the health hazards and exposures associated with gasoline containing MTBE

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ABSTRACT

This report compares the toxicological properties of gasoline with and without MTBE. It also reviews the available occupational and consumer exposure data for MTBE.

KEYWORDS

MTBE, gasoline, toxicology, occupational exposure, consumer exposure, occupational exposure limit.

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SUMMARY

Review of the animal toxicity data available suggests that the toxicities of MTBE and gasoline are broadly similar. Although both materials produce kidney tumours (male rats) and liver tumours (female mice), it is possible that their mechanisms of action may differ. These data, together with limited data available on the toxicity of gasoline/MTBE blends, indicate that the presence of up to 15% (%$_v$) MTBE is unlikely to increase the toxicity of motor gasoline.

The ACGIH recommends an 8h TWA TLV of 144 mg/m^3 (40 ppm), for MTBE but does not make a recommendation for a short-term exposure limit.

The available exposure data indicate that for personnel engaged in handling gasoline containing MTBE average 8h TWA concentrations of MTBE ranged from 0.3 to 2.8 mg/m^3. Shorter term exposures were somewhat higher and average exposures ranged from 3.6 to 45.5 mg/m^3.

Data from North America and recent European studies are consistent with the data from CONCAWE member companies.

1. INTRODUCTION

Methyl tertiary butyl ether (MTBE) is used as a component in gasoline where its primary purpose is as an octane enhancer. MTBE can be present in gasoline at levels up to about 15% by volume (EU, 1985).

There have been many reports of the use of MTBE as a solvent to dissolve gallstones.

MTBE has been present in fuels in the USA since 1979, initially without significant problems. In 1992, due to the introduction of the 1990 Clean Air Act amendments, the use of oxygenated fuels at higher levels was mandated in 37 specific areas of the USA.

During the winter of 1992 there were a number of complaints from some of these areas that the use of gasoline containing MTBE was associated with headaches, eye irritation, nausea and dizziness. This was unexpected as previously there had been few complaints, and there was little indication from studies in animals that MTBE presented any unusual problems.

This report summarises the available information on the mammalian toxicity and health effects of MTBE and compares these data with similar information from studies of formulated gasoline. The report also summarises the available occupational exposure data available on MTBE.

2. SUMMARY OF INFORMATION ON MTBE

2.1. PHYSICAL/CHEMICAL PROPERTIES OF MTBE

MTBE is a volatile, colourless liquid with a characteristic ethereal odour. Its physical and chemical characteristics are listed below.

Molecular weight	: 88.15
Boiling point (°C)	: 55.2
Melting point (°C)	: -109
Flash point (°C)	: -28
Spontaneous ignition temperature (°C)	: 460
Relative density (water =1)	: 0.75
Relative vapour density (air =1)	: 3.1
Vapour pressure (hPa, 25°C)	: 326
Odour recognition threshold (ppb)	: 125
Solubility in water at 25°C (% $^{w}/_{w}$)	: 4.8

2.2. TOXICITY OF MTBE TO ANIMALS

The toxicity of MTBE has been extensively studied. MTBE has a low order of acute toxicity, and is not teratogenic, mutagenic, neurotoxic, nor a reproductive toxicant. Repeated exposure resulted in early mortality in male mice and rats due to obstructive uropathy and renal effects, respectively. Additionally, at high exposure levels, there were significant increases in tumours of the male rat kidney and female mouse liver. Studies of the mechanism(s) of male rat kidney toxicity induced by MTBE and its role in the carcinogenic process are currently ongoing. A summary of the toxicity data is given below.

2.2.1. Acute Toxicity

The acute toxicity in mammals is low by all routes tested : oral LD_{50} (rat) - 3.9 g/kg (Sivak and Murphy, 1991); dermal LD_{50} (rabbit) - 10 ml/kg (Kirwin and Galvin, 1983); inhalation LC_{50} (rat, 4-hour) - 23,630 - 39,000 ppm (Sivak and Murphy, 1991).

MTBE was slightly irritating to the skin and eyes of rabbits (Kirwin and Galvin, 1983) and was negative in sensitisation assays in guinea pigs (ARCO Chemical Company, 1980).

2.2.2. Subchronic Toxicity

In a 90 day inhalation study, rats were exposed to MTBE vapours of 800, 4000, or 8000 ppm. There was no mortality nor any indication of significant toxicity at exposure levels up to 8000 ppm. There were some minor blood chemistry differences noted in the exposed groups. The No Observed Adverse Effect Level (NOAEL) was 800 ppm (Lington et al., 1997). The main findings were increased organ weights (without histological changes) in the mid- and high-dosed groups. These findings suggest mild

toxicity which may be secondary to the stress-induced effects caused by prolonged, high-level exposures (Duffy et al., 1992).

2.2.3. Reproductive Toxicity

No teratogenic or other developmental effects were seen in rats or mice at exposure levels up to 1000 ppm (NOEL). At higher concentrations, structural malformations such as cleft palate, reduced body weights, and increased skeletal variations were observed in mice but only at maternally toxic levels. No teratogenic or developmental toxicity was noted in rabbits at exposures up to 8000 ppm (Bevan et al., 1997a).

No adverse effects were observed in a two-generation reproductive toxicity study of inhaled MTBE in rats. Animals were initially exposed 6 hours/day, 5 days/week for 10 weeks at levels of 400, 3000 or 8000 ppm MTBE; exposures were increased to 6 hours/day, 7 days/week during mating, gestation and lactation. Litter size and viability of offspring were unaffected by parental and post-natal exposure to MTBE (Bevan et al., 1997b).

2.2.4. Mutagenicity

MTBE has been found to be negative in genetic toxicity tests including Salmonella (ARCO Chemical Company, 1980), in vitro chromosome aberration or sister chromatid exchange (ARCO Chemical Company, 1980), drosophila sex-linked recessive lethal (McKee et al., 1997) and in vivo rat bone marrow cytogenetics (McKee et al., 1997). However, MTBE was weakly active in a mouse lymphoma assay when an S9 rat liver metabolic activation system was present (ARCO Chemical Company, 1980). The overwhelming evidence from these studies indicates that MTBE does not affect genetic materials and is not considered to have mutagenic potential (Duffy et al., 1992; MTBE Task force, 1994).

2.2.5. Chronic Toxicity/Carcinogenicity

A carcinogenicity study was conducted in rats and mice. Animals were exposed 6 hours/day, 5 days per week for either 18 months (mice) or two years (rats) to 400, 3000 or 8000 ppm MTBE. Both species demonstrated reversible CNS depression at 8000 ppm. Additionally, mice exposed to 8000 ppm experienced decreased body weight gain and early mortality; male mice developed an obstructive uropathy and female mice had increased liver weights and decreased spleen weights.

- There was early mortality in male rats exposed to 3000 or 8000 ppm MTBE due to severe chronic progressive nephrosis. Survival of female rats was similar to controls.

Preliminary evaluation indicates that early mortality in male mice from obstructive uropathy and in male rats from kidney failure may have been an exacerbation of existing conditions specific to those species (Bird et al., 1997).

Increased frequencies of liver tumours were observed in female rats in the 8000 ppm group and kidney tumours in the male rats were observed in the 3000 and 8000 ppm groups. The incidence of testicular tumours was also significantly increased in exposed rats but was within the historical control range for the species utilized, the Fischer-344 rat. Both kidney and liver tumours appear to occur:

- at dose levels producing profound toxicity in the animals
- through non-mutagenic events
- through mechanisms that are species-specific and secondary to toxicity and are not expected to occur in the workplace or in the routine use of the chemical.

In a lifetime carcinogenicity study (Belpoggi et al., 1995), rats were administered oral doses of MTBE dissolved in olive oil, four days/week, at treatment levels of 0, 250, or 1000 mg/kg body weight. Following 104 weeks of treatment, animals remained untreated until their natural death; the last animal died 166 weeks after treatment started. The authors highlight two main findings as follows:

- An increased incidence of Leydig cell, testicular tumours in male rats exposed to 1000 mg/kg (11 animals compared to 2 in each of the control and 250 mg/kg groups).

- A dose-related increase in the total number (combined) of lymphomas and leukaemias in female rats (number of animals were 2, 6 and 11 - at 0, 250 and 1000 mg/kg respectively). In addition an increased incidence of 'hyperplastic lymphoid tissue' in female rats was reported. This finding was not dose related however (incidence of 1, 15 and 9 at 0, 250 and 1000 mg/kg respectively).

The published results of this study contain insufficient detail to comment fully on the significance of these effects. However, it is possible to make the following observations:

- No historical data were presented on the expected, spontaneous tumour incidence in rats up to 174 weeks of age.
- Survival rates were acceptable at 112 weeks (end of treatment) but intergroup differences in survival were apparent after this time. Hence, comparison of tumour incidence beyond 112 weeks is extremely difficult and, in the absence of sound historical data, is of questionable validity.
- Only combined data were presented for the incidence of 'lymphoma and leukaemia'. The relevance of this is questionable in the absence of separate data on the incidence of each effect.
- The increased incidence of lymphomas/leukaemias and 'hyperplastic lymphoid tissue' was only observed in female animals.
- The testicular tumours had a long latent period (first tumour appeared at 96 weeks).
- A recent review (Prentice & Meikle, 1995) questioned the relevance of rat testicular tumours and concluded that these probably arise by a mechanism which does not operate in man.

2.2.6. Neurotoxicity

Transient CNS effects (depression and neurobehavioural changes) were noted in a number of studies. However, there were no prolonged or persistent functional changes or effects on motor activity. Additionally prolonged treatment did not result in any histopathological changes in tissues of the peripheral or central nervous system (Daughtrey et al., 1997).

2.2.7. Metabolism and Pharmacokinetics

Male and female rats were exposed to either 400 or 8000 ppm MTBE once for 6 hours or to 400 ppm 6 hours/day for 15 consecutive days. The data indicated that there was no accumulation of either MTBE or its metabolites after repeated inhalation exposure. The biotransformation of MTBE as well as the elimination half-life (t½) of 0.5 - 0.6 hours was similar for both the single and repeated exposures. The major metabolite was t-butanol which had a half life (t½) in the animal of about 3 hours after a single exposure but about 1.7 hours after multiple exposures (Miller et al, 1997).

2.3. HUMAN EFFECTS OF MTBE

Human effects related to exposure to MTBE, either directly, or as a gasoline constituent can be characterised as transient and subjective. As indicated below, there is no compelling evidence of any adverse effects at low exposure levels.

2.3.1. Workers

There have been some worker complaints of odour, nausea, headache, and irritation of the eyes and respiratory tract. In general, these effects have been associated with exposures at levels greater than 100 ppm (Raabe, 1993a).

2.3.2. Community

A number of complaints were received during the winter of 1992/1993, a period of time during which the use of MTBE became widespread in the USA as a means of reducing carbon monoxide emissions. The complaints were concentrated in Anchorage and Fairbanks, Ak., and Missoula, Mt. In other communities complaints were much less prevalent, even when the gasoline contained similar levels of MTBE.

To address these complaints, the EPA, API, and several other organisations initiated a series of studies to more fully quantify MTBE exposures, and to try to relate these exposure levels to human effects. The data were discussed at a conference in Washington D.C. (July 26-28, 1993). The main findings were that :

- Exposures in non-occupational settings are generally much less than 1 ppm, although they could reach 10 ppm during refuelling under unusual circumstances. Occupational exposures are usually less than 10 ppm, but short-term, isolated exposures may reach 300 ppm.

- The animal data suggest that adverse human effects are unlikely, particularly at low exposure levels.

- The epidemiological data do not generally support a causal relationship between subjective health effects and MTBE exposure.

- Controlled human exposures to MTBE at 1.4 and 1.7 ppm for 1 hour produced no clinically significant subjective or objective health effects.

Although the data indicated that adverse effects at low exposure levels were extremely unlikely, no definitive conclusions were drawn, and a research agenda was developed. For MTBE, possible areas of investigation included additional work on exposure assessment, mechanistic studies of rodent carcinogenicity, and risk assessment.

Subsequently, a study in which volunteers were exposed to 18, 90 or 180 mg/m^3 (equivalent to 5, 25 and 50 ppm) MTBE for 2 hours showed a dose unrelated increase in nasal peak expiratory flow. There were no signs of eye or mucous irritation in this study, nor were there any significant subjective effects (Johanson et al., 1995).

The study by Johansen et al. has been supported by work by Riihinäski et al, who exposed healthy male volunteers to 0, 25, and 75 ppm MTBE for one and three hours. The subjects reported subjective effects by means of questionnaires and the investigators also conducted some clinical examinations. It was concluded that mild symptoms, mainly a feeling of heaviness in the head and to a smaller extent slight mucous membrane irritation, was caused by exposure to MTBE at concentrations of 75 ppm for 3 hours (Riihinäski et al., 1996).

3. SUMMARY OF INFORMATION ON GASOLINE

3.1. PHYSICAL/CHEMICAL PROPERTIES

Formulated gasoline is a complex mixture of hydrocarbons. It has a boiling range of approximately 30-220°C, a vapour pressure of 400-775 mm Hg at 20°C, and has very low water solubility (less than 1%). The odour recognition limit is approximately 0.8 ppm (API, 1994). The odour threshold of gasoline is altered by the presence of MTBE which also imparts a more recognisable odour to the gasoline.

3.2. TOXICITY OF GASOLINE TO ANIMALS

The toxicity of gasoline has been studied extensively and this has been summarised elsewhere (Scala, 1988; von Burg, 1989; CONCAWE, 1992). Gasoline has a low order of acute toxicity, it is slightly irritating to the skin, is not an eye irritant nor a skin sensitizer. In subchronic toxicity studies, the only effect noted was hyaline droplet nephropathy in male rat kidneys at the highest concentration tested (3316 ppm). This effect is not considered to be clinically significant for man.

Chronic Toxicity/Carcinogenicity

A significant increase in renal cell carcinomas was noted in male Fisher 344 rats after chronic exposure to 292 or 2056 ppm gasoline (Raabe, 1993b). There was also a statistically significant increase in liver tumours in female B6C3F1 mice after exposure to 2056 ppm. The female rats and male mice did not develop tumours. The kidney tumours in male rats have been shown to have resulted from hyaline droplet nephropathy and are not believed to be clinically significant for humans (US EPA, 1991). The underlying mechanism for the liver tumours in female mice is not known.

Mutagenicity

Gasoline is not considered mutagenic.

Reproductive Toxicity

No teratogenic or other developmental effects were seen following exposure of rats to gasoline vapour. The effects of exposure to gasoline on fertility have not been investigated.

Neurotoxicity

Exposure to gasoline produced transient CNS depression but did not cause persistent functional or pathological changes.

3.3. HUMAN EFFECTS ASSOCIATED WITH EXPOSURE TO FORMULATED GASOLINE

Exposure to gasoline vapours at concentrations between 200 and 500 ppm can be irritating to the eyes; at 500 ppm it can be irritating to the nose and throat and may produce symptoms of CNS depression. Depression, numbness and anaesthesia may occur following 15-60 minute exposures to 1000-5000 ppm vapour. Exposure to levels above 5000 ppm may result in loss of consciousness, coma, and death.

Epidemiological studies have revealed little evidence that exposure to gasoline is associated with significant adverse health risks except under conditions of gasoline abuse.

4. EXPOSURE DATA

4.1. DATA FROM CONCAWE MEMBER COMPANIES

4.1.1. Sources of information

Data on exposure to and levels of MTBE in air, collected over the period 1981 to 1995 were obtained from seven companies. Personal and fixed-position samples relate to exposures to gasoline in bulk storage, from blending and movements, distribution, retail forecourts, maintenance and the laboratory. MTBE exposures from neat MTBE were obtained from some of these activities plus plant operation.

4.1.2. Scope

Data are given for 177 personal and 75 fixed position samples for gasoline and 24 personal samples for neat MTBE, all of which provide sufficient data for ranges and averages (arithmetic means) to be reported. Additional incomplete data are recorded for information. The data are shown in sets, categorised by sampling time, which varied from 2 to 599 minutes, using terminology as reported by the originator.

4.1.3. General trends

For the complete data, average personal exposures to MTBE from gasoline for all sample times ranged from 1.1 to 85.6 mg/m^3; fixed position samples averaged from 0.2 to 18 mg/m^3. Average personal exposures to neat MTBE ranged from <3.6 to 45.5 mg/m^3. The variability of the data was greatest in the samples collected for the shorter times, as expected (**Table 1** and **Table 2**).

4.1.4. Exposures from gasoline

Average personal MTBE exposures for 480 minute periods from gasoline were within the range 1.1 mg/m^3 to 2.8 mg/m^3 with a maximum value of 20.2 mg/m^3. Driver bottom loading, supervisor, maintenance worker and laboratory worker were in this exposure band. Samples collected for up to 99 minutes had averages of <3.6 to 85.6 mg/m^3, top loading being at the top of this range, and having a maximum of 162 mg/m^3. A relatively high average level was observed for filter change, 23.4 mg/m^3. Average exposures associated with bottom loading were one quarter of those found for top loading (**Table 2**).

Fixed position samples produced similar average trends and values but with a lower maximum of 18 mg/m^3. Samples taken in the laboratory gave the highest average levels of 7.2 and 18 mg/m^3 (**Table 3**).

4.1.5. Exposures from neat MTBE

Average personal exposures from MTBE product were not available for 480 min periods. Samples for 100 to 390 min gave averages ranging from <3.6 to 45.5 mg/m^3 the higher values being due to ship loading and associated tasks (**Table 4**). Comparisons are restricted due to low sample numbers in the groups.

4.1.6. Other data

The range of values for all other data was <1 to 227 mg/m^3 derived from samples taken over periods from 2 to 599 min. While these data are incomplete, they are generally consistent with the trends and levels described above. In these results, average equals arithmetic mean.

4.2. DATA FROM EUROPEAN STUDIES

Two major European studies in Italy and Scandinavia carried out since 1991 have focussed on MTBE exposures and levels in air in marketing.

Personal exposures of shift duration for service station attendants ranged form 0.1 to 2.5 mg/m^3, with averages in the range 0.4 to 0.7 mg/m^3 (Giacomello, 1996).

Personal samples taken in four locations whilst customers were dispensing gasoline gave concentrations ranging from 0.2 to 245 mg/m^3 with geometric means of 4.4 to 7.4 mg/m^3 (Vainiotalo, 1996). These values relate to sample times of less than one minute.

Ambient levels of MTBE in air on service stations were also reported in these studies. Giacomello (1996) quotes average levels around pump units of 107 to 247 µg/m^3. Vainiotalo (1996) found levels that were higher by the pumps than at the service station perimeter, average levels being in the order of 200 to 1400 and 4 to 14 µg/m^3 respectively. In these studies, average equals arithmetic mean.

4.3. DATA FROM NORTH AMERICAN STUDIES

A review of petroleum industry data by McCoy and Johnson for the API (1995), quotes personal exposure data for the handling of both gasoline and neat MTBE.

For gasoline, shift average (arithmetic mean) personal exposures ranged from 0.036 to 95 mg/m^3 with median values of the order of 0.5 mg/m^3 for distribution and transport. For the transport of MTBE product the range was <0.036 to 895 mg/m^3, with a median value of 0.6 mg/m^3. For manufacturing the range was 0.03 to 2563 mg/m^3 with a median of 0.1 mg/m^3. Personal exposures of service station attendants ranged from 0.32 to 122 mg/m^3 with a median of 2.1 mg/m^3. Personal exposures of service station attendants are also reported by Hartle (1993), ranging from 0.1 to 14 mg/m^3 with geometric means of 0.5 to 1.1 mg/m^3.

Area samples in gasoline transport in the API review ranged from 0.07 to 1054 mg/m^3 with a median 0.1 mg/m^3. For transporting neat MTBE the range was 0.14 to 792 mg/m^3 with a median 1.6 mg/m^3.

4.4. CONCLUSION

The scope of the data collected from member companies provides a partial but informative view of the order of levels of exposure and related sources.

Overall, for gasoline, average worker exposures to MTBE in four jobs ie driver, supervisor, maintenance worker and laboratory technician were less than 5 mg/m^3. Samples taken over shorter periods indicate the potential for higher levels in tanker loading, particularly top loading and maintenance activities. Under adverse conditions, levels may exceed 100 mg/m^3. Fixed position samples were generally indicative of low ambient levels with the possible exception of the laboratory.

Data on MTBE exposures and levels from the handling of neat MTBE were less comprehensive. No comment can be made on full shift exposures due to absence of data but there is an indication that ship loading and related activities have a potential to cause high short term exposures and average exposures in the region of 50 mg/m^3.

Data from the recent European studies give good insight into exposures arising from refuelling with gasoline at service stations. Shift average exposures of attendants (less than 1 mg/m^3) tend to be lower than in manufacturing and distribution activities. The higher levels reported for self service customers need to be seen in relation to the very short exposure periods.

The average exposures in transport and distribution of gasoline, reported in the API studies, are consistent with the findings in this report, although the upper levels of the ranges in the API review are up to one order of magnitude greater. A similar effect is seen with the exposures arising from neat MTBE. There is insufficient background information to explain these discrepancies.

Table 1 MTBE from gasoline and neat MTBE - overall summary table for fully documented data

Origin of MTBE	Type of measurement	Time (min)	No. of measurements	mg/m^3
Gasoline				
	PERSONAL			
	Range of averages	480	117	0.3-2.8
	Maximum			20.2
	Range of averages	2-599	60	<3.6-85.6
	Maximum			162
	FIXED POSITION			
	Range of averages	480	59	0.2-3.5
	Maximum			6.5
	Range of averages	23-420	16	0.04-18
	Maximum			18
Neat MTBE				
	PERSONAL			
	Range of averages	15-390	24	<3.6-45.5
	Maximum			46

Table 2 MTBE from gasoline: summary of all data from personal monitoring

Job type/activity	Average (mg/m^3)	No. of measurements	Minimum (mg/m^3)	Maximum (mg/m^3)	Time (min)
Complete data					
Driver bottom loading	2.8	49	0.01	10	480
Supervisor	2.2	45	nd [1]	13.6	
Maintenance worker	2.3	13	nd	20.2	
Laboratory technician	1.1	10	nd	3.2	
TEL[2] operator	<3.6	10	<3.6	3.6	126-420
Area operator	<3.6	6	<3.6	<3.6	
Ship loading	<3.6	7	<3.6	<3.6	
Bottom loading	20.6	14	7.2	36	2-99
Top loading	85.6	6	28.8	162	
Sampling	<3.6	6	<3.6	36	
Dewater tanks	<3.6	9	<3.6	<3.6	
Filter change lab.	23.4	2	14.4	32.4	
Incomplete data					
Retail deliveries		20	<0.1	10.5	126-599
Retail deliveries		17	<0.1	10.4	2-99
Dipping, temp measure		6	<0.1	31	
Draining water bottoms		5	<0.1	115	
Ship offloading		7	<0.1	10.5	
Laboratory octane test		1	<3.6		
Bottom loading		6	<0.1	7	
Top loading		6	<0.1	21.3	

[1] nd - no data
[2] TEL - Tetra ethyl lead

Table 3 MTBE from gasoline: summary of all data from fixed position monitoring

	Average (mg/m^3)	No. of measurements	Minimum (mg/m^3)	Maximum (mg/m^3)	Time (Min)
Complete data					
Bottom loading platform	2.5	12	0.25	5.5	480
Top loading platform	3.5	11	1.2	6.5	
Floating roof tanks	0.2	7	nd	0.4	
Reception terminal	0.2	12	nd	0.5	
Outside office	0.5	17	0.01	0.7	
Octane test room	<3.6	2	<3.6	<3.6	180-420
Laboratory	7.2	6	<3.6	14.4	
Dewater tanks	<3.6	6	<3.6	<3.6	2-30
Laboratory	18	2	18	18	
Incomplete data					
Storage area pump repair		1	<3.6		180-420
Storage area change mixer		1	<3.6		23-40
Storage area change lighting		1	<3.6		

Table 4 MTBE from neat MTBE : summary of all data from personal and fixed position monitoring

	Average (mg/m^3)	No. of measurements	Minimum (mg/m^3)	Maximum (mg/m^3)	Time (Min)
Complete data			**PERSONAL**		
Plant operator	2.4	10	0.08	19.3	100-390
Plant operator	<3.6	5	<3.6	<3.6	
Ship loading	45.5	2	45	46	
Plant operator	<3.6	3	<3.6	<3.6	15-40
Check tank levels	2.7	2	1.2	4.2	
Hose disconnection	23.3	2	8.3	38.3	
Incomplete data			**PERSONAL**		
Roadcar loading			nd	10.8	480
Plant operator			10.8		
Plant operator		1	36		15-40
Hose connection		1	3.5		
Hose disconnection		1	60.8		
Hose disconnection		1	<1		
Hose disconnection		1	0.07		
			FIXED		
Plant			nd	19.1	480
Roadcar loading			nd	32.8	
Roadcar loading			nd	227.2	

5. COMPARISON OF THE HEALTH HAZARDS OF GASOLINE AND GASOLINE/MTBE BLENDS

The toxicities of MTBE and gasoline are essentially indistinguishable as is clear from the data given in **Sections 2** and **3** and the comparative presentation in **Appendix 1**. The only quantitative difference is that the MTBE is more acutely toxic by the oral route. One other difference may be related to mechanism of tumour formation. Although both gasoline and MTBE produce kidney tumours in male rats and liver tumours in female mice it is possible that they may do so by different mechanisms. Otherwise the data are very similar. Hence, it is unlikely that it would be possible to distinguish between gasoline and gasoline/MTBE blends in toxicity tests.

There is one study which directly assessed the toxicity of gasoline containing 15% MTBE (Amoco, 1993). Rats were exposed to 0, 500, 2000, or 4000 ppm hydrocarbon, 6 hours/day, 5 days/week for 4 weeks. Corresponding MTBE levels were 0, 98, 269, and 618 ppm. There were no deaths, and no clinical signs of CNS depression. Body weight gain was significantly reduced in the two highest groups. There were some significant changes in clinical chemistry values. However, the only pathological effect was the appearance of hyaline droplet nephropathy in the kidneys of the male rats.

These results seem grossly similar to those obtained in a 90 day study of unleaded gasoline, without MTBE (Kuna and Ulrich, 1984), although organ weights and clinical chemistry measurements were not included in the study. The results are also similar to those obtained in a 90 day inhalation study of MTBE (Ridlon et al., 1991). As the combination of gasoline and MTBE produces effects similar to those produced by the two components tested individually, there is no evidence for a synergistic response.

In conclusion, as the toxicities of MTBE and gasoline are similar, and the toxicity of an MTBE/gasoline blend approximates that expected based on the toxicities of the constituents, there is no reason to suspect that the presence of MTBE at up to 15% by volume would increase the toxicity of motor gasoline.

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APPENDIX 1

COMPARISON OF THE TOXICITY OF MTBE AND GASOLINE

ACUTE TOXICITY	MTBE	GASOLINE
Oral LD_{50} (rat)	3.9 g/kg	14.6 g/kg
Dermal LD_{50} (rabbit)	>7.4 g/kg	>3.75 g/kg
Inhalation LC_{50} (rat, 4 hr)	23,630 - 39,600 ppm	estimated >1300 ppm
Eye irritation	slight	non-irritating
Skin irritation	slight	slight
Sensitisation	non-sensitising	non-sensitising

SUBCHRONIC (90-DAY) INHALATION TOXICITY

MTBE - No mortality or indications of significant toxicity at levels up to 8000 ppm. Some increased organ weights but without histopathological changes; some minor blood chemistry differences, possibly stress-related.

GASOLINE - At levels up to 3316 ppm, the only effect seen was male rat kidney nephropathy.

CHRONIC TOXICITY/CARCINOGENICITY

MTBE - Increased frequencies of liver tumours in female mice at 8000 ppm and kidney tumours in male rats at 3000 and 8000 ppm. Testicular tumours in male rats also increased but not significantly different from control.

GASOLINE - Increased frequencies of liver tumours in female mice at 2056 ppm and kidney tumours in male rats at 292 and 2056 ppm. The kidney tumours are believed to be the result of hyaline droplet nephropathy.

MUTAGENICITY	MTBE	GASOLINE (*)
Salmonella	negative	negative
Mouse lymphoma	positive with activation negative without activation	mixed results
Chromosome aberrations (in vitro)	negative	not tested
Sister chromatid exchange (in vitro)	negative	negative
Drosophila sex-linked recessive lethal	negative	not tested

(*) Results from studies of commercially-available gasoline where available, otherwise results are from studies of blending stocks.

REPRODUCTIVE TOXICITY	MTBE	GASOLINE (*)
Teratogenicity	NOAEL (Rat/Mouse)= 1000 ppm Higher levels produced developmental effects but were also maternally toxic NOAEL (Rabbit) = > 8000 ppm	No effects in rats at levels up to 1600 ppm
Multi-generation	No effects in rats at levels up to 8000 ppm	no data

NEUROTOXICITY	MTBE	GASOLINE (*)
	CNS depression and transient neurobehavioural changes at 4000 and 8000 ppm. No persistent effects or pathological changes in central or peripheral nervous system.	No pathological changes at levels up to 2056 ppm (highest level tested)