Petrol

Toxicological overview

Key Points

**Kinetics and metabolism**

- As petrol is a mixture of chemicals, there is no definitive ADME (absorption, distribution, metabolism and excretion) data

**Health effects of acute exposure**

- Exposure to petrol vapour in confined or poorly ventilated areas may cause rapid onset of unconsciousness
- The main hazard associated with petrol is chemical pneumonitis that may arise following aspiration of vomitus (secondary to ingestion) or inhalation of aerosol (or aspiration of liquid) during manual siphoning
- Inhalation may cause dizziness, excitement and incoordination
- Ingestion may cause nausea, vomiting and diarrhoea
- Petrol vapour may be irritating to the eyes and respiratory system

**Health effects of chronic exposure**

- Prolonged skin exposure to petrol may cause a variety of dermatitic conditions and is generally a result of inadequate or inappropriate use of personal protective equipment
- Chronic exposure to high levels (particularly arising from recreational inhalation) is associated with a range of neurological disorders
- Petrol does not have a measurable effect on human reproduction or development
- There is currently no unequivocal evidence to link petrol with the incidence of cancer in humans but there is limited evidence for carcinogenicity in animals

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Toxicological Overview

Petrol is a complex mixture of aliphatic and aromatic hydrocarbons derived from blending fractions of crude oil with brand-specific additives. The actual composition of petrol will vary according to the source of crude oil, the manufacturing process and between batches. A representative composition of European petrol is given at Annex I.

Unless otherwise stated, this document pertains to unleaded petrol and not products of combustion or individual chemical components (e.g. benzene, toluene, xylene, butadiene, etc). Vapour concentrations are expressed as ppm and refer to total hydrocarbon present. However, it should be noted that this conventional measure of concentration introduces a source of error and should be considered at best an approximation, as the average molecular weight (on which the calculation of ppm is based) may vary according to temperature, brand or batch of technical product.

Summary of Health Effects

At low doses, petrol vapour is irritating to the eyes, respiratory tract and skin. Exposure to higher concentrations of vapour may produce CNS effects such as staggered gait, slurred speech and confusion. Very high concentrations may result in rapid unconsciousness and death due to respiratory failure [1].

Prolonged dermal exposure to liquid petrol or inhalation of vapour has been associated with renal dysfunction, attributed to lipid degeneration of the proximal convoluted tubules and glomeruli [2, 3], the clinical manifestations of which include haematuria, proteinuria and myoglobinuria. A late-onset autoimmune glomerulonephritis has also been described [4].

Pulmonary sequelae following inhalation of petrol vapour or secondary to pulmonary elimination of volatile hydrocarbons (following ingestion or dermal absorption) include persistent atelectasis [2] and petachial haemorrhage [1]. This may be associated with concomitant ‘hydrocarbon hepatitis’ secondary to vascular endothelial damage, possibly due to hydrocarbon-induced degeneration of fatty tissue [4-6].

The critical health effect of petrol is chemical pneumonitis, arising from aspiration of liquid petrol or inhalation of petrol-contaminated vomitus [7].
Kinetics and metabolism

Petrol is a complex mixture of hydrocarbons and so there is no definitive ADME data available for animals or humans. The onset of local or systemic effects following dermal, oral and inhalation exposure indicates that these are all potential routes of entry for petrol vapour or liquid.

Dermal exposure to petrol can be retrospectively identified following solvent extraction of hydrocarbons from the skin surface. However, the profile of hydrocarbons found in the systemic circulation after cutaneous exposure is markedly different to that extracted from the skin [8], indicating selective uptake and distribution of individual hydrocarbon components.

There is some evidence to suggest that petrol exposure may alter hepatic enzyme activity in rats and humans [9, 10], although the clinical relevance of such observations has not been established.

The predominant route of elimination for volatile components of petrol is considered to be via expired air. This assumption is based on clinical observation; there are no experimental studies to confirm this route of elimination in humans.

Sources and route of exposure

Petrol contains mixture of volatile hydrocarbons and so inhalation is the most common form of exposure [11]. Petrol vapour can reach supra-lethal concentrations in confined or poorly ventilated areas, although such exposures are rare [12-14]. A representative sample of petrol vapour concentrations under different exposure scenarios are summarised in Table 1. It should be noted that the chemical composition (hydrocarbon profile) of petrol vapour differs substantially from the corresponding liquid (Annex I). Petrol vapour is predominantly (>70%) composed of light (C4 & C5) hydrocarbons [15] whereas liquid petrol contains mainly (>80%) C6-12 compounds [16]. The intentional inhalation of vapour (‘sniffing’ or ‘huffing’) has been extensively documented [17-22].

Table 1: Representative vapour concentrations, expressed in parts per million (ppm) or mass of total hydrocarbons per unit volume (mg m⁻³) under different conditions.

<table>
<thead>
<tr>
<th>Vapour concentration (ppm)</th>
<th>Scenario</th>
<th>Notes</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>25,000</td>
<td>Air above open barrel in unventilated out-house on ‘hot’ day.</td>
<td>Environmental conditions not reported.</td>
<td>[12]</td>
</tr>
<tr>
<td>5 – 320</td>
<td>Air around tanker during bulk-loading.</td>
<td>Environmental conditions not reported.</td>
<td>[23]</td>
</tr>
<tr>
<td>2 – 100</td>
<td>Air around petrol pump in service station.</td>
<td>Environmental conditions not reported.</td>
<td>[24]</td>
</tr>
<tr>
<td>1 – 5</td>
<td>Air within petrol service station.</td>
<td>Temperature varied from 4.5 – 25°C. Recovered petrol components were predominantly (72%) C4 and C5 aliphatic hydrocarbons.</td>
<td>[25]</td>
</tr>
<tr>
<td>174</td>
<td>Worker at bulk loading facility.</td>
<td>Average exposure values. Environmental conditions not reported. Vapour concentration reported as the sum of all detected hydrocarbon constituents.</td>
<td>[16]</td>
</tr>
<tr>
<td>13</td>
<td>Road tanker driver.</td>
<td></td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>Service station worker.</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
It is generally considered that dermal absorption of petrol does not contribute significantly to systemic signs of toxicity.

Accidental ingestion of petrol by adults is often the result of siphoning petrol tanks whereas the incidence of petrol ingestion in children is relatively low [7, 12].
Health Effects of Acute / Single Exposure

**Human Data**

**General toxicity**

The acute health risks involved in handling and using petrol are minimal, provided that the product(s) are used in accordance with appropriate health and safety practices [26].

The main health effect associated with petrol exposure is chemical pneumonitis, resulting from pulmonary aspiration of vomitus following ingestion [27]. A rare complication of petrol intoxication may be cardiac arrhythmia and ventricular fibrillation, attributed to increased myocardial sensitivity to endogenous catecholamines [28].

Vascular endothelial damage of the lung, liver, kidney and spleen has been described following severe intoxication with associated renal lipid degeneration confined mainly to the proximal tubules [1, 6].

**Inhalation**

Petrol vapour is readily detectable by most individuals at concentrations below 1 to 2 ppm [29] (as reviewed by [7]) although prior exposure within 24 hours or chronic, occupational exposure may increase the olfactory threshold [30].

It has been suggested that the concentration of petrol vapour is the primary determinant of acute toxicity rather than duration of exposure [31]. This assumption is based on exposures of less than 30 minutes and relates to one study of three dogs dosed with different petrol products [32].

The minimum concentration of petrol vapour required to elicit a mild response (cough) is probably less than 140 ppm (Table 2), although there are no human studies which have determined the exact threshold for this effect.

Following inhalation, effects on the CNS are readily apparent above 900 ppm within a few minutes, the morbidity of which resembles alcohol intoxication (dizziness, excitement, incoordination, etc.).

In sufficient concentration (>10,000 ppm), petrol may act as an anaesthetic, sometimes resulting in immediate loss of consciousness [1]. Indeed, the rapidity of this effect has been implicated as a significant factor in fatal incidents [12-14, 31].

**Ingestion**

Ingestion of petrol may cause acute, generalised signs of GI tract irritation, including nausea, vomiting, colic and diarrhoea [7]. The relatively low oral toxicity of petrol is comparable to that of other petrochemical products such as kerosene (2 – 17 g kg⁻¹) [33] and ingestion of 7.5 g kg⁻¹ has been reported to be the lethal dose in adult humans in the absence of pulmonary effects caused by aspiration of ingested petrol or vomitus [1].
A critical, delayed health effect associated with ingestion of petrol is chemical pneumonitis, resulting from aspiration of petrol during the swallowing process or of vomitus following emesis [34].

Table 2: Summary of the human inhalation toxicity of petrol vapour. *Refers to estimated concentrations based on post-incident measurements: See also Annex II.

<table>
<thead>
<tr>
<th>Study type</th>
<th>Concentration (ppm)</th>
<th>Duration</th>
<th>Temperature</th>
<th>Effect(s)</th>
<th>Ref</th>
</tr>
</thead>
<tbody>
<tr>
<td>Human volunteer studies</td>
<td>140 – 270</td>
<td>8 h</td>
<td>23 °C</td>
<td>Mild irritation (coughing, sore throat), conjunctival hyperaemia.</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>200</td>
<td>0.5 h</td>
<td></td>
<td>Threshold level for eye irritation.</td>
<td>[35]</td>
</tr>
<tr>
<td></td>
<td>900</td>
<td>8 h</td>
<td>22 °C</td>
<td>Mild CNS effects (dizziness). Tolerable.</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>2,600</td>
<td>1 h</td>
<td>n/s</td>
<td>Onset of neuromuscular effects (incoordination)</td>
<td>[30]</td>
</tr>
<tr>
<td></td>
<td>&gt; 10,700</td>
<td>&lt; 5 min</td>
<td>n/s</td>
<td>Rapid onset of dizziness and 'drunkenness' (ataxia, confusion). Threshold level for onset of anaesthetic effects.</td>
<td>[30]</td>
</tr>
<tr>
<td>Case studies</td>
<td>8,000 – 35,000*</td>
<td>Minutes</td>
<td>'hot'</td>
<td>Death occurred sometime within 45 minutes of initial exposure.</td>
<td>[12]</td>
</tr>
<tr>
<td></td>
<td>5,000 – 16,000*</td>
<td>Minutes</td>
<td>n/s</td>
<td>Death occurred sometime within five minutes of exposure.</td>
<td>[31]</td>
</tr>
</tbody>
</table>

Dermal / ocular exposure

Mild ocular irritation may follow prolonged (8 h) exposure to low concentrations (140 ppm) of petrol vapour [30] or shorter (30 minute) exposure to vapours above 200 ppm [35]. More pronounced signs of ocular toxicity (lacrimation) occur above concentrations of 1000 ppm [35]. One study attributed ocular irritation to the presence of hydrocarbon component(s) present in the most volatile fraction of petrol: “The substance causing eye irritation was distilled from gasoline at extremely low temperatures and in very small amounts” [30].

Skin lesions resulting from acute exposure to liquid petrol are rare and generally result only from prolonged contact (hours) with undiluted product [5]. Thus, the extent of skin injury is primarily related to the duration of the exposure rather than concentration. Petrol "burns" resemble scalding, with an initial erythema leading to blister formation [5]. Prolonged dermal exposure (45 minutes – 12 hours) may lead to partial or full thickness burns with associated loss of epidermis and coagulation necrosis [3, 6]. Discolouration of the skin (brown / yellow / gold) has been observed and attributed to dye additives.

Dermal exposure to petrol is not considered to be a major factor in systemic toxicity [1]: this is based upon the assumption that skin contamination will occur concomitantly to inhalation of petrol vapour (which is considered the predominant route of entry). However, several clinical reports have suggested that dermal exposure may substantially contribute to systemic toxicity [2, 6] and it has been recommended that debridement of contaminated skin
may limit continued systemic absorption in cases where prolonged dermal exposure has occurred [2]. Systemic toxicity resulting from dermal exposure has been noted with other hydrocarbon mixtures such as diesel [36].

**Neurotoxicity**

As with other hydrocarbon solvents, petrol has anaesthetic (narcotic) properties (Table 2). Petrol also contains a number of potentially neurotoxic chemicals including n-hexane, benzene, butadiene, toluene, ethylbenzene, xylene and trimethyl pentane [37]. The approximate concentration of each constituent in liquid petrol and vapour are given in Table 3.

**Table 3: Average concentration of potentially neurotoxic constituents of liquid petrol and vapour [11, 38]. Numbers in brackets refer to range of values. Vapour values expressed as percentage of total hydrocarbons recovered from air samples obtained during the manual filling of cars (conditions and duration not reported).**

<table>
<thead>
<tr>
<th>Chemical</th>
<th>Liquid (%w/w)</th>
<th>Vapour (%w/w)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benzene</td>
<td>2.5 (0.2 – 4.7)</td>
<td>1.77 (0 – 5.4)</td>
</tr>
<tr>
<td>1,3-Butadiene</td>
<td>&lt;0.1</td>
<td>0.65 (0 – 4.6)</td>
</tr>
<tr>
<td>Ethylbenzene</td>
<td>2.6 (1.0 – 5.4)</td>
<td>.009 (0 – 0.1)</td>
</tr>
<tr>
<td>n-Hexane</td>
<td>2.5 (0.8 – 5)</td>
<td>1.37 (0 – 6.5)</td>
</tr>
<tr>
<td>Toluene</td>
<td>11.4 (2.7 – 21.0)</td>
<td>1.63 (0 – 7.1)</td>
</tr>
<tr>
<td>Xylene</td>
<td>10.6 (5.8 – 15.8)</td>
<td>0.48 (0 – 2.1)</td>
</tr>
</tbody>
</table>

Historically, lead (as tetraethyl lead; TEL) has been identified as the principal component of petrol responsible for neurological deficits following intentional (recreational) inhalation or massive acute exposure. However, European legislation has prohibited the use of TEL in petrol since January 2000 [39]. Therefore, there is currently a paucity of human data pertaining to the acute neurological effects of current (unleaded) petrol products other than narcosis.

**Delayed effects following an acute exposure**

A variety of delayed, neurological deficits have historically been associated with the acute inhalation of petrol vapour, including peripheral neuritis, impairment of memory, paresthesia, ataxis and epilepsy [1]. A late-onset autoimmune glomerulonephritis has also been observed following acute exposure [4].

There is limited evidence to suggest that long-term pulmonary residual effects may occur following chemical pneumonitis (as a result of aspiration-induced pneumonitis) [27, 40], the effects of which are of unknown clinical relevance [41].
Animal and In-Vitro Data

General toxicity

The acute toxicity of petrol in a variety of animal species is broadly consistent with that reported in humans, being predominantly associated with CNS, pulmonary and renal effects [42]. Data on LD$_{50}$ and skin and eye irritation are shown in Table 4.

Table 4: Acute toxicity data for petrol [43].

<table>
<thead>
<tr>
<th>Test</th>
<th>Species</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute oral (LD$_{50}$)</td>
<td>Rat</td>
<td>13.6 g kg$^{-1}$</td>
</tr>
<tr>
<td>Sensitisation</td>
<td>Guinea pig</td>
<td>Not sensitising</td>
</tr>
<tr>
<td>Primary dermal irritancy</td>
<td>Rabbit</td>
<td>slight</td>
</tr>
<tr>
<td>Acute dermal</td>
<td>Rabbit</td>
<td>No mortalities</td>
</tr>
<tr>
<td>Primary eye</td>
<td>Rabbit</td>
<td>Non irritating</td>
</tr>
</tbody>
</table>
Health Effects of Chronic / Repeated Exposure

Human Data

General toxicity

Dysfunction of the central nervous system is the predominant pathological condition associated with chronic exposure to high levels and such effects arising from frequent, recreational exposure (‘sniffing’ or ‘huffing’) have been extensively documented [17-22, 44-49]. There is currently insufficient evidence to unequivocally link chronic (occupational) exposure to petrol with other pathological conditions [50]. This may be because petrochemical workers are potentially exposed to a wide range of chemicals in addition to other confounding factors [42].

Historically, lead has been identified as the principal component of petrol responsible for neurotoxicity [51] and studies have demonstrated a link between lead body burden and neurological deficits as a result of petrol abuse (‘sniffing’ or ‘huffing’) [52]. However, it should be noted that the volatility of tetraethyl lead (TEL) is relatively low (0.4 mm Hg at 25°C) and so prolonged dermal exposure associated with the practice of petrol sniffing is likely to be the predominant route of entry for TEL rather than inhalation [7]. Since 2000, petrol has only been commercially available in ‘unleaded’ form within the UK and most of Europe. This policy limits the concentration of lead in marketable petrol to less than 0.005 g L$^{-1}$ as defined at Annex I of the 1998 EU Directive [39].

Whilst there is a known association between chronic petrol exposure and renal cancer in male rats [53-55], there is currently no evidence to link petrol exposure and renal cancer in humans [56, 57]. It is generally accepted that the susceptibility of male rats is mediated via a specific protein ($\alpha$-2-microglobin) which is absent in other mammals [54, 58].

Genotoxicity

At relatively high concentrations (1000 – 2500 ppm) in cell culture medium, petrol was mutagenic in drosophila melanogaster [59].

Negative results have been reported when petrol was investigated for its ability to induce gene mutations in bacteria (Salmonella assay) and mammalian cells using the mouse lymphoma assay [60]. Negative results were also obtained in another mammalian cell assay for gene mutation using a human lymphoblastoid cell line [61]. Negative results were reported in an in vivo bone marrow assay for clastogenicity in the rat [60].

There is a report of positive results being obtained using the UDS (unscheduled DNA synthesis) assay: limited studies in vitro (essentially only one dose level used) gave a positive result using rat hepatocytes and marginal effect in human and mouse hepatocytes. In the same report, negative results were obtained from in vivo UDS assays in the rat, but a slight increase in UDS was observed in mice [62].

Overall, it can be concluded that petrol does not have significant mutagenic activity.
**Carcinogenicity**

Epidemiological studies have not demonstrated a statistically significant link between cancer and occupational exposure to petrol [63-71]. However, the IARC has classified petrol as “possibly carcinogenic to humans” (Group 2B) mainly on the basis that there was inadequate evidence for the carcinogenicity in humans but there was limited evidence for the carcinogenicity in experimental animals. It was also noted that certain components of petrol are known or possible human carcinogens such as benzene and 1,3-butadiene. [57].

Petrol is assigned the Risk Phrase R45 ("may cause cancer") under the Chemical Hazard Information and Packaging for Supply (CHIPS) Regulations.

**Reproductive and developmental toxicity**

No reports specifically pertaining to the human reproductive or developmental toxicity of petrol were identified. The NOAEL for reproductive toxicity in a two-generation rat study was reported to be 20 000 mg m⁻³ [72].

Petrol is not classified under CHIPS (Chemical Hazards Information and Packaging Supply) regulations as a reproductive or developmental hazard.
References


PETROL– TOXICOLOGICAL OVERVIEW


Annex I: Average composition of (European) petrol liquid and vapour.

This document will be reviewed no later than 3 years or sooner if substantive evidence becomes available.