylaniline and ethoxyaniline, and non-traditional gasoline blendstocks such as isobutyl acetate. FCA's report refers to serious issues and the disruption of three engine families due to the presence of the nitrogen-containing octane boosters in petrol. The main identified causes for the engine failure included progressive accumulation of the compounds in engine oil, and formation of resins on engine components, most likely N-aromatic. Information on aniline and its derivatives when used as blending components in unleaded petrol was published by CEN in their report (CEN-TR17491).



In the aviation field, several aromatic amine octane boosters have been investigated as potential replacements for tetraethyllead (TEL) in gasoline for piston aircrafts. These include aniline (Shell patent application AU2014206198B2), various xylydines and toluidines (Exxon Patent 5,470,358, CRC Report No. AV-7-07), and N-alkylated toluidines (GAMI patents US 10,377,959 B2, US 10,364,399 B2). Unlike organometallic additives that produce >100 MON fuels³ at concentrations well below 1 weight %, aromatic amine octane boosters must be used at the 5-15 volume % level to achieve acceptable detonation resistance for the most demanding engines in the general aviation fleet. At these levels, they can affect key properties of the fuel such as corrosion, density, reactivity (gum formation), and compatibility with

³ The term 'MON' refers to the motor octane number and describes the performance of an engine fuel at high temperatures and high speed.



materials of construction (paints, polysulfide sealants and fuel bladder materials). This likely make fuels based on these octane boosters unsuitable as 'drop-in' replacements for 100 LL (low-lead), the current industry standard for aviation gasoline as defined in ASTM D910.

5. CONCLUDING REMARKS AND FUTURE DIRECTIONS

The present literature review was conducted to evaluate the impact of the most commonly used aniline-type nitrogen-containing octane boosters in today's fuel market, namely N-methylaniline (NMA), N,N-dimethylaniline, xylidines, and toluidines, on human health, the environment, air quality, and engines.



As a group, nitrogen-containing octane boosters are acutely toxic or harmful, often irritating to eyes and/or skin or sensitizing, and cause damage to organs following prolonged exposure (often targeting the blood system). *o*-Toluidine is suspected of causing genetic defects, and N,N-dimethylaniline, *o*-toluidine and *p*-toluidine are classified for carcinogenicity ('suspected of causing cancer' or 'may cause cancer'). Furthermore, aniline-type nitrogen-containing octane boosters are harmful or toxic to aquatic life, causing long-term effects.

Nitrogen-containing octane boosters are much less effective anti-knock agents than organometallic substances and must therefore be used at higher concentrations for satisfactory knock suppression. A number of studies indicate deleterious effects on internal combustion vehicle engines resulting from their use, including pre-ignition, shortened induction period, and an increase in deposits (gum, tar, sludge), all of which may lead to decreased efficiency or engine failure.

Due to their chemical composition, the use of nitrogen-containing octane boosters results in an additional release of nitrogen during fuel combustion, leading to higher end levels of NO_x greenhouse gases, poorer air quality, and well-known toxicity to man and the environment.

Aniline-type compounds, especially NMA, are banned or strictly regulated as fuel blending components in many countries (e.g., Russia, The People's Republic of China, the Republic of Belarus, The Republic of Kazakhstan, Vietnam) and others are considering a similar ban (e.g., Australia). Europe is currently assessing potential issues with gasoline components such as aniline, N-methyl aniline, N-ethylaniline, N,N di-methyl aniline, and secondary-butyl acetate. A CEN taskforce has been activated to identify a suitable engine-no-harm test procedure to assess which chemicals at which dosages can or cannot be safely blended into gasoline. Among the aniline compounds, only NMA is registered as an octane booster under the REACH legislation. Under Section 211 of the US Clean Air Act, all fuel additives must be registered with the Environmental Protection Agency (EPA) before being sold in the United States. NMA is not in the US EPA's list of registered gasoline additives. In the rest of the world, the Aniline and Aniline Derivatives section of the 2019 Sixth Edition of the World Fuel Charter, which has been developed by car manufacturers, mentions that "*N-methyl-aniline (NMA) is a commonly used solvent that has been used as an octane-enhancing additive for gasoline; other aniline derivatives, such as N-ethyl aniline, also are a concern. Besides being toxic, this class of compounds can have serious adverse effects on engine parts and the emission control system*".



Work is ongoing to favour the development of more sustainable compounds with favourable anti-knock properties. Viayna and coworkers for example published an integrated holistic approach involving high throughput screening that considers physico-chemical factors, structural resemblance, susceptibility to participate in chemical reactions with radical species, and production viability, and environmental / toxicological risks. Their holistic strategy led to the identification of N-methyl-p-anisidine, N',N'-diethyl-2-methyl-p-phenylenediamine and N-nitroso-diphenylalanine as promising future aniline-like anti-knock additives (Viayna et al. 2021). Badia and colleagues conducted a broad review of octane booster molecules appropriate for modern gasolines. In their paper, they identify a few chemical families with promising technical and safety properties, either as high-octane components (e.g., ethers, ketones, and esters), or as octane booster additives (e.g., anilines, N-nitrosamines, and phenols) (Badia et al. 2021).



A current global trend can be observed towards achieving higher octane petrol grades as an effective means to enhance transport decarbonization by increasing the thermodynamic efficiency of internal combustion engines (CONCAWE 2020; Leach et al. 2014; Speth et al. 2014). However, blend stocks suitable to increase octane must be safe and clean. In this regard, aromatic-amines-based blending in petrol is projected to grow in the next 7 years as well, by 6% each year, and the EU market is anticipated to grow from 148,000 to over 240,000 tons per year in 2028 (VMR, 2021). Considering that aniline derivatives are highly octane-effective at relatively low dosages, these numbers translate into millions of tons of petrol-containing amines in the EU.

Aniline derivatives, when used as petrol octane boosters, have already been recognized as a matter of potential concern by the European Committee for Standardization (CEN) that, in one of its latest reports (CEN 2020), identified the potential technical consequences on engine parts and fuel systems when some types of chemical compounds such as aniline derivatives are used as blending components in unleaded petrol. While other chemical compounds are not addressed by the report, one needs to bear in mind that the CEN Standard EN 228 requires that *"unleaded petrol be free from any adulterant or contaminant that can render the fuel unacceptable for use"*.

In conclusion, the existing human health, environmental and technical data suggest that aniline-type nitrogen-containing octane boosters such as N-methylaniline (NMA), N,N-dimethylaniline, xylidines, and toluidines show lower performance than metal-based octane boosters, have an unfavourable human health and environment profile, and are detrimental to air quality and car and aircraft engines. Existing and future nitrogen-containing octane boosters should only be allowed to be blended into fuels if they successfully pass a properly designed screening that consider both their efficacy and their safety for man and the environment.



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7. GLOSSARY

ACEA	European Automobile Manufacturers' Association
ACFA	Asian Clean Fuels Association
ATC	Additives Technical Committee
CEFIC	European Chemical Industry Council
CEN	European Committee for Standardisation
CLP	Classification, Labelling, and Packaging
CO ₂	Carbon Dioxide
CoRAP	Community Rolling Action Plan
EC	European Commission
ECHA	European Chemicals Agency
EEA	European Environment Agency
ETBE	Ethyl Tert-Butyl Ether
EU	European Union
FCA	FIAT Chrysler Automobiles
GHS	Globally Harmonised System
MAK	Maximale Arbeitsplatz-Konzentration
MMT	Methylcyclopentadienyl Manganese Tricarbonyl
MTBE	Methyl Tert-Butyl Ether
NICNAS	Australian National Industrial Chemicals Notification and Assessment Scheme
NMA	N-Methylaniline
N	Nitrogen
NO	Nitrogen Oxide
NO ₂	Nitrogen Dioxide
NO _x	Nitrogen Oxide gases
NTP	National Toxicology Program

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O3	Ozone
OECD	Organisation for Economic Cooperation and Development
PBT	Persistent, Bioaccumulative, and Toxic
POP	Persistent Organic Pollutant
ppm	Part Per Million
REACH	Registration, Evaluation, Authorisation and Restriction of Chemical
TEL	Triethyl Lead
US	United States
VOC	Volatile Organic Compounds
WHO	World Health Organisation



DECLARATIONS

Funding: This work was undertaken with funds provided by Sustainable Fuels, a sector group of the European Chemical Industry Council (CEPIC), and by the European Automobile Manufacturers' Association (ACEA).

Conflicts of interest/Competing interests: The authors have no financial or proprietary interests in any material discussed in this article.

Availability of data and material: All data used for this article was obtained from the published literature or from proprietary reports for which authorization to refer was obtained.

ACKNOWLEDGEMENTS

This work was undertaken with funds provided by Sustainable Fuels, a sector group of the European Chemical Industry Council (CEPIC), and by the European Automobile Manufacturers' Association (ACEA). The authors also wish to acknowledge the valuable support provided by Dr. Monica Autiero and Ms. Céline De Roy in the proof-reading of the article.

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About Sustainable Fuels:

Sustainable Fuels, the association of the European fuel ethers industry, is dedicated to the responsible production, usage and promotion of clean, high quality, high-efficiency petrol components. Sustainable Fuels bring together producers of MTBE | BIO-MTBE | BIO-ETBE | TAME | BIO-TAME | BIO-TAEE. Sustainable Fuels (former EFOA) has been created in 1986 as part of CEPIC, the European Chemical Industry Association and sits within Petrochemicals Europe department.
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