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January 30, 1998

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**Chevron Research and
Technology Company**
100 Chevron Way
Richmond, California
P.O. Box 1627
Richmond, CA 94802-0627

Richard D. Cavalli
Manager
Toxicology and Health
Risk Assessment
242 7011
2 7022



89980000125

Document Processing Center
Attention: TSCA 8(e) Coordinator
Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street S. W.
Washington, DC 20460

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RE: Supplemental TSCA 8(e) Submission for Tertiary Amyl Methyl Ether (TAME)

Dear Sir or Madam:

This information is submitted as supplement to a previous TSCA 8(e) notification filed on behalf of Amerada Hess Corporation, Chevron Products Company, CITGO Petroleum, Exxon Company USA, Marathon Oil Company, Sun Refining and Marketing, and Texaco Refining and Marketing. This information is based on test results obtained under the Enforceable Consent Agreement (54 FR 14910 -- March 21, 1995) for TAME (CAS No. 994-05-8). The required studies are being coordinated by staff from the American Petroleum Institute.

On January 23, 1997, a TSCA 8(e) letter was submitted to EPA describing results from an ongoing 2-Generation Reproduction Study in Rats (copy of letter attached). This whole-body inhalation study was conducted at 3000, 1500, and 250 ppm TAME (OPPTS Guidelines 870.3800). A draft report on the full study is now available. It contains information pertinent to the previous submission regarding the reproductive toxicity of TAME in rats. Included in this supplemental submission are data on developmental landmarks (Tables 1,2,3), pup survival through weaning (Table 4), and adult male reproductive toxicity (Table 5).

As reported in the previous submission, the F1 females showed a dose-dependent delay in vaginal opening and the F1 males showed a dose-dependent delay in preputial separation. At that time, data had not been analyzed by Analysis of Covariance with body weight. Because of the delayed developmental landmarks in the F1 animals, the anogenital distance and body weight of the F2 pups of both sexes were measured at birth. Vaginal opening and preputial separation were

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also measured in the F2 animals. However in the F2 animals, exposure to TAME was not resumed at day 28 as it was with the F1 generation.

Anogenital distance was significantly shortened in both F2 male and females at 3000 ppm, accompanied by (and most likely due to) significantly reduced body weights in both F2 male and females on postnatal day zero (Table 1). When the developmental landmarks were analyzed by Analysis of Covariance with body weight (Tables 2 and 3) acquisition of preputial separation was significantly delayed in F1 males at 1500 and 3000 ppm and in F2 males at 3000 ppm. Acquisition of vaginal patency was significantly delayed at 3000 ppm for F1 females and at 250 and 3000 ppm (but not at 1500 ppm) for F2 females. We believe the effects on acquisition of reproductive landmarks in F1 and F2 offspring and on anogenital distance in F2 offspring were due to delayed prenatal and postnatal growth of the offspring. This in turn was due to the compromised status of the dams at these exposure concentrations during lactation.

While survival indices were unaffected for the F1 offspring, survival indices appear significantly reduced for the F2 pups (Table 4). There is no clear explanation for the increased mortality in the F2 pups. However, inhalation studies generally are more stressful to the pups and these F2 pups appeared to have more systemic toxicity based on greater body weight effects.

Also observed in this study were several statistically significant measurements of male reproductive toxicity in the high dose group (Table 5). The endpoints affected were relative testes weight, absolute prostate weight, epididymal sperm concentration, and percentage abnormal sperm. None of these effects were statistically significant in the mid-dose or low-dose males. The biological significance of the findings is unclear because there was no treatment effect on mating or fertility indices. Many other measures of male reproductive toxicity were not affected in either the F0 or F1 animals. Endpoints not affected included: absolute or relative weights of the epididymides or seminal vesicles with coagulating gland, percentage motile or progressively motile sperm, testicular homogenization-resistant spermatid head counts, and daily sperm production. There were also no treatment-related gross or histopathologic findings in the reproductive organs in the F0 or F1 males.

TAME and other aliphatic ethers are used as gasoline additives to meet the fuel oxygen requirements of the Clean Air Act Amendments of 1990. Typical occupational and consumer exposures to these gasoline additives are orders-of-magnitude less than the exposures used in this animal study. This margin of exposure makes the occurrence of adverse health effects from the use of TAME in gasoline extremely unlikely.

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A final report of this study will be forwarded to EPA under the conditions of the Enforceable Consent Agreement, Docket Number OPPTS-4205Q. If you have any questions about this submission, please contact Ms. CeCe Sharp at the American Petroleum Institute (202) 682-8333.

Sincerely,



Richard D. Cavalli
Manager, Toxicology & Health Risk Assessment

Enclosures: 6 (5 tables and one copy of old 8(e) letter)

cc. Mr. Gary Timm
Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street S. W.
Washington, DC 20460

Ms. CeCe Sharp
American Petroleum Institute
1220 L Street, NW
Washington, DC 20005



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January 23, 1997

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Non-Confidential Information**

**Chevron Research and
Technology Company**
1003 West Cutting Boulevard
Richmond, California
P.O. Box 4054
Richmond, CA 94804-0054

Richard D. Cavalli
Manager
Toxicology and Health
Risk Assessment
Phone 510 242 7011
Fax 510 242 7022

Document Processing Center
Attention: TSCA 8(e) Coordinator
Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street S. W.
Washington, DC 20460

TSCA 8(e) Submission for Tertiary Amyl Methyl Ether (TAME)

Dear Sir or Madam:

This notice is submitted pursuant to Section 8(e) of the Toxic Substances Control Act on behalf of Amerada Hess Corporation, Chevron Products Company, CITGO Petroleum, Exxon Company USA, Marathon Oil Company, Sun Refining and Marketing, and Texaco Refining and Marketing. This notice is based on test results obtained under the Enforceable Consent Agreement (54 FR 14910 - March 21, 1995) for Tertiary Amyl Methyl Ether (CAS No. 994-05-8). The required studies are being coordinated by staff from the American Petroleum Institute.

We are advising the EPA of results from an ongoing 2-Generation Reproduction Study in Rats conducted at 3000, 1500, and 250 ppm TAME (OPPTS Guidelines 870.3800). The F1 females were examined once a day beginning postnatal day 22 for vaginal patency until the event occurred. The F1 females showed a dose-dependent delay in vaginal opening that was statistically significant at all dose levels. The F1 males were examined once a day beginning postnatal day 35 for preputial separation until the event occurred. The F1 males showed a dose-dependent delay in preputial separation that was statistically significant at 1500 and 3000 ppm.

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The results are summarized in the Table below.

| | 0 PPM | 250 PPM | 1500 PPM | 3000 PPM |
|---|-----------------------------------|------------------------|------------------------|-------------------------|
| Mean Day of Vaginal Opening ¹ | 32.5 ± 0.4 $\Phi \zeta$ n = 30 | 32.7 ± 0.3 * n = 30 | 33.3 ± 0.3 * n = 30 | 36.0 ± 0.6 ** n = 29 |
| Median Day of Vaginal Opening | 32 | 33 | 33 | 35 |
| Mean Day of Preputial Separation ² | 43.6 ± 0.4 $\Phi \zeta$ n = 30 | 43.9 ± 0.4 n = 30 | 45.3 ± 0.5 * n = 30 | 47.8 ± 0.4 ** n = 29 |
| Median Day of Preputial Separation | 44 | 44 | 45 | 48 |

¹Because Bartlett's test was significant (p<0.001) nonparametric statistics were used in analysis of data from the F1 females.

²Parametric statistics were used in analysis of data from the F1 males.

Φ p < 0.001; Kruskal-Wallis Test or ANOVA

ζ p < 0.001; Jonckheere's Test or Test for Linear Trend

* p < 0.05; Mann Whitney U Test or Dunnett's Test

** p < 0.001; Mann Whitney U Test or Dunnett's Test

Considering previous Agency guidance for reporting of reproductive effects, we are notifying the EPA of these statistically significant findings. Because of the delayed developmental landmarks in the F1 animals, the study design will be modified to measure anogenital distance on the F2 pups of both sexes at birth.

There is no confirmed mechanism for causing the observed developmental delays in both sexes. However, the body weight of treated animals is being investigated as a possible confounder of these observations. A covariant analysis of body weight with day of event will be appended to the final report.

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Results of this study will be forwarded to EPA under the conditions of the Enforceable Consent Agreement, Docket Number OPPTS-4205Q. If you have any questions about this submission, please contact Dr. Richard Rhoden at the American Petroleum Institute (202) 682-8480.

Very truly yours,

A handwritten signature in black ink that reads "Richard D. Cavalli". The signature is written in a cursive style with a horizontal line at the end.

Richard D. Cavalli
Manager, Toxicology & Health Risk Assessment

cc. Mr. Gary Timm
Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street S. W.
Washington, DC 20460

Dr. Richard Rhoden
American Petroleum Institute
1220 L Street, NW
Washington, DC 20005

TABLE 1

Summary and Statistical Analysis of the F₂ Litter Size, Postnatal Day 0 Anogenital Distance and Pup Body Weights during Lactation

| | Tertiary Amyl Methyl Ether (ppm, inhaled) | | | |
|--|---|------------------------|------------------------|---------------------------|
| | 0 | 250 | 1500 | 3000 |
| Average Pup Anogenital Distance (mm) per Litter on Postnatal Day 0 ^k | | | | |
| | 1.52 ± 0.05 N=28 | 1.46 ± 0.04 N=24 | 1.44 ± 0.04 N=28 | 1.44 ± 0.05 N=27 |
| Average Male Anogenital Distance (mm) per Litter on Postnatal Day 0 ^k | | | | |
| | 2.25 ‡‡ ± 0.03 §§§ N=28 | 2.28 ± 0.03 N=24 | 2.23 ± 0.03 N=28 | 2.11 ° ± 0.04 N=27 |
| Average Female Anogenital Distance (mm) per Litter on Postnatal Day 0 ^k | | | | |
| | 0.73 ‡‡ ± 0.03 §§ N=28 | 0.70 ± 0.02 N=24 | 0.67 ± 0.02 N=28 | 0.63 °° ± 0.01 N=27 |
| Average Pup Body Weight (g) per Litter (pnd 0) ^k | | | | |
| | 6.29 ‡‡ ± 0.11 §§ N=28 | 6.36 ± 0.09 N=24 | 6.29 ± 0.12 N=28 | 5.84 ° ± 0.12 N=27 |
| Average Male Body Weight (g) per Litter (pnd 0) ^k | | | | |
| | 6.47 ‡‡ ± 0.11 §§ N=28 | 6.58 ± 0.10 N=24 | 6.45 ± 0.13 N=28 | 6.02 ° ± 0.12 N=27 |
| Average Female Body Weight (g) per Litter (pnd 0) ^k | | | | |
| | 6.08 ‡‡ ± 0.11 §§ N=28 | 6.18 ± 0.09 N=24 | 6.12 ± 0.12 N=28 | 5.64 ° ± 0.12 N=27 |

^kReported as the mean ± S.E.M.; pnd=postnatal day.

^lOne litter was inadvertently culled to 9 pups rather than 10 on postnatal day 4.

^mOne litter was inadvertently culled to 11 pups rather than 10 on postnatal day 4.

ⁿTwo litters had only female pups.

^oOne litter had only male pups.

^pOne litter had only female pups.

[#]Bartlett's test for homogeneity of variances was significant (p<0.001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed.

[‡]p<0.05; ANOVA Test.

^{‡‡}p<0.01; ANOVA Test.

^{‡‡‡}p<0.001; ANOVA Test.

[§]p<0.05; Test for Linear Trend.

^{§§}p<0.01; Test for Linear Trend.

^{§§§}p<0.001; Test for Linear Trend.

^{*}p<0.05; Dunnett's Test.

^{**}p<0.01; Dunnett's Test.

[‡]p<0.05; Jonckheere's Test.

Source: Table 3-48 "Two Generation Reproductive Toxicity Evaluation of Inhaled Tertiary Amyl Methyl Ether (TAME) Vapor in CD® (Sprague-Dawley) Rats" (CIIT Protocol 96020).

TABLE 2

Summary and Statistical Analysis of the F₁ Female Vaginal Opening and the F₁ Male Preputial Separation Data

| | Tertiary Amyl Methyl Ether (ppm, inhaled) | | | |
|--|---|-------------------|----------------------|----------------------------------|
| | 0 | 250 | 1500 | 3000 |
| Number of Females Evaluated | 30 | 30 | 30 | 29 |
| Average Day of Vaginal Opening ^a | | | | |
| # | 32.5 TTT XXX YYY | 32.7 □ | 33.3 □ | 36.0 □□ ++ |
| | ± 0.4 §§§ YYY | ± 0.3 | ± 0.3 | ± 0.6 |
| | N=30 | N=30 | N=30 | N=29 |
| Average Body Weight (g) ^{a,b} | | | | |
| | 99.52 | 100.04 | 97.27 | 91.97 |
| | ± 3.18 § | ± 2.46 | ± 3.53 | ± 2.63 |
| | N=30 | N=30 | N=30 | N=29 |
| Number of Males Evaluated | 30 | 30 | 30 | 29 |
| Average Day of Preputial Separation ^a | | | | |
| | 43.6 +++ XXX | 43.9 | 45.3 * ++ | 47.8 ** ++ |
| | ± 0.4 §§§ YYY | ± 0.4 | ± 0.5 | ± 0.4 |
| | N=30 | N=30 | N=30 | N=29 |
| Average Body Weight (g) ^{a,b} | | | | |
| | 210.72 +++ | 197.94 | 206.52 | 184.83 ** |
| | ± 3.95 §§§ | ± 4.57 | ± 4.30 | ± 3.70 |
| | N=30 | N=30 | N=30 | N=29 |

^aReported as the mean ± S.E.M. with average day being postnatal day.

^bAnimals were not weighed on the day they were positive, the body weight used was the body weight taken closest to the day the animal was positive.

#Bartlett's test for homogeneity of variances was significant (p<0.001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed.

~~TTT~~ p<0.001; Kruskal-Wallis Test.

~~XXX~~ p<0.001; Jonckheere's Test.

~~YYY~~ p<0.05; Mann-Whitney U Test.

~~□~~ p<0.01; Mann-Whitney U Test.

~~□□~~ p<0.001; Analysis of Covariance.

~~□□□~~ p<0.001; Linear Trend Analysis of Covariance.

~~++~~ p<0.01; Least Squares Means Test.

~~+++~~ p<0.001; ANOVA Test.

§ p<0.05; Test for Linear Trend.

§§§ p<0.001; Test for Linear Trend.

* p<0.05; Dunnett's Test.

** p<0.01; Dunnett's Test.

Source: Table 3-33 "Two Generation Reproductive Toxicity Evaluation of Inhaled Tertiary Amyl Methyl Ether (TAME) Vapor in CD® (Sprague-Dawley) Rats" (CIIT Protocol 96020).

TABLE 3

Summary and Statistical Analysis of the F₂ Female Vaginal Opening and the F₂ Male Preputial Separation Data

| | Tertiary Amyl Methyl Ether (ppm, inhaled) | | | |
|--|---|-----------------------|-------------------|------------------------|
| | 0 | 250 | 1500 | 3000 |
| Number of Females Evaluated | 30 | 30 | 30 | 30 |
| Average Day of Vaginal Opening ^a | | | | |
| # | 31.7 TTT XXX | 32.6 XXX * | 32.1 | 33.8 XXX ** |
| | ± 0.1 TTT XXX | ± 0.3 | ± 0.2 | ± 0.4 |
| | N=30 | N=30 | N=30 | N=30 |
| Average Body Weight on Day of Vaginal Opening(g) ^a | | | | |
| | 104.24 TTT XXX | 102.27 | 96.99 * | 88.43 ** |
| | ± 1.82 TTT XXX | ± 1.90 | ± 2.49 | ± 1.75 |
| | N=30 | N=30 | N=29 ^b | N=29 ^b |
| Number of Males Evaluated | 30 | 30 | 30 | 30 |
| Average Day of Preputial Separation ^a | | | | |
| # | 41.2 TTT XXX | 41.8 | 41.9 | 44.9 XXX ** |
| | ± 0.4 TTT XXX | ± 0.5 | ± 0.4 | ± 0.4 |
| | N=30 | N=30 | N=30 | N=30 |
| Average Body Weight on Day of Preputial Separation(g) ^a | | | | |
| | 201.98 | 195.22 | 197.55 | 191.67 |
| | ± 2.46 | ± 2.22 | ± 3.64 | ± 3.12 |
| | N=30 | N=30 | N=30 | N=30 |

^aReported as the mean ± S.E.M. with average day being postnatal day.

^bDecrease in N is due to one body weight inadvertently not being recorded.

#Bartlett's test for homogeneity of variances was significant (p<0.001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed.

~~TTT~~ p<0.001; Kruskal-Wallis Test.

~~XXX~~ p<0.001; Jonckheere's Test.

~~XXX~~ p<0.01; Mann-Whitney U Test.

~~XXX~~ p<0.001; Analysis of Covariance.

~~XXX~~ p<0.001; Linear Trend Analysis of Covariance.

* p<0.05; Least Squares Means Test.

** p<0.01; Least Squares Means Test.

~~TTT~~ p<0.001; ANOVA Test.

~~TTT~~ p<0.001; Test for Linear Trend.

* p<0.05; Dunnett's Test.

** p<0.01; Dunnett's Test.

Source: Table 3-63 "Two Generation Reproductive Toxicity Evaluation of Inhaled Tertiary Amyl Methyl Ether (TAME) Vapor in CD₁ (Sprague-Dawley) Rats" (CIIT Protocol 96020).

TABLE 4

Summary of the F₁ Pup and F₂ Pup Survival through Weaning

| | TAME (ppm) | | | |
|---------------------------------|-------------------|------------|-------------|-------------|
| | 0 | 250 | 1500 | 3000 |
| F₁ pup deaths | 14 | 11 | 18 | 23 |
| F₂ pup deaths | 43 | 42 | 99 | 186 |

Table 4 Source:

F₁ Pups, Table 3-18 "Two Generation Reproductive Toxicity Evaluation of Inhaled Tertiary Amyl Methyl Ether (TAME) Vapor in CD® (Sprague-Dawley) Rats" (CIIT Protocol 96020).

F₂ Pups, Table 3-49 "Two Generation Reproductive Toxicity Evaluation of Inhaled Tertiary Amyl Methyl Ether (TAME) Vapor in CD® (Sprague-Dawley) Rats" (CIIT Protocol 96020).

TABLE 5

Summary of the F₀ and F₁ Male Reproductive Effects at 3000 ppm Exposure

| | F ₀ | | F ₁ | |
|--|--|---------------------------------------|--|-------------------------------|
| TAME Concentration ppm | 0 | 3000 | 0 | 3000 |
| Relative Testes Weight (% sacrifice weight) ^a | 0.6376 ††† ± 0.0138 §§§ N=28 | 0.7028 ** ± 0.0152 N=30 | 0.6541 ††† ± 0.0142 §§§ N=29 | 0.7510 ** ± 0.0136 N=29 |
| Absolute Prostate Weight (g) ^a | 1.1101 ± 0.1111 N=28 | 0.8893 ± 0.0370 N=30 | 1.1464 † ± 0.0435 §§§ N=29 | 0.9300 ** ± 0.0412 N=29 |
| Epididymal Sperm Concentration (10 ⁶ /g) ^a | 1039.95 ± 24.53 § N=28 | 964.60 ± 25.42 N=30 | 1046.09 † ± 36.54 §§ N=28 ^d | 918.25 * ± 31.03 N=29 |
| Percent Abnormal Sperm ^a | 2.26 ††† ± 0.21 ††† N=28 | 5.49 ‡‡‡ ± 2.14 N=30 | 2.5 ± 0.2 ††† N=29 | 3.5 ± 0.4 N=29 |

^aReported as the mean ± S.E.M.

^bDecrease in N is due to one spleen weight inadvertently not being recorded.

^cDecrease in N is due to one epididymis inadvertently being placed in formalin prior to a sample being taken for motility analysis.

^dDecrease in N is due to one sample being spilled prior to analysis.

[#]Bartlett's test for homogeneity of variances was significant (p<0.001) or could not be done because there was zero variance in one or more groups, therefore nonparametric statistical procedures were employed.

†p<0.05; ANOVA Test.

††p<0.01; ANOVA Test.

†††p<0.001; ANOVA Test.

§p<0.05; Test for Linear Trend.

§§p<0.01; Test for Linear Trend.

§§§p<0.001; Test for Linear Trend.

*p<0.05; Dunnett's Test.

**p<0.01; Dunnett's Test.

†p<0.05; Kruskal-Wallis Test.

†††p<0.001; Kruskal-Wallis Test.

††p<0.01; Jonckheere's Test.

†††p<0.001; Jonckheere's Test.

‡p<0.05; Mann-Whitney U Test.

‡‡p<0.01; Mann-Whitney U Test.

Sources: Tables 3-28, 3-59 "Two Generation Reproductive Toxicity Evaluation of Inhaled Tertiary Amyl Methyl Ether (TAME) Vapor in CD® (Sprague-Dawley) Rats" (CIIT Protocol 96020).

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