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Via Courier



TSCA Confidential Business Information Center (7407M)  
 EPA EAST - Room 6428 Attn: Section 8(e)  
 United States Environmental Protection Agency  
 1201 Constitution Avenue, NW  
 Washington DC 20460-0001

August 8, 2008

Attention: TSCA 8(e) Coordinator

RE: Ethyl tertiary butyl ether (CASRN: 637-92-3): Results from a Single Generation Reproduction in Rodents (Oral-Rat) and a Soil Biodegradation Study as part of The ETBE Utilization Study Working Group, Testing Program and Risk Assessment.

Dear Sir or Madam:

Lyondell Chemical Company (Lyondell) hereby submits this letter pursuant to Section 8(e) of the Toxic Substances Control Act (TSCA) and EPA's 1991 Section 8(e) Reporting Guide because it includes findings that EPA may consider reportable. Lyondell has not made a determination as to whether a significant risk of injury to health or the environment is actually presented by the findings.

As part of Japan's Kyoto Protocol Objective Achievement Plan, The "ETBE Utilization Study Working Group" under the auspices of the Japanese Ministry of Economy Trade and Industry (METI) has recently completed a risk assessment of ethyl tertiary butyl ether (ETBE), CASRN: 637-92-3.

A summary of the risk assessment has been published by the International Fuel Quality Center (IFQC) in its June 18, 2008, *Special Report - Japan: ETBE Testing Program and Risk Assessment*. With permission from the IFQC, a copy of the publication is attached.

While much of the Japanese risk assessment and toxicity data concur with previous studies, the following information being reported for ETBE may not have been previously observed or reported:

1. Single Generation Reproduction in Rodents (Oral) - a finding of increased deaths in the pups of dams that received 1000 mg/kg/bw/day.
2. Biodegradation Tests - Under unsaturated and saturated soil conditions, in surface water conditions, both in aerobic and anaerobic conditions and with and without nutrient addition, ETBE exhibited very slow rates of degradation.

The finding of reproductive toxicity in the Japanese single generation study is questionable, however, as a two-generation study also conducted orally at doses up to 1000 mg/kg bw/day

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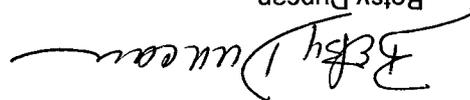
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in the same strain of rat did not show an increase in pup deaths (McGregor D, *Critical Reviews in Toxicology*, 37:287-312, 2007). There were no effects on reproduction or development attributed to ETBE exposure in the two generation reproductive toxicity study.

Should you have any questions or require additional details, please do not hesitate to call me at 713-309-7791. I may also be reached by facsimile at 713-951-1574 or by e-mail at [betsy.duncan@lyondellbasell.com](mailto:betsy.duncan@lyondellbasell.com).

Sincerely,



Betsy Duncan  
Business Consultant - Chemical Control  
Corporate TSCA Coordinator  
Lyondell Chemical Company

Attachment

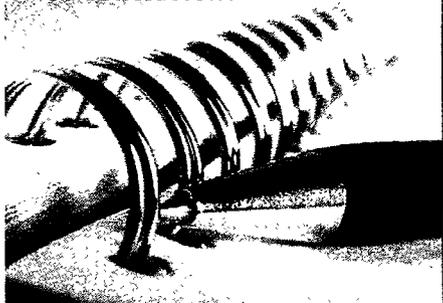


### KEY POINTS

- ETBE used as gasoline blendstock is not expected to pose any human health risk from either inhalation or ingestion exposure.
- ETBE demonstrated very little biodegradation under limited testing conditions; however, further investigation may show degradation potential and
- Proper gasoline storage tank management, including leak prevention and detection, and prompt corrective actions for releases, ensures environmental protection.

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# Special Report

## Japan: ETBE Testing Program and Risk Assessment

June 18, 2008

As part of the initiative to help reduce greenhouse gas (GHG) emissions (mainly CO<sub>2</sub>), Japan is evaluating the use of biomass-based fuel products. To help meet the Kyoto Protocol Target, the Petroleum Association of Japan (PAJ), which is composed of Japanese refiners, set a target in April 2005 to replace crude with 500,000 kiloliters oil equivalent of biofuels by 2010. In January 2006, PAJ announced that it aims to blend 36,000 kiloliters of fuel ethanol (210,000 kiloliters oil equivalent or 840,000 kiloliters of ETBE – ethyl tertiary butyl ether) with gasoline by 2010. The current maximum oxygen and ethanol limits in gasoline are set at 1.3 wt% and 3 vol% (E3), respectively.

PAJ and the Ministry of Environment (MOE) have different views about how bioethanol should be blended with gasoline. MOE has been promoting E3 through direct blending of ethanol with gasoline, whereas PAJ prefers ETBE over ethanol as a blendstock in gasoline, as the ETBE formula can be blended through existing petroleum refining facilities. In contrast, the direct blending of E3 requires additional capital spending and cooperation from many downstream companies. Furthermore, because of an ethanol-related explosion known as the “Gaiax incident” that occurred years ago, consumers are hesitant to use ethanol blends, requiring reassurance from government and industry.

As of April 2008, ETBE at 7 vol% (which is equivalent to E3 by bioethanol content) is blended into gasoline at 100 service stations in Tokyo and adjacent prefectures. PAJ has set a target to make ETBE-blended gasoline available at all service stations nationwide by 2010.

Concerns raised by Japanese auto manufacturers regarding potential fuel system and engine compatibility with bioethanol blends resulted in cooperative efforts to consider this alternative strategy for ETBE blending. As part of the evaluations necessary for this strategy, health and environmental testing and assessments of ETBE were conducted and the initial summary report issued. Based on these results and analyses, the report indicated that the use of ETBE as a blendstock in gasoline is not expected to pose an increased health risk due to inhalation exposures. As for the potential for health impacts due to ingestion exposures in the event of gasoline release from underground fuel storage tanks, minimal risks may occur only when leak detection and remediation steps are not adequately implemented. The report includes recommendations for long-term experimental testing with laboratory animals to expand the risk assessment. These long-term tests are currently being carried out.

### 1. Background

Within the Kyoto Protocol Objective Achievement Plan adopted by the Japanese Cabinet in 2005, biomass-based fuels were included as part of the implementation objectives for transportation fuels use. The “ETBE Utilization Study Working Group” (Working Group) was established within the Total Resources and Energy Investigation Committee, Petroleum Subcommittee, Petroleum Section of the Ministry of Economy, Trade and Industry (METI) for the purposes of gathering information, generating datasets, and conducting hazard and risk analysis on the use of ETBE in  
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gasoline. Using available information, the Working Group determined that:

*(S)ince ETBE was categorized under the Type II Monitoring Chemical Substance under the Law Concerning the Evaluation of Chemical Substances and Regulation of Their Manufacturing, etc. (Japanese Chemical Substances Control Act) upon using ETBE, it is important to conduct talks and seminars regarding the risk evaluation of ETBE as well as proper risk management and risk reduction.*

The Chemical Substances Control Law adopted in 1973 (amended in 1986 and 2003) regulates the manufacturing, importation and use of chemical substances either already in use or proposed for use based on toxicity and environmental impacts potential, and on existing or anticipated production volumes.

ETBE is an oxygenate gasoline component that is used to help improve combustion properties and reduce emissions, thus contributing to overall air quality improvement. ETBE is produced by reacting ethanol and isobutylene within a heat and catalyst system. As a gasoline additive, ETBE does not increase vapor pressure and thus helps lower evaporative emissions. It does not absorb moisture, so it therefore has greater fungibility for blending as well as product transportation and delivery. As mentioned, potential ETBE consumption in gasoline for Japan is estimated to be as much as 840,000 kL (equivalent to approximately 210,000 kL of bioethanol used in ETBE production) based on blending levels of 7 vol% in 20% of the national gasoline pool. This anticipated production/consumption level and classification warranted the risk evaluation that was initiated in July 2006. The evaluation considered these elements of risk determination:

- testing design and methodology;
- hazard analysis based on toxicology

testing results;

- exposure analysis for human risk potential via inhalation and oral exposures;
- quantitative risk determination using exposure assessment and hazard analysis; and
- biodegradation testing.

## 2. Scope of Risk Evaluation

Environmental release of gasoline and its constituents can occur from manufacture and import, transportation-delivery-storage, dispensing from service station pumps, and from accidental spills and releases from storage tanks. ETBE use as a gasoline component means that human exposure potential is primarily from inhalation; however, in the event of gasoline release into the subsurface, potential ingestion exposure is possible should the product reach ground water resources used as drinking water supply.

The Working Group's review of available and reliable datasets determined that additional testing information was needed to conduct quantitative health risk evaluation based on No-Observed-Adverse-Effect-Level (NOAEL) from toxicology studies under anticipated human exposure potential. Further assumptions used for the risk determination included general population exposure that can occur via air or water, and that the entire gasoline pool would convert to ETBE-gasoline blend. Occupational exposure scenarios (workers at manufacturing or blending sites) and severe underground storage tank (UST) spills and sudden releases resulting in detectable taste and odor impacts were not included within the current evaluation scope.

Using the conventional methodologies for hazard analysis and exposure estimation, the Work Group established from screening evaluations that ETBE:

- has very limited biodegradation under typical conditions,

- does not bioaccumulate in body tissues,
- does not cause mutagenic response, and
- does not cause exotoxicity impacts.

Under 28-day repeated oral-dose toxicity testing, animal liver weight increases occurred as indicated by increased primary liver tissue development.

Based on these data, the Work Group decided on the following scope of hazard testing:

- 180-day repeated dose oral toxicity study in rodents;
- 90-day repeated dose inhalation toxicity study in rodents;
- developmental toxicity study in rodent and rabbit (oral administration);
- single generation reproductive toxicity study in rodent (oral administration); and
- toxicokinetics (pharmacokinetics/metabolism) in rodent (multi-exposure routes).

The toxicology studies applied OECD Test Guideline 414 and Good Laboratory Practices (GLP) standards. The toxicokinetics (PK) studies used Japan Pharmaceutical Affairs Law standards and GLP.

The Work Group examined potential emissions sources and exposure routes for ETBE, as shown in figure 1. Under the Pollutant Release and Transfer Registry program, the Work Group concluded that inhalation exposure potential was the primary evaluation target. Based on ETBE's greater solubility compared to other gasoline components, the Work Group determined that oral (ingestion) exposure was the secondary evaluation target in the limited occurrence of groundwater impact due to underground gasoline storage releases. An estimate model was used

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**Table 1: ETBE Research Programs and Results**

Test	Facility	Dose Levels	Key Results
180-day Repeated Oral Dose in Rodents	Japan Petroleum Energy Center, ETBE Nichida Lab	5, 25, 100, or 400 mg/kg/day	400 mg/kg/day: centrilobular hepatocyte hypertrophies in male/female liver; increased liver weights in male/female; increased cholesterol level in male. NOAEL = 100 mg/kg/day
90-day Repeated Dose Inhalation in Rodents	Japan Petroleum Energy Center, ETBE Nichida Lab	150, 500, 1,500, or 5,000 ppm for 6 hr/day, 5 day/ week	5,000 ppm: lower glucose levels in male; centrilobular hepatocyte hypertrophies in male/female; increased adrenal gland weights in male; increased liver weight in female. 1,500 ppm: unsteady gait, rhinorrhea & salivation in male/female. NOAEL = 500 ppm
Developmental Toxicity in Rodents	Japan Petroleum Energy Center, ETBE Nichida Lab	100, 300 or 1,000 mg/kg/day	No significant effects observed. NOAEL = at least 1,000 mg/kg/day
Developmental Toxicity in Rabbits	Bozo Research Center, Inc.	100, 300, 1,000 mg/kg/day	1,000 mg/kg/day: depressed body weight gain; decreased food consumption. No significant effects observed in off-spring. NOAEL = 300 mg/kg/day
Single Generation Reproduction in Rodents (Oral)	Institute of Environmental Toxicology, Chemical Compound Safety Lab	100, 300 or 1,000 mg/kg/day	1,000 mg/kg/day: increased liver weights in male/female; increased deaths in F1 off-spring; slight decrease in survival rates. NOAEL = 300 mg/kg/day
Toxicokinetics in Rodent	Mitsubishi Chemical Safety Institute Ltd., Kumamoto Research Center	5, 50 or 400 mg/kg single dose; 5 mg/kg/day repeated dose (5 days)	Plasma concentrations dose dependent; no tissue residues (no bioaccumulation); low protein binding; primary excretion via inhalation followed by urine; repeated dosing profile similar to single dose. Major metabolites: 2-hydroxyisobutyrate; 2-methyl-1,2-propanediol; tert-butyl alcohol; glucuronide of tert-butyl alcohol.
Soil Biodegradation	Shimadzu Analytical & Measuring Center, Inc., K.K. SVC Tokyo	Unsaturated, saturated conditions	Slow rate of degradation observed under all conditions.
ETBE Purity Analysis	Toray Research Center, Inc.	N/A	N/A
Risk Evaluation Estimate	Nat'l Institute of Advanced Industrial Science & Technology, Research Ctr for Chemical Risk Mgmt	Inhalation Exposure & Oral Exposure	Primary exposure route is inhalation; secondary exposure is ingestion. MOE via inhalation – no risk estimated. MOE via ingestion – no risk estimated. UST release prevention & detection, prompt corrective action important.

Source: Japan Ministry of Economy, Trade and Industry

(continued from p2) to calculate the potential ambient national exposure concentration level for ETBE. Following review of existing available data, the Work Group determined that other potential exposures, such as from industrial wastewater discharge or surface water releases, were unlikely to contribute to risk levels

and therefore were not incorporated in the assessment.

### 3. Results for Toxicology Studies

The general design, facility and results for the toxicology studies are summarized in table 1.

#### 3.1 180-Day Repeated Oral Toxicity Study

Male and female Crl:CD Sprague-Dawley (SD) rats were orally administered ETBE doses of 5 mg/kg/day, 25 mg/kg/day, 100 mg/kg/day or 400 mg/kg/day for a period of 180 days. Significant findings included

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hypertrophies in the centrilobular hepatocytes of the livers of male and female rats at 400 mg/kg/day; significant increase of relative liver weights of male and female rats at 400 mg/kg/day; and significant increase in cholesterol level of male rats at 400 mg/kg/day. The NOAEL for the study was determined to be 100 mg/kg/day.

### 3.2 Developmental Toxicity Studies

Oral administration of 100 mg/kg/day, 300 mg/kg/day or 1,000 mg/kg/day of ETBE was given to Crl:CD (SD) female rats prior to and during pregnancy. No significant effects were observed from the administration of ETBE. The NOAEL for the study was at least 1,000 mg/kg/day.

New Zealand white rabbits were orally administered ETBE doses of 100 mg/kg/day, 300 mg/kg/day or 1,000 mg/kg/day during pregnancy. In the 1,000 mg/kg/day dosed animals, body weight gains were depressed and decreased food consumption was observed on days 12, 14 and 16 of pregnancy. The NOAEL for pregnant females was determined to be 300 mg/kg/day. There were no observed significant effects observed in embryos or fetuses. The NOAEL for the study, based on effects observed in the pregnant females, was 300 mg/kg/day.

### 3.3 Single Generation Reproductive Toxicity Study

Male and female Crl:CD (SD) rats were orally administered 100 mg/kg/day, 300 mg/kg/day or 1,000 mg/kg/day of ETBE over 10 week period prior to mating, during reproduction or during mating,

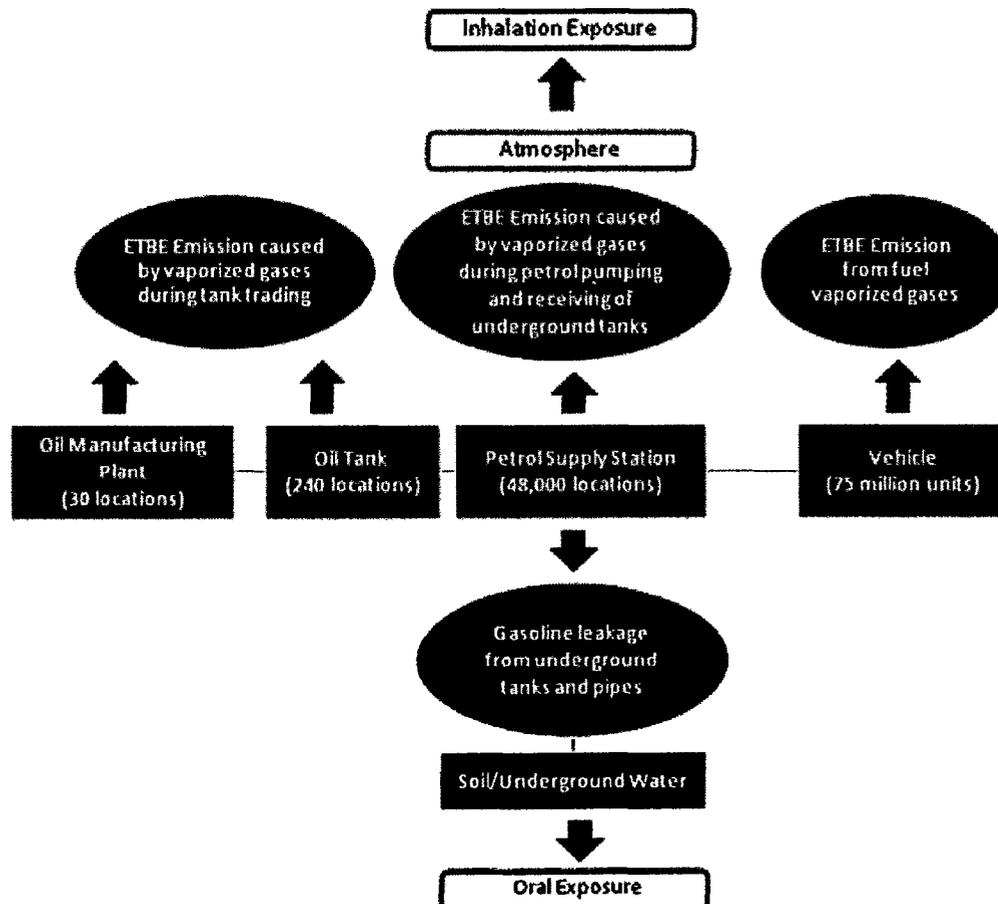
pregnancy and nursing. At the 1,000 mg/kg/day dosing group, significant findings in the study were increased liver weights for both sexes; increased deaths in the F1 nursing offspring and insignificantly slight decrease in survival rates. The NOAEL for this study was determined to be 300 mg/kg/day.

### 3.4 Toxicokinetics (Pharmacokinetics) Study

Radiolabeled [<sup>14</sup>C] ETBE was given to male Crl:CD (SD) rats by single oral, vein or repeated (14 - exposures) oral administration. Various adsorption, distribution, metabolism and excretion analyses were carried out. The key results for the single 5 mg/kg, 50 mg/kg or 400 mg/kg oral dosing were:

- concentrations in plasma were dose dependent;
- no tissue residues observed;
- low protein binding observed;
- most excretion via exhalation, followed by urine;
- low excretion via bile and no radiolabelled compound found in feces;
- main metabolized compounds in plasma were 2-hydroxyisobutyrate, 2-methyl-1,2-propanediol and tert-butyl alcohol;
- main metabolized compounds in urine were 2-hydroxyisobutyrate; glucuronide of tert-butyl alcohol and 2-methyl-1,2-propanediol; and
- main metabolized compounds in bile were 2-hydroxyisobutyrate; glucuronide of tert-butyl alcohol and 2-methyl-1,2-propanediol. (continued on p5)

Figure 1: ETBE Exposure Route Assumptions



Source: Japan Ministry of Economy, Trade and Industry



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The key results for the repeated 5 mg/kg/day oral administration study were:

- $C_{max}$  and AUC equilibrated after five days at approximately two times the single oral dose level;
- no bioaccumulation in tissues observed and fat body clearance declined;
- excretion followed similar pattern to single dosing, little bile excretion and no label material in feces; and
- metabolized compounds in plasma and urine the same as during single dosing.

### 3.5 90-day Repeated Inhalation Toxicity Study

Male and female Crl:CD (SD) rats received whole body repeated inhalation exposures of 150 ppm, 500 ppm, 1,500 ppm or 5,000 ppm of ETBE for six hours per day, five days per week over a period of 13 weeks (total exposures of 65 times). Key observations from this study included:

- at 5,000 ppm exposures: male rats had significantly lower glucose levels; both males and females had significant centrilobular hepatocyte hypertrophies; males had significantly increased adrenal gland weights; females had significantly increased liver weights;
- at 1,500 ppm exposures: male and female rats had unsteady gait, rhinorrhea and salivation; and
- anesthetic effects dissipated during recovery period after exposures.

Based on these observations, the NOAEL for the study was 500 ppm (2,090 mg/m<sup>3</sup>).

### 4. Ambient Exposure Estimation

Based on existing data on gasoline emissions and physical-chemical proper-

ties of ETBE, the total estimated emissions for ETBE were determined as follows:

**Table 2: Estimated ETBE Emissions**

Source	Emissions Estimate
Refining, Tank Storage	~ 2,100 t/yr
Gasoline Supply Station	~ 4,700 t/yr
Vehicle	~ 6,300 t/yr

Source: Japanese Ministry of Economy, Trade and Industry

The Atmospheric Dispersion Model for Exposure and Risk Assessment (ADMER), from the National Institute of Advanced Industrial Science and Technology, was used to estimate the maximum ambient atmospheric ETBE concentration throughout the country based on total emissions. This estimate was determined to be 38 µg/m<sup>3</sup> max.

### 5. Risk Estimate from Inhalation Exposure

Based on the NOAEL established for the 90-day repeated inhalation exposure toxicity study for rats of 500 ppm (2,090 mg/m<sup>3</sup>) and uncertainty factors of 1,000 (for 10x for individual differences; 10x for species differences; and 10x for less than chronic exposure test data), the Work Group developed a risk estimate from inhalation exposure using a Margin of Exposure (MOE) method. The resulting MOE was 55,000 (NOAEL/Estimated Maximum Inhalation Exposure Concentration). The Work Group concluded that there is no risk to human health from ambient exposure to ETBE.

### 6. Risk Estimate from Ingestion Exposure(s)

The Work Group recognized that determination of the oral exposure estimate posed challenges because of the very infrequent release of ETBE into the subsurface via gasoline UST systems. In addition, UST leak prevention and detec-

tion, and in the event of release, dispersion and remediation of soil and water resources further minimize potential ingestion exposures. To remedy this situation, the Work Group assumed a set of standard conditions for detection of UST leaks and for distribution of groundwater concentration and intake volumes. Using published data and the

U.S. Environmental Protection Agency's (EPA) Hydrocarbon Spill Screening Model (HSSM), the Work Group developed an estimated groundwater concentration for ETBE during UST release.

The Work Group further developed the Lifetime Average Daily Intake Volume by estimating the Lifetime Average Exposure Concentration, and assuming 2L/day of average water intake over 70-year lifetime. Standard conditions for UST releases - continuous-low-volume release or one-time-large-volume spill - and detection and remediation actions based on current laws and regulations were employed for estimations. The Consumption Prohibited Concentration (maximum daily dose) was determined using the NOAEL of 100 mg/kg/day from the 180-day repeated oral exposure toxicity study and uncertainty factors of 100 (10x for individual differences and 10x for species differences). Applying the MOE method using NOAEL/Lifetime Average Daily Oral Intake Volume, the risk estimates for human health were determined for the various release conditions.

Under continuous-low-volume release with one-month discharge before detection and corrective action, the MOE was 5,400 using the maximum Lifetime Average Exposed Concentration. For the one-time-large-volume release and immediate detection and corrective action, the MOE was 41,000 using the maximum

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Lifetime Average Exposed Concentration. Considering the actual release incidence documented in the country and applying worst-case conditions, the Work Group determined that virtually no health risk exists from potential ingestion exposures.

The Work Group acknowledged that failure to adequately detect UST releases and promptly implement corrective actions could potentially result in ETBE levels exceeding the Consumption Prohibited Concentration.

### 7. Biodegradation Tests

The Work Group carried out biodegradation tests of ETBE under unsaturated soil conditions, saturated conditions, and in surface water conditions. Under both aerobic and anaerobic conditions, with or without nutrient addition, ETBE exhibited very slow rates of degradation. The Work Group concluded, however, that the testing conditions carried out were limited and did not represent sufficiently broad overall conditions in Japan.

### 8. Further Evaluations Recommended

The Work Group determined that additional research and evaluations were recommended to further enhance the ETBE risk assessments:

- complete the animal carcinogenicity studies implemented separately under the overall research structure;
- ensure continued enforcement and implementation of release prevention and de-

tection measures for fuels, including when blended with ETBE;

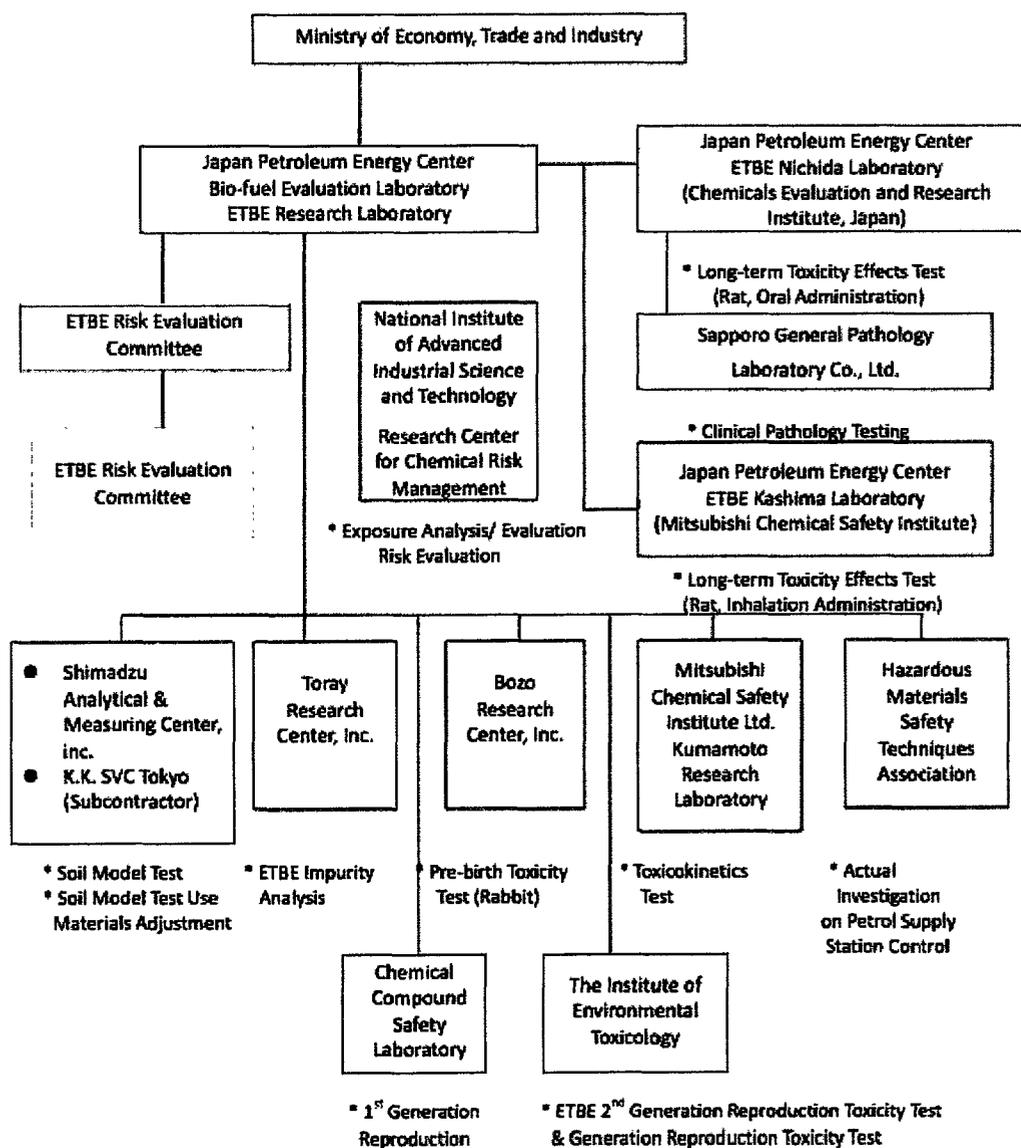
- conduct more in-depth assessment of occupational and worker exposures;
- evaluate the impact of taste and odor on water quality;
- evaluate other potential exposure conditions that may occur; and
- conduct additional testing on biodegradation, fate and transportation, and dispersion and collect environmental monitoring data as full-scale introduction occurs.

### 9. Conclusions

The ETBE Utilization Study Working Group (figure 2) was organized to estimate exposure levels and potential health risks to the general population from the introduction and expanded use of 7% by volume blending of ETBE into gasoline. As part of the hazard analysis, toxicology testing was carried out using both ingestion (oral) and inhalation routes of exposure. Modeling estimates were used

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Figure 2: ETBE Investigation Research Structure



Source: Japan Ministry of Economy, Trade and Industry



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to derive potential exposure levels for atmospheric inhalation and ingestion by impacted groundwater from environmental releases of ETBE. The Working Group's main findings were:

- primary potential route of exposure is via inhalation from emissions in gasoline blending, transportation, storage and vehicle refueling;
- secondary potential route of exposure is via ingestion from unlikely release or spills from underground gasoline storage tanks;
- based on Margin of Exposure risk assessment, inhalation exposure to ETBE does not pose any human health risk levels;
- based on Margin of Exposure risk assessment, ingestion exposure to ETBE from groundwater does not pose any human health risk level due extremely low frequency of UST releases; and
- release prevention and detection, along with prompt and effective correction actions for any UST releases will further reduce potential risk factors for ETBE use.

If you have any questions or feedback on this Special Report, please contact John Kneiss, director, Technical and Regulatory Services at +1.703.891.4812.

