T-BUTANOL PRELIMINARY SEARCH RESULTS: CHRONIC AND LESS-THAN-LIFETIME TOXICITY STUDIES
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POTENTIAL KEY REFERENCES (34)

1. Aarstad K, Zahlsen, K, Nilsen, OG. (1985) Inhalation of butanols: changes in the cytochrome P-450 enzyme system. Arch Toxicol Suppl. 8:418-421.
   After inhalation of different butanol isomers for 3 days (2000 ppm) and 5 days (500 ppm), liver and kidney parameters of the microsomal cytochrome P-450 enzyme system were increased. sec-Butanol caused the highest increase in cytochrome P-450 concentration with a 47% rise in the kidneys (500 ppm for 5 days) and 33% in the liver (2000 ppm for 3 days). A concomitant increase of the in vitro n-hexane metabolism in liver microsomes was observed with a 77% increased formation of the preneurotoxic metabolite 2-hexanol compared with control. iso-Butanol did not alter total cytochrome P-450 concentration but caused a significant 30% decrease in the formation of 2-hexanol. Inhalation of all butanols slightly decreased the enzyme levels in the lung. Changes in microsomal enzymes did not correlate with measured serum concentrations of the different butanols showing different inducing capacities among the butanol isomers themselves or the participation of metabolites in the inducing process. As a conclusion sec-butanol, probably through its metabolite methyl-ethyl-ketone, is the most potent inducer of microsomal cytochrome P-450 in liver and kidney while iso-butanol does not alter total cytochrome P-450.

2. Acharya S, Mehta K, Rodrigues S, Pereira J, Krishnan S, Rao CV. (1995) Administration of subtoxic doses of t-butyl alcohol and trichloroacetic acid to male Wistar rats to study the interactive toxicity Toxicology Letters 80(1):97-104.
   Tertiary butyl alcohol and trichloroacetic acid (TCA) are known to be contaminants in drinking water. In order to evaluate the interactive toxicity of t-butyl alcohol (TBA) with TCA, young male Wistar rats were dosed through water at a dose level of TBA (0.5% v/v), 25 ppm TCA and a combined dose of TBA + TCA (0.5% v/v TBA, 25 ppm TCA) for a period of 10 weeks ad libitum and were maintained on normal diet. The control animals received plain water and normal diet. There was remarkable loss of body weight and significantly decreased liver triglycérides in the treatment groups in the order of TBA + TCA, TCA, TBA and increased liver weights were observed. Serum succinate dehydrogenase (SDH) levels were significantly increased in TCA- and TBA + TCA-treated groups. There was no significant change in serum alanine (GPT), aspartate (GOT) aminotransferase, serum alkaline (ALP) and acid (ACP) phosphatase levels as well as liver glutathione (GSH) and liver and serum cholestrol levels in the treated groups. But serum triglycerides, liver glycogen, serum glucose (only in TBA- and TCA-treated animals) were significantly high in the treated groups. Lipid peroxidation measured by diene conjugation was significant in TBA + TCA-treated group and kidney GSH levels were significantly low in the treated groups. These results show that interaction of TBA + TCA does bring about alteration in biochemical parameters which may play a pivotal role in toxic responses on long-term exposure.

3. Acharya S, Mehta K, Rodriguez S, Pereira J, Krishnan S, Rao CV. (1997) A histopathological study of liver and kidney in male Wistar rats treated with subtoxic doses of t-butyl alcohol and trichloroacetic acid. Exp Toxicol Pathol 49(5):369-373.
   Tertiary butyl alcohol and trichloroacetic acid are known to be contaminants in drinking water. In order to evaluate the interactive toxicity of t-butyl alcohol with trichloroacetic acid, young male Wistar rats were dosed through water at a dose level of t-butyl alcohol (TBA)-0.5% (v/v), trichloroacetic acid (TCA)-25 ppm and a combined dose of TBA + TCA (0.5% v/v TBA-25 ppm TCA) for a period of 10 weeks ad libitum and were maintained on normal diet. The control animals received plain water and normal diet. The liver and kidney histology was undertaken to see whether subtoxic administration of TBA and TCA individually as well as combined administration for a period of 10 weeks would bring about any histological alterations. It was observed that TBA, TCA and TBA + TCA caused histological alterations in the liver such as centrilobular necrosis, vacuolation in hepatocytes and loss of hepatic architecture. TBA

and TBA + TCA caused periportal proliferation and lymphocytic infiltration. Hypertrophy of hepatocytes in the periportal area was a characteristic feature in the liver of TCA treated rats. Moreover, in the histology of the kidney, in the three treated groups, degeneration of renal tubules, with syncitial arrangements of the nucleus of renal tubular epithelial cells was evident. In addition to this, degeneration of the basement membrane of the Bowmans capsule, diffused glomeruli and vacuolation of glomeruli was also evident in the three treated rat kidneys. Renal tubular proliferation in certain areas was also evident in certain areas of the kidney in TCA treated rats. The results indicate that, TBA and TCA do bring about alterations in histology of liver and kidney, but on combined administration, do not show enhanced toxicity in the form of increased hepatic and renal injury.

4. Amberg A, Rosner E, Dekant W. (1999) Biotransformation and kinetics of excretion of methyl-tert-butyl ether in rats and humans. Toxicol Sci 51(1):1-8.
   Methyl-tert-butyl ether (MTBE) is widely used as an additive to gasoline to increase oxygen content and reduce tail pipe emission of pollutants. Therefore, widespread human exposure may occur. To contribute to the characterization of potential adverse effects of MTBE, its biotransformation was compared in humans and rats after inhalation exposure. Human volunteers (3 males and 3 females) and rats (5 each, males and females) were exposed to 4 (4.5 +/- 0.4) and 40 (38.7 +/- 3.2) ppm MTBE for 4 h in a dynamic exposure system. Urine samples from rats and humans were collected for 72 h in 6-h intervals, and blood samples were taken in regular intervals for 48 h. In urine, MTBE and the MTBE metabolites tertiary-butanol (t-butanol), 2-methyl-1,2-propane diol, and 2-hydroxyisobutyrate were quantified; MTBE and t-butanol were determined in blood samples. After the end of the exposure period, inhalation of 40 ppm MTBE resulted in blood concentrations of MTBE 5.9 +/- 1.8 microM in rats and 6.7 +/- 1.6 microM in humans. The MTBE blood concentrations after inhalation of 4 ppm MTBE were 2.3 +/- 1.0 in rats and 1.9 +/- 0.4 microM in humans. MTBE was rapidly cleared from blood with a half-life of 2.6 +/- 0.9 h in humans and 0.5 +/- 0.2 h in rats. The blood concentrations of t-butanol were 21.8 +/- 3.7 microM in humans and 36.7 +/- 10.8 microM in rats after 40 ppm MTBE, and 2.6 +/- 0.3 in humans and 2.9 +/- 0.5 in rats after 4 ppm MTBE. In humans, t-butanol was cleared from blood with a half-life of 5.3 +/- 2.1 h. In urine samples from controls and in samples collected from the volunteers and rats before the exposure, low concentrations of t-butanol, 2-methyl-1,2-propane diol and 2-hydroxyisobutyrate were present. In urine of both humans and rats exposed to MTBE, the concentrations of these compounds were significantly increased. 2-Hydroxyisobutyrate was recovered as a major excretory product in urine; t-butanol and 2-methyl-1,2-propane diol were minor metabolites. All metabolites of MTBE excreted with urine were rapidly eliminated in both species after the end of the MTBE exposure. Elimination half-lives for the different urinary metabolites of MTBE were between 7.8 and 17.0 h in humans and 2.9 to 5.0 h in rats. The obtained data indicate that MTBE biotransformation and excretion are similar in rats and humans, and MTBE and its metabolites are rapidly excreted in both species. Between 35 and 69% of the MTBE retained after the end of the exposure was recovered as metabolites in urine of both humans and rats.

5. Amberg A, Rosner E, Dekant W. (2000) Biotransformation and kinetics of excretion of ethyl tert-butyl ether in rats and humans. Toxicol Sci 53(2):194-201.
   Ethyl tert-butyl ether (ETBE) may be used in the future as an additive to gasoline to increase oxygen content and reduce tailpipe emissions of pollutants. Therefore, widespread human exposure may occur. To contribute to the characterization of potential adverse effects of ETBE, its biotransformation was compared in humans and rats after inhalation exposure. Human volunteers (3 males and 3 females) and rats (5 males and 5 females) were exposed to 4 (4.5+/-0.6) and 40 (40.6+/-3.0) ppm ETBE for 4 h in a dynamic exposure system. Urine samples from rats and humans were collected for 72 h at 6-h intervals, and blood samples were taken in regular intervals for 48 h. In urine, ETBE and the ETBE-metabolites tert-butanol (t-butanol), 2-methyl-1,2-propane diol, and 2-hydroxyisobutyrate were quantified; ETBE and t-butanol were determined in blood samples. After the end of the exposure period to inhalation of 40-ppm ETBE, blood concentrations of ETBE were found at 5.3+/-1.2 microM in rats and 12.1+/-4.0 microM in humans. The ETBE blood concentrations, after inhalation of 4-ppm ETBE, were 1.0+/-0.7 microM in rats and 1.3+/-0.7 microM in humans. ETBE was rapidly cleared from blood. After the end of the 40-ppm ETBE exposure period, the blood concentrations of t-butanol were 13.9+/-2.2 microM in humans and 21.7+/-4.9 microM in rats. After 4-ppm ETBE exposure, blood concentrations of t-butanol were 1.8+/-0.2 microM in humans and 5.7+/-0.8 microM in rats. t-Butanol was cleared from human blood with a half-life of 9.8+/-1.4 h in humans after 40-ppm ETBE exposure. In urine samples from controls and in samples collected from the volunteers

and rats before the exposure, low concentrations of t-butanol, 2-methyl-1,2-propane diol, and 2-hydroxyisobutyrate were present. In the urine of both humans and rats exposed to ETBE, the concentrations of these compounds were significantly increased. 2-Hydroxy-isobutyrate was recovered in urine as the major excretory product formed from ETBE; t-butanol and 2-methyl-1,2-propane diol were minor metabolites. All metabolites of ETBE excreted with urine were rapidly eliminated in both species after the end of the ETBE exposure. Excretion half-lives for the different urinary metabolites of ETBE were between 10.2 and 28.3 h in humans and 2.6 and 4.7 h in rats. The obtained data indicate that ETBE biotransformation and excretion are similar for rats and humans, and that ETBE and its metabolites are rapidly excreted by both species. Between 41 and 53% of the ETBE retained after the end of the exposure was recovered as metabolites in the urine of both humans and rats.

6. Amberg A, Rosner E, Dekant W. (2001) Toxicokinetics of methyl tert-butyl ether and its metabolites in humans after oral exposure. Toxicol Sci 61(1):62-67.
Methyl tert-butyl ether (MTBE) is widely used as an additive to gasoline, to increase oxygen content and reduce tailpipe emission of pollutants. Widespread human exposure to MTBE may occur due to leakage of gasoline storage tanks and a high stability and mobility of MTBE in ground water. To compare disposition of MTBE after different routes of exposure, its biotransformation was studied in humans after oral administration in water. Human volunteers (3 males and 3 females, identical individuals, exposures were performed 4 weeks apart) were exposed to 5 and 15 mg 13C-MTBE dissolved in 100 ml of water. Urine samples from the volunteers were collected for 96 h after administration in 6-h intervals and blood samples were taken in intervals for 24 h. In urine, MTBE and the MTBE-metabolites tert-butanol (t-butanol), 2-methyl-1,2-propane diol, and 2-hydroxyisobutyrate were quantified, MTBE and t-butanol were determined in blood samples and in exhaled air in a limited study of 3 male volunteers given 15 mg MTBE in 100 ml of water. MTBE blood concentrations were 0.69 +/- 0.25 microM after 15 mg MTBE and 0.10 +/- 0.03 microM after 5 mg MTBE. MTBE was rapidly cleared from blood with terminal half-lives of 3.7 +/- 0.9 h (15 mg MTBE) and 8.1 +/- 3.0 h (5 mg MTBE). The blood concentrations of t-butanol were 1.82 +/- 0.63 microM after 15 mg MTBE and 0.45 +/- 0.13 microM after 5 mg MTBE. Approximately 30% of the MTBE dose was cleared by exhalation as unchanged MTBE and as t-butanol. MTBE exhalation was rapid and maximal MTBE concentrations (100 nmol/l) in exhaled air were achieved within 10-20 min. Clearance of MTBE by exhalation paralleled clearance of MTBE from blood. T-butanol was cleared from blood with half-lives of 8.5 +/- 2.4 h (15 mg MTBE) and 8.1 +/- 1.6 h (5 mg MTBE). In urine samples, 2-hydroxyisobutyrate was recovered as major excretory product, t-butanol and 2-methyl-1,2-propane diol were minor metabolites. Elimination half-lives for the different urinary metabolites of MTBE were between 7.7 and 17.8 h. Approximately 50% of the administered MTBE was recovered in urine of the volunteers after both exposures, another 30% was recovered in exhaled air as unchanged MTBE and t-butanol. The obtained data indicate that MTBE-biotransformation and excretion after oral exposure is similar to inhalation exposure and suggest the absence of a significant first-pass metabolism of MTBE in the liver after oral administration.

7. Benson JM, Barr EB, Krone JR. (2001) MTBE inhaled alone and in combination with gasoline vapor: uptake, distribution, metabolism, and excretion in rats. Res Rep Health Eff Inst(102):73-94; discussion 95-109.
The purpose of these studies was to extend previous evaluation of methyl tert-butyl ether (MTBE)* tissue distribution, metabolism, and excretion in rats to include concentrations more relevant to human exposure (4 and 40 ppm) and to determine the effects of coinhalation of the volatile fraction of unleaded gasoline on the tissue distribution, metabolism, and excretion of MTBE. Groups of male F344 rats were exposed nose-only for 4 hours to 4, 40, or 400 ppm 14C-MTBE or to 20 or 200 ppm of the light fraction of unleaded gasoline (LFG) containing 4 or 40 ppm 14C-MTBE, respectively. To evaluate the effects of repeated inhalation of LFG on MTBE tissue distribution, metabolism, and excretion, rats were exposed for 4 hours on each of 7 consecutive days to 20 or 200 ppm LFG with MTBE (4 or 40 ppm) followed on the eighth day by a similar exposure to LFG containing 14C-MTBE. Subgroups of rats were evaluated for respiratory parameters, initial body burdens, rates and routes of excretion, and tissue distribution and elimination. The concentrations of MTBE and its chief metabolite, tert-butyl alcohol (TBA), were measured in blood and kidney immediately after exposure, and the major urinary metabolites-2-hydroxyisobutyric acid (IBA) and 2-methyl-1,2-propanediol (2MePD)-were measured in urine. Inhalation of MTBE alone or as a component of LFG had no concentration-dependent effect on respiratory minute volume. The initial body burdens of MTBE equivalents achieved after 4 hours of exposure to MTBE did not increase linearly with exposure

concentration. MTBE equivalents rapidly distributed to all tissues examined, with the largest percentages distributed to liver. The observed initial body burden did not increase linearly between 4 and 400 ppm. At 400 ppm, elimination half-times of MTBE equivalents from liver increased and from lung, kidney, and testes decreased compared with the two smaller doses. Furthermore, at 400 ppm the elimination half-time for volatile organic compounds (VOCs) in breath was significantly shorter and the percentage of the initial body burden of MTBE equivalents eliminated as VOCs in breath increased significantly. These changes probably reflect a saturation of blood with MTBE at 400 ppm and strongly suggest that the uptake and fate of MTBE are notably different at exposure concentrations above and below 400 ppm. Single and repeated coexposure to 20 and 200 ppm LFG with MTBE had opposite effects on the total body burden of MTBE equivalents present at the end of exposures compared with those achieved after 4 and 40 ppm MTBE exposures: 20 ppm LFG increased and 200 ppm LFG significantly decreased the burdens of MTBE equivalents present. The effects of coexposure to LFG on blood levels of MTBE equivalents paralleled the effects on body burden. These differences in overall uptake of MTBE equivalents cannot be attributed to alterations of minute volume. The reason for the increase in overall uptake after 20-ppm LFG exposure is not clear. Decreased MTBE absorption (uptake) after single and repeated coexposure to 200 ppm LFG may be due to a decrease in solubility of MTBE in blood caused by inhalation of other hydrocarbons. Investigations on the blood/air partition coefficient of MTBE in the absence and presence of LFG would be needed to confirm this hypothesis. Single and repeated coexposure to either 20 or 200 ppm LFG significantly decreased the percentage of the initial body burden from MTBE equivalents in tissues, including liver, kidney, and testes, immediately and 72 hours after

8. Bernauer U, Amberg A, Scheutzow D, Dekant W. (1998) Biotransformation of 12C- and 2-13C-labeled methyl tert-butyl ether, ethyl tert-butyl ether, and tert-butyl alcohol in rats: identification of metabolites in urine by 13C nuclear magnetic resonance and gas chromatography/mass spectrometry. Chem Res Toxicol 11(6):651-658.
   The biotransformation of the fuel oxygenates methyl tert-butyl ether (MTBE) and ethyl tert-butyl ether (ETBE) was studied in rats after inhalation exposure; the biotransformation of the initial metabolite of these ethers, tert-butyl alcohol, was studied after oral gavage. To study ether metabolism, rats were exposed for 6 h to initial concentrations of 2000 ppm of MTBE or ETBE, respectively [2-13C]MTBE and [2-13C]ETBE. Urine was collected for 48 h after the end of the exposure, and urinary metabolites were identified by 13C NMR (13C-labeled ethers) and gas chromatography/mass spectrometry (GC/MS) (12C- and 13C-labeled ethers). To study tert-butyl alcohol metabolism, rats were dosed either with tert-butyl alcohol at natural carbon isotope ratio or with 13C-enriched tert-butyl alcohol (250 mg/kg of body weight), urine was collected, and metabolites were identified by NMR and GC/MS. tert-Butyl alcohol was identified as a minor product of the biotransformation of MTBE and ETBE. In addition, small amounts of a tert-butyl alcohol conjugate, likely a glucuronide, were present in the urine of the treated animals. Moreover, the mass spectra obtained indicate the presence of small amounts of [13C]acetone in the urine of [13C]MTBE and [13C]ETBE-treated rats. 2-Methyl-1,2-propanediol, 2-hydroxyisobutyrate, and another unidentified conjugate of tert-butyl alcohol, most probably a sulfate, were major urinary metabolites of MTBE and ETBE as judged by the intensities of the NMR signals. In [13C]-tert-butyl alcohol-dosed rats, [13C]acetone, tert-butyl alcohol, and its glucuronide represented minor metabolites; as with the ethers, 2-methyl-1,2-propanediol, 2-hydroxyisobutyrate, and the presumed tert-butyl alcohol sulfate were the major metabolites present. In one human individual given 5 mg/kg [13C]-tert-butyl alcohol orally, 2-methyl-1,2-propanediol and 2-hydroxyisobutyrate were major metabolites in urine detected by 13C NMR analysis. Unconjugated tert-butyl alcohol and tert-butyl alcohol glucuronide were present as minor metabolites, and traces of the presumed tert-butyl alcohol sulfate were also present. Our results suggest that tert-butyl alcohol formed from MTBE and ETBE is intensively metabolized by further oxidation reactions. Studies to elucidate mechanisms of toxicity for these ethers to the kidney need to consider potential toxicities induced by these metabolites.

9. Borghoff SJ, Murphy JE, Medinsky MA. (1996) Development of physiologically based pharmacokinetic model for methyl tertiary-butyl ether and tertiary-butanol in male Fisher-344 rats. Fundam Appl Toxicol 30(2):264-275.
   Methyl tertiary-butyl ether (MTBE) and its metabolite tertiary-butanol (TBA) both cause renal tumors in chronically exposed male rats. Knowledge of the kinetic behavior of MTBE and TBA in rats and its comparison to the kinetics of these chemicals in humans will aid in assessing human risk. The objective of

this study was to develop a physiologically based pharmacokinetic (PBPK) model for MTBE and TBA in rats that will form the basis for a human model. Physiological parameters such as blood flows, tissue volumes, and alveolar ventilation were obtained from the literature. Chemical-specific parameters such as the solubility of MTBE and TBA in blood and selected tissues and metabolic rate constants to describe whole-body metabolism of MTBE in rats were measured using vial equilibration and gas uptake techniques, respectively. MTBE metabolism was described in the model as occurring through two saturable pathways. The model was able to predict gas uptake data (100 to 2000 ppm starting concentrations) and levels of MTBE in blood of rats exposed to MTBE by inhalation (400 to 8000 ppm, 6 hr), i.v. (40 mg/kg), and oral (40 or 400 mg/kg) administration. Two different models to describe the dosimetry of TBA in a rat were tested for their ability to predict TBA blood levels after MTBE exposure. TBA blood levels were predicted best at low MTBE exposure concentrations using a two-compartment model. The pharmacokinetics of TBA appear to be far more complex than those of MTBE, and additional experimental data on TBA distribution and elimination will be necessary to refine the submodel. With a quantitative description of the important determinants of MTBE and TBA dosimetry understood, a better assessment of the potential toxic and cancer risk for humans exposed to MTBE can be made.

10. Borghoff SJ, Prescott JS, Janszen DB, Wong BA, Everitt JI. (2001) alpha 2u-Globulin nephropathy, renal cell proliferation, and dosimetry of inhaled tert-butyl alcohol in male and female F-344 rats. Toxicol Sci 61(1):176-186.
    tert-Butyl alcohol (TBA) has been shown to cause kidney tumors in male rats following chronic administration in drinking water. The objective of the present study was to determine whether TBA induces alpha 2u-globulin (alpha 2u) nephropathy (alpha 2u-N) and enhanced renal cell proliferation in male, but not female, F-344 rats, and whether the dosimetry of TBA to the kidney is gender specific. Male and female F-344 rats were exposed to 0, 250, 450, or 1750 ppm TBA vapors 6 h/day for 10 consecutive days to assess alpha 2u-nephropathy and renal cell proliferation and for 1 and 8 days to evaluate the dosimetry of TBA following a single and repeated exposure scenario. Protein droplet accumulation was observed in kidneys of male rats exposed to 1750 ppm TBA, with alpha 2u-globulin immunoreactivity present in these protein droplets. A statistically significant increase in alpha 2u concentration in the kidney, as measured by an enzyme-linked immunosorbent assay, was observed in male rats exposed to 1750 ppm TBA with a exposure-related increase in renal cell proliferation. Renal alpha 2u concentration was positively correlated with cell proliferation in male rat kidney. No histological lesions or increased renal cell proliferation was observed in female rats exposed to TBA compared to controls. The TBA kidney:blood ratio was higher at all concentrations and time points in male rats compared with female rats, which suggests that TBA is retained longer in male rat kidney compared with female rat kidney. Together these data suggest that TBA causes alpha 2u-N in male rats, which is responsible for the male rat-specific increase in renal cell proliferation.

11. Buckley TJ, Prah JD, Ashley D, Zweidinger RA, Wallace LA. (1997) Body burden measurements and models to assess inhalation exposure to methyl tertiary butyl ether (MTBE). J Air Waste Manag Assoc 47(7):739-752.
    Biomarkers of methyl tertiary butyl either (MTBE) exposure and the partitioning of inhaled MTBE into the body were investigated in a human chamber study. Two subjects were exposed to an environmentally relevant nominal 5,011 micrograms/m3 (1.39 ppm) MTBE for 1 hour, followed by clean-air exposure for 7 hours. Breath and blood were simultaneously sampled, while total urine was collected at prescribed times before, during, and after the exposure. Mass-balance and toxicokinetic analyses were conducted based upon the time series measurement of multiple body-burden endpoints, including MTBE in alveolar breath, and MTBE and tertiary butyl alcohol (TBA) in venous blood and urine. The decay of MTBE in the blood was assessed by fitting the post-exposure data to a 2- or 3-exponential model that yielded residence times(tau) of 2-3 min, 15-50 min, and 3-13 h as measured by alveolar breath, and 5 min, 60 min, and 32 h as evaluated from venous blood measurements. Based on observations of lower than expected blood and breath MTBE during uptake and a decreasing blood-to-breath ratio during the post-exposure decay period, we hypothesize that the respiratory mucous membranes were serving as a reservoir for the retention of MTBE. The decay data suggest that 6-9% of the MTBE intake may be retained by this non-blood reservoir. The compartmental modeling was further used to estimate important parameters that define the uptake of inhaled MTBE. The first of these parameters is f, the fraction of C(air) exhaled at equilibrium, estimated as 0.60 and 0.46 for the female and male subject, respectively. The second parameter is the blood-to-breath

partition coefficient (P) estimated as approximately 18. The product of these parameters provides an estimate of the blood concentration at equilibrium as 8-11 times the air concentration. Blood TBA lagged MTBE levels and decayed more slowly (tau = 1.5-3 h), providing a more stable indication of longer term integrated exposure. The concentration ranges of MTBE and TBA in urine were similar to that of the blood, ranging from 0.37 to 15 micrograms/L and 2 to 15 micrograms/L, respectively. In urine, MTBE and TBA by themselves bore little relationship to the exposure. However, the MTBE:TBA ratio followed the pattern of exposure, with peak values occurring at the end of the exposure (20- and 60-fold greater than pre-exposure values) before decaying back to pre-exposure levels by the end of the 7-h decay period. Urinary elimination accounted for a very small fraction of total MTBE elimination (< 1%).

12. Cirvello JD, Radovsky A, Heath JE, Farnell DR, Lindamood C, 3rd. (1995) Toxicity and carcinogenicity of t-butyl alcohol in rats and mice following chronic exposure in drinking water. Toxicol Ind Health 11(2):151-165.
    t-Butyl alcohol (TBA) was administered in drinking water to F344/N rats and B6C3F1 mice for two years using 60 animals/dose/sex/species. Male rats received doses of 0, 1.25, 2.5, or 5 mg/ml and females received 0, 2.5, 5, or 10 mg/ml, resulting in average daily doses of approximately 85, 195, or 420 mg TBA/kg body weight for males and 175, 330, or 650 mg/kg for females. Ten rats per group were evaluated after 15 months. Male and female mice received doses of 0, 5, 10, or 20 mg/ml, resulting in average daily doses of approximately 535, 1,035, or 2,065 mg TBA/kg body weight for males and 510, 1,015, or 2,105 mg/kg for females. Survival was significantly reduced in male rats receiving 5 mg/ml, female rats receiving 10 mg/ml, and male mice receiving 20 mg/ml. Long-term exposure to TBA produced increased incidences of renal tubule adenoma and carcinoma in male rats; transitional epithelial hyperplasia of the kidney in male and female rats; follicular cell adenoma of the thyroid in female mice; and follicular cell hyperplasia of the thyroid and inflammation and hyperplasia of the urinary bladder in male and female mice. In addition, a slight increase in follicular cell adenoma or carcinoma of the thyroid (combined) in male mice may have been related to the administration of TBA.

13. Faulkner TP, Hussain AS. (1989) The pharmacokinetics of tertiary butanol in C57BL/6J mice. Res Commun Chem Pathol Pharmacol 64(1):31-39.
    Doses of 5.0, 10.0, and 20.0 mmoles/kg of t-butanol were given to C57BL/6J mice in order to study the in vivo pharmacokinetics of the alcohol in this strain. A pseudozero order decline in blood concentrations which was directly proportional to dose suggested Michaelis-Menten kinetics. PCNONLIN analysis of the data, however, yielded Vmax estimates which increased with dose and VD estimates which decreased with dose. These results are inconsistent with the Michaelis-Menten model and suggest either multiple elimination pathways or dose related effects on distribution or elimination.

14. Faulkner TP, Wiechart JD, Hartman DM, Hussain AS. (1989) The effects of prenatal tertiary butanol administration in CBA/J and C57BL/6J mice. Life Sciences 45(21):1989-1995.
    Pregnant mice of the CBA/J and C57BL/6J strains were given either tertiary butanol (10.5 mmoles/kg, p.o.) or an equivalent volume of tap water twice daily from day 6 through day 18 of gestation. Examination on day 18 revealed significantly more resorptions per litter in the t-butanol-treated animals but no interstrain difference. Tertiary butanol did not significantly affect the body weight of the survivors nor produce significant abnormalities in either strain. Subsequent blood concentration profiles in female C57BL/6J mice indicated that the treatment regimen produced blood levels equivalent to teratogenic ethanol treatment. Mice receiving 3 days of t-butanol treatment did not eliminate the drug more rapidly than control animals, indicating that tolerance was not a factor in the treatment regimen. Since t-butanol shares membrane disordering effects with ethanol but is not metabolized by the same pathway, a role for acetaldehyde or the process of ethanol metabolism is suggested in ethanol teratogenicity.

15. Groth G, Freundt KJ. (1994) Inhaled tert-butyl acetate and its metabolite tert-butyl alcohol accumulate in the blood during exposure. Hum Exp Toxicol 13(7):478-480.
    1. A continuous 5 h-exposure to approximately 440 ppm tert-butyl acetate in air (via a tracheal canule) resulted in continuously increasing concentrations of tert-butyl acetate and tert-butyl alcohol (metabolite of tert-butyl acetate) in the blood of rats. 2. This accumulation of tert-butyl acetate and tert-butyl alcohol was reproduced during a continuous exposure to about 900 ppm tert-butyl acetate in air over a period of 4 h and 15 min. After the inhalation approximately 50% of the blood level of tert-butyl acetate decreased within 45

min, but that of tert-butyl alcohol remained unchanged at a high level. 3. The accumulation of tert-butyl acetate and tert-butyl alcohol should be relevant for the health risk assessment at the workside.

16. Johanson G, Nihlen A, Lof A. (1995) Toxicokinetics and acute effects of MTBE and ETBE in male volunteers. Toxicol Lett 82-83:713-718.
Methyl tertiary butyl ether (MTBE) is widely used in gasoline as an oxygenator and octane enhancer. There is also an interest in using the ethyl tertiary butyl (ETBE) and methyl tertiary amyl (TAME) ethers. We measured the blood, water, and olive oil/air partition coefficients in vitro of MTBE, ETBE, TAME and tertiary butyl alcohol (TBA), a metabolite of MTBE and ETBE. The results indicate similar uptake and distribution behavior for the three ethers and a slight affinity for fatty tissues. The partition coefficients of TBA indicate that this metabolite is not excreted via the lungs to any great extent and that it is preferentially distributed in body water. Further, we exposed 10 healthy male volunteers to MTBE vapor at 5, 25 and 50 ppm for 2 h during light physical exercise. Uptake and disposition were studied by measuring MTBE and TBA in inhaled and exhaled air, blood and urine. Low uptake, high post-exposure exhalation, and low blood clearance indicate slow metabolism of MTBE relative to many other solvents. A low recovery of TBA in urine (below 1% of uptake) indicates further metabolism of TBA. The concentration of MTBE and TBA in blood was proportional to exposure level suggesting linear kinetics up to 50 ppm. The half life of 7-10 h in blood and urine indicates that TBA would be more suitable than the parent compound as a biomarker for MTBE exposure. Subjective ratings (discomfort, irritative symptoms, CNS effects) and eye (redness, tear film break-up time, conjunctival damage, blinking frequency) and nose (peak expiratory flow, acoustic rhinometry, inflammatory markers in nasal lavage) measurements indicated no or minimal effects of MTBE.

17. Kim D, Andersen ME, Pleil JD, Nylander-French LA, Prah JD. (2007) Refined PBPK model of aggregate exposure to methyl tertiary-butyl ether. Toxicol Lett 169(3):222-235.
Aggregate (multiple pathway) exposures to methyl tertiary-butyl ether (MTBE) in air and water occur via dermal, inhalation, and oral routes. Previously, physiologically based pharmacokinetic (PBPK) models have been used to quantify the kinetic behavior of MTBE and its primary metabolite, tertiary-butyl alcohol (TBA), from inhalation exposures. However, the contribution of dermal and oral exposures to the internal dose of MTBE and TBA were not characterized well. The objective of this study was to develop a multi-route PBPK model of MTBE and TBA in humans. The model was based entirely on blood MTBE and TBA measurements from controlled human exposures. The PBPK model consists of nine primary compartments representing the lungs, skin, fat, kidney, stomach, intestine, liver, rapidly perfused tissue, and slowly perfused tissue. The MTBE and TBA models are linked by a single metabolic pathway. Although the general structure of the model is similar to previously published models of volatile organic compounds, we have now developed a detailed mathematical description of the lung, skin, and gastrointestinal tract. This PBPK model represents the most comprehensive and accurate description of MTBE and TBA pharmacokinetics in humans to date. The aggregate exposure model application for MTBE can be generalized to other environmental chemicals under this framework given appropriate empirical measurement data.

18. Lee CW, Mohr SN, Weisel CP. (2001) Toxicokinetics of human exposure to methyl tertiary-butyl ether (MTBE) following short-term controlled exposures. J Expo Anal Environ Epidemiol 11(2):67-78.
Methyl tertiary-butyl ether (MTBE) is an oxygenated compound added to gasoline to improve air quality as part of the US Federal Clean Air Act. Due to the increasing and widespread use of MTBE and suspected health effects, a controlled, short-term MTBE inhalation exposure kinetics study was conducted using breath and blood analyses to evaluate the metabolic kinetics of MTBE and its metabolite, tertiary-butyl alcohol (TBA), in the human body. In order to simulate common exposure situations such as gasoline pumping, subjects were exposed to vapors from MTBE in gasoline rather than pure MTBE. Six subjects (three females, three males) were exposed to 1.7 ppm of MTBE generated by vaporizing 15 LV% MTBE gasoline mixture for 15 min. The mean percentage of MTBE absorbed was 65.8 +/- 5.6% following exposures to MTBE. The mean accumulated percentages expired through inhalation for 1 and 8 h after exposure for all subjects were 40.1% and 69.4%, respectively. The three elimination half-lives of the triphasic exponential breath decay curves for the first compartment was 1-4 min, for the second compartment 9-53 min, and for the third compartment 2-8 h. The half-lives data set for the breath second and blood first compartments suggested that the second breath compartment rather than the first breath

compartment is associated with a blood compartment. Possible locations for the very short breath half-life observed are in the lungs or mucous membranes. The third compartment calculated for the blood data represent the vessel poor tissues or adipose tissues. A strong correlation between blood MTBE and breath MTBE was found with mean blood-to-breath ratio of 23.5. The peak blood TBA levels occurred after the MTBE peak concentration and reached the highest levels around 2-4 h after exposures. Following the exposures, immediate increases in MTBE urinary excretion rates were observed with lags in the TBA excretion rate. The TBA concentrations reached their highest levels around 6-8 h, and then gradually returned to background levels around 20 h after exposure. Approximately 0.7-1.5% of the inhaled MTBE dose was excreted as unchange urinary MTBE, and 1-3% was excreted as unconjugated urinary TBA within 24 h after exposure.

19. Lindamood C, Farnell DR, Giles HD, Prejean JD, Collins JJ, Takahashi K, Maronpot RR. (1992) Subchronic toxicity studies of t-butyl alcohol in rats and mice. Fundamental and Applied Toxicology 19(1):91-100.
The purpose of this study was to evaluate the toxicity of t-butyl alcohol, an important commodity chemical, an additive to unleaded gasoline, and a contaminant of drinking water. Ninetyday toxicity studies were conducted in B6C3F1 mice and Fischer 344 (F344) rats of both sexes using dosed water. Dose levels of t-butyl alcohol were 0, 0.25, 0.5, 1, 2, and 4% (w/v). Lethality was observed at the 4% level of both sexes and species. Weight-gain depression was present in all dose levels of male rats; 4% female rats; 1, 2, and 4% male mice; and 2 and 4% female mice. Water consumption was increased at lower dose levels in male rats and decreased in the higher dose levels of both sexes of rats and female mice. Clinical signs in rats were ataxia in both sexes and hypoactivity in males. Clinical signs in mice were ataxia. abnormal posture, and hypoactivity. In rats, urine volumes were reduced, in association with crystalluria. Gross lesions at necropsy were urinary tract calculi, renal pelvic and ureteral dilatation, and thickening of the urinary bladder mucosa. Microscopic lesions were hyperplasia of transitional epithelia and inflammation of the urinary bladder. In male rats treated with t-butyl alcohol, microscopic renal changes were suggestive of α-2μ-globulin nephropathy. No-effect levels for the urinary tract lesions were 1% in male rats and mice (803.7 mg/kg/day for the male rats and 1565.8 mg/kg/day for the male mice) and 2% in female rats and mice (1451.5 mg/kg/day for the female rats and 4362.9 mg/kg/day for the female mice). The results indicate that in rodents the urinary tract is the target organ for t-butyl alcohol toxicity, and males are more sensitive to t-butyl alcohol toxicity than females.

20. Miller MJ, Ferdinandi ES, Klan M, Andrews LS, Douglas JF, Kneiss JJ. (1997) Pharmacokinetics and disposition of methyl t-butyl ether in Fischer-344 rats. J Appl Toxicol 17 Suppl 1:S3-12.
Methyl t-butyl ether (MTBE) is a commonly used octane booster in gasoline. This study examines the pharmacokinetics and disposition of MTBE in Fischer-344 rats after i.v., oral, dermal and inhalation routes of administration. Groups of male and female rats were given single i.v. (40 mg kg-1), oral (40 and 400 mg kg-1) and dermal (40 and 400 mg kg-1 in occluded chambers) doses of [14C]MTBE. For inhalation studies, rats were exposed nose-only for 6 h to low (400 ppm), high (8000 ppm) and repeated daily 6-h low (400 ppm x 15 days) chamber concentrations of [14C]MTBE. Blood, expired air, and excreta (urine and feces) were collected at selected times up to 7 days post-dose and quantified for 14C content. Plasma concentrations of MTBE and t-butyl alcohol (TBA) were quantified and mean values used for pharmacokinetic analysis. The mean total recoveries of 14C ranged from 91 to 105%. Methyl t-butyl ether was rapidly and completely absorbed after oral and inhalation exposures; dermal absorption was low. After all routes, MTBE was rapidly eliminated from blood (ti = 0.5 h) by exhalation and metabolism to TBA. At the high doses, metabolism was saturated and the proportion of renal 14C excretion decreased relative to the pulmonary route. At 48 h post-exposure, virtually all of the 14C was eliminated. The major metabolites recovered in urine were 2-methyl-1,2-propanediol and alpha-hydroxyisobutyric acid. There were no significant gender or route-dependent differences in the pharmacokinetics and disposition of MTBE.

21. Nelson BK, Brightwell WS, Khan A, Burg JR, Goad PT. (1989) Lack of selective developmental toxicity of three butanol isomers administered by inhalation to rats. Fundam Appl Toxicol 12(3):469-479.
As part of an ongoing study of the developmental toxicology of industrial alcohols, this report presents the results of the teratology assessments of 1-butanol, 2-butanol, and t-butanol administered by inhalation to rats. Groups of approximately 15 Sprague-Dawley rats were exposed at 8000, 6000, 3500, or 0 ppm 1-butanol, 7000, 5000, 3500, or 0 ppm 2-butanol, or 5000, 3500, 2000, or 0 ppm t-butanol for 7 hr/day on Gestation Days 1-19 (sperm = 0). In each case, the highest concentration was selected to produce maternal

toxicity. Dams were sacrificed on Gestation Day 20, and fetuses were individually weighed, tagged, and examined for external malformations. One-half of the fetuses were stained and examined for skeletal abnormalities, and the other half were examined for visceral defects using the Wilson technique. For each butanol isomer examined, the highest concentration (and the intermediate in some cases) was maternally toxic, as manifest by reduced weight gain and feed intake. Even at a maternally toxic dose, and in spite of a dose-dependent reduction in fetal weights for each isomer, the only teratogenicity observed was a slight increase in skeletal malformations (primarily rudimentary cervical ribs), seen with the highest concentration of 1-butanol. Thus, although teratogenicity was observed at 8000 ppm 1-butanol, and developmental toxicity was observed with each of the butyl alcohol isomers studied, concentrations 50 times the current permissible exposure limits for these three butanol isomers do not produce teratogenicity in rats.

22. Nihlen A, Johanson G. (1999) Physiologically based toxicokinetic modeling of inhaled ethyl tertiary-butyl ether in humans. Toxicol Sci 51(2):184-194.
A physiologically based toxicokinetic (PBTK) model was developed for evaluation of inhalation exposure in humans to the gasoline additive, ethyl tertiary-butyl ether (ETBE). PBTK models are useful tools to relate external exposure to internal doses and biological markers of exposure in humans. To describe the kinetics of ETBE, the following compartments were used: lungs (including arterial blood), liver, fat, rapidly perfused tissues, resting muscles, and working muscles. The same set of compartments and, in addition, a urinary excretion compartment were used for the metabolite tertiary-butyl alcohol (TBA). First order metabolism was assumed in the model, since linear kinetics has been shown experimentally in humans after inhalation exposure up to 50 ppm ETBE. Organ volumes and blood flows were calculated from individual body composition based on published equations, and tissue/blood partition coefficients were calculated from liquid/air partition coefficients and tissue composition. Estimates of individual metabolite parameters of 8 subjects were obtained by fitting the PBTK model to experimental data from humans (5, 25, 50 ppm ETBE, 2-h exposure; Nihlen et al., Toxicol. Sci., 1998; 46, 1-10). The PBTK model was then used to predict levels of the biomarkers ETBE and TBA in blood, urine, and exhaled air after various scenarios, such as prolonged exposure, fluctuating exposure, and exposure during physical activity. In addition, the interindividual variability in biomarker levels was predicted, in the eight experimentally exposed subjects after a working week. According to the model, raising the work load from rest to heavy exercise increases all biomarker levels by approximately 2-fold at the end of the work shift, and by 3-fold the next morning. A small accumulation of all biomarkers was seen during one week of simulated exposure. Further predictions suggested that the interindividual variability in biomarker levels would be higher the next morning than at the end of the work shift, and higher for TBA than for ETBE. Monte Carlo simulations were used to describe fluctuating exposure scenarios. These simulations suggest that ETBE levels in blood and exhaled air at the end of the working day are highly sensitive to exposure fluctuations, whereas ETBE levels the next morning and TBA in urine and blood are less sensitive. Considering these simulations, data from the previous toxicokinetic study and practical issues, we suggest that TBA in urine is a suitable biomarker for exposure to ETBE and gasoline vapor.

23. Nihlen A, Lof A, Johanson G. (1998) Controlled ethyl tert-butyl ether (ETBE) exposure of male volunteers. I. Toxicokinetics. Toxicol Sci 46(1):1-10.
Ethyl tert-butyl ether (ETBE) might replace methyl tert-butyl ether (MTBE), a widely used additive in unleaded gasoline. The aim of this study was to evaluate uptake and disposition of ETBE, and eight healthy male volunteers were exposed to ETBE vapor (0, 5, 25, and 50 ppm) during 2 h of light physical exercise. ETBE and the proposed metabolites tert-butyl alcohol (TBA) and acetone were analyzed in exhaled air, blood, and urine. Compared to a previous MTBE study (A. Nihlen et al., 1998b, Toxicol. Appl. Pharmacol. 148, 274-280) lower respiratory uptake of ETBE (32-34%) was seen as well as a slightly higher respiratory exhalation (45-50% of absorbed ETBE). The kinetic profile of ETBE could be described by four phases in blood (average half-times of 2 min, 18 min, 1.7 h, and 28 h) and two phases in urine (8 min and 8.6 h). Postexposure half-times of TBA in blood and urine were on average 12 and 8 h, respectively. The 48-h pulmonary excretion of TBA accounted for 1.4-3.8% of the absorbed ETBE, on an equimolar basis. Urinary excretion of ETBE and TBA was low, below 1% of the ETBE uptake, indicating further metabolism of TBA or other routes of metabolism and elimination. The kinetics of ETBE and TBA were linear up to 50 ppm. Based upon blood profile, levels in blood and urine, and kinetic profile we suggest that TBA is a more appropriate biomarker for ETBE than the parent ether itself. The acetone level in blood was

higher after ETBE exposures compared to control exposure, and acetone is probably partly formed from ETBE.

24. Nihlen A, Lof A, Johanson G. (1998) Experimental exposure to methyl tertiary-butyl ether. I. Toxicokinetics in humans. Toxicol Appl Pharmacol 148(2):274-280.
Methyl tertiary-butyl ether (MTBE) is widely used in gasoline as an oxygenate and octane enhancer. The aim of this study was to evaluate the uptake, distribution, metabolism, and elimination of MTBE in humans. Ten healthy male volunteers were exposed to MTBE vapor (5, 25, and 50 ppm) on three different occasions during 2 h of light physical exercise (50 W). MTBE and the metabolite tertiary-butyl alcohol (TBA) were monitored in exhaled air, blood, and urine. Blood and urine were collected at selected time intervals, during and up to 3 days after the exposure, and analyzed by head space gas chromatography. MTBE in exhaled air was collected with sorbent sample tubes and subsequently analyzed by gas chromatography. The respiratory uptake of MTBE was rather low (42-49%), and the respiratory exhalation was high (32-47%). A relatively low metabolic blood clearance (0.34-0.52 L/h/kg) was seen compared to many other solvents. The kinetic profile of MTBE in blood could be described by four phases, and the average half-lives were 1 min, 10 min, 1.5 h, and 19 h. The post-exposure decay curve of MTBE in urine was separated into two linear phases, with average half-lives of 20 min and 3 h. The average post-exposure half-lives of TBA in blood and urine were 10 and 8.2 h, respectively. The urinary excretion of MTBE and TBA was less than 1% of the absorbed dose, indicating further metabolism of TBA, other routes of metabolism, or excretion. The kinetics of MTBE and TBA were linear up to the highest exposure level of 50 ppm. We suggest that TBA in blood or urine is a more appropriate biological exposure marker for MTBE than the parent ether itself.

25. NSF_International. 2003. T-Butanol (CAS # 75-65-0) Oral Risk Assessment Document.
This document has been prepared to allow toxicological evaluation of the unregulated contaminant t-butanol in drinking water, as an extractant from one or more drinking water system components evaluated under NSF/ANSI 61 (2002), or as a contaminant in a drinking water treatment chemical evaluated under NSF/ANSI 60 (2002). Both non-cancer and cancer endpoints have been considered, and risk assessment methodology developed by the U.S. Environmental Protection Agency (U.S. EPA) has been used.

26. NTP. 1995. NTP Toxicology and Carcinogenesis Studies of t -Butyl Alcohol (CAS No. 75-65-0) in F344/N Rats and B6C3F1 Mice (Drinking Water Studies). National Toxicology Program, NIH, DHHS. Report nr NIH Publication 95-3167, TR 436. 1-305 p.
t -Butyl alcohol is widely used in the manufacture of perfumes and a variety of cosmetics. It is also used as a raw material in the production of isobutylene, which may be used to produce methyl tertiary butyl ether, a common gasoline additive, or to produce butyl elastomers used in the production of automobile tires. Male and female F344/N rats and B6C3F1 mice were given t -butyl alcohol (greater than 99% pure) in drinking water for 13 weeks or 2 years. The genetic toxicity of t -butyl alcohol was assessed by testing the ability of the chemical to induce mutations in various strains of Salmonella typhimurium and in L5178Y mouse lymphoma cells, sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and by measuring the frequency of micronucleated erythrocytes in mouse peripheral blood. 13-WEEK STUDY IN RATS: Groups of 10 male and 10 female F344/N rats were given 0, 2.5, 5, 10, 20, or 40 mg/mL t -butyl alcohol in drinking water for 13 weeks. All males and six females given 40 mg/mL died during the study. Final mean body weights of 10 and 20 mg/mL males and of 40 mg/mL females were 12%, 17%, or 21% less than those of the corresponding controls, respectively. Serum sorbitol dehydrogenase activities in 10 and 20 mg/mL males were greater than that in the controls after 13 weeks. Serum alanine aminotransferase activity in 40 mg/mL females was greater than that in the controls after 2 weeks and greater in all exposed females after 13 weeks. Urine volumes of 10, 20, and 40 mg/mL males and females decreased, and urine specific gravity values increased. Transitional epithelial hyperplasia and inflammation of the urinary bladder were observed in 20 and 40 mg/mL males and 40 mg/mL females. Absolute and relative liver weights of all exposed groups of females and relative liver weights of 5, 10, and 20 mg/mL males were significantly greater than those of the controls. Absolute and relative kidney weights of all exposed groups of males and females were significantly greater than those of the controls. Incidences of mineralization of the kidney were significantly increased in 10, 20, and 40 mg/mL males. The severity of nephropathy in 2.5, 5, 10, and 20 mg/mL males was significantly greater than that of the controls as was the accumulation of hyaline droplets in the kidney of 5, 10, and 20 mg/mL males. The incidences of

nephropathy in 10, 20, and 40 mg/mL females were significantly greater than that of the controls. 13-WEEK STUDY IN MICE: Groups of 10 male and 10 female B6C3F1 mice were given 0, 2.5, 5, 10, 20, or 40 mg/mL t -butyl alcohol in drinking water for 13 weeks. The deaths of two males and one female in the 40 mg/mL group were attributed to exposure to t -butyl alcohol. The final mean body weights of 20 and 40 mg/mL males and 40 mg/mL females were significantly lower than those of the controls. There were no biologically significant differences in hematology parameters of exposed and control groups of mice. Transitional epithelial hyperplasia and inflammation were observed in the urinary bladder of 20 and 40 mg/mL males and 40 mg/mL females. 2-YEAR STUDY IN RATS: Groups of 60 F344/N rats were given 0, 1.25, 2.5, or 5 mg/mL t -butyl alcohol (males) or 0, 2.5, 5, or 10 mg/mL t -butyl alcohol (females) in drinking water for 2 years. These correspond to average daily doses of approximately 90, 200, or 420 mg t -butyl alcohol/kg body weight for males and approximately 180, 330, or 650 mg t -butyl alcohol/kg body weight for females. Ten rats per group were evaluated after 15 months of chemical administration. Survival, Body Weights, and Water Consumption: Survival rates of 5 mg/mL males and 10 mg/mL females were significantly lower than those of the controls. The final mean body weights of exposed groups of males were 15% to 24% lower than that of the controls, and the final mean body weight of 10 mg/mL females was 21% lower than that of the controls. Water consumption by males increased with dose; water consumption by females decreased with dose. Hematology and Urinalysis: At the 15-month inte. Hematology and Urinalysis: At the 15-month interim evaluation, there were no significant differences in hematology parameters in males and females, and there were no significant differences in urinalysis parameters in males. Females given 5 or 10 mg/mL had increased urine specific gravities and decreased urine volumes. Pathology Findings: At the 15-month interim evaluation, relative kidney weights of 2.5 and 5 mg/mL males and absolute and relative kidney weights of 2.5, 5, and 10 mg/mL females were significantly greater than those of the controls. At 2 years, the incidence of mineralization in the kidney increased with dose and that of 5 mg/mL males was significantly greater than that of the controls. In the standard evaluation at the end of the study, the incidences of focal renal tubule hyperplasia and of adenoma were increased in exposed males and a carcinoma was observed in one 5 mg/mL male. Renal tubule hyperplasia occurred in one 10 mg/mL female. An extended evaluation of the kidney identified additional male rats with hyperplasia (control, 11/50; 1.25 mg/mL, 13/50; 2.5 mg/mL, 11/50; 5 mg/mL, 19/50) and renal tubule adenoma (7/50, 8/50, 15/50, 10/50); renal tubule carcinomas were identified in two 1.25 mg/mL males and in one 2.5 mg/mL male. Renal tubule adenoma was identified in one 5 mg/mL male from the 15-month extended evaluation. In the standard and extended evaluations combined, there were dose-related increased incidences of hyperplasia and adenoma. The severity of nephropathy and the incidence and severity of transitional cell hyperplasia of the kidney were increased in exposed male and female rats. Linear foci of mineralization were present in the renal papilla of exposed males. 2-YEAR STUDY IN MICE: Groups of 60 male and 60 female B6C3F1 mice were given 0, 5, 10, or 20 mg/mL t -butyl alcohol in drinking water for 2 years. Exposure levels of 5, 10, or 20 mg/mL delivered average daily doses of approximately 540, 1,040, or 2,070 mg t -butyl alcohol/kg body weight to males and approximately 510, 1,020, or 2,110 mg/kg to females. Survival, Body Weights, and Water Consumption: Survival of 20 mg/mL males was significantly lower than that of the controls. The final mean body weights of exposed groups of males were similar to those of the controls. The mean body weights of females given 20 mg/mL were 10% to 15% lower than those of the controls from week 13 to the end of the study. Water consumption by exposed groups of males and females was similar to that by the controls. Pathology Findings: Incidences of thyroid gland follicular cell hyperplasia were significantly increased in all exposed groups of males and in 10 and 20 mg/mL females. The incidence of follicular cell adenoma or carcinoma (combined) was marginally increased in 10 mg/mL males (0 mg/mL, 1/60; 5 mg/mL, 0/59; 10 mg/mL, 4/59; 20 mg/mL, 2/57). The incidence of follicular cell adenoma was significantly increased in 20 mg/mL females (2/58, 3/60, 2/59, 9/59). The incidences of chronic inflammation and transitional epithelial hyperplasia of the urinary bladder were increased in 20 mg/mL males and to a lesser extent in 20 mg/mL females. GENETIC TOXICOLOGY: t -Butyl alcohol was tested for induction of genetic damage in vitro and in vivo, and all results were negative. In vitro, t -butyl alcohol was negative in Salmonella typhimurium and mouse lymphoma cell mutation tests, and it did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells. These in vitro studies were conducted with and without metabolic activation (S9). In vivo, no increase in micronucleated erythrocytes was observed in peripheral blood samples from mice administered t -butyl alcohol in drinking water for 13 weeks. CONCLUSIONS: Under the conditions of these 2-year drinking water studies, there was some evidence of carcinogenic activity of t -butyl alcohol in male F344/N rats based on increased incidences of renal tubule adenoma or

carcinoma (combined). There was no evidence of carcinogenic activity in female F344/N rats receiving 2.5, 5, or 10 mg/mL t -butyl alcohol. There was equivocal evidence of carcinogenic activity of t -butyl alcohol in male B6C3F1 mice based on the marginally increased incidences of follicular cell adenoma or carcinoma (combined) of the thyroid gland. There was some evidence of carcinogenic activity of t -butyl alcohol in female B6C3F1 mice based on increased incidences of follicular cell adenoma of the thyroid gland. Exposure to t -butyl alcohol was associated with mineralization and renal tubule hyperplasia in male rats, transitional epithelial hyperplasia and increased severity of nephropathy of the kidney in male and female rats, follicular cell hyperplasia of the thyroid gland in male and female mice, and chronic inflammation and hyperplasia of the urinary bladder in male mice and to a lesser extent in female mice. Synonyms: 2-Methyl-2-propanol, 2-methylpropan-2-ol, TBA, t -butanol, tertiary butyl alcohol, t -butyl hydroxide, trimethyl carbinol, trimethyl methanol

27. NTP. 1997. NTP Technical Report on Toxicity Studies of t-Butyl Alcohol (CAS No. 75-65-0) Administered by Inhalation to F344/N Rats and B6C3F1 Mice. Research Triangle Park, NC National Toxicology Program, National Institutes of Health, United States Department of Health and Human Services. Report nr NIH Publication 97-3942 (July 1997). 1-56, A51-D59 p.
t-Butyl alcohol is widely used in the manufacture of perfumes and a variety of cosmetics. It is also used as a raw material in the production of isobutylene, which may be used to produce methyl tertiary butyl ether, a common gasoline additive, or to produce butyl elastomers used in the production of automobile tires. The National Cancer Institute nominated t-butyl alcohol to the NTP for study as a result of a review of chemicals found in drinking water. In addition to the high annual production and the potential for occupational exposure, there is also a potential for human exposure to t-butyl alcohol by the inhalation route from its use as an additive in unleaded gasoline. Therefore, toxicity studies of t-butyl alcohol were conducted in male and female F344/N rats and B6C3F1 mice by whole-body inhalation. Animals were evaluated for hematology, clinical chemistry, urinalysis, reproductive toxicity, and histopathology. The genetic toxicity of t-butyl alcohol was assessed by testing the ability of the chemical to induce mutations in various strains of Salmonella typhimurium and L5178Y mouse lymphoma cells or sister chromatid exchanges and chromosomal aberrations in cultured Chinese hamster ovary cells, and by measuring the frequency of micronucleated erythrocytes in rat bone marrow and mouse peripheral blood. In the 18-day inhalation studies, groups of five male and five female rats and mice were exposed to t-butyl alcohol by inhalation at concentrations of 450, 900, 1,750, 3,500, and 7, 000 ppm for 6 hours per day, 5 days per week, for 12 exposure days. All rats and mice exposed to 7,000 ppm were killed moribund following a single 6-hour exposure. One 3,500 ppm male mouse died on day 3. Final mean body weights of 3,500 ppm male and female rats were significantly lower than those of the controls. Final mean body weights and body weight gains of all other exposed groups were similar to those of the controls. In animals exposed to 3.500 ppm, the thymus weights of male and female rats and female mice were less than those of the controls. The liver weights of male and female mice exposed to 3,500 ppm were greater than those of the controls. No grss or microscopic lesion were present in rats or mice. In the 13-week inhalation studies, groups of 10 male and 10 female rats and mice were exposed to t-butyl alcohol at concentrations of 0, 135, 270, 540, 1,080, and 2,100 ppm for 6 hours per day, 5 days per week, for 13 weeks. One 2,100 ppm and five 1,080 ppm male mice died before the end of the studies. The final mean body weight of 2,100 ppm female mice and the mean body weight gains of 1,080 and 2,100 ppm female mice were significantly lower than those of the controls. Clinical findings of toxicity in the 1,080 ppm male mice died during the studies included rough coats and emaciated appearance, hypoactivity, and prostration. Minimal decreases in hematocrit values, hemoglobin concentrations, and erythrocyte counts occurred in the 1,080 and 2,100 ppm male rats at week 13. Hemoglobin concentrations and/or hematocrit values were also minimally decreased in male rats in the lower exposure groups. At week 13, a minimal decrease in urine pH occurred in the 1,080 ppm female and 2,100 ppm male and female rats. Neutrophilia occurred in the 2,100 ppm male mice. Organ weight differences in exposed rats included increased absolute and relative kidney weights of 1,080 ppm males and 2,100 ppm males and females and increased relative liver weights of 1,080 and 2,100 ppm females. There were no treatment-related gross findings in male or female rats or mice; no microscopic lesion occurred in female rats or male or female mice that survived to the end of the study. In male rats, there was an exposure concentration-related increase in the severity of chronic nephropathy. Splenic lymphoid depletion was present in male mice that died during the studies; this lesion was presumed to be secondary to stress. t-butyl alcohol produced no adverse effects on reproductive parameters in male or female rats or mice. The results of all tests of t-butyl alcohol for induction of genetic damage in vitro and in vivo were negative. In vitro, t-

butyl alcohol was negative in Salmonella typhimurium and mouse lymphoma cell mutation test, and it did not induce sister chromatid exchanges or chromosomal aberrations in cultured Chinese hamster ovary cells. These in vitro studies were conducted with and without metabolic activation (S9). In vivo, no increase in the frequency of micronucleated erythrocytes was observed in peripheral blood samples from mice administered t-butyl alcohol in drinking water for 13 weeks. Also, induction or micronucleated erythrocytes was noted in bone marrow cells of rats administered t-butyl alcohol by intraperitoneal injection. In summary, inhalation exposure of rats and mice to t-butyl alcohol resulted in deaths following a single 7,000 ppm exposure and clinical findings of alcohol toxicity (hyper- and hypoactivity, ataxia) at concentrations of 900 ppm and greater in rats and 1,750 ppm and greater in mice. In 13-week studies at concentrations up to 2,100 ppm, only one death (that of a 2,100 ppm mouse) was attributed to chemical exposure. The most notable evidence of toxicity at the end of 13 weeks was limited to males and consisted of increased kidney weights, which correlated microscopically to increased severity of chronic nephropathy. Reproductive parameters in male and female rats and mice were unaffected after 13 weeks of exposure, and the results of all tests for genetic toxicity were negative.

28. Poet TS, Valentine JL, Borghoff SJ. (1997) Pharmacokinetics of tertiary butyl alcohol in male and female Fischer 344 rats. Toxicol Lett 92(3):179-186.
Tertiary butyl alcohol (TBA) is a small aliphatic alcohol with multiple industrial and scientific uses. A comprehensive pharmacokinetic profile for TBA has not been determined in rats. The purpose of this study was to fully characterize the pharmacokinetics of TBA in male and female F-344 rats following intravenous administration of 37.5, 75, 150 and 300 mg/kg TBA. TBA was observed to undergo a rapid distribution phase followed by a slower elimination phase. The steady-state volume of distribution for TBA was roughly 4.5 times greater than total body water, and the clearance was lower than the estimated glomerular filtration rate. The elimination of TBA appears to saturate at higher doses, as evidenced by a disproportional increase in area under the concentration-time curve and decreased rate of clearance.

29. Prah J, Ashley D, Blount B, Case M, Leavens T, Pleil J, Cardinali F. (2004) Dermal, oral, and inhalation pharmacokinetics of methyl tertiary butyl ether (MTBE) in human volunteers. Toxicol Sci 77(2):195-205.
Methyl tertiary butyl ether (MTBE), a gasoline additive used to increase octane and reduce carbon monoxide emissions and ozone precursors, has contaminated drinking water and can lead to exposure by oral, inhalation, and dermal routes. To determine its dermal, oral, and inhalation kinetics, 14 volunteers were exposed to 51.3 microg/ml MTBE dermally in tap water for 1 h, drank 2.8 mg MTBE in 250 ml Gatorade(R), and inhaled 3.1 ppm. MTBE for 1 h. Blood and exhaled breath samples were then obtained. Blood MTBE peaked between 15 and 30 min following oral exposure, at the end of inhalation exposure, and ~5 min after dermal exposure. Elimination by each route was described well by a three-compartment model (Rsq >0.9). The Akaike Information Criterion for the three-compartment model was smaller than the two-compartment model, supporting it over the two-compartment model. One metabolite, tertiary butyl alcohol (TBA), measured in blood slowly increased and plateaued, but it did not return to the pre-exposure baseline at the 24-h follow-up. TBA is very water-soluble and has a blood:air partition ratio of 462, reducing elimination by exhalation. Oral exposure resulted in a significantly greater MTBE metabolism into TBA than by other routes based on a greater blood TBA:MTBE AUC ratio, implying significant first-pass metabolism. The slower TBA elimination may make it a better biomarker of MTBE exposure, though one must consider the exposure route when estimating MTBE exposure from TBA because of first-pass metabolism. Most subjects had a baseline blood TBA of 1-3 ppb. Because TBA is found in consumer products and can be used as a fuel additive, it is not a definitive marker of MTBE exposure. These data provide the risk assessment process of pharmacokinetic information relevant to the media through which most exposures occur-air and drinking water.

30. Rao HV, Ginsberg GL. (1997) A physiologically-based pharmacokinetic model assessment of methyl t-butyl ether in groundwater for a bathing and showering determination. Risk Anal 17(5):583-598.
Methyl t-butyl ether (MTBE) is a gasoline additive that has appeared in private wells as a result of leaking underground storage tanks. Neurological symptoms (headache, dizziness) have been reported from household use of MTBE-affected water, consistent with animal studies showing acute CNS depression from MTBE exposure. The current research evaluates acute CNS effects during bathing/showering by application of physiologically-based pharmacokinetic (PBPK) techniques to compare internal doses in animal toxicity studies to human exposure scenarios. An additional reference point was the delivered dose

associated with the acute Minimum Risk Level (MRL) for MTBE established by the Agency for Toxic Substances and Disease Registry. A PBPK model for MTBE and its principal metabolite, t-butyl alcohol (TBA) was developed and validated against published data in rats and humans. PBPK analysis of animal studies showed that acute CNS toxicity after MTBE exposure can be attributed principally to the parent compound since the metabolite (TBA) internal dose was below that needed for CNS effects. The PBPK model was combined with an exposure model for bathing and showering which integrates inhalation and dermal exposures. This modeling indicated that bathing or showering in water containing MTBE at 1 mg/L would produce brain concentrations approximately 1000-fold below the animal effects level and twofold below brain concentrations associated with the acute MRL. These findings indicate that MTBE water concentrations of 1 mg/L or below are unlikely to trigger acute CNS effects during bathing and showering. However, MTBE's strong odor may be a secondary but deciding factor regarding the suitability of such water for domestic uses.

31. Saarinen L, Hakkola M, Pekari K, Lappalainen K, Aitio A. (1998) Exposure of gasoline road-tanker drivers to methyl tert-butyl ether and methyl tert-amyl ether. Int Arch Occup Environ Health 71(2):143-147.
Organic oxygenates, namely, methyl tert-butyl ether (MTBE) and methyl tert-amyl ether (MTAE), are added to gasoline to reduce carbon monoxide in exhausts and to enhance the octane number. The aim of this study was to investigate road-tanker drivers' exposure to oxygenate vapors during road-tanker loading and unloading as well as to evaluate the measurements of these ethers and their metabolites in the urine as a means of assessing the uptake of the ethers. A total of 11 drivers in different parts of Finland were trained to monitor their exposure with personal samplers, to report their working conditions, and to collect their whole-day urine samples. Charcoal tubes of the air samples were analyzed for MTBE, MTAE, benzene, toluene, and aliphatic hydrocarbons. For biological monitoring purposes the two main oxygenates, tertiary ethers MTBE and MTAE, as well as their main metabolites, tertiary alcohols tert-butanol (TBA) and tert-amyl alcohol (TAA), were determined in urine specimens. On average the drivers were exposed to vapors for short periods (21 +/- 14 min) three times during a work shift. The mean concentrations of MTBE and MTAE (mean +/- SD) were 8.1 +/- 8.4 and 0.3 +/- 0.4 mg/m3. The total MTBE uptake during the shift was calculated to be an average of 106 +/- 65 mumol. The mean concentrations of MTBE, TBA, MTAE and TAA detected in the first urine after the work shift were 113 +/- 76, 461 +/- 337, 16 +/- 21, and 40 +/- 38 nmol/l, and those found the next morning, 16 h later, were 18 +/- 12, 322 +/- 213, 9 +/- 10, and 20 +/- 27 nmol/l. The good relationship (r = 0.84) found between MTBE exposure and postshift excretion suggests that urinary MTBE can be used for biological monitoring of exposure, but at the present low level of exposure the corresponding metabolite TBA is not equally reliable. The determination of MTAE and its metabolite TAA in urine is sensitive enough to detect the low degree of exposure to MTAE, but in this study the data were too scarce to allow calculation of the correlations due to very low levels of MTAE exposure.

32. Strubelt O, Deters M, Pentz R, Siegers CP, Younes M. (1999) The toxic and metabolic effects of 23 aliphatic alcohols in the isolated perfused rat liver. Toxicological Sciences 49(1):133-142.
BIOSIS COPYRIGHT: BIOL ABS. We investigated the acute toxic and metabolic effects of 23 aliphatic alcohols (16 saturated and 7 unsaturated) in the isolated perfused rat liver at a concentration of 65.1 mmol/l (0.3% ethanol). The capacity of the straight chain primary alcohols (methanol, ethanol, 1-propanol, 1-butanol and 1-pentanol) to release the enzymes glutamate-pyruvate transaminase (GPT), lactate dehydrogenase (LDH) and glutamate dehydrogenase (GLDH) into the perfusate was strongly correlated with their carbon chain rfusion flow of the isolated livers. Statistically significant correlations exist between parameters of alcohol-induced hepatotoxicity and the membrane/buffer partition coefficents of the alcohols. With the exception of methanol, all alcohols tested increased the lactate/pyruvate ratio of the perfusate, although this effect was not correlated to the degree of hepatic injury. Hepatic ATP concentrations decreased in most cases in line with hepatic injury and were particularly corre

33. Takahashi K, Lindamood C, 3rd, Maronpot RR. (1993) Retrospective study of possible alpha-2 mu-globulin nephropathy and associated cell proliferation in male Fischer 344 rats dosed with t-butyl alcohol. Environ Health Perspect 101 Suppl 5:281-285.
Tert-butyl alcohol, an important commodity chemical, additive to unleaded gasoline, and contaminant of drinking water, was evaluated for toxicity and was found to enhance nephropathy in male Fischer 344 rats. Because male rats treated with t-butyl alcohol for 2 years had a low incidence of renal cortical tumors,

additional renal sections for the 90-day toxicity study were examined for the presence of hyaline droplet accumulation, nephropathy, and evidence of replicative DNA synthesis (S-phase nuclei) to indirectly and retrospectively investigate a possible role of alpha-2 mu-globulin in the pathogenesis of the nephropathy. Dose levels for t-butyl alcohol were 0, 0.25, 0.5, 1, 2, and 4% (w/v) administered in drinking water. Significant body weight gain depressions were observed in all treated males, and there was an absolute weight loss in the 4% male group, none of which survived to the end of the study. Except for the 4% dose group, there was a treatment-related increase in hyaline droplet accumulation in the renal proximal tubules with crystalline, rectangular, and rhomboid forms of the protein evident. The severity of nephropathy was enhanced in treated rats, except for the 4% dose group. Replicative DNA synthesis, as measured by immunohistochemical staining for proliferating cell nuclear antigen, was increased in proximal tubules of rats dosed with 2% t-butyl alcohol. It is concluded that t-butyl alcohol exacerbated nephropathy in male Fischer 344 rats and increased renal accumulation of hyaline protein material consistent with alpha-2 mu-globulin deposition.

34. Williams TM, Borghoff SJ. (2001) Characterization of tert-butyl alcohol binding to alpha2u-globulin in F-344 rats. Toxicol Sci 62(2):228-235.
tert-Butyl alcohol (TBA) is widely used in the manufacturing of certain perfumes, cosmetics, drugs, paint removers, methyl tert-butyl ether (MTBE), and industrial solvents. In both rodents and humans, TBA is a major metabolite of MTBE, an oxygenated fuel additive. Chronic TBA exposure causes protein droplet nephropathy, alpha2u-globulin (alpha2u) accumulation, renal cell proliferation, and with chronic exposure, renal tumors in male, but not female, rats. These effects suggest an alpha2u-mediated mechanism for renal tumors. The objective of the present study was to determine whether TBA or its metabolites bind to alpha2u. Mature male and female F-344 rats were administered a single gavage dose of 500 mg/kg TBA, 500 mg/kg (14)C-TBA, or corn oil. TBA equivalents/gram or ml of tissue in the male rat kidney, liver, and blood were higher than the levels measured in female rat tissue 12 h after (14)C-TBA administration. Gel filtration and anion-exchange chromatography demonstrated that (14)C-TBA-derived radioactivity co-eluted with alpha2u from male kidney cytosol. Protein dialysis studies demonstrated that the interaction between (14)C-TBA-derived radioactivity and alpha2u was reversible. Incubations of the low-molecular-weight protein fraction (LMWPF) isolated from (14)C-TBA-treated male rat kidneys with d-limonene oxide (a chemical with a high affinity to alpha2u) demonstrated that (14)C-TBA-derived radioactivity was displaced. Gas chromatography-mass spectrometry analysis confirmed that TBA was present in this LMWPF fraction. These results demonstrate that TBA interacts with alpha2u, which explains the accumulation of alpha2u in the male rat kidney following TBA exposure.

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2. 1992. Initial submission: acute percutaneous toxicity of t-butanol with cover letter dated 081092. EPA/OTS; Ntis/ots0538658; Doc #88-920007738.

3. 1992. Initial submission: letter submitting preliminary results from subchronic toxicity studies of tertiary butyl alcohol in rats and mice dated 101492 and attachments. EPA/OTS; Ntis/ots0538283; Doc #88-930000018.

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5. 1994. Eye irritation study in rabbits using t-butyl alcohol with cover letter dated 03/24/94. EPA/OTS; Ntis/ots0572355; Doc #86940000252.

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8. 1994. Ld50 acute inhalation toxicity evaluation in rats using t-butyl alcohol with cover letter dated 03/24/94. EPA/OTS; Ntis/ots0572353; Doc #86940000250.

9. 1994. Primary dermal irritation test in rabbits with t-butyl alcohol with cover letter dated 03/24/94. EPA/OTS; Ntis/ots0572354; Doc #86940000251.

10. 1994. Repeated dose test of t-butanol (c55367) in b6c3f1 mice and fischer 344 rats with cover letter dated 031594. EPA/OTS; Ntis/ots0556768; Doc #86940000173.

11. 1994. Report on animal toxicity experiments with ethyl alcohol, tertiary butyl alcohol, and stoddard's solvent with cover letter dated 03/28/94 (sanitized). EPA/OTS; Ntis/ots0572373; Doc #86940000270S.

12. 1994. Salmonella/mammalian-microsome preincubation mutagenicity assay with t-butyl alcohol with cover letter dated 03/24/94. EPA/OTS; Doc #86940000253.

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Pregnant rats consumed liquid diets containing methanol (1.6%, 0.9%, 0.6% v/v) or t-butanol (10.9%, 1.3%, 0.65% v/v) beginning on gestation day 8 until parturition. Each group had its own pair-fed controls. After parturition mothers were put on lab chow ad lib. Methanol did not affect fecundity but reduced maternal weight gain, decreased litter sizes (from 12 to 5 pups per litter), increased perinatal mortality (from 4% to 25%) and postnatal mortality (from 0% for controls to 100% for offspring in the highest dose group), and decreased weights at weaning for survivors in the other methanol groups. Since methanol treated animals did not differ from pair fed controls in weight gain, these effects could not be due to decreased maternal weight gain. T-butanol reduced maternal weight gain, litter sizes (from 11 to 3 pups per litter), birth weights, and weights at weaning and increased perinatal mortality (from 2% to 14%) and postnatal mortality (from 6% to 100%). These results indicate that prenatal exposure to methanol and t-butanol can result in very high postnatal mortality rates. These rates are much higher than we have previously seen in connection with prenatal alcohol exposure.

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19. Atkinson J, Sullivan, TJ, Kelly, JP, Parker, CW. (1977) Stimulation by alcohols of cyclic AMP metabolism in human leukocytes. Possible role of cyclic AMP in the anti-inflammatory effects of ethanol. J Clin Invest 60(2):287-294.
In this study ethanol and certain other short-chain aryl (benzyl and phenethyl) and aliphatic (methyl, propyl, butyl, and amyl) alcohols produced up to 10-fold increases in cyclic AMP (cAMP) concentrations in purified human peripheral blood lymphocytes. Ethanol concentrations as low as 80 mg/dl produced significant elevations in lymphocyte cAMP. Significant but less marked augmentation of cAMP in response to alcohols was observed in human platelets, human granulocytes, and rabbit alveolar macrophages. The mechanism of the alcohol-induced cAMP accumulation is probably secondary to membrane perturbation and consequent activation of adenylate cyclase, because ethanol directly stimulated this enzyme in lymphocyte membrane preparations but had no effect on lymphocyte phosphodiesterase activity.Lysosomal enzyme release, by phagocytosing human leukocytes, and aminoisobutyric acid transport in mitogen-stimulated human lymphocytes were shown to be inhibited by ethanol and other alcohols at concentrations which also elevate cAMP. In general, the magnitude of the inhibition of these inflammatory processes correlated with the ability of the alcohol to elevate cAMP concentrations. Lectin- and anti-thymocyte globulin-induced lymphocyte mitogenesis was inhibited or unaffected depending upon both the concentration and type of mitogenic stimulus and the concentration and type of alcohol utilized. Inflammatory mediator release from rat mast cells also was inhibited by ethanol and certain other alcohols, but whole cell cAMP was not increased. Ethanol may alter these inflammatory responses and other biologic processes at least in part by modulating cellular levels of cAMP.

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The mechanisms of ethanol's hyperglycemic and hypothermic effects were investigated by comparing the effects of ethanol with those of tertiary butanol. Tertiary butanol is an intoxicant like ethanol, but unlike ethanol it is only minimally metabolized. Consequently, tertiary butanol does not produce appreciable amounts of active metabolites or energy. Tertiary butanol exerts its neural effects primarily by directly altering the physico-chemical properties of nerve cell membranes. It was found that ethanol and tertiary butanol produce hyperglycemic and hypothermic effects whose magnitude and time course are nearly identical. These data suggest that the hyperglycemic and hypothermic effects of ethanol represent a primary physico-chemical effect on nerve cell membranes and are not secondary to its energy content or metabolites.

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The purpose of these studies was to evaluate the tissue uptake, distribution, metabolism, and excretion of methyl tertiary-butyl ether (MTBE) in rats and to determine the effects of coinhalation of the volatile fraction of unleaded gasoline on these parameters. Male F344 rats were exposed nose-only once for 4 h to 4, 40, or 400 ppm 14C-MTBE and to 20 and 200 ppm of the light fraction of unleaded gasoline (LFG)

containing 4 and 40 ppm 14C-MTBE, respectively. To evaluate the effects of repeated inhalation of LFG on the fate of inhaled MTBE, rats were exposed for 7 consecutive days to 20 and 200 ppm LFG followed on d 8 by exposure to LFG containing 14C-MTBE. Three subgroups of rats were included for evaluation of respiratory parameters, rates and routes of excretion, and tissue distribution and elimination. MTBE and its chief metabolite, tertiary-butyl alcohol, were quantitated in blood and kidney (immediately after exposure), and the major urinary metabolites, 2-hydroxyisobutyric acid and 2-methyl-1,2- propanediol, were identified and quantified in urine. Inhalation of MTBE alone or as a component of LFG had no concentration-dependent effect on respiratory minute volume. The initial body burdens (IBBs) of MTBE equivalents achieved after 4 h of exposure to MTBE did not increase linearly with exposure concentration. MTBE equivalents rapidly distributed to all tissues examined, with the largest percentages distributed to liver. Between 40 and 400 ppm, there was a significant reduction in percentage of the IBB present in the major organs examined, both immediately and 72 h after exposure. At 400 ppm, the elimination rates of MTBE equivalents from tissues changed significantly. Furthermore, at 400 ppm there was a significant decrease in the elimination half-time of volatile organic compounds (VOCs) in breath and a significant increase in the percentage of the IBB of MTBE equivalents eliminated as VOCs in breath. LFG coexposure significantly decreased the percentage of the MTBE equivalent IBBs in tissues and increased rates of elimination of MTBE equivalents. The study results indicate that the uptake and fate of inhaled MTBE are altered upon increasing exposure levels from 4 to 400 ppm, suggesting that toxic effects observed previously upon repeated inhalation of concentrations of 400 ppm or greater may not necessarily be linearly extrapolated to effects that might occur at lower concentrations. Furthermore, coexposure to LFG, whether acute or repeated, decreases tissue burdens of MTBE equivalents and enhances the elimination rate of MTBE and its metabolites, thereby potentially reducing the toxic effects of the MTBE compared to when it is inhaled alone.

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26. Brady JF, Xiao F, Ning SM, Yang CS. (1990) Metabolism of methyl tertiary-butyl ether by rat hepatic microsomes. Arch Toxicol 64(2):157-160.
Exposure to methyl tertiary-butyl ether (MTBE), a commonly used octane booster in gasoline, has previously been shown to alter various muscle, kidney, and liver metabolic activities. In the present study, the metabolism of MTBE by liver microsomes from acetone- or phenobarbital-treated Sprague-Dawley rats was studied at concentrations of up to 5 mM MTBE. Equimolar amounts of tertiary-butanol, as measured by head-space gas chromatography, and formaldehyde were formed. The Vmax for the demethylation increased by 4-fold and 5.5-fold after acetone and phenobarbital treatments, respectively. The apparent Km value of 0.70 mM using control microsomes was decreased slightly after acetone treatment, but was increased by 2-fold after phenobarbital treatment. The metabolism of MTBE (1 mM) was inhibited by 35% by monoclonal antibodies against P450IIE1, the acetone/ethanol inducible form of cytochrome P450, suggesting a partial contribution by this isozyme. A single 18-h pretreatment of rats with 1 or 5 ml/kg MTBE (i.p.) resulted in a 50-fold induction of liver microsomal pentoxyresorufin dealkylase activity but no change in N-nitrosodimethylamine demethylase activity. These trends in activity agreed with immunoblot analysis which showed an elevation in P450IIB1 but no change in P450IIE1 levels.

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We reviewed toxicological studies, both experimental and epidemiological, that appeared in international

literature in the period 1990-1997 and included both leaded and unleaded gasolines as well as their components and additives. The aim of this overview was to select, arrange, and present references of scientific papers published during the period under consideration and to summarize the data in order to give a comprehensive picture of the results of toxicological studies performed in laboratory animals (including carcinogenic, teratogenic, or embryotoxic activity), mutagenicity and genotoxic aspects in mammalian and bacterial systems, and epidemiological results obtained in humans in relation to gasoline exposure. This paper draws attention to the inherent difficulties in assessing with precision any potential adverse effects on health, that is, the risk of possible damage to man and his environment from gasoline. The difficulty of risk assessment still exists despite the fact that the studies examined are definitely more technically valid than those of earlier years. The uncertainty in overall risk determination from gasoline exposure also derives from the conflicting results of different studies, from the lack of a correct scientific approach in some studies, from the variable characteristics of the different gasoline mixtures, and from the difficulties of correctly handling potentially confounding variables related to lifestyle (e.g., cigarette smoking, drug use) or to preexisting pathological conditions. In this respect, this paper highlights the need for accurately assessing the conclusive explanations reported in scientific papers so as to avoid the spread of inaccurate or misleading information on gasoline toxicity in nonscientific papers and in mass-media messages.

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Tertiary butyl alcohol has often been used experimentally as a “non-metabolizable” alcohol. In this report, evidence is presented that t-butanol serves as a substrate for rat liver microsomes and that it is oxidatively demethylated to yield formaldehyde. The apparent Km for t-butanol is 30 mM while Vmax is about 5.5 nmol per min per mg microsomal protein. Formaldehyde production is stimulated by azide, which prevents destruction of H2O2 by catalase. Hydroxyl radical scavenging agents, such as benzoate, mannitol, and 2-keto-4-thiomethylbutyrate, suppress formaldehyde production. Therefore, the microsomal reaction pathway appears to involve the interaction of t-butanol with hydroxyl radicals generated from H2O2 by the microsomes. Formaldehyde is also produced when t-butanol is incubated with model hydroxyl radical-generating systems such as the iron-EDTA-stimulated oxidation of xanthine by xanthine oxidase or the iron-EDTA-catalyzed autoxidation of ascorbate. These results indicate that t-butanol cannot be used to distinguish metabolically-linked from non-metabolically-linked actions of ethanol.

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t-Butyl alcohol is not a substrate for alcohol dehydrogenase or for the peroxidatic activity of catalase and, therefore, it is used frequently as an example of a non-metabolizable alcohol. t-Butyl alcohol is, however, a scavenger of the hydroxyl radical. The current report demonstrates that t-butyl alcohol can be oxidized to formaldehyde plus acetone by hydroxyl radicals generated from four different systems. The systems studied were: (a) two chemical systems, namely, the iron catalyzed oxidation of ascorbic acid and the Fenton reaction between H2O2 and iron; (b) an enzymatic system, the coupled oxidation of xanthine by xanthine oxidase; and (c) a membrane-bound system, NADPH-dependent microsomal electron transfer. The oxidation of t-butyl alcohol appeared to be mediated by hydroxyl radicals, or by a species with the oxidizing power of the hydroxyl radical, because the production of formaldehyde plus acetone was (a) inhibited by competing scavengers of the hydroxyl radical; (b) stimulated by the addition of iron-EDTA; and (c) inhibited by catalase. The last observation suggests that H2O2 served as the precursor of the hydroxyl radical in all three systems. A possible mechanism is hydrogen abstraction to form the alkoxyl radical [CH3)3-C-O.), spontaneous fission of the alkoxyl radical to produce acetone and the methyl radical (CH3.), interaction of the methyl radical with O2 to form the methyl peroxy radical (CH300.), and decomposition of the later to formaldehyde. These results extend the alcohol oxidizing capacity of the microsomal alcohol oxidizing system to a tertiary alcohol. Since t-butyl alcohol is not a substrate for alcohol dehydrogenase or catalase, the ability of microsomes to oxidize t-butyl alcohol lends further support for a role for hydroxyl radicals in the microsomal alcohol oxidation system. In view of the production of formaldehyde, and the reactivity as well as further metabolism of this aldehyde, caution should be used in interpreting experiments in which t-butyl alcohol is used as a presumed "non-metabolizable" alcohol

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Experiments were carried out to evaluate whether the molecular mechanism for ethanol oxidation by microsomes, a minor pathway of alcohol metabolism, involved generation of hydroxyl radical (.OH). Microsomes oxidized chemical .OH scavengers (KMB, DMSO, t-butyl alcohol, benzoate) by a reaction sensitive to catalase, but not SOD. Iron was required for microsomal .OH generation in view of the potent inhibition by desferrioxamine; however, the chelated form of iron was important. Microsomal .OH production was effectively stimulated by ferric EDTA or ferric DTPA, but poorly increased with ferric ATP, ferric citrate, or ferric ammonium sulfate. By contrast, the latter ferric complexes effectively increased microsomal chemiluminescence and lipid peroxidation, whereas ferric EDTA and ferric DTPA were inhibitory. Under conditions that minimize .OH production (absence of EDTA, iron) ethanol was oxidized by a cytochrome P-450-dependent process independent of reactive oxygen intermediates. Under conditions that promote microsomal .OH production, the oxidation of ethanol by .OH becomes more significant in contributing to the overall oxidation of ethanol by microsomes. Experiments with inhibitors and reconstituted systems containing P-450 and NADPH-P-450 reductase indicated that the reductase is the critical enzyme locus for interacting with iron and catalyzing production of reactive oxygen species. Microsomes isolated from rats chronically fed ethanol catalyzed oxidation of .OH scavengers, light emission, and inactivation of added metabolic enzymes at elevated rates, and displayed an increase in ethanol oxidation by a .OH-dependent and a P-450-dependent pathway. It is possible that enhanced generation of reactive oxygen intermediates by microsomes may contribute to the hepatotoxic effects of ethanol.

33. Chen M. (2005) Amended final report of the safety assessment of t-Butyl Alcohol as used in cosmetics. Int J Toxicol 24 Suppl 2:1-20.
t-Butyl Alcohol (t-BuOH) is a tertiary aliphatic alcohol that is used as a solvent or an alcohol denaturant and as a perfume carrier in cosmetics. t-BuOH was reported as an ingredient in 32 formulations of eye makeup, fragrance, and shaving preparations, at concentrations ranging from 0.00001% and 0.3%. There is little acute oral toxicity in animals; e.g., the acute oral LD(50) in rats was 3.0 to 3.7 g/kg. In short-term oral studies in rats, t-BuOH at 2% (w/v) or less in drinking water did not cause gross organ or tissue damage in mice, although weight loss was reported and microscopic damage to livers and kidney and alterations such as centrilobular necrosis, vacuolation in hepatocytes, and loss of hepatic architecture were noted. Subchronic oral dosing with t-BuOH increased the mineralization of the kidney, nephropathy, and urinary bladder transitional cell epithelial hyperplasia in rats; and liver damage, chronic inflammation, hyperplasia of transitional cell epithelium urinary, and proliferative changes including hyperplasia and neoplasia in the thyroid in mice. Male rats exposed to t-BuOH were susceptible to alpha 2mu-globulin nephropathy. t-BuOH (99.9%) was a moderate to severe ocular irritant to rabbits and caused mild to moderate dermal irritation to rabbits. It was not considered to be a primary dermal irritant to rabbits. In animal studies, fetotoxicity generally increased with concentration, and fetal weights were slightly depressed at concentrations of 0.5% to 1% t-BuOH. t-BuOH produced a significant increase in the number of resorptions per litter. There was also a significant decrease in the number of live fetuses per litter. t-BuOH reduced maternal weight gain, litter sizes, birth weights, and weights at weaning, and increased perinatal and postnatal mortality. t-BuOH was not mutagenic in several bacterial and mammalian test systems. The principal effects from 2 years of exposure to t-BuOH in drinking water (up to 10 mg/ml for rats and 20 mg/ml for mice) were proliferative lesions (hyperplasia, adenoma, and carcinoma) in the kidneys of exposed male rats, and nephropathy in all exposed groups of female rats. There was some evidence of carcinogenic activity, but it was not consistent between species, sexes, or doses. A repeat-insult patch test (RIPT) test showed no potential for eliciting either dermal irritation or sensitization by 100% t-BuOH. Dermatitis can result from dermal exposure of humans to t-BuOH. In consideration of these data, it was concluded that t-BuOH was (at most) a weak carcinogen and unlikely to have significant carcinogenic potential as currently used in cosmetic formulations. In addition, the renal tubule effects found in male rats were likely an effect of alpha 2mu-globulin. In consideration of the reproductive and developmental toxicity data, the increased incidence of still births occurred at high exposure levels and was likely secondary to maternal toxicity. Based on the available animal and clinical data in this report, it was concluded that t-BuOH is safe as used in cosmetic products.

34. Clark J. Tert-butyl Alcohol: Chemical Properties, Production and Use, Fate and Transport, Toxicology, and Detection in Groundwater and Regulatory Standards. In: Diaz A, editor; 2002; ACS Symp. Ser. 799 (Oxygenates in Gasoline). Am. Chem. Soc.: Washington, DC. pp 92-106.

35. Clary JJ. (1997) Methyl tert butyl ether systemic toxicity. Risk Anal 17(6):661-672.
In male F344 rats exposed in a chronic inhalation study to methyl tertiary butyl ether (MTBE) a treatment related increase in severity of chronic nephropathy and mortality and an increase in hyaline droplets in the kidney were noted. Liver weights were increased in both rats and mice but no histological lesions other than hypertrophy are seen. Transient CNS effects but no indications of permanent nervous system effects were noted. MTBE is not a reproductive or developmental hazard. MTBE is rapidly absorbed. MTBE with some metabolite, tertiary butyl alcohol (TBA) and a little CO2 are excreted in the air. The urinary excretion products in animals are TBA metabolites, while in humans the urinary excretion products are MTBE and TBA. A comparison of the systematic responses of the possible metabolites TBA and formaldehyde indicate that they are not responsible for toxicity associated with MTBE, except that TBA may be partially responsible for the kidney effects reported. Animals and humans are similar in the uptake and excretion though with some differences in metabolism of MTBE. This supports the use of the animal data as a surrogate for humans.

36. Cooper S, Raymer, JH, Pellizzari, ED, Thomas, KW. (1995) The identification of polar organic compounds found in consumer products and their toxicological properties. J Expo Anal Environ Epidemiol 5(5):57-75.
Exposure to volatile organic compounds (VOCs) in the indoor environment has received substantial research attention in the past several years, with the goal of better understanding the impact of such exposures on human health and well-being. Many VOCs can arise from consumer products used within the indoor environment. The VOCs emitted from five representative consumer products were collected onto Tenax-GC and subjected to thermal desorption and analysis by gas chromatography, in combination with low-resolution mass spectrometry (MS), high-resolution MS, and matrix-isolation Fourier transform infrared spectroscopy for structural characterization. An emphasis was placed on the polar organic compounds often used to provide fragrance in these products. The structures of a number of these compounds were confirmed, and an electronic literature search was carried out on them to determine any known toxic properties. The search revealed that many of the VOCs possess toxic properties when studied at acute, relatively high-level exposures. In addition, toxic effects were reported for a few of the chemicals, such as benzaldehyde, alpha-terpineol, benzyl acetate, and ethanol, at relatively low dose levels of 9-14 mg/kg. In general, the data were unclear as to the effect of chronic, low-level exposures. The widespread use of such chemicals suggests that the health effects of chronic exposures need to be determined. Validated analytical methods for the quantitative characterization of polar organic compounds at low concentrations will be required to make such work possible.

37. Drogos D, Diaz, AF. Physical Properties of Fuel Oxygenates and Additives. In: Diaz A, editor; 2002; ACS Symp. Ser. 799 (Oxygenates in Gasoline). Am. Chem. Soc.: Washington, DC. pp 258-279.

38. ECETOC. 1997. Methyl tert-Butyl ether (MTBE). Health risk characterisation. 124 p.
Toxicity. Biotransformation of MTBE leads to the formation of tert-butanol (TBA) and formaldehyde, which in turn are further metabolised. TBA excretion proceeds relatively slowly (half-life of 8 h in humans). For formaldehyde the detoxification rate is much faster than its rate of formation from MTBE and therefore this route of metabolism is judged not to contribute to the toxic effects of MTBE discussed in this report. Toxicokinetic data do not indicate reasons for concern with regard to bioaccumulation of MTBE or any of its metabolises. Skin and respiratory irritation are regarded as effects of prime concern following acute exposure. MTBE posesses a low order of acute toxicity in experimental animals exposed via oral, dermal and inhalation routes. LDso values exceed 2,000 mg/kg for oral and dermal exposure, and the inhalation LC50 value is 85,000 mg/m3 for 4 hours. Sub-lethal acute exposure evokes local irritation at the site of contact and transient clinical signs characteristic of central nervous system (CNS) depression. Skin contact with MTBE causes reversible moderate to severe irritation in rabbits whereas MTBE was found to be only slightly irritant to the rabbit eye. MTBE vapour at concentrations above 300 mg/m3 evokes slight and transient irritation to the respiratory system of laboratory animals. For sensory and respiratory irritation an RDso value (50% reduction of breathing rate) of 16,600 mg/m3 was determined for MTBE in the mouse. The Task Force recommended that MTBE be labelled as irritant (Xi) with the corresponding R-

phrase 38 (irritating to skin). There have been no cases reported of sensitisation to MTBE in humans exposed by skin contact to the neat material or to gasoline containing MTBE. Studies in animals also failed to demonstrate skin sensitising potential on the part of MTBE, adding weight to the conclusion that MTBE is not a skin sensitiser. MTBE caused anaesthesia in experimental animals when inhaled at concentrations of 28,800 mg/m3. Reversible CNS effects were detected in a rat study at 14,400 mg/m3 (LOAEL) using a functional observation battery and 6 hours of exposure. The NOAEL in this study was 2,880 mg/m3. Observations suggesting transient CNS depression were consistently made also in animal studies using repeated inhalation and oral exposure. However, all effects were reversed when exposure ended and repeated exposure did not lead to NOAELs that were lower than for single exposure. Principle effects observed following repeat oral and inhalation exposure of rats and mice to MTBE are local irritation, transient anaesthetic effects (as observed with many other low molecular weight ethers), chronic nephropathy and hepatocellular hypertrophy. The NOAEL for sub-chronic oral exposure is 300 mg/kg and for chronic inhalation exposure 1,440 mg/m3. The latter value corresponds to daily retained doses (for calculation see page 29) of 102 and 113 mg/kg for male and female rats, respectively and 182 and 184 mg/kg for male and female mice, respectively. MTBE has been tested extensively in vitro and in vivo for its genotoxic potential. The weight of evidence shows MTBE is not genotoxic. This conclusion is supported by the information for TBA, which is not genotoxic in several in vitro and in vivo tests, and formaldehyde, which though genotoxic in a number of tests, is rapidly detoxified by the body thereby removing the potential to damage the cell. Tumours in rodents result from exposure to MTBE at doses exceeding the Maximum Tolerated Dose (MTD). An inhalation study in rats demonstrated a tumourigenic response in the male kidney at 10,800 and 28,800 mg/m3 (corresponding to daily retained doses of 384 and 1023 mg/kg, respectively), but a non-genotoxic mechanism unique to the male rat is probably involved. An apparent increase in the incidence of Leydig cell tumours in male rats treated via inhalation was not considered to be relevant to humans. An inhalation study with mice showed an increase in the incidence of liver adenomas in female animals at 28,800 mg/m3 (corresponding to a daily retained dose of 1824 mg/kg). A nongenotoxic mechanism is likely to be involved. Further mechanistic studies are currently under way to clarify the mechanisms for the induction of these tumours. Effects reported in an oral gavage study include an increase in rat Leydig cell tumour incidence and elevated combined lymphoma/leukaemia incidence in female rats. The Task Force considered the rat Leydig cell tumour findings as not predictive of hazard to humans. Furthermore, the importance of the combined lymphoma/leukaemia incidence from this oral gavage study was unclear due to deficiencies in the study report. Overall, the Task Force concluded that the doses necessary to evoke neoplastic effects are equal to or greater than the doses that induce non-neoplastic effects in female mouse liver and male rat kidney. Therefore, protection against non-neoplastic effects should also protect from any theoretical carcinogenic effect. The Task Force concluded that MTBE is not carcinogenic according to the criteria in EU Directive on Dangerous Substances 67/548/EEC (EEC, 1993B). Effects of MTBE vapour on reproduction and development have been evaluated in well-conducted inhalation studies with rats, mice and rabbits. Foetal toxicity and developmental toxicity were observed only at concentrations clearly toxic to the mother. MTBE was not embryotoxic or teratogenic at exposure levels not causing maternal toxicity and did not adversely affect reproduction. Human Experience. A large body of data is available from human experience with MTBE, including case reports of clinical use of MTBE for gallstone dissolution, studies reporting subjective complaints by garage workers and service station attendants, large population studies with sophisticated study design and controlled short-term exposure of volunteers. Whereas the early studies suggested a relationship between MTBE exposure concentration and health complaints, this has not been confirmed in subsequent studies. This absence of an association is in line with short-term experimental studies that showed no specific effects at concentrations (< 3.6-180 mg/m3) similar to or greater than those observed in the population studies. Human experimental data do not indicate irritation of the respiratory tract at concentrations of 180 mg/m3 for two hours. Exposure to 270 mg/m3 for three hours caused mild mucous membrane irritation in some volunteers. Objective symptoms on the CNS have not been observed in volunteer studies up to 270 mg/m3. Subjective symptoms at this concentration were reported by volunteers (mainly feeling of heaviness in the head). At 180 mg/m3 no symptoms were reported. Risk Characterisation. Table 1 on page 5 summarises the conclusions with regard to MTBE-related health effects. Irritation observed after short-term exposure in humans as well as liver and kidney toxicity observed after longterm exposure in experimental animals are considered to be the critical effects for the health risk characterisation of MTBE. Mild respiratory irritation occurred at a concentration of 270 mg/m3 for three hours in human volunteers, whereas 180 mg/m3 for two hours did not evoke such effects. The lowest NOAEL for liver and kidney effects after chronic inhalation

exposure was 102 mg/kg/day (retained dose in male rats). The basis for the risk characterisation is a comparison of these three different doses/concentrations with occupational and consumer exposure data. The available data on short-term peak exposure levels (about 200 mg/m3) did not indicate concerns with regard to respiratory irritation. Comparison of the NOAEL for long-term liver and kidney effects revealed margins of safety between 180 to 300 fold for workers involved in MTBE production, about 70 fold for workers handling gasolines containing MTBE, and between 250 to 800 fold for service station attendants and garage workers. A 17,000 fold margin of safety was calculated for consumer exposure during car refuelling. Compliance with an occupational exposure limit of 90 mg/m3 or 25 ppm MTBE (8-h TWA) is considered by the Task Force to protect workers from any potential health hazards. This concentration corresponds to a daily retained MTBE dose of about 5.1 mg/kg for a 70-kg adult (on the basis of a ventilation volume of 10 m3/8-h shift and a relative respiratory uptake of 40%) and provides a margin of safety of 20 when compared with the lowest NOAEL determined in chronic animal inhalation experiments. Respiratory irritation is regarded as the critical effect for higher short-term exposures. In humans, no effects were observed at a concentration of 180 mg/m3 for 2 hours, while at 270 mg/m3 for three hours only weak irritating effects on the mucous membranes were reported in some volunteers. Therefore, a limit of three times the TWA (270 mg/m3 or 75 ppm) is considered to be an appropriate short-term, peak exposure limit (15-min STEL). Conclusion. The risk characterisation for MTBE does not indicate concern for human health with regard to current occupational and consumer exposures.

39. Gosselin RE, R.P. Smith, H.C. Hodge. . (1984) Clinical Toxicology of Commercial Products, 5th ed: Baltimore: Williams and Wilkins, p. III-14; pp.

40. Hong JY, Wang YY, Bondoc FY, Lee M, Yang CS, Hu WY, Pan J. (1999) Metabolism of methyl tert-butyl ether and other gasoline ethers by human liver microsomes and heterologously expressed human cytochromes P450: identification of CYP2A6 as a major catalyst. Toxicol Appl Pharmacol 160(1):43-48. To reduce the production of carbon monoxide and other pollutants in motor vehicle exhaust, methyl tert-butyl ether (MTBE), ethyl tert-butyl ether (ETBE), and tert-amyl methyl ether (TAME) are added to gasoline as oxygenates for more complete combustion. Previously, we demonstrated that human liver is active in metabolizing MTBE to tert-butyl alcohol (TBA) and that cytochrome P450 (CYP) enzymes play a critical role in the metabolism of MTBE. The present study demonstrates that human liver is also active in the oxidative metabolism of ETBE and TAME. A large interindividual variation in metabolizing these gasoline ethers was observed in 15 human liver microsomal samples. The microsomal activities in metabolizing MTBE, ETBE, and TAME were highly correlated among each other (r, 0.91-0. 96), suggesting that these ethers are metabolized by the same enzyme(s). Correlation analysis of the ether-metabolizing activities with individual CYP enzyme activities in the liver microsomes showed that the highest degree of correlation was with human CYP2A6 (r, 0. 90-0.95), which is constitutively expressed in human livers and known to be polymorphic. CYP2A6 displayed the highest turnover number in metabolizing gasoline ethers among a battery of human CYP enzymes expressed in human B-lymphoblastoid cells. Kinetic studies on MTBE metabolism with three human liver microsomes exhibited apparent Km values that ranged from 28 to 89 microM and the V(max) values from 215 to 783 pmol/min/mg, with similar catalytic efficiency values (7.7 to 8.8 microl/min/mg protein). Metabolism of MTBE, ETBE, and TAME by human liver microsomes was inhibited by coumarin, a known substrate of human CYP2A6, in a concentration-dependent manner. Monoclonal antibody against human CYP2A6 caused a significant inhibition (75% to 95%) of the metabolism of MTBE, ETBE, and TAME in human liver microsomes. Taken together, these results clearly indicate that in human liver, CYP2A6 is the major enzyme responsible for the metabolism of MTBE, ETBE, and TAME.

41. Hong JY, Yang CS, Lee M, Wang YY, Huang WQ, Tan Y, Patten CJ, Bondoc FY. (1997) Role of cytochromes P450 in the metabolism of methyl tert-butyl ether in human livers. Arch Toxicol 71(4):266-269. Methyl tert-butyl ether (MTBE) is widely used as a gasoline oxygenate for more complete combustion in order to reduce the air pollution caused by motor vehicle exhaust. The possible adverse effects of MTBE on human health is a major public concern. However, information on the metabolism of MTBE in human tissues is lacking. The present study demonstrates that human liver is active in metabolizing MTBE to tert-butyl alcohol (TBA), a major circulating metabolite and a marker for exposure to MTBE. The activity is localized in the microsomal fraction (125 +/- 11 pmol TBA/ min per mg protein, n = 8) but not in the cytosol. This activity level in human liver microsomes is approximately one-half of the value in rat and

mouse liver microsomes. Formation of TBA in human liver microsomes is NADPH-dependent, and is significantly inhibited by carbon monoxide (CO), an inhibitor of cytochrome P450 (CYP) enzymes, suggesting that CYP enzymes play a critical role in the metabolism of MTBE in human livers. Both CYP2A6 and 2E1 are known to be constitutively expressed in human livers. To examine their involvement in MTBE metabolism, human CYP2A6 and 2E1 cDNAs were individually co-expressed with human cytochrome P450 reductase by a baculovirus expression system and the expressed enzymes were used for MTBE metabolism. The turnover number for CYP2A6 and 2E1 was 6.1 and 0.7 nmol TBA/min per nmol P450, respectively. The heterologously expressed human CYP2A6 was also more active than 2E1 in the metabolism of two other gasoline ethers, ethyl tert-butyl ether (ETBE) and tert-amyl methyl ether (TAME). Although the contributions of other human CYP forms to MTBE metabolism remain to be determined, these results strongly suggest that CYP enzymes play an important role in the metabolism of MTBE in human livers.

42. IPCS. 1987. Butanols:four isomers -- 1 butanol 2 butanol tert butanol isobutanol. International Programme on Chemical Safety (IPCS). Geneva: World Health Organization; Albany, NY: WHO Publications Center USA. Report nr ISBN: 9241542659 9789241542654 | OCLC: 20898054 3-141 p.
Evaluation of the toxicity data available on the 4 butyl alcohol isomers. Contents: properties and analysis; sources of exposure (man, environment); metabolism; animal studies; effects on man; evaluation of risks to health and to the environment. tert-Butanol is a colourless liquid or white crystalline solid with a camphor-like odour. It has a melting point of 25 xC, a boiling point of 81.5 - 83 xC, is freely soluble in water, and its n-octanol/water partition coefficient is 0.37. Its vapour is 2-6 times denser than air. It is used primarily as a solvent, a dehydrating agent, and as an intermediate in the manufacture of other chemicals. It is also used as a denaturant for alcohols. Human exposure will be mainly occupational. Data on exposure of the general population are not available, but it may result from industrial emissions. tert-Butanol is inherently biodegradable and does not bioaccumulate. At ambient levels, it is not toxic for fish, amphibia, crustacea, algae, or bacteria (Fish, 24-h LC50 > 3000; Green algae, EC50 = 24 200). In animals, tert-butanol is absorbed through the lungs and gastrointestinal tract; no information is available on dermal absorption. tert-Butanol is not a substrate for alcohol dehydrogenase and is slowly metabolized by mammals. Up to 24% of the dose is eliminated in the urine as the glucuronide, and up to 10% of the dose can be excreted in the breath and urine as acetone or carbon dioxide. The rat oral LD50 is 3.5 g/kg body weight; it is, therefore, slightly toxic according to the classification of Hodge & Sterner. The primary acute effects observed in animals are signs of alcoholic intoxication. Its potency for intoxication is approximately 1.5 times that of ethanol. Animal data regarding skin and eye irritation are not available. tert-butanol produces physical dependance in animals and post-natal effects in offspring exposed in utero. Data concerning the pathological effects of repeated exposure of animals are not available. From the animal studies available, it is not possible to determine a no-observed-adverse-effect level. tert-Butanol has been found not to be mutagenic. Adequate data are not available on carcinogenicity, teratogenicity, or effects on reproduction. In man, tert-butanol is a mild irritant to the skin. No other effects on man have been reported, and there have been no reports of poisonings.

43. IPCS. 1987. Tert-Butanol Health and Safety Guide. World Health Organization, International Program on Chemical Safety (IPCS), Switzerland. 40 p.
Chemical safety information sheet based on WHO Environmental Health Criteria 65: Butanols - Four isomers (CIS 87-1025). Toxicity: is absorbed through the skin; irritant.

44. IPCS. 1995. International Chemical Safety Card (ICSC) for Tert-Butanol. Commission of the European Communities, 2920 Luxembourg, Grand Duchy of Luxembourg; International Programme on Chemical Safety (IPCS), World Health Organization, 1211 Genáeve 27, Switzerland, 1991. 2p.
International chemical safety card.

45. Johnson JH. (1988) Automotive emissions. In: Watson aY, R. R. Bates and D. Kennedy (Ed.). , editor. Air Pollution, the Automobile, and Public Health Washington, D.C., USA. : National Academy Press. pp 39-76.

46. Kool H, Van Kreijl, CF, Zoeteman, BCJ (1982) Toxicology Assessment of Organic Compounds in Drinking Water. Crit. Rev. Env. Control 12:307-357.

47. Kotter K, Klein J. (1999) Ethanol inhibits astroglial cell proliferation by disruption of phospholipase D-mediated signaling. Journal of Neurochemistry 73(6):2517-2523.
BIOSIS COPYRIGHT: BIOL ABS. The activation of phospholipase D (PLD) is a common response to mitogenic stimuli in various cell types. As PLD-mediated signaling is known to be disrupted in the presence of ethanol, we tested whether PLD is involved in the ethanol-induced inhibition of cell proliferation in rat cortical primary astrocytes. Readdition of fetal calf serum (FCS) to serum-deprived astroglial cultures caused a rapid, threefold increase of PLD activity and a strong mitogenic response; both effects were dependent on tyrosine kinases but not on protein kinase C. Ethanol (0.1-2%) suppressed the FCS-induced, PLD-mediated formation of phosphatidic acid (PA) as well as astroglial cell proliferation in a concentration-dependent manner. Moreover, exogenous bacterial PLD increased astroglial proliferation in an ethanol-sensitive manner, whereas exogenous PA or lysophosphatidic acid was less effective. Formation of PA and astroglial proliferation were strongly inhibited by 1-butanol (0.1-1%), a substrate of PLD, butwere unaffected by t-butanol, a non-substrate; 2-butanol had intermediate effects. Platelet-derived growth factor and endothelin-1 mimicked the mitogenic effect of FCS; their effects were also inhibited by the butanols in the potency order 1-butanol > 2-butanol > tert-butanol. Our results, in particular, the differential effects of 1-, 2-, and tert-butanol with respect to PA formation and astroglial proliferation, strongly suggest that the antiproliferative effects of ethanol in glial cells are due to the disruption of the PLD signaling pathway. This mechanism may also contribute to the inhibition of astroglial growth and brain development observed in alcoholic embryopathy.

48. Lewis RJV-NY, NY: Van Nostrand Reinhold, 1996., p. 559. (2004) Sax's Dangerous Properties of Industrial Materials, 11th ed: John Wiley & Sons, Inc.

49. Lindbohm R, Wallgren, H. (1962) Changes in respiration of rat brain cortex slices induced by some aliphatic alcohols. Acta Pharmacol Toxicol 19(1):53-58.

50. Lyon R, McComb, JA, Schreurs, J, Goldstein, DB. (1981) A relationship between alcohol intoxication and the disordering of brain membranes by a series of short-chain alcohols. J Pharmacol Exp Ther 218(3):669-675.
This study has established a correlation between the hypnotic potencies of aliphatic alcohols and their abilities to disrupt the structure of neuronal membranes in vitro. The hypnotic potency was determined in mice from the ED50 for loss of righting reflex. The alcohol-induced perturbation of mouse brain synaptosomal plasma membranes was measured by a sensitive electron paramagnetic resonance technique. The membrane disordering potency was determined from the slope of the concentration-dependent decrease in order parameter observed for each alcohol. Significant reductions in the order parameter were observed at nerve blocking concentrations. The following alcohols were investigated: ethanol, 1-propanol, 2-propanol, 1-butanol, 2-butanol, 2-methyl-1-propanol, 2-methyl-2-propanol, 1-pentanol, 2-pentanol, 3-methyl-1-butanol, 1-hexanol and 1-octanol. The disordering potency of each alcohol was closely related to its membrane solubility, based on published oil/water partition coefficients. Structural disorganization resulting from the incorporation of alcohols into neuronal membranes may be an integral step in the mechanism of alcohol intoxication. For a given degree of membrane disorder, intramembrane alcohol concentrations and intramembrane alcohol volumes were estimated from published partitioning and molecular volume data and compared for constancy. The data did not favor either the intramembrane drug concentration or the intramembrane drug volume as a more effectual determinant of disordering potency.

51. McGregor D, Hard GC. (2001) Renal tubule tumor induction by tertiary-butyl alcohol. Toxicol Sci 61(1):1-3.

52. McGregor DB, Brown A, Cattanach P, Edwards I, McBride D, Caspary WJ. (1988) Responses of the L5178Y tk+/tk- mouse lymphoma cell forward mutation assay. II: 18 coded chemicals. Environ Mol Mutagen 11(1):91-118.
Eighteen chemicals were tested for their mutagenic potential in the L5178Y tk+/- mouse lymphoma cell forward mutation assay by the use of procedures based upon those described by Clive and Spector [Mutat Res 44:269-278, 1975] and Clive et al [Mutat Res 59:61-108, 1979]. Cultures were exposed to the chemicals for 4 hr, then cultured for 2 days before plating in soft agar with or without trifluorothymidine (TFT), 3 micrograms/ml. The chemicals were tested at least twice. Significant responses were obtained with benzofuran, benzyl chloride, bromodichloromethane, butylated hydroxytoluene, chlorendic acid, o-

chlorobenzalmalonitrile, 1,2,3,4-diepoxybutane, dimethyl formamide, dimethyl hydrogen phosphite, furfural, glutaraldehyde, hydroquinone, 8-hydroxyquinoline, and resorcinol. Apart from bromodichloromethane, butylated hydroxytoluene and dimethyl hydrogen phosphite, rat liver S9 mix was not a requirement for the activity of any of these compounds. Chemicals not identified as mutagens were water, tert-butyl alcohol, pyridine, and witch hazel.

53. McGregor DB, Cruzan G, Callander RD, May K, Banton M. (2005) The mutagenicity testing of tertiary-butyl alcohol, tertiary-butyl acetate and methyl tertiary-butyl ether in Salmonella typhimurium. Mutat Res 565(2):181-189.
Tertiary-Butyl alcohol (TBA), tertiary-butyl acetate (TBAc) and methyl tertiary-butyl ether (MTBE) are chemicals to which the general public may be exposed either directly or as a result of their metabolism. There is little evidence that they are genotoxic; however, an earlier publication reported that significant results were obtained in Salmonella typhimurium TA102 mutagenicity tests with both TBA and MTBE. We now present results of testing these chemicals and TBAc against S. typhimurium strains in two laboratories. The emphasis was placed on testing with S. typhimurium TA102 and the use of both dimethyl sulphoxide and water as vehicles. Dose levels up to 5000 microg/plate were used and incubations were conducted in both the presence and absence of liver S9 prepared from male rats treated with either Arochlor 1254 or phenobarbital-beta-naphthoflavone. The experiments were replicated, but in none of them was a significant mutagenic response observed, thus the current evidence indicates the TBA, TBAc and MTBE are not mutagenic in bacteria.

54. Mennear JH. (1997) Carcinogenicity studies on MTBE: critical review and interpretation. Risk Anal 17(6):673-681.
Chronic inhalation of toxic concentrations of MTBE caused renal tubular cell neoplasms in male Fischer 344 rats and hepatocellular adenomas in female CD-1 mice. In Sprague-Dawley rats the oral administration of MTBE was associated with increased incidences of Leydig cell tumors and of lymphomas and leukemias (combined) in males and females, respectively. Neither lymphomas nor leukemias were individually increased in treated females. leydig cell tumors are common in rats and do not predict human responses to drugs and chemicals. Neither MTBE nor its metabolite, t-butyl alcohol, possess mutagenic potential and a second metabolite, formaldehyde, is mutagenic in vitro but in vivo results are equivocal. MTBE-induced neoplasms are most likely produced through a nongenetic mechanism which requires chronic exposure to toxic doses. Because of the intense odor (and taste) of MTBE, humans will not tolerate either air or water concentrations sufficient to produce the cytotoxic precursors required to promote cellular proliferation.

55. National_Library_of_Medicine. Hazardous Substances Data Bank (HSDB). TOXNET.
HSDB is peer-reviewed by the Scientific Review Panel (SRP), a committee of sixteen experts in major subject areas such as toxicology, chemistry, pharmacology, industrial hygiene, medicine, emergency response procedures, environmental science, hazardous waste handling, and regulatory requirements. The panel meets three or four times a year to conduct a comprehensive review of the scientific information in new and updated chemical records.

56. Nelson BK, Brightwell WS, Khan A, Shaw PB, Krieg EF, Jr., Massari VJ. (1989) Behavioral Teratology Investigation of Tertiary-Butanol Administered by Inhalation to Rats. Teratology 39(5):504.
A study was conducted of physical and behavioral fetal side effects following exposure of pregnant Sprague-Dawley-rats to tertiary- butanol (75650). Tertiary-butanol was administered by inhalation at concentration levels of 12,000 and 6,000mg/m3 to pregnant female rats throughout their gestation period. Exposures were also made to adult male rats subsequently mated to control females. The offspring were treated for neuromotor coordination, activity, and learning. Brains from ten offspring per exposure group were dissected and assayed for protein and the neurotransmitter acetylcholine, dopamine, norepinephrine, serotonin, met-enkephalin, B-endorphin, and substance-P. Maternal toxicity was apparent, but only limited behavioral or neurochemical effects were noted in the offspring on tests conducted through 90 days of age. The authors conclude that exposure to tertiary-butanol does not appear to produce remarkable behavioral or neurochemical deviations in offspring at the concentrations tested.

57. Nihlen A, Lof A, Johanson G. (1997) Liquid/air partition coefficients of methyl and ethyl T-butyl ethers, T-amyl methyl ether, and T-butyl alcohol. Journal of Clean Technology Environmental Toxicology and

Occupational Medicine 6(2):205-213.
BIOSIS COPYRIGHT: BIOL ABS. Partition coefficients are essential to a description of the uptake and distribution Of volatile substances in humans and in the development of physiologically based pharmacokinetic models. Liquid/air partition coefficients (lambda) of three ethers, methyl t-butyl ether (MTBE), ethyl t-butyl ether (ETBE), and t-amyl methyl ether (TAME) were determined in vitro by head space-gas chromatography. These ethers, and especially MTBE, are used in unleaded gasoline to enhance the oxygen and octane conte and to reduce the output of carbon monoxide during combustion. Partition coefficients of t-butyl alcohol (TBA), a metabolite of MTBE, were determined also. The liquids tested were fresh human blood, water (physiological saline), and olive oil. The deltablood/air values were: 17.7 (95% confidence interval 17.0-18.4) for MTBE; 11.7 (11.3-12.1) for ETBE; and 17.9 (17.3-18.6) for TAME. Corresponding lambdawater/air values were 15.2 (14.9-15.5), 8.39 (8.19-8.59), and 11.9 (11.7-12.1).

58. NIOSH. 1989. National Occupational Exposure Survey (NOES), 1981 - 1983: Estimated Numbers of Employees Potentially Exposed to Specific Agents by Occupation -- Tert-butyl alcohol.

59. NIOSH. 1992. Occupational Safety and Health Guidelines for Chemical Hazards (Publication No. 81-123): Tert-Butyl alcohol. 4676 Columbia Parkway, Cincinnati, OH: National Institute of Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention (CDC), Department of Health and Human Services (DHHS). 7 p.
Chemical safety information sheet taken from the newly revised edition of the NIOSH publication "Occupational Safety and Health Guidelines for Chemical Hazards".

60. NIOSH. 2005. NIOSH Pocket Guide to Chemical Hazards (2005-149) : tert-Butyl alcohol. National Institute for Occupational Safety and Health (NIOSH), Centers for Disease Control and Prevention, Department Of Health And Human Services.
Colorless solid or liquid (above 77°F) with a camphor-like odor. [Note: Often used in aqueous solutions.

61. OHS/MDL. 2007. Material Safety Data Sheet (MSDS) for Tert-Butyl Alcohol. MDL Information Systems, Inc.

62. Olajos EJ, Morgan EW, Renne RA, Salem H, McVeety B, Johnson R, Phelps RL. (1998) Acute inhalation toxicity of neutralized chemical agent identification sets (CAIS) containing agent in chloroform. J Appl Toxicol 18(5):363-371.
An acute head-only inhalation study was conducted in rats exposed for 1 h to product solution (wastestream) resultant from the chemical neutralization of Chemical Agent Identification Sets (CAIS) containing agent (sulfur mustard (HD), nitrogen mustard (HN-1) or lewisite (L)) in chloroform. Groups of Sprague-Dawley rats were exposed to varying concentrations (24000, 18000, 12000 or 6000 ppm) of CAIS wastestream. An additional group was exposed to the vehicle (chloroform/t-butanol) only, at a concentration equivalent to the concentration of vehicle at the highest exposure level. Animals were evaluated for toxic effects, including assessment of toxicant-induced alterations to the ocular and respiratory systems. Mortality on exposure to 24000 ppm of test article or to vehicle alone was high. Mortality in the other exposure groups was roughly proportional to the concentration of test article (wastestream). Toxic signs were consistent with exposure to solvent system components (chloroform/t-butanol) and to agent decomposition products/by-products. Incidence and severity of ocular effects were similar in vehicle control and treatment groups. The salient respiratory effect observed was a decreased minute volume, which was also noted in vehicle and treatment groups.

63. OSHA. 1996. Occupational Safety and Health Guideline for tert-butyl alcohol. Washington, DC: Occupational Safety and Health Administration, Department of Labor.
Disclaimer: The information contained in these guidelines is intended for reference purposes only. It provides a summary of information about chemicals that workers may be exposed to in their workplaces.

64. OSHA. 2007. tert-Butyl Alcohol.
NIOSH/OSHA Health Guideline. Summarizes pertinent information about for workers and employers as well as for physicians, industrial hygienists,and other occupational safety and health professionals who may need such information to conduct effective occupational safety and health programs.

65. Pellizzari ED HT, Harris BS 3rd, Waddell RD, Whitaker DA, Erickson MD. (1982) Purgeable organic compounds in mother's milk. Bull Environ Contam Toxicol 28(3):322-328.
HUMAN//EXP

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Toxicokinetics of Ethyl Tertiary-butyl Ether (ETBE) and Methyl Tertiary-butyl Ether (MTBE) in men and women. NIOSHTIC No. 20023640 Methyl tertiary butyl ether (MTBE) and ETBE are used as gasoline components to reduce tailpipe emissions in 39 areas of the United States which exceed the National Ambient Air Quality Standards for carbon monoxide and in the 9 metropolitan regions with the most elevated summertime ozone levels. MTBE and ETBE exposures occur during gasoline production and refueling, and as recently documented in California and Washington, potentially through contact with groundwater contaminated by leaking underground storage tanks. However, little is known about how the body handles MTBE, ETBE and their metabolites; nor about reliable biological indicators or occupational and environmental exposure. We conducted controlled exposures of men and women to 2.5 ppm 2H12-MTBE + 2.5 ppm ETBE for two hours with alternating periods of work and rest, and sampled blood, breath and urine during and for three days following exposure. Concurrently, a physiologically-based kinetic (KBK) model was developed to include data from other research efforts, to incorporate parameter variability through Bayesian fitting and Monte Carlo simulation techniques, and to determine a biological index of exposure Post-exposure blood and breath levels exhibited two half-lives for both 2H12-MTBE and ETBE of about 1 and 8.4 hours, and 1.5 and 10.6 hours, respectively. Tertiary-butyl-alcohol (TBA) breath concentration from each ether appeared to be a valuable index of exposure with a single half-life of 20-40 hours.

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Methyl t-butyl ether (MTBE) and ethyl t-butyl ether (ETBE) are commonly used in unleaded gasoline to increase the oxygen content of fuel and to reduce carbon monoxide emissions from motor vehicles. This study was undertaken to investigate: (1) the effect of administration to rats of ETBE and its metabolite, t-butanol, on the induction and/or inhibition of hepatic P450 isoenzymes; (2) the oxidative metabolism of MTBE and ETBE by liver microsomes from rats pretreated with selected P450 inducers and purified rat P450(s), (2B1, 2E1, 2C11, 1A1). ETBE administration by gavage at a dose of 2 ml/kg for 2 days induced hepatic microsomal P4502E1-linked p-nitrophenol hydroxylase and the P4502B1/2-associated PROD and 16beta-testosterone hydroxylase, verified by immunoblot experiments. t-Butanol treatments at doses of 200 and 400 mg/kg i.p. for 4 days did not alter any liver microsomal monoxygenases. Both MTBE and ETBE were substrates for rat liver microsomes and were oxidatively dealkylated to yield formaldehyde and acetaldehyde, respectively. The dealkylation rates of both MTBE and ETBE were increased c. fourfold in phenobarbital (PB)-treated rats. In rats pretreated with pyrazole, an inducer of 2E1, only the demethylation of MTBE was increased (c. twofold). When the oxidations of MTBE and ETBE were investigated with purified P450(s) in a reconstituted system, it was found that P4502B1 had the highest activities towards both solvents, whereas 1A1 and 2C1 were only slightly active; P4502E1 had an appreciable activity on MTBE but not against ETBE. Metyrapone, a potent inhibitor of P450 2B, consistently inhibited both the MTBE and ETBE dealkylations in microsomes from PB-treated rats. Furthermore, 4-methylpyrazole (a probe inhibitor of 2E1) and anti-P4502E1 IgG showed inhibition, though modest, only on MTBE

demethylation, but not on ETBE deethylation. Inhibition experiments have also suggested that rat 2A1 may exert an important role in MTBE and ETBE oxidation. Taken together, these results indicate that 2B1, when expressed, is the major enzyme involved in the oxidation of these two solvents and that 2E1 may have a role, although minor, in MTBE demethylation. The implications of these data for MTBE and ETBE toxicity remain to be established.

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Methyl-tert-butylether (MTBE) is an oxygenate widely used in the United States as a motor vehicle fuel additive to reduce emissions and as an octane booster [National Research Council, Toxicological and Performance Aspects of Oxygenated Motor Vehicle Fules, National Academy Press, Washington, DC, 1996]. But it is the potential for MTBE to enter drinking water supplies that has become an area of public concern. MTBE has been shown to induce liver and kidney tumors in rodents but the biochemical process leading to carcinogenesis is unknown. MTBE was previously shown to be non-mutagenic in the standard Ames plate incorporation test with tester strains that detect frame shift (TA98) and point mutations (TA100) and in a suspension assay using TA104, a strain that detects oxidative damage, suggesting a non-genotoxic mechanism accounts for its carcinogenic potential. These strains are deficient in excision repair due to deletion of the uvrB gene. We hypothesized that the carcinogenic activity of MTBE may be dependent upon a functional excision repair system that attempts to remove alkyl adducts and/or oxidative base damage caused by direct interaction of MTBE with DNA or by its metabolites, formaldehyde and tert-butyl alcohol (TBA), established carcinogens that are mutagenic in some Ames strains. To test our hypothesis, the genotoxicity of MTBE-induced DNA alterations was assayed using the standard Ames test with TA102, a strain similar to TA104 in the damage it detects but uvrB + and, therefore, excision repair proficient. The assay was performed (1) with and without Aroclor-induced rat S-9, (2) with and without the addition of formaldehyde dehydrogenase (FDH), and (3) with human S-9 homogenate. MTBE was weakly mutagenic when tested directly and moderately mutagenic with S-9 activation producing between 80 and 200 TA102 revertants/mg of compound. Mutagenicity was inhibited 25%-30% by FDH. TA102 revertants were also induced by TBA and by MTBE when human S-9 was substituted for rat S-9. We conclude that MTBE and its metabolites induce a mutagenic pathway involving oxidation of DNA bases and an intact repair system. These data are significant in view of the controversy surrounding public safety and the environmental release of MTBE and similar fuel additives.

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