ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)

FOR

AUTOMOTIVE GASOLINE (UNLEADED)

(CAS Reg. No. 86290-81-5; 8006-61-9)

PROPOSED

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels – AEGL-1, AEGL-2 and AEGL-3 – are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL.

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SUMMARY

Automotive gasoline (CAS No. 86290-81-5) is a clear, amber colored volatile and flammable liquid with a characteristic odor. The most serious immediate hazard from the accidental release of gasoline is the threat of fire or explosion. Gasoline is a complex substance made by blending various refinery streams containing many hydrocarbon components. The hydrocarbons consist of paraffins, cycloparaffins and aromatic and olefinic hydrocarbons having carbon numbers predominantly in the C_3 to C_{11} range. Composition is variable depending on the crude oil or petroleum source, refining facilities, and total petroleum product demand. Carbon numbers in gasoline vapor range from C_4-C_6. The major hydrocarbon found in gasoline vapor is isopentane (C_5H_{12}, 34%). Automotive gasoline may also contain oxygenates such as ethanol or ethers and proprietary additives.

A level of distinct odor awareness (LOA) of 7.4 ppm (approximately 22 mg/m^3) was calculated for a gasoline blend comprised of summer and winter blends. The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception.

Relatively high concentrations of gasoline vapor may be irritating to the eyes. Data on sensory irritation were available from a clinical study. At sufficiently high vapor concentrations, gasoline is neurotoxic, inducing narcosis. Data were available on acute, repeat-exposure, subchronic exposure, neurotoxicity, reproductive and developmental toxicity, and chronic toxicity/carcinogenicity. Most of these studies used the rat as the animal model. Results of the available toxicity studies indicate that various blending streams of gasoline have similar toxicity.

The AEGL-1 is based on the sensory irritation study of Davis et al. (1960) in which volunteers were exposed to three different blends of gasoline vapor on separate occasions. Each blend was tested at approximately 880, 2200, and 4400 mg/m^3 for 30 minutes. The 30-minute exposure to all three blends of gasoline vapor at 2200 mg/m^3 produced subjective eye irritation at a higher incidence (15/30 subjects) than under control conditions (1/20 subjects). The incidence of objective eye irritation, although scored as slight (+1 on a scale of 1 to 4), was higher in the 2200 mg/m^3 group (15/30) than in the control group (2/20). Incidences of ocular tearing were similar in this group (3/30) and the control group (2/20). Incidences of subjective and objective eye irritation, including tearing, were higher at the higher concentration of 4400 mg/m^3. Because the eye irritation when measured objectively was slight (less than marked), an intraspecies uncertainty factor of 3 (instead of 10) was applied to protect sensitive subjects. There is adaptation to the slight irritation that defines the AEGL-1. Therefore, the same value of 730 mg/m^3 (2200 mg/m^3/3) was used across all exposure durations.

Although anecdotal human experience indicates acute inhalation of high concentrations can cause acute neurological effects (gasoline sniffers), tested concentrations in rodent studies of acute duration were not high enough to induce narcotic effects. The acute studies were conducted for 4 hours at the limit concentration of 5000 mg/m^3. The AEGL-2 values were based on the subchronic study of Schreiner et al. (2000) in which male and female Sprague-Dawley rats inhaled 22,500 mg/m^3 gasoline vapor (whole-body) for 6 hours/day, 5 days/week for 13

weeks. This concentration was the highest tested concentration in the subchronic studies. At this concentration, the rats failed to show clinical signs indicative of neurotoxicity during exposure. The point of departure, the 6-hour exposure to 22,500 mg/m^3, was divided by interspecies and intraspecies uncertainty factors of 1 and 3, respectively for a total uncertainty factor of 3. An interspecies uncertainty factor of 1 is sufficient because solvent uptake is generally greater in rodents than in humans based on higher blood:air partition coefficients for related hydrocarbons. In addition, the higher respiratory rate and greater cardiac output in rodents, on a body weight basis compared with humans, indicates faster uptake. Although humans differ in the rate at which they metabolize chemicals, the susceptibility of the general population to central nervous system depressants varies by no more than 2- to 3-fold as indicated by the minimum alveolar concentration, the concentration of an anesthetic that produces immobility in 50% of patients. Therefore, an intraspecies uncertainty factor of 3 is considered sufficient. Higher uncertainty factors would result in values inconsistent with the clinical study of Davis et al. (1960). Time scaling may not be relevant for hydrocarbons that act as anesthetics because blood concentrations of the major light components of gasoline rapidly approach steady-state. Therefore, the 6-hour value of 7500 mg/m^3 (22,500 mg/m^3/3) was used across all AEGL-2 exposure durations. The 7500 mg/m^3 value is supported by the study of Kuna and Ulrich (1984) in which no toxic signs were observed in squirrel monkeys exposed to 6350 mg/m^3 for six hours/day for 13 weeks. Partially vaporized gasoline was not a reproductive or developmental toxicant following repeat exposures to 20,000 to 23,900 mg/m^3 (McKee et al. 2000; Roberts et al. 2001).

None of the concentrations tested in acute or subchronic studies with rodents resulted in mortality, and there are no reports of human fatalities from exposure to gasoline vapors. It is not apparent that concentrations high enough to cause death from inhalation of gasoline vapor can be attained. Based on the likelihood that lethal concentrations of gasoline vapor cannot be attained/sustained under ambient conditions, an AEGL-3 was not determined.

The calculated values are listed in the table below.

TABLE S 1. Summary of AEGL Values for Gasoline

Classification	10-min	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL–1 (Nondisabling)	730 mg/m^3	730 mg/m^3	730 mg/m^3	730 mg/m^3	730 mg/m^3	Slight eye irritation in humans (Davis et al. 1960)
AEGL–2 (Disabling)	7500 mg/m^3 *	7500 mg/m^3 *	7500 mg/m^3 *	7500 mg/m^3 *	7500 mg/m^3 *	No clinical signs at highest tested concentration of 22,500 mg/m^3 – rat (Schreiner et al. 2000)
AEGL–3 (Lethal)	Not determined	Not determined	Not determined	Not determined	Not determined	No data**

*The AEGL-2 value is higher than 1/10 of the lower explosive limit (LEL) of gasoline in air (LEL = 14,000 ppm). Therefore, safety considerations against hazard of explosion must be taken into account.

**A lethal concentration was not attained in the available acute, subchronic, and chronic toxicity studies. Automotive gasoline vapor may act as a simple asphyxiant in sensitive individuals at 990,000 mg/m^3.

1. INTRODUCTION

Automotive gasoline (CAS No. 86290-81-5) is a clear, amber colored volatile and flammable liquid with a characteristic odor. Gasoline is a complex substance made by blending various refinery streams with many hydrocarbon components. The hydrocarbons consist of paraffins, cycloparaffins and aromatic and olefinic hydrocarbons having carbon numbers predominantly in the C_3 to C_{11} range. Definitions and examples of these classes of chemicals are provided in Appendix A. Carbon numbers of the major components of liquid gasoline range from C_5-C_9. Composition is variable depending on the crude oil or petroleum source, refining facilities, and total petroleum product demand. Ranges of major hydrocarbons in gasoline (vol%) are paraffins and cycloparaffins (59-66%), aromatics (26-32%), and olefins (8-9%). Carbon numbers in gasoline vapor range from C_4-C_6; at room temperature the C_4 hydrocarbons are gases. The major hydrocarbon found in gasoline vapor is isopentane (C_5H_{12}, 35%). Predominant components found in gasoline vapor and gasoline vapor containing 10% ethanol are listed in Appendix A. The lighter components, primarily isomers of butane and pentane are present in the vapor.

Various additives are blended into automotive gasoline (Appendix A). These include octane enhancers such as methyl *t*-butyl ether (MTBE; 15% v/v), *t*-amyl methyl ether (TAME), ethyl *t*-butyl ether (ETBE 17% v/v), *t*-butyl alcohol (TBA), ethanol (EtOH, 10%), and methanol; antioxidants such as butylated methyl, ethyl, and dimethyl phenols; metal deactivators; ignition controllers; icing inhibitors; corrosion inhibitors; and detergents/dispersants. These additives have low vapor pressures. Gasoline sold in the United States is unleaded and contains 10% ethanol. Ethanol is added at the marketing terminal (ATSDR 1995; API 2002; White 2009). Chemical and physical properties of automotive gasoline are listed in Table 1.

The commercial production of gasoline begins with crude oil which is refined into the following fractions: light naphtha, heavy naphtha, kerosene and light gas-oil, heavy gas-oil, and reduced crude. Each refinery stream has been assigned a CAS number. The light naphtha is used as a component of finished gasoline without further refining. Heavy oils can be treated by catalytic or thermal cracking which breaks down the higher boiling hydrocarbons into lower boiling ones; these can be used as components of gasoline. After various streams have been blended, sulfur compounds may be removed by hydrogenation. Additives and blending agents are added to improve the performance and stability of the gasoline. Typical retail gasoline contains 200-300 compounds. The benzene content of finished gasoline is 1-1.5% (ATSDR 1995; White 2009). European blends of gasoline may contain up to 7.5% benzene (Dutch Intervention Values 2009).

Gasoline is a high volume commercial product (McKee et al. 2000). U.S. production volume of motor gasoline in 1989 was 306.6 million gallons/day (ATSDR 1995). Several million gallons/day are imported. Recent production data were not located.

The most serious immediate hazard from the accidental release of gasoline is the threat of fire or explosion (Anonymous 1989). The lower and upper flammability limits are 1.4 and 7.4% or 14,000 and 74,000 ppm. The autoignition temperature is between 280 and 486ºC, and the flashpoint is -46ºC (ATSDR 1995).

A review of monitoring studies of workplaces for a variety of jobs in the manufacture, transport, and sale of gasoline shows that C_4 and C_5 compounds represent 54-81% of the total hydrocarbons in industrial hygiene samples (Dalbey et al. 1996). Thus, although the hydrocarbons comprising gasoline are predominantly in the range of C_3 to C_{11}, exposure of humans would be to the more volatile components in the range of C_4 to C_6 (Bruckner et al. 2008; White 2009). The C_4 to C_5 hydrocarbons are generally regarded as less toxic than the higher-molecular-weight counterparts (Reese and Kimbrough 1993). Studies that address the toxicity of both wholly vaporized gasoline and gasoline vapor containing the more volatile components are discussed in the following sections.

Because gasoline is a complex substance, concentrations are reported in mg/m^3. Many of the studies reviewed here reported concentrations in ppm. Concentrations are listed as they were reported. Appropriate conversions were made for calculation of AEGL values.

TABLE 1. Chemical and Physical Properties

Parameter	Value	Reference
Synonyms	Petrol; benzin; motor fuel;	O'Neil 2001; ATSDR 1995
Chemical formula	Not applicable (mixture)	
Molecular weight	108 (avg. whole gasoline); 72.6-80 (vapor)	ATSDR 1995; AIHA 2008
CAS Reg. No.	86290-81-5; 8006-61-9*	
Physical state	liquid, clear, amber-colored	AIHA 2008
Solubility in water	Insoluble 20ºC	O'Neil 2001
Vapor pressure	275-475 mm Hg at 20ºC	Amerada Hess 2004
Vapor density, saturated (air =1)	3 to 4	Amerada Hess 2004
Liquid density (water =1)	0.7-0.8 g/cm at 21ºC	AIHA 2008; ATSDR 1995
Melting point	not relevant	
Boiling point	32-210 ºC	O'Neil 2001
Flammability limits in air	1.4-7.4%	ATSDR 1995
Conversion factors	Whole gasoline: 1 ppm = 4.42 mg/m^3 1 mg/m^3 = 0.23 ppm Gasoline vapor: 1 ppm = 2.99 mg/m^3 1 mg/m^3 = 0.33 ppm	Calculated (based on average molecular weights of 108 and 73, respectively)

* CAS No. 86290-81-5 is unleaded gasoline that meets 1990 industry average specifications. CAS No. 8006-61-9 is assigned to natural gasoline, a complex combination of hydrocarbons separated from natural gas by processes such as refrigeration or absorption. Individual refinery process streams have additional CAS numbers.

2. HUMAN TOXICITY DATA

2.2.1. Odor Threshold

Gasoline has a characteristic odor. The odor threshold and odor recognition concentrations have been reported for gasoline and gasoline containing MTBE and TAME (Amerada Hess 2004). For non-oxygenated gasoline the odor detection and odor recognition thresholds were 0.5-0.6 ppm and 0.8-1.1 ppm. For gasoline with 15% MTBE, the respective thresholds were 0.2-0.3 ppm and 0.4-0.7 ppm, and for gasoline with 15% TAME, the respective thresholds were 0.1 ppm and 0.2 ppm.

The American Petroleum Institute (API 1994) reported odor threshold, recognition, and intensity thresholds for summer and winter blends of gasoline and for blends containing oxygenates (Table 2). Trained panelists participated in a forced choice sniff test by identifying which of three ports contained the odor. The lowest average odor detection and recognition thresholds were for the summer blend of gasoline containing 15% ETBE (97% purity). For MTBE, the odor detection threshold decreased with increases in MTBE concentration. Odor intensity values for gasoline blends without oxygenates ranged from 2.03-3.33. Odor intensity values for the blends ranged from 2.95-4.60. Most panelists described the odor for both the blends of gasoline as well as gasoline containing oxygenates as gasoline.

Using the data of API (1994) a level of distinct odor awareness (LOA) was calculated for gasoline. The LOA of 7.4 ppm (approximately 22 mg/m^3) was calculated for gasoline based on the odor detection value of 0.474 ppm for a composite of summer and winter blends. The calculation is shown in Appendix B. The LOA represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity.

TABLE 2. Odor Detection and Odor Recognition Thresholds for Gasoline

Gasoline blend	Odor Detection	Odor Recognition
Gasoline – summer blend	0.576 ppm	0.802 ppm
Gasoline – winter blend	0.479 ppm	1.121 ppm
Gasoline – composite	0.474 ppm	0.765 ppm
Gasoline – summer blend + 3% MTBE	0.500 ppm	0.696 ppm
Gasoline – summer blend + 11% MTBE	0.275 ppm	0.710 ppm
Gasoline – summer blend + 15% MTBE	0.264 ppm	0.686 ppm
Gasoline – winter blend + 15% MTBE	0.219 ppm	0.398 ppm
Gasoline – composite + 15% MTBE	0.085 ppm	0.185 ppm
Gasoline – summer blend + 15% ETBE	0.064 ppm	0.139 ppm
Gasoline – summer blend + 15% TAME	0.114 ppm	0.207 ppm
MTBE (97% purity)	0.053 ppm	0.125 ppm

Source: API 1994.

2.2.2. Clinical Studies

Drinker et al. (1943) conducted a clinical study with male and female volunteers exposed to various concentrations of straight lead-free commercial gasoline and the volatile fraction of gasoline distilled below 110ºC. Except for two exposures with a face mask, the exposures took place in a 16x22x9-ft chamber. Gasoline was metered into the ventilating air at the top of the chamber and exited at the floor. Concentrations were computed from the volume of gasoline vaporized and checked by vapor pressure and charcoal adsorption methods. Male volunteers, ages 23 to 45 years, and female volunteers, ages 17-32 years, participated in the study as outlined in Table 3. At concentrations up to 900 ppm, only slight sensory irritation was reported. While no dizziness was reported during the exposure to 900 ppm, two of six men reported feeling unsteady following the exposure. One subject experienced nausea during the 1-hour exposure to 2600 ppm, and all subjects felt slightly lightheaded. The slight irritation reported at low concentrations of whole gasoline was not present during the exposure to the light fraction.

The authors also noted that inhalation of gasoline causes slight gastrointestinal disturbance in about 10% of the population.

TABLE 3. Clinical Study with Gasoline and Gasoline Vapor (Drinker et al. 1943)

Concentration in ppm/Subjects	Exposure Duration	Response
Whole Gasoline Vapor		
160 (8 females)	8 hours	Odor detection for various periods of time; slight irritation of eyes and throat
270 (13 males)	8 hours	Odor detection throughout day, slight irritation of eyes and throat
11,200 (3 males, 1 female) vapor delivered by face mask	5-5.5 minutes	Nose and throat irritation within 20 seconds; feeling of incoordination
Gasoline Vapor Distilled below 110ºC		
140 (10 females)	8 hours	Odor detection; no definitive irritation
150 (8 females)	8 hours	Odor detection; very slight irritation of the eyes and throat
500 (9 males)	1 hour	Slight irritation of the eyes and throat
900 (6 males)	1 hour	Slight irritation of the eyes and throat; threshold for unsteadiness
2600 (5 males, 1 female)	1 hour	Strong odor; slight dizziness, transient eye irritation
10,700 (4 men) vapor delivered by face mask	4-7 minutes	Unsteadiness (compared to euphoria from alcohol or ether)

Ten healthy male volunteers, ages 23 to 40 years, were exposed to three varieties of unleaded vaporized gasoline for 30 minutes (Davis et al. 1960). The subjects were blind to the test material. The gasoline sample composition varied as follows: A: 25% paraffins, 30% naphthenes (cycloparaffins), 40% aromatics; B: 40% paraffins, 35% naphthenes, 20% aromatics; and C: 30% paraffins, 5% naphthenes, 65% aromatics. Volunteers were exposed individually in a 10x7x9.5-ft chamber. Gasoline was metered into the top of the chamber and exhausted near the floor. Chamber air samples were collected on silica gel, eluted with *n*-dodecane, and analyzed by gas chromatography. Concentrations averaged 200, 500, and 1000 ppm. Because three different blends were tested, it is assumed that the gasoline was almost wholly vaporized. Therefore, concentrations in mg/m^3 would be 880, 2200, and 4400 mg/m^3, respectively. Each subject filled out a 21-part questionnaire following exposure. The questionnaire addressed odor; irritation of the eyes, nose, and throat; headache, dizziness, drowsiness/fatigue, and headache. A photograph of each subject's left eye was taken before and after exposure. The photographs showed conjunctival blood vessels in detail (graded over a range of 1-4, with 1 representing very slight change, 2 and 3 representing intermediate change, and 4 representing marked change). Total positive responses of the 10 subjects to 12 questions and the highest responses are summarized in Table 4.

TABLE 4. Clinical Study with Gasoline Vapor (Davis et al. 1960)

Concentration in ppm (mg/m^3)	Total Responses[a]	Highest Response (number of subjects)[b]
Control 1	6	Transient cough (2); drowsiness (2)
Control 2	4	Responses evenly distributed

Sample A		
200 (880)	9	Itching or burning of eyes (3); headache (3)
528 (2323)	15	Itching or burning of eyes (7); headache (2)
1054 (4638)	9	Itching or burning of eyes (4)
Sample B		
186 (818)	7	Transient cough (2)
497 (2187)	12	Itching or burning of eyes (6); ocular tearing (2)
996 (4382)	26	Itching or burning of eyes (9); ocular tearing (4); nose irritation, cough, nausea, drowsiness, fatigue (2)
Sample C		
164 (722)	8	Itching or burning of eyes (3); drowsiness (2)
501 (2204)	11	Itching or burning of eyes (5); headache (2)
984 (4330)	16	Itching or burning of eyes (9); ocular tearing (3) itching of nose (2)

n = ten subjects.
All exposure durations were 30 minutes.
[a] Total responses of 10 subjects answering 12 questions (possible score of 120).
[b] Single responses not recorded.

The data in Table 4 show that the response to itching or burning eyes was most frequent, with an apparent concentration-response relationship. An analysis of variance of the rescored data (corrected for control responses) showed that the responses as a group lacked significance. Incidences of drowsiness in the control and 4400 mg/m^3 exposure were 3/30 and 2/20. Ocular tearing was similar in the control and 2200 mg/m^3 groups (10%), but was higher (27%) in the group exposed to 4400 mg/m^3. Objective eye irritation was graded +1 (very slight) or +2 (intermediate) with only one subject's eye graded +3 (in one group exposed to 4400 mg/m^3); this subject's scores were +1 and 0 following the other two exposures to 4400 mg/m^3. In the 4400 mg/m^3 exposure group, objective eye irritation scores averaged 0.9 to 1.4 out of 4. Numerous negative scores of -1 and 0 were also recorded following exposure. Subjective eye irritation was concentration related, with the higher scores at the higher concentrations. Subjective eye irritation did not fully correlate with responses of objective (photographed) eye irritation. No differences in irritation were noted between the gasoline vapor samples at approximately the same concentrations.

Neurological effects have been observed in individuals that habitually sniff gasoline for its euphoric/hallucinogenic properties (ATSDR 1995). These effects include postural tremor, ataxia, abnormal gait, affected speech, fatigue, headaches, memory loss, and sleep problems.

Cytogenetic monitoring studies and cancer epidemiology studies of workers exposed to gasoline have produced inconclusive results (ATSDR 1995). Most of these studies were considered inadequate due to inherent limitations including unreported exposure concentrations, length of exposure, and concurrent exposure to other substances. Exposure of human lymphoblastoid cells to 0.6% and 1.2% unleaded gasoline, with or without metabolic activation, failed to induce mutations at the TK+ locus (Richardson et al. 1986). Assays for mutagenicity and sister chromatid exchange were also negative.

3. ANIMAL TOXICITY DATA

Using standard protocols, ARCO clear gasoline with MTBE was tested for acute oral and dermal toxicity and skin and eye irritation and sensitization (ARCO Chemical Co. 1984). The

acute oral LD_{50} was >5.0 g/kg in rats. The acute dermal toxicity in rabbits was >2.0 g/kg. The ARCO gasoline was considered a moderate dermal irritant and was a minimal irritant to the rabbit eye (instillation of 0.1 mL). Gasoline was a weak sensitizing agent in the guinea pig.

3.1. Acute Toxicity

The acute inhalation toxicity of various blending streams of gasoline has been reported with the rat as the test species (Table 5). All exposure durations were for four hours. All studies followed the same methodology (provided in the following example). A group of five male and five female Sprague-Dawley rats inhaled a measured concentration of 5200 mg/m^3 sweetened naphtha (API No. 81-08; CAS No. 64741-87-3), whole-body, for 4 hours (API 1982). A second group was exposed to air only and served as the control group. Exposures took place in 160-L glass and stainless steel chambers. The atmospheres were generated by delivering test material liquid to a glass bead column. Air, heated to 55ºC and delivered in a counter-current manner relative to the liquid, vaporized the liquid. The vapor was diluted with air and piped to the exposure chamber. Concentrations were measured throughout the exposure period by a total hydrocarbon analytical method. Animals were observed for clinical signs during the exposure period, hourly for four hours following the exposure, and twice daily for 14 days post-exposure. Rats were weighed prior to exposure and on days 7 and 14. Surviving rats were sacrificed and organs and tissues were examined macroscopically. The lungs and trachea were examined microscopically. There were no deaths and no significant clinical signs observed during or following exposure. Two male rats and one female rat showed a slight clear nasal discharge during exposure. Females gained slightly less weight than expected over the 14-day recovery period. There were no microscopic changes in the lungs or trachea that could be attributed to treatment.

In some of the studies listed in Table 5, languid behavior (hypoactivity) was observed during exposure (light alkylate naphtha) and nasal discharge was observed in two animals on day 2 post-exposure (light, catalytically cracked naphtha) (API 1995). Lower body weight gain, seen with API 81-08 was not observed in most of the studies. There were no significant gross observations at necropsy and no histological changes observed in the lungs in any study.

TABLE 5. Acute Toxicity of Gasoline Blending Stream Vapor to Rats

Blending Stream	LC_{50} (mg/m^3)
Naphtha, light catalytic cracked (API 81-04)	>5300
Naphtha, heavy catalytic cracked (API 83-18)	>5000
Naphtha, light catalytic reformed (API 83-04)	>5200
Naphtha, heavy catalytic reformed (API 83-06)	>5000
Naththa, full range catalytic reformed (API 83-05)	>5000
Naphtha, sweetened (API 81-08)	>5200
Naphtha, light alkylate (API 83-19)	>5000
Naphtha, heavy thermally cracked (API 84-02)	>5000

All studies were conducted for four hours at the limit concentration of 5000 mg/m^3.
Sources: API 2008a,b; CONCAWE 1992.

A group of five male and five female Sprague-Dawley rats inhaled 5200 mg/m^3 of ARCO clear gasoline with MTBE for 4 hours (ARCO Chemical Co. 1984). Chamber atmospheres were generated by metering the test material to a flask maintained at 100ºC and then mixing with

room air. Rats were observed during exposure and at set intervals for 14 days post-exposure. Animals appeared unaffected during exposure. Upon removal from the chamber, lacrimation was noted in 2 of 10 animals, mucoid nasal discharge in 7 of 10 animals, red nasal discharge and dry rales in 2 of 10 animals, and reduced righting reflex in 4 of 10 animals. These signs continued into the next day, but generally abated during the 14-day observation period. There were no deaths, and rats gained weight during the post-exposure period. At necropsy, discolored kidneys were observed in 4 of 5 males and 2 of 5 females.

3.2. Repeat-Exposure and Subchronic Studies

Groups of 5-6 $B6C3F_1$ mice inhaled 0 (filtered air), MTBE (7814 ppm), API-91-01 unleaded gasoline (2014 ppm), or PS-blend unleaded gasoline (2028 ppm) for 6 hours/day, 5 days/week, for 3 or 21 days (Moser et al. 1996) (Table 6). Neither blend of gasoline contained significant amounts of MTBE. The API-91-01 blend contains a slightly greater percentage of aromatics and olefins than the PS-6 blend. Mice were sacrificed 18 hours after the last exposure. During exposure, abnormal gait, hypoactivity, decreased muscle tone, and increased lacrimation were observed in the group exposed to MTBE. Occasional hypoactivity was observed in mice exposed to the unleaded gasolines. Compared to the control, relative liver weight was increased in all groups after 3 and 21 days, and relative uterine weight was decreased for all groups after 3 days and in the MTBE- and API-91-01-treated groups after 21 days.

Chu et al. (2005) exposed groups of 15 male and 15 female Sprague-Dawley rats to filtered air, 6130 ppm ethanol, 500 ppm gasoline, or a mixture of 85% ethanol and 15% gasoline (6130 ppm ethanol and 500 ppm gasoline) for 6 hours/day, 5 days/week for 4 weeks. Ten rats of each gender were sacrificed after 4 weeks, and the remaining rats were held for a 4-week recovery period. No clinical signs of toxicity were observed. Body weight gain was reversibly suppressed by 21% in female rats that inhaled the ethanol-gasoline mixture. Reversible inflammation of the upper respiratory tract was observed only in the gasoline-ethanol group. The authors concluded that treatment with gasoline and ethanol produced mild, reversible biochemical, hematological, and histological effects (adrenal cortical vacuolation), with some indication of interaction when the vapors were co-administered.

Halder et al. (1986) exposed groups of ten Sprague-Dawley rats/sex to 0, 120, 1150, or 11,800 mg/m^3 of the C_4 and C_5 hydrocarbons that comprise typical gasoline vapor. Atmospheres consisted of 25% each *n*-butane, *n*-pentane, isobutene and isopentane. Exposure was for 6 hours/day, 5 days/week for 3 weeks. No adverse clinical signs were observed. No treatment-related changes were found in body weight, serum chemistry, hematology, histopathology of tissues, or organ weight.

Groups of 20 male and 20 female Sprague-Dawley rats inhaled vapor of either unleaded gasoline at concentrations of 0, 1570 or 6350 mg/m^3 or leaded gasoline at 420 or 1530 mg/m^3 for 90 days (Kuna and Ulrich 1984). Groups of four male and four female squirrel monkeys inhaled the same concentrations. Exposures were for 6 hours/day, 5 days/week. Gasoline was wholly vaporized in an atomizer with heated nitrogen; and then mixed with the exposure chamber air inflow. Atmospheres were analyzed with a total hydrocarbon analyzer connected to an automatic sampling device. No "remarkable" changes were observed in body weight; hematology; CNS response (flash-evoked response time, tested in monkeys); pulmonary function

tests (in monkeys); urinalysis; deposition of IgG in the renal glomerulus; lead levels in blood, urine, and tissue; organ weight; organ-to-body weight ratio; or histopathology. Minor changes in some parameters in rats are listed in Table 6. Male rats exposed to 6350 mg/m^3 unleaded gasoline showed male-rat-specific changes in the kidney tubules.

Groups of 20 Sprague-Dawley rats (10/sex) and 20 CD-1 mice (10/sex) were exposed whole body to vapors of light catalytically cracked naphtha at measured concentrations of 0, 530, 2060, or 7690 mg/m^3 for 13 weeks (Dalbey et al. 1996). Exposure was for 6 hours/day, 5 days/week. Atmospheres were analyzed by gas chromatography. No significant treatment-related changes were found in clinical signs, body weight, serum chemistry, hematology, histopathology of 24 tissues, or organ weight. In rats, a marginal increase was noted in the number of sperm per gram of epididymis in the 7690 mg/m^3 group, compared to sham-exposed controls, but not compared to untreated controls.

In a study conducted in the same manner, groups of 15 male and 15 female Sprague-Dawley rats inhaled 0, 410, 1970, or 8050 mg/m^3 of partially vaporized full range catalytic reformed naphtha for 13 weeks (Dalbey and Feuston 1996). No significant treatment-related effects were found in clinical signs, serum chemistry, hematology, or histopathology of 24 organs. Body weight and weights of liver and kidney were marginally increased in males in the 8050 mg/m^3 group.

Additional studies including neurotoxicity, developmental toxicity, and chronic toxicity/carcinogenicity are summarized in Table 6.

TABLE 6. Repeat-Exposure, Subchronic and Chronic Exposure, Developmental Toxicity, and Genotoxicity Studies with Gasoline Vapor

Type of Study (species)	Material Characterization	Concentrations (mg/m^3)	Effect	Reference
General toxicity 3, 21 days (mouse)	PS-6 blend API-91-01	0, 2056 ppm 0, 2014 ppm	Occasional hypoactivity Occasional hypoactivity	Moser et al. 1996
General toxicity 4 weeks (rat)	ethanol gasoline ethanol+gasoline	6130 ppm 500 ppm 6130+500 ppm	No clinical signs No clinical signs Reversible body weight suppression in female rats; reversible nasal inflammation; biochemical changes	Chu et al. 2005
General toxicity, 3 weeks (rat)	Combination of 25% n-butane, 25% isobutene, 25% n-pentane, 25% isopentane	0, 120, 1150, 11,800	No adverse clinical signs or effects	Halder et al. 1986
General toxicity, subchronic (rat, monkey)	Wholly vaporized leaded and unleaded gasoline	0, 1570, 6350	Alpha 2-microglobulin mediated nephropathy in male rats; slight increases in thrombocyte and reticulocyte counts and liver weight in male rats receiving 6570 mg/m^3; slight increase in tissue lead content in rats receiving leaded	Kuna and Ulrich 1984

			gasoline Monkeys – no significant toxic effect	
General toxicity, subchronic (rat, mouse)	Partially vaporized light catalytically cracked naphtha	0, 530, 2060, 7690	No treatment related clinical signs, or changes in body weight, serum chemistry, hematology, histopathology, organ weight; marginal decrease in sperm in male rats at 7690 mg/m^3	Dalbey et al. 1996
General toxicity, subchronic (rat)	Partially vaporized full range catalytic reformed naphtha	0, 410, 1970, or 8050	No treatment-related clinical signs, no effect on serum chemistry or male reproductive parameters; lower white blood cell count (up to 24% at highest concentration); increased liver and kidney weight; no microscopic lesions	Dalbey and Feuston 1996
Neurotoxicity, subchronic (rat)	Vapor from light catalytic reformed naphtha	0, 750, 2500, 7500 ppm (0, 2250, 7500, 22,500)	No clinical signs during exposure; no change in motor activity other parameters during an FOB; transient decreases in hematology parameters	Schreiner et al. 2000
Neurotoxicity, subchronic (rat)	Gasoline vapor condensate with or without additives: MTBE, ETBE, TAME, DIPE, ethanol, TBA	0, 2000, 10,000, 20,000	No neuropathology; negative FOB; motor activity affected by gasoline containing TBA with effect resolving during recovery	O'Callaghan et al. 2004
Reproductive toxicity, two generation (rat)	volatile fraction from a gasoline terminal	5076, 10,247, or 20,241	No significant effects other than male rat specific nephropathy	McKee et al. 2000
Reproductive toxicity, one-generation; two generation (rat)	GVC with or without additives: MTBE, ETBE, TAME, DIPE, ethanol, TBA	0, 2000, 10,000, 20,000	No impact on reproduction	Gray et al. 2004
Developmental toxicity, GD 6-19 (rat)	Gasoline vapor condensate (API 94-02)	0, 2653, 7960, 23,900	No maternal toxicity; no developmental effects	Roberts et al. 2001
Developmental toxicity, GD 0-19 (rat)	Light catalytically cracked naphtha	0, 2150, 7660 GD 6-19	No treatment-related clinical signs or effects on reproductive parameters other than increased resorptions at 7660 mg/m^3	Dalbey et al. 1996
Developmental toxicity GD 6-19 (rat)	Partially vaporized full range catalytic reformed naphtha	0, 2160, 7800	Reproductive performance unaffected; no affect on body weight gain; serum glucose decreased and serum potassium increased	Dalbey and Feuston 1996
Genetic toxicity	GVC with or without additives:	0, 2000, 10,000, 20,000	Assay results negative for micronuclei formation in bone marrow; sister chromatid	Schreiner et al. 2004

	MTBE, ETBE, TAME, DIPE, ethanol, TBA		exchange assay positive for gasoline vapor condensate and condensate containing MTBE	
Chronic toxicity/ carcinogenicity (rat, mouse)	Wholly vaporized gasoline containing 2% benzene	296, 1290. 9080	Survival unaffected; decreased body weight gain at 9080 mg/m^3 both species; male rat nephropathy; liver tumors in sensitive strain of female mice	MacFarland et al. 1984
Chronic toxicity/ carcinogenicity (rat)	GVC with or without additives: MTBE, ETBE, TAME, DIPE, ethanol, TBA	0, 2000, 10,000 or 20,000	Survival unaffected; reversible changes in body weight (gasoline +ethanol and gasoline + ETBE); reversible FOB motor activity change (gasoline + TBA); neuropathology negative;	Benson et al. 2004

Subchronic exposures are for 13 weeks, 6 hours/day, 5 days/week.
Rat studies were conducted with male and female Sprague-Dawley rats; CD-1 mice were additionally tested in the toxicity study of Dalbey et al. (1996), and squirrel monkeys were additionally tested in the study of Kuna and Ulrich 1984.
FOB = functional observational battery.
GVC = gasoline vapor condensate consisting of approximately 15-20% of starting gasoline which was slowly vaporized at near maximum gasoline in-use tank temperature (130ºC) and condensed.
GD = gestation day.

3.3. Neurotoxicity

Neurotoxicity assessments were not performed following acute exposures. Clinical signs were generally absent with the exception of languid behavior and hunched appearance exhibited during a 4-hour exposure of rats to 5000 mg/m^3 light alkylate naphtha (API 1995).

In a subchronic (13 week) study, Schreiner et al. (2000) exposed groups of 16 male and 16 female Sprague–Dawley rats (whole-body) to 0, 750, 2500, or 7500 ppm (approximately 0, 2250, 7500, or 22,500 mg/m^3) of vapors of a light catalytic reformed naphtha distillate (CAS No. 64741-63-6).[1] Standard parameters of subchronic toxicity were measured throughout the study. At necropsy, organs were weighed and tissues were examined microscopically. There was no mortality and no clinical signs such as tremors, ataxia, or lethargy were seem. Compared to the control group, there were no changes in motor activity or other parameters during a standard functional observational battery (FOB). Changes in some hematology parameters such as a decrease in white blood cell count in males in the 22,500 mg/m^3 group generally abated during a four-week recovery period. In male rats that inhaled 22,500 mg/m^3, a small increase in relative kidney weight and decreases in absolute and relative spleen weight were reversible at the end of the recovery period. These parameters were unaffected in female rats. Rats in the 22,500 mg/m^3 group showed a male-rat specific light hydrocarbon nephropathy.

A 13-week neurotoxicity study was conducted with gasoline vapor generated by vaporizing gasoline at near-maximum in-use automotive fuel tank temperature conditions (O'Callaghan et al. 2004). The starting material, described in Daughtrey et al. (2004), was

[1] Light catalytic reformed naphtha is comprised of hydrocarbons having carbon numbers predominantly in the C_5-C_{11} range. It contains a relatively large proportion of aromatics and branched chain hydrocarbons and may contain as much as 10% benzene by volume. Finished gasoline contains 20-30% of this light catalytic reformed naphtha.

slowly vaporized, separated, condensed and recovered. This fraction, termed gasoline vapor condensate (GVC) was used in multiple studies. Samples of GVC to which one of four ethers or one of two alcohols was added were also tested (See Appendix A for volume percent additives). Male and female Sprague Dawley rats were exposed to 0, 2000, 10,000 or 20,000 mg/m^3 of each test material, 6 hours/day, 5 days/week for 13 weeks. A standard FOB and motor activity tests were administered at 3 weeks and several times thereafter. At study termination, brains were evaluated for glial fibrillary acidic protein (GFAP), a biomarker of brain damage. Except for vapor containing the oxygenate *t*-butyl alcohol, FOB and motor activity were unaffected. Behavioral effects (undefined change in motor activity) for the group exposed to gasoline vapor containing t-butyl alcohol resolved during a recovery period. Neuropathology was negative in all groups. Analysis of GFAP revealed a mild gliosis only in males exposed to gasoline vapor condensate containing ethyl alcohol.

3.4. Developmental/Reproductive Toxicity

In a two-generation reproductive toxicity study, groups of 30 male and female Sprague-Dawley rats inhaled gasoline vapor daily for 6 hours/day, 7 days/week, for 10 weeks prior to mating and throughout the mating period (up to 3 weeks) (McKee et al. 2000). Selected first generation pups were treated in the same manner. The study was conducted in accordance with United States and European guidelines (OECD Guideline 416). In order to assess vapor representative of the exposure of handlers and customers at gasoline service stations, the vapor consisted of the volatile fraction from a gasoline terminal vapor recovery unit at a distribution terminal in the Netherlands. The assigned CAS Reg. No. was 68514-15-8. Exposure took place in 1.5 m^3 chambers; measured concentrations were 5076, 10,247, and 20,241 mg/m^3 (the latter reported as 50% of the LEL). The vapor consisted of primarily C_4 and C_5 hydrocarbons. There were no treatment-related effects in parental animals. Microscopic changes were limited to males and involved hydrocarbon droplet nephropathy of the kidney, specific to male rats. There were no deleterious effects on offspring survival and growth. The potential for endocrine modulation was assessed by analysis of sperm count and quality as well as time to onset of developmental landmarks in females. No toxicologically significant effects were observed. The NOAEL for reproductive toxicity in this study was >20,000 mg/m^3.

In a one-generation study, groups of 26 male and 26 female Sprague-Dawley rats inhaled the evaporative emissions of gasoline or gasoline containing the ether or alcohol oxygenates, TAME, ETBE, DIPE, ethanol, or TBA, at 0, 2000, 10,000, or 20,000 mg/m^3, 6 hours/day prior to mating and up to weaning of the F_1 on lactation day 28 (Gray et al. 2004). There were no differences in male or female fertility with any exposure. Reduced weight gain was observed in groups inhaling gasoline vapor and gasoline/MTBE, ethanol, ETBE, and TBA. All exposures caused increases in the kidney weight of male rats. Weight changes and discolorations in other organs were not accompanied by histopathological changes, and so were not considered adverse.

A developmental toxicity study was conducted according to U.S. EPA TSCA Guideline No. 798-4350 (Roberts et al. 2001). Groups of 21 to 24 pregnant Sprague-Dawley rats inhaled measured concentrations of 0, 2653, 7960, or 23,900 mg/m^3 (the latter reported as 75% of the LEL), 6 hours/day, on days 6 to 19 of gestation. The test material was gasoline vapor condensate derived from unleaded gasoline that met 1990 industry average specification (the 1990 Clean Air Act required increased oxygen content in gasoline). All rats were sacrificed on

gestation day 20. No maternal toxicity was observed. Developmentally, there were no differences between treated and control groups in fetal malformations, total variations, resorptions, body weight or viability. Under conditions of this study, the developmental NOAEL was >23,900 mg/m^3.

Groups of 15 pregnant Sprague Dawley rats inhaled vapor of light catalytically cracked naphtha, whole-body, at concentrations of 0, 2150, or 7660 mg/m^3 for 6 hours/day on gestation days 0-19 (Dalbey et al. 1996). Dams were sacrificed on gestation day 20. There were no skeletal or visceral effects in the fetuses. The only observed effect was an increase in resorptions in the dams that received 7660 mg/m^3. In a study conducted in the same manner, groups of 11-12 pregnant Sprague-Dawley rats inhaled 0, 2160, or 7800 mg/m^3 of partially vaporized full range catalytic reformed naphtha for 6 hours/day on gestation days 6-19 (Dalbey and Feuston 1996). At sacrifice on day 20, no maternal or fetal effects were observed.

3.5. Genotoxicity

The genetic toxicity of gasoline was reviewed by ATSDR (1995). The weight of evidence from *in vivo* animal studies suggests that unleaded gasoline is not genotoxic to rats and not strongly genotoxic to mice. *In vitro* rodent studies produced mixed results. Mutagenicity tests with Salmonella typhimurium TA1535, TA1537, TA1538, TA98, or TA100, with and without metabolic activation were largely negative. Mutations were observed only at toxic concentrations. Assays for gene mutation in rodent lymphoma cells were negative. Assays for unscheduled DNA synthesis in rodent primary hepatocytes were positive only as gasoline concentrations approached toxic levels. Results of an assay for unscheduled DNA synthesis in rat kidney cells were negative.

In a subchronic inhalation study with male and female Sprague-Dawley rats exposed to 0, 2000, 10,000, or 20,000 mg/m^3 of gasoline vapor concentrate, with and without oxygenates, all assays for micronucleus formation in bone marrow were negative (Schreiner et al. 2004). Statistically significant increases in sister chromatid exchange over several doses were observed in cultured lymphocytes of rats that inhaled gasoline vapor condensate or gasoline vapor condensate containing MTBE. Females appeared more sensitive than males. Gasoline vapor condensate containing TAME induced increased sister chromatid exchanges in both sexes at the highest dose only.

3.6. Chronic Toxicity/Carcinogenicity

Gasoline vapor with and without MTBE was tested for chronic toxicity and carcinogenicity in male and female F344 rats (Benson et al. 2004). Whole-body exposures were to 0, 2000, 10,000, or 20,000 mg/m^3, 6 hours/day, 5 days/week for 104 weeks. Survival to study termination was unaffected by either concentrate. Final body weight in males and females inhaling 20,000 mg/m^3 gasoline vapor condensate was decreased by 9% and 8% respectively. Reductions in final body weight in male and females rats inhaling gasoline vapor containing MTBE were both 8%. Incidences of hepatic adenomas or carcinomas were unaffected by either exposure compared with the respective control groups. Male-rat specific nephropathy was observed in both control and treated rats.

In an earlier study, chronic inhalation of unleaded gasoline vapor resulted in increased hepatocellular adenomas and carcinomas in $B6C3F_1$ female mice (MacFarland et al. 1984). Tumors appeared in female mice between 18 months and terminal sacrifice in the highest exposure group, 2056 ppm, 6 hours/day. This increase may have been due to the promotion of spontaneously initiated cells that occur with unusually high frequency in this mouse strain (Bruckner et al. 2008). Male rats also exhibited male-rat-specific nephropathy. Inhalation of unleaded gasoline vapor promoted the development of *N*-nitrosodiethylamine initiated tumors in male but not female $B6C3F_1$ mice (Standeven et al. 1995).

In addition to increased hepatocellular adenomas and carcinomas in $B6C3F_1$ mice, gasoline has been shown to induce P450 activity and produce hepatomegaly and a transient increase in hepatocyte proliferation, all considered relevant to tumor-promoting activity (Bruckner et al. 2008). However, based on epidemiological evidence, an association between gasoline exposure and cancer in humans is inconclusive (IARC 1989).

3.7. Summary

Acute toxicity is similar for all blending streams of gasoline. No deaths were reported in male and female rats that inhaled the limit concentration of 5000 mg/m^3 of various blending streams of gasoline for 4 hours (API 2008a,b). No mortality was reported in male and female rats that inhaled 20,000 mg/m^3 gasoline for more than 10 weeks (McKee et al. 2000) or in male and female rats that inhaled 22,500 mg/m^3 of a blending stream for 13 weeks (Schreiner et al. (2000). In the latter study, no clinical signs were noted during exposure. Studies of subchronic and chronic duration and studies that addressed developmental and reproductive toxicity showed no significant toxic effects. Genotoxicity studies were generally negative.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

There are no relevant studies of rates or extent of absorption, distribution, metabolism, or excretion of gasoline in humans. The metabolic pathways of many of the components of gasoline have been studied in animal models, but information on the toxicokinetics of complex substances is sparse. Individual hydrocarbons such as pentane are hydroxylated by hepatic cytochrome P-450 enzymes to pentanol, conjugated with glucuronic acid and excreted. Dennison et al. (2003) used physiologically-based pharmacokinetic (PBPK) modeling to characterize the pharmacokinetics of gasoline in rats. Most gasoline components are metabolized or oxidized primarily in the liver by cytochrome P-450/2E1. It was assumed that essentially all of the components of gasoline serve as competitive inhibitors of oxidation of the other components. Therefore, a lumped approach was used to model the pharmacokinetics of whole gasoline. Selected target components of gasoline were *n*-hexane, benzene, toluene, ethylbenzene, and *o*-xylene. Male F344 rats were exposed in a closed chamber for 6 hours to the single chemicals at concentrations between 500 and 2000 ppm, to various mixtures of all five chemicals at 50 to 1000 ppm each, to mixtures of the chemicals at the same concentration of 100-500 ppm each, and to winter and summer blends of gasoline at 500, 1000, and 1500 ppm. The experimental data from all combinations of chemicals and computer simulation results from the model matched well. The PBPK model analysis indicated that metabolism of individual components was inhibited up to 27% during the 6-hour experiments of gasoline uptake.

4.2. Mechanism of Toxicity

Automotive gasoline is a complex substance consisting of many hydrocarbon components. Although gasoline components vary within limits with octane number and engine requirements, the acute toxic effects do not differ significantly (ACGIH 1992; Niemeier 2001). Some gasoline additives are of toxic interest, but their generally low concentration and low volatility make a negligible contribution to the vapor phase.

Exposure to very high concentrations of hydrocarbons may cause excitement, loss of equilibrium, stupor, and coma (Cavender 1994a, 1994b, 1994c; Bruckner et al. 2008). The effectiveness of the individual components of gasoline as CNS depressants is related to their volatilization, potency, and blood/air partition coefficients. Recovery from CNS effects is rapid and complete in the majority of cases. Death is postulated to be due to either central nervous system depression due to asphyxia leading to respiratory failure, or cardiac sensitization to circulating catecholamines leading to a fatal arrhythmia (ATSDR 1995).

Because hydrocarbons are lipophilic, they partition into and accumulate in neuronal membranes and myelin. The more lipophilic the hydrocarbon (i.e., the higher its neuronal tissue:blood partition coefficient), the more potent a CNS depressant it is. The mere presence of hydrocarbons has generally been thought to disrupt the ability of the neuron to propagate an action potential and repolarize. Recent research has revealed that hydrocarbons might act by more specific mechanisms and might affect specific neurotransmitters and membrane receptors (i.e., by enhancing gamma-aminobutyric $acid_A$ receptor function, or activating dopaminergic systems).

Many volatile hydrocarbons are of low acute toxicity. Concentrations that cause CNS depression are generally non-injurious to the lung. Exposure of rats to gasoline vapor at 20,000 mg/m^3 for more than 10 weeks was without effect (McKee et al. 2000). The aromatic hydrocarbons are more toxic than the aliphatic and alicyclic hydrocarbons but, due to their lower boiling point, are present to a much smaller extent in gasoline vapor.

Long-term exposure to some hydrocarbons results in α_{2u}-globulin nephropathy and associated renal carcinogenicity specific to male rats (Bruckner et al. 2008). The nephropathy is characterized by hyaline droplet formation and necrosis of kidney cells. The toxic affect is attributed to the α_{2u}-microglobulin protein which is unique to the male rat. The α_{2u}-microglobulin protein is synthesized in the liver of male rats and is readily excreted in the glomerular filtrate. Select hydrocarbons combine with the protein to form poorly digestible complexes and prevent efficient catabolism of the protein following resorption from the glomerular filtrate. The tubular epithelial cells become engorged with the protein, resulting in metabolic disturbances followed by cell death and exfoliation. Exfoliated necrotic cells form tubular casts which plug the nephron near the corticomedullary junction. The casts become mineralized and may be flushed into the medullary segments where they may remain. α_{2u}-Microglobulin nephropathy is unique to male rats. This protein is not synthesized in humans (U.S. EPA 1991). Therefore, this adverse effect is not considered relevant to human exposure to gasoline vapor.

4.3. Structure-Activity Relationships

Gasoline vapor is a complex substance composed of volatile hydrocarbons, primarily in the C_4 to C_6 range. The predominant hydrocarbons in vapor such as butane and pentane, have high vapor pressures, low blood/air partition coefficients (Dahl et al. 1988) and are practically nontoxic (Galvin and Marashi 1999). Individual components of gasoline vapor are not addressed in detail in this document.

4.4. Other Relevant Information

4.4.1. Species Variability

All acute toxicity studies were conducted with the rat as the test species. Therefore, no information on species variability during acute inhalation exposure could be ascertained. Subchronic studies with rats, mice (up to 7690 mg/m^3), and monkeys (up to 6570 mg/m^3) failed to provide data on relative sensitivity. Although data were available only for a few hydrocarbons, the C_7 hydrocarbon *n*-heptane and xylene components, *in vitro* studies of blood/air partition coefficients show that uptake of hydrocarbons is greater by rat blood than human blood (Gargas et al. 1989). Human and rat blood to air partition coefficients for *n*-heptane were 2.9 and 4.8, respectively, and human and rat blood to air partition coefficients for *m*-xylene were 33 and 46. Greater chemical uptake by rats than humans is also due to the more rapid respiration rate and greater cardiac output in rodents compared with humans on a body weight basis.

4.4.2. Susceptible Populations

No information was available on susceptible human populations. No information was located on age-related sensitivity. Children and the elderly may be more or less sensitive to the toxic effects of solvents and vapors, but age-dependent susceptibility to acute effects of such vapors usually differs by no more than two- to threefold (Bruckner et al. 2008). Although humans differ in the rate at which they metabolize chemicals, the susceptibility of the general population to central nervous system depressants varies by no more than 2- to 3-fold as indicated by the minimum alveolar concentration, the concentration of an inhaled anesthetic that produces immobility in 50% of patients (Kennedy and Longnecker 1996; Marshall and Longnecker 1996).

4.4.3. Concentration-Exposure Duration Relationship

No data were located that provided information on the concentration-exposure duration relationship for either the slight eye irritation experienced at gasoline vapor concentrations ≤4400 mg/m^3 (Drinker et al. 1943; Davis et al. 1960) or the vapor's effect on the central nervous system. For the endpoints of both sensory irritation and depression of the central nervous system by solvents, there is generally a concentration threshold. For neurotoxicity, time to steady state for individual components depends on lipophilicity as well as chemical interactions. Once steady-state is attained, the CNS effect observed with exposure to high concentrations is most likely a concentration-dependent effect with exposure duration of lesser importance. For example, for *n*-nonane, inhaled by F344 rats at 100, 500, or 1000 ppm for 4 hours, steady-state was approached in the blood within two hours at the two higher concentrations (Robinson 2000). The blood:air partition coefficient was 5.13.

4.4.4. Concurrent Exposure Issues

Gasoline is a complex substance of hydrocarbon components. The effect of inhalation of multiple similar hydrocarbons appears to be additive (Dennison et al. 2003). The highly volatile "light ends" which include hydrocarbons such as isopentane (C_5H_{12}), are practically non-toxic. The 4-hour LC_{50} for isopentane is 280,000 mg/m^3 (Matheson Tri-Gas, Inc. 2009). The aromatics such as toluene are more toxic, with a 3-hour LC_{50} value in the mouse of 32,250 mg/m^3 (U.S. EPA 2002).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

Drinker et al. (1943) exposed male and/or female subjects to whole gasoline vapor (unleaded) at concentrations of 160 and 270 ppm and to gasoline vapor distilled below 110ºC at concentrations of 140 and 150 ppm for 8 hours. Male and/or female subjects were also exposed to the distillate vapor at 500, 900 or 2600 ppm for 1 hour. Additional exposures via face masks and lasting only a few minutes utilized concentrations of 11,200 ppm (whole gasoline vapor) and 10,700 ppm (distillate vapor). Odor detection and very slight irritation were reported at concentrations up to and including 900 ppm. At this concentration, a slight neurotoxic effect was apparent only after the exposure. Unfortunately, the study employed a 17-year-old female college student and thus does not meet the U.S. EPA ethical criteria for human exposure.

On separate occasions, Davis et al. (1960) exposed 10 male subjects to three different samples of unleaded gasoline vapor for 30 minutes. Target concentrations were 880, 2200, and 4400 mg/m^3. Concentration-related itching or burning of the eyes was the primary reported symptom. Objective irritation of the eye, as measured by redness, was negative or slight at 880 and 2200 mg/m^3 (score range of -2 to +1) and intermediate at 4400 mg/m^3 (score range of -1 to +3 in the three exposures). The scores in the control groups ranged from -1 to +1, but the eyes of more subjects in the 880 and 2200 mg/m^3 groups were assigned a +1 than in the control groups. Incidences of ocular tearing in the control, 880, 2200, and 4400 mg/m^3 groups were 2/20, 1/30, 3/30, and 8/30, respectively. Drowsiness was reported by two subjects inhaling 4400 mg/m^3 and as well as by two control subjects.

5.2. Summary of Animal Data Relevant to AEGL-1

All acute inhalation studies were conducted with rats as the test animal. A 4-hour exposure to 5000 mg/m^3 vapor of various gasoline blending streams was generally without a significant toxic effect (API 2008a,b). In subchronic studies, the highest concentrations tested, 20,000 and 22,500 mg/m^3 (rat), 7690 mg/m^3 (mouse), and 6570 mg/m^3 (monkey) were without toxic effects (Schreiner et al. 2000; O'Callaghan et al. 2004; Dalbey et al. 1996; Kuna and Ulrich 1984).

5.3. Derivation of AEGL-1

The AEGL-1 is based on the sensory irritation study of Davis et al. (1960). The 30-minute exposures to three different blends of gasoline vapor at approximately 2200 mg/m^3

(measured concentrations of 2323, 2187, and 2204 mg/m^3) produced subjective eye irritation at a higher incidence (15/30) than under control conditions (1/20). The incidence of objective eye irritation, although scored as slight (+1 on a scale of 1 to 4), was higher in the 2200 mg/m^3 group (15/30) than in the control group (2/20). Incidences of subjective and objective eye irritation, including ocular tearing were higher at the higher concentration of 4400 mg/m^3. Incidences of ocular tearing were similar in the 2200 mg/m^3 group (3/30) and the control group (2/20). Because the eye irritation when measured objectively was slight (less than marked), an intraspecies uncertainty factor of 3 was applied to protect sensitive subjects. There is adaptation to the slight irritation that defines the AEGL-1. Therefore, the same value of 730 mg/m^3 (2200 mg/m^3/3) was used across all exposure durations. AEGL-1 values are summarized in Table 7. Calculations are in Appendix C and a category graph of the toxicity data in relation to AEGL values is in Appendix D.

TABLE 7. AEGL-1 Values for Automotive Gasoline Vapor

10-min	30-min	1-h	4-h	8-hour
730 mg/m^3	730 mg/m^3	730 mg/m^3	730 mg/m^3	730 mg/m^3

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

Davis et al. (1960) exposed 10 male subjects to three different samples of unleaded gasoline vapor for 30 minutes. Target concentrations were 880, 2200, and 4400 mg/m^3. Drowsiness was reported by two subjects inhaling 4400 mg/m^3 and in two control subjects.

6.2. Summary of Animal Data Relevant to AEGL-2

All acute inhalation studies were conducted with rats as the test model. A 4-hour exposure to 5000 mg/m^3 of vapor of various gasoline blending streams was generally without a toxic effect (API 2008a,b; ARCO Chemical Co. 1984). No higher concentrations were tested in acute studies. In subchronic studies, the highest concentrations tested, 20,000 and 22,500 mg/m^3 (rat), 7690 mg/m^3 (mouse), and 6570 mg/m^3 (monkey) were also without apparent toxic effects (Schreiner et al. 2000; O'Callaghan et al. 2004; Dalbey et al. 1996; Kuna and Ulrich 1984), although clinical signs were specifically addressed only in the study of Schreiner et al. (2000). Schreiner et al. (2000) reported an absence of neurotoxicity (tremors, ataxia, lethargy) in rats during subchronic exposure to 22,500 mg/m^3.

6.3. Derivation of AEGL-2

The study of Davis et al. (1960) does not address effects helpful in determining an AEGL-2. For substances with anesthetic effects, the threshold for neurotoxicity is the point of departure. In a series of studies of the acute inhalation toxicity of blending streams of gasoline, the limit concentration of 5000 mg/m^3 (range, 5000-5300 mg/m^3) was generally without effect. Clinical signs of slight nasal discharge, lacrimation in a few animals, and reduced righting reflex were observed in some of the studies (API 2008a,b; ARCO Chemical Co. 1984).

Because acute studies do not address endpoints consistent with the definition of the AEGL-2, observations from longer-term studies are relevant. Male and female Sprague-Dawley rats exposed to 22,500 mg/m^3 of a gasoline blending stream failed to show neurotoxic signs during a 6 hour/day exposure over 90 days (Schreiner et al. 2000). Rats were observed specifically for tremors, ataxia, and lethargy. The point of departure, 22,500 mg/m^3, was divided by interspecies and intraspecies uncertainty factors of 1 and 3, respectively, for a total of 3, giving an AEGL-2 value of 7500 mg/m^3 (22,500 mg/m^3/3). An interspecies uncertainty factor of 1 is sufficient because solvent uptake is generally greater in rodents than in humans (based on higher blood:air partition coefficients for related hydrocarbons (Bruckner et al. 2008; Gargas et al 1989)]. In addition, chemical uptake is faster in rodents than in humans based on higher respiratory rate and greater cardiac output on a body weight basis. Although humans differ in the rate at which they metabolize chemicals, the susceptibility of the general population to central nervous system depressants varies by no more than 2- to 3-fold as indicated by the minimum alveolar concentration, the concentration of an inhaled anesthetic that produces immobility in 50% of patients (Kennedy and Longnecker 1996; Marshall and Longnecker 1996). Therefore, an intraspecies uncertainty factor of 3 (rather than the default of 10) is considered sufficient. Higher uncertainty factors would result in values inconsistent with the clinical study of Davis et al. (1960). Time scaling may not be relevant for hydrocarbons that act as anesthetics as blood concentrations rapidly approach steady-state. Therefore, the 6-hour value of 7500 mg/m^3 was used across all exposure durations. AEGL-2 values are summarized in Table 8. Calculations are in Appendix C and a category graph of the toxicity data in relation to AEGL values is in Appendix D.

TABLE 8. AEGL-2 Values for Automotive Gasoline Vapor

10-min	30-min	1-h	4-h	8-h
7500 mg/m^3*	7500 mg/m^3*	7500 mg/m^3*	7500 mg/m^3*	7500 mg/m^3*

*The AEGL-2 value is higher than 1/10 of the lower explosive limit (LEL) of gasoline in air (LEL = 14,000 ppm or 42,000 mg/m^3). Therefore, safety considerations against hazard of explosion must be taken into account.

The subchronic study of Kuna and Ulrich (1984) in which squirrel monkeys inhaling 6350 mg/m^3 for 6 hours/day showed no toxic signs supports the calculated AEGL-2 value, and by extension, the interspecies uncertainty factor of 1. Lack of toxicologically significant effects in reproductive and developmental repeat-exposure studies at concentrations of 20,000 to 23,900 mg/m^3 (McKee et al. 2000; Roberts et al. 2001; Gray et al. 2004) support the key study.

The toxicity of individual hydrocarbons comprising gasoline vapor may also be supportive of the values derived for gasoline vapor. In a subchronic study of *n*-pentane toxicity with male and female Sprague-Dawley rats, 20,000 mg/m^3/day for 6 hours/day, 5 days/week for 13 weeks was a NOAEL for lethality and changes in body weight gain, hematology parameters, clinical chemistry, gross findings, ophthalmology, and histopathology of major tissues and organs (McKee et al. 1998). This value is similar to the NOAEL for a blending stream in the AEGL-2 key study.

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to calculation of AEGL-3 values were located.

7.2. Summary of Animal Data Relevant to AEGL-3

None of the acute or subchronic studies with gasoline vapor or gasoline vapor plus additives resulted in mortality in rats. The highest exposures for 4-hour acute and 6 hour/day subchronic studies were approximately 5000 mg/m^3 (API 2008a,b) and 22,500 mg/m^3 (Schreiner et al. 2000), respectively. There was no mortality in these studies. The 4-hour LC_{50} for isopentane is 280,000 mg/m^3 (Matheson Tri-Gas, Inc. 2009).

7.3. Derivation of AEGL-3

It is not apparent that concentrations high enough to cause death from inhalation of automotive gasoline vapor can be attained except in occasional accidental or misuse cases. Based on the likelihood that lethal concentrations of gasoline vapor cannot be attained/sustained under ambient conditions, an AEGL-3 was not determined (Table 9).

At sufficiently high concentrations, toxicologically inert chemicals may act as simple asphyxiants by displacing atmospheric oxygen (Leikauf and Prows 2001). For the sensitive population of people with pulmonary diseases (edema or emphysema) or cardiovascular diseases, an arterial oxygen saturation of 65% may be the threshold for a life threatening condition. Using the SatCur model (2009), 65% oxygen saturation in a sensitive subject performing light exercise corresponds to 14% atmospheric oxygen. This corresponds to a 33% atmosphere of a simple asphyxiant (330,000 ppm or 990,000 mg/m^3).

TABLE 9. AEGL-3 Values for Automotive Gasoline Vapor

10-min	30-min	1-h	4-h	8-h
Not determined*	Not determined*	Not determined	Not determined	Not determined

* AEGL-3 values were not determined due to insufficient data. Automotive gasoline vapor may act as a simple asphyxiant in sensitive individuals at 990,000 mg/m^3.

8. SUMMARY OF AEGLs

8.1. AEGL Values and Toxicity Endpoints

AEGL values are summarized in Table 10. Derivations summaries are in Appendix E.

TABLE 10. Summary of AEGL Values for Gasoline Vapor

Classification	Exposure Duration				
	10-min	30-min	1-h	4-h	8-h
AEGL-1 (Nondisabling)	730 mg/m^3	730 mg/m^3	730 mg/m^3	730 mg/m^3	730 mg/m^3
AEGL-2 (Disabling)	7500 mg/m^3*	7500 mg/m^3*	7500 mg/m^3*	7500 mg/m^3*	7500 mg/m^3*
AEGL-3 (Lethal)**	Not determined	Not determined	Not determined	Not determined	Not determined

*The AEGL-2 value is higher than 1/10 of the lower explosive limit (LEL) of gasoline in air (LEL = 14,000 ppm). Therefore, safety considerations against hazard of explosion must be taken into account.
**AEGL-3 values were not determined due to insufficient data. Automotive gasoline vapor may act as a simple asphyxiant in sensitive individuals at 990,000 mg/m^3.

8.2. Comparison with Other Standards and Guidelines

Standards and guidelines for automotive gasoline are listed in Table 11. The American Conference of Government Industrial Hygienists (ACGIH) Threshold Limit Value of 300 ppm (890 mg/m^3) is based on Runion (1975). Runion (1975) cites the study of Drinker et al. (1943) as showing eye irritation at 160-270 ppm during 8-hour exposures. The ACGIH short-term exposure limit is 500 ppm (1480 mg/m^3).

The Emergency Response Planning Guideline-1 (ERPG-1) of 200 ppm (654 mg/m^3) is based on the study of Drinker et al. (1943) in which eye irritation was reported at 140 ppm during an 8-hour exposure. It is believed that the threshold for eye irritation would be 200 ppm for shorter exposure periods. The ERPG-2 of 1000 ppm (3270 mg/m^3) was based on the onset of mild central nervous system depression in workers. The ERPG-3 of 4000 ppm (13,080 mg/m^3) was considered non-life-threatening. The ERPG values used the conversion factor of 3.27 (molecular weight of 80 for gasoline vapor) to convert from ppm to mg/m^3.

TABLE 11. Standards and Guidelines for Automotive Gasoline Vapor

Guideline	Exposure Duration				
	10 min	**30 min**	**1 h**	**4 h**	**8 h**
AEGL-1	730 mg/m^3	730 mg/m^3	730 mg/m^3	730 mg/m^3	730 mg/m^3
AEGL-2	7500 mg/m^3*	7500 mg/m^3*	7500 mg/m^3*	7500 mg/m^3*	7500 mg/m^3*
AEGL-3**	Not determined	Not determined	Not determined	Not determined	Not determined
ERPG-1 (AIHA)[a]			654 mg/m^3		
ERPG-2 (AIHA)			3270 mg/m^3		
ERPG-3 (AIHA)			13,080 mg/m^3		
Dutch VRW[b]			2 mg/m^3		
Dutch AGW			1000 mg/m^3		
Dutch LBW			5000 mg/m^3		
IDLH (NIOSH)[c]		─Ca			
REL-TWA (NIOSH)[d]					Ca
OSHA PEL (NIOSH)[e]					─
TLV-TWA (ACGIH)[f]					890 mg/m^3; 1480 mg/m^3 (15-min STEL)
MAK (Germany)[g]					─
MAC (The Netherlands)[h]					240 mg/m^3; 480 mg/m^3 (15-min excursion)

*The AEGL-2 value is higher than 1/10 of the lower explosive limit (LEL) of gasoline in air (LEL = 14,000 ppm or 42,000 mg/m^3). Therefore, safety considerations against hazard of explosion must be taken into account.
** Automotive gasoline vapor may act as a simple asphyxiant in sensitive individuals at 990,000 mg/m^3.
VRW = Voorlichtingsrichtwaarde, threshold at which the general public needs to be informed (based on odor).
AGW = Alarmeringsgrenswaarde, threshold for irritation.
LBW = Levensbedreigende waarde, neurotoxicity.
Ca = potential occupational carcinogen.

[a]**ERPG (Emergency Response Planning Guidelines, American Industrial Hygiene Association** (AIHA 2008). The ERPG-1 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing other than mild, transient adverse health effects or without

perceiving a clearly defined objectionable odor.
The ERPG-2 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing irreversible or other serious health effects or symptoms that could impair an individual's ability to take protective action.
The ERPG-3 is the maximum airborne concentration below which it is believed nearly all individuals could be exposed for up to one hour without experiencing or developing life-threatening health effects.

[b]**Dutch Intervention Values** are similar to the ERPG values and the 1-hour AEGL values, but are based on slighter effects – odor, irritation, and neurotoxicity, respectively.

[c]**IDLH (Immediately Dangerous to Life and Health, National Institute of Occupational Safety and Health)** (NIOSH 2005) represents the maximum concentration from which one could escape within 30 minutes without any escape-impairing symptoms, or any irreversible health effects.

[d]**NIOSH REL-TWA (National Institute of Occupational Safety and Health, Recommended Exposure Limits - Time Weighted Average)** (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA.

[e]**OSHA PEL-TWA (Occupational Safety and Health Administration, Permissible Exposure Limits - Time Weighted Average)** (NIOSH 2005) is defined analogous to the ACGIH-TLV-TWA, but is for exposures of no more than 10 hours/day, 40 hours/week (no value assigned).

[f]**ACGIH TLV-TWA (American Conference of Governmental Industrial Hygienists, Threshold Limit Value - Time Weighted Average)** (ACGIH 1992) is the time-weighted average concentration for a normal 8-hour workday and a 40-hour workweek, to which nearly all workers may be repeatedly exposed, day after day, without adverse effect.

[g]**MAK (Maximale Arbeitsplatzkonzentration [Maximum Workplace Concentration])** (Deutsche Forschungsgemeinschaft [German Research Association 2008] is defined analogous to the ACGIH-TLV-TWA (no value assigned).

[h]**MAC (Maximaal Aanvaarde Concentratie [Maximal Accepted Concentration])** (SDU Uitgevers [under the auspices of the Ministry of Social Affairs and Employment], The Hague, The Netherlands is defined similar to the ACGIH TLV. The 15-minute ceiling is 480 mg/m^3. Note: automotive gasoline is called benzene.

8.3. Data Adequacy and Research Needs

The data base for gasoline is rich. Clinical studies addressed subjective and objective eye irritation. Studies with laboratory rodents addressed acute and subchronic toxicity, chronic toxicity/carcinogenicity, neurotoxicity, reproductive and developmental toxicity and genotoxicity.

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APPENDIX A: Major Hydrocarbons found in Gasoline Vapor Condensate (representative composition)

Hydrocarbon	Gasoline Vapor Condensate (%)	Gasoline Vapor Condensate containing 10% Ethanol (%)
Isobutane (C_4H_{10})	2.8	2.2
n-Butane (C_4H_{10})	13.1	11.6
Isopentane (C_5H_{12})	34.8	34
n-Pentane (C_5H_{12})	13.7	10.2
trans-2 Pentene (C_5H_{10})	2.6	2.1
2-Methylpentane (C_6H_{14})	6.8	5.1
n-Hexane (C_6H_{14})	3.1	2.4
Benzene (C_6H_6)	2.2	1.6
3-Methyl hexane (C_7H_{16})	1.4	1.2
Isooctane (C_8H_{18})	1.5	1.3
Toluene (C_7H_8)	3.3	2.4
Ethanol (C_2H_6O)	0.0	13.3

Note: as measured by % gas chromatography area.
Source: White (2009).

Typical Oxygenate Levels (v/v)
(only one used in any gasoline)

Methyl *t*-butyl ether (MTBE)	21.3
t-Amyl methyl ether (TAME)	11.9
Ethyl *t*-butyl ether (ETBE)	16.3
Diisopropyl ether (DIPE)	17.8
Ethanol	13.3
t-Butyl alcohol (TBA)	16.8

Source: Daughtrey et al. (2004).

Petroleum Chemistry Definitions (Source: API n.d.):

Paraffins: C_nH_{2n+2}: carbon atoms are joined by a single bond; may be linear or branched
example: *n*-pentane
Olefins: C_nH_{2n}: contain at least one double bond; may be linear, branched, or cyclic
example: cyclohexene
Cycloparaffins (naphthenes): 5-6 carbon atoms arranged in a ring, saturated
example: cyclohexane
Aromatics: carbon atoms arranged in a ring, unsaturated
examples: benzene, toluene

APPENDIX B: Derivation of Level of Odor Awareness

The level of distinct odor awareness (LOA) represents the concentration above which it is predicted that more than half of the exposed population will experience at least a distinct odor intensity, and about 10% of the population will experience a strong odor intensity. The LOA should help chemical emergency responders in assessing the public awareness of the exposure due to odor perception. The LOA derivation follows the guidance given by van Doorn et al. (2002).

The lowest odor detection threshold (OT_{50}) for gasoline without additives was for the summer and winter composite blend, 0.474 ppm. (API 1994).

The concentration (C) leading to an odor intensity (I) of distinct odor detection (I=3) is derived using the Fechner function:

$I = kw \times \log (C / OT_{50}) + 0.5$

For the Fechner coefficient, the default of kw = 2.33 will be used due to the lack of chemical-specific data:

$3 = 2.33 \times \log (C / 0.474) + 0.5$ which can be rearranged to
$\log (C / 0.474) = (3 - 0.5) / 2.33 = 1.07$ and results in
$C = (10^{1.07}) \times 0.474 = 5.6$ ppm

The resulting concentration is multiplied by an empirical field correction factor. It takes into account that in every day life factors such as sex, age, sleep, smoking, upper airway infections and allergy, as well as distraction, may increase the odor detection threshold by up to a factor of 4. In addition, it takes into account that odor perception is very fast (about 5 seconds) which leads to the perception of concentration peaks. Based on the current knowledge, a factor of 1/3 is applied to adjust for peak exposure. Adjustment for distraction and peak exposure lead to a correction factor of 4 / 3 = 1.33

LOA = C x 1.33 = 5.57 ppm x 1.33 = 7.4 ppm

The LOA for gasoline is 7.4 ppm (approximately 22 mg/m^3).

APPENDIX C: Derivation of Gasoline AEGLs

Derivation of AEGL-1 Values

Key Study:	Davis, A., L. Schafer, and Z. Bell. 1960. The effects on human volunteers of exposure to air containing gasoline vapor. Arch. Environ. Health 1:545-554.
Toxicity endpoint:	Slight to subjective and objective eye irritation in human subjects at 2200 mg/m^3 for 30 minutes
Time scaling	None; there is adaptation to the slight irritation that defines the AEGL-1
Uncertainty factors:	Interspecies: not applied to human subjects Intraspecies: 3, generally applied to slight to mild sensory irritation studies to protect sensitive individuals; adaptation to irritation was demonstrated
Calculations:	2200 $mg/m^3/3 = 730$ mg/m^3
10-min AEGL-1:	C = 730 mg/m^3
30-min AEGL-1:	C = 730 mg/m^3
1-h AEGL-1:	C = 730 mg/m^3
4-h AEGL-1:	C = 730 mg/m^3
8-h AEGL-1:	C = 730 mg/m^3

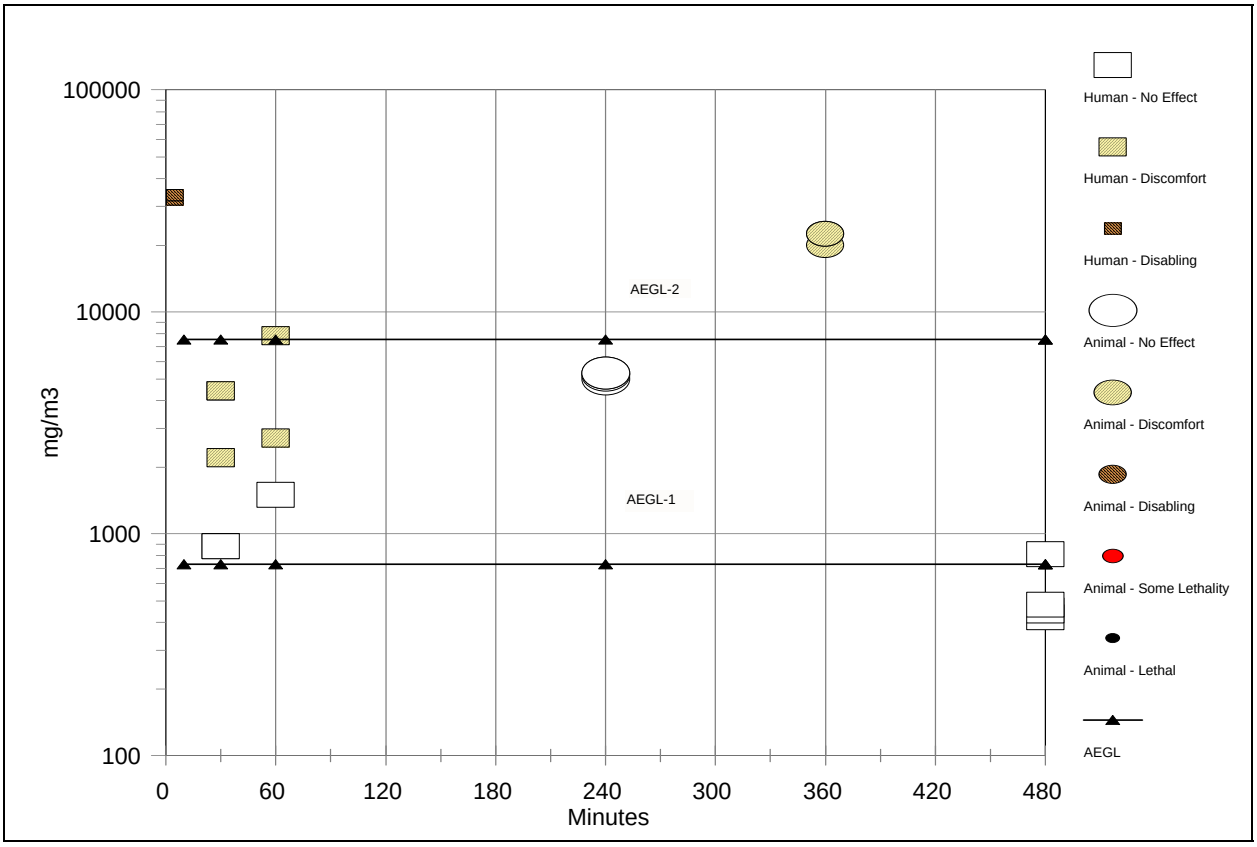
Derivation of AEGL-2 Values

Key Study:	Schreiner, C., Q. Bui, R. Breglia, D. Burnett, F. Koschier, E. Lapadula, P. Podhasky, and R. White. 2000. Toxicity evaluations of petroleum blending streams: inhalation subchronic toxicity/neurotoxicity study of a light catalytic reformed naphtha distillate in rats. J. Toxicol. Environ. Health, Part A, 60:489-512.
Toxicity endpoint:	No clinical signs in rats at highest chronic exposure, 22,5000 mg/m^3 for 6 hours/day, 5 days/week, subchronic
Time scaling	None applied; steady-state in the blood is rapidly approached by hydrocarbon solvents
Uncertainty factors:	Interspecies: 1, rodents have higher blood:air partition coefficients for many chemicals; in addition they have higher respiratory rates and cardiac output resulting in greater chemical uptake than in humans Intraspecies: 3, for hydrocarbon solvents the minimum alveolar concentration at which narcosis occurs differs by no more than two- to threefold among humans.
Calculations:	22,500 mg/m^3/3 = 7500 mg/m^3
10-min AEGL-2:	C = 7500 mg/m^3
30-min AEGL-2:	C = 7500 mg/m^3
1-h AEGL-2:	C = 7500 mg/m^3
4-h AEGL-2:	C = 7500 mg/m^3
8-h AEGL-2:	C = 7500 mg/m^3

Derivation of AEGL-3 Values

Not determined. None of the rodent studies reported lethality at the highest concentrations tested. Therefore, AEGL-3 values cannot be determined. Gasoline vapor may act as a simple asphyxiant in sensitive individuals at a concentration of 990,000 mg/m^3.

APPENDIX D: Category Graph of AEGL Values and Toxicity Data for Gasoline



Data:

For Category: 0 = No effect, 1 = Discomfort, 2 = Disabling, SL = Some Lethality, 3 = Lethal				
Source	**Species**	**mg/m^3**	**Minutes**	**Category**
NAC/AEGL-1		730	10	AEGL
NAC/AEGL-1		730	30	AEGL
NAC/AEGL-1		730	60	AEGL
NAC/AEGL-1		730	240	AEGL
NAC/AEGL-1		730	480	AEGL
NAC/AEGL-2		7500	10	AEGL
NAC/AEGL-2		7500	30	AEGL
NAC/AEGL-2		7500	60	AEGL
NAC/AEGL-2		7500	240	AEGL
NAC/AEGL-2		7500	480	AEGL
NAC/AEGL-3		Not determined	10	AEGL
NAC/AEGL-3		Not determined	30	AEGL
NAC/AEGL-3		Not determined	60	AEGL
NAC/AEGL-3		Not determined	240	AEGL
NAC/AEGL-3		Not determined	480	AEGL

Drinker et al. 1943	Human	420	480	0 (no irritation)
	Human	450	480	0 (very slight irritation)
	Human	480	480	0 (slight irritation)
	Human	810	480	0 (slight irritation)
	Human	1500	60	0 (slight irritation)
	Human	2700	60	1 (slight irritation; threshold for unsteadiness)
	Human	7800	60	1 (slight dizziness)
	Human	32,100	5	2 (unsteadiness)
	Human	33,600	5	2 (feeling of incoordination)
Davis et al. 1960	Human	880	30	0 (minor irritation)
	Human	2200	30	1 (slight eye irritation)
	Human	4400	30	1 (slight to intermediate eye irritation)
API 2008a	Rat	5000	240	0 (no effect)
	Rat	5200	240	0 (no effect)
	Rat	5300	240	0 (no effect)
ARCO Chemical Co. 1984	Rat	5200	240	0 (no effect)
Multiple studies: McKee et al. 2000 Benson et al. 2004	Rat	20,000	360	0 (no effect)
Schreiner et al. 2000	Rat	22,500	360	0 (no effect)

The 360-minute data points (20,000 and 22,500 mg/m^3) are repeat-exposure (McKee et al. 2000), chronic exposure (Benson et al. 2004), and subchronic exposure (Schreiner et al. 2000) studies.

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APPENDIX E: Derivation Summary for Gasoline AEGLs

Acute Exposure Guideline Levels For Gasoline

(CAS Reg. No. 86290-81-5)

AEGL-1 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-hour**
730 mg/m^3	730 mg/m^3	730 mg/m^3	730 mg/m^3	730 mg/m^3

Key Reference: Davis, A., L. Schafer, and Z. Bell. 1960. The effects on human volunteers of exposure to air containing gasoline vapor. Arch. Environ. Health 1:545-554.

Test Species/Strain/Sex/Number: Human/males/10

Exposure Route/Concentration/Duration: Inhalation/0, 880, 2200, 4400 mg/m^3 for 30 minutes

Effects: Slight subjective and objective eye irritation at 2200 mg/m^3

Endpoint/Concentration/Rationale: Slight subjective and objective eye irritation at 2200 mg/m^3)

Uncertainty Factors/Rationale:

Total uncertainty factor: 3

Interspecies: None, human subjects

Intraspecies: 3, generally applied to slight irritation in sensory irritation studies; adaptation to the irritation

Modifying Factor: None

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: None; there is adaptation to the slight irritation that defines the AEGL-1.

Data Adequacy: The study was well-conducted and reported. Older clinical studies reported in several reviews support the derived values.

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AEGL-2 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
7500 mg/m^3*	7500 mg/m^3*	7500 mg/m^3*	7500 mg/m^3*	7500 mg/m^3*

Key Reference: Schreiner, C., Q. Bui, R. Breglia, D. Burnett, F. Koschier, E. Lapadula, P. Podhasky, and R. White. 2000. Toxicity evaluations of petroleum blending streams: inhalation subchronic toxicity/neurotoxicity study of a light catalytic reformed naphtha distillate in rats. J. Toxicol. Environ. Health, Part A, 60:489-512.

Test Species/Strain/Number: Rat/Sprague-Dawley/15/sex/group

Exposure Route/Concentration/Duration: Inhalation/0, 2250, 7500, 22,500 mg/m^3/6 hours/day, 5 days/week, for 13 weeks

Effects: No clinical signs of lethargy

Endpoint/Concentration/Rationale: Although no lethargy/narcosis was observed, 22,500 mg/m^3 was the highest exposure in any study

Uncertainty Factors/Rationale:

Total uncertainty factor: 3

Interspecies: 1, for many hydrocarbons, rodents have higher blood:air partition coefficients; in addition they have higher respiratory rates and cardiac output resulting in greater chemical uptake than in humans

Intraspecies: 3, for hydrocarbon solvents the minimum alveolar concentration at which narcosis occurs differs by no more than two- to threefold among humans.

Modifying Factor: None applied

Animal to Human Dosimetric Adjustment: Not applicable

Time Scaling: None;

Data Adequacy: The data base for gasoline is rich with studies at similar concentrations (20,000 mg/m^3) and using different blending streams addressing general toxicity, neurotoxicity, reproductive and developmental toxicity and chronic toxicity/carcinogenicity.

2 *The AEGL-2 value is higher than 1/10 of the lower explosive limit (LEL) of gasoline in air (LEL = 14,000 ppm).
3 Therefore, safety considerations against hazard of explosion must be taken into account.
4
5

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AEGL-3 VALUES				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
Not determined	Not determined	Not determined	Not determined	Not determined
Key References:				
Test Species/Strain/Number:				
Exposure Route/Concentration/Duration:				
Effect:				
Endpoint/Concentration/Rationale:.				
Uncertainty Factors/Rationale: **Total uncertainty factor**: **Interspecies:** **Intraspecies**: :				
Modifying Factor:				
Animal to Human Dosimetric Adjustment:				
Time Scaling:				
Data Adequacy: No studies were available that reported the threshold for lethality				

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