Ethylene Glycol Monomethyl Ether and Propylene Glycol Monomethyl Ether: Metabolism, Disposition, and Subchronic Inhalation Toxicity Studies

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Short-term and subchronic vapor inhalation studies have shown that there are pronounced differences in the toxicological properties of ethylene glycol monomethyl ether (EGME) and propylene glycol monomethyl ether (PGME). Overexposure to EGME has resulted in adverse effects on testes, bone marrow and lymphoid tissues in laboratory animals. PGME does not affect these tissues, and instead, overexposure to PGME has been associated with increases in liver weight and central nervous system depression.

EGME is primarily oxidized to methoxyacetic acid in male rats, while PGME apparently undergoes O-demethylation to form propylene glycol. Since methoxyacetic acid has been shown to have the same spectrum of toxicity as EGME in male rats, the observed differences in the toxicological properties of EGME and PGME are thought to be due to the fact that the two materials are biotransformed via different routes to different types of metabolites.

Introduction

Ethylene glycol monomethyl ether (EGME, 2-methoxyethanol) is a primary alcohol while propylene glycol monomethyl ether (PGME, 1-methoxy-2-propanol) is a secondary alcohol. Despite the similarities in chemical structure and physical properties (Table 1), recent vapor inhalation studies discussed herein have shown remarkable differences in the toxicological properties of EGME and PGME (1-3). Moreover, the observed differences in toxicity are apparently the result of biotransformation of EGME and PGME via different routes to different types of metabolites (4).

| Table 1. Chemical structures and physical properties of EGME and PGME. |
|-----------------------------|-----------------------------|
| EGME                      | PGME                      |
| CH₃O-CH₂-CH₂-OH            | CH₃O-CH₂-CH(CH₃)-OH        |
| 2-methoxyethanol           | 1-methoxy-2-propanol       |
| Molecular weight           | 76.1                       | 90.1 |
| Boiling point, °C          | 124.6                      | 120.1|
| Specific gravity           | 0.963                      | 0.919|
| Vapor pressure, mm Hg at 25°C | 9.5                       | 12.5 |

EGME and PGME Subchronic Vapor Inhalation Studies

The subchronic vapor inhalation studies were conducted using male and female rats and rabbits. Sprague-Dawley rats and New Zealand White rabbits were used in the EGME study, while Fischer 344 rats and New Zealand White rabbits were used in the PGME study. The animals were exposed 6 hr/day, 5 days/week, for a total of 13 weeks. The exposure concentrations for the EGME study were 0, 30, 100 and 300 ppm; the PGME exposure concentrations (0, 300, 1000 and 3000 ppm) were 10-fold higher than for EGME. The criteria of response included daily observations for signs of toxicity, weekly body weight measurements, hematology analyses, clinical chemistry analyses, urinalyses (rats), and organ weights, as well as gross and histopathologic examinations.

Two male and two female rabbits exposed to 300 ppm EGME, and two female rabbits exposed to 100 ppm EGME died or were sacrificed moribund during the course of the study. One of the two rabbits in the 100 ppm group was sacrificed moribund with an inner ear infection unrelated to exposure. Otherwise, the relationship of the deaths to EGME exposure was uncertain.

Hematologic analyses revealed decreases in hemoglobin concentration, packed cell volume, white blood cell counts, and platelet counts, as well as a tendency

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toward decreased red blood cell counts in both male and female rats exposed to 300 ppm EGME (Table 2). There were no significant hematologic changes in either male or female rats in the 100 ppm or 30 ppm groups.

Male and female rabbits exposed to 300 ppm EGME had the same sort of hematologic changes as occurred in rats, including significant decreases in red blood cell counts (Table 3). There were no hematologic effects in rabbits in the 100 or 30 ppm groups.

Body weights of male and female rats in the 300 ppm group, as well as female rats in the 100 ppm group, were significantly lower than for controls as a result of exposure to EGME (Table 4). Relative thymus weights of male and female rats, and relative testes weights of males in the 300 ppm group were significantly lower than for controls. Relative liver weights of rats were not appreciably altered by exposure to concentrations of EGME as high as 300 ppm.

Relative thymus and testes weights of rabbits exposed to 300 ppm EGME were significantly lower than for controls (Table 5), as also occurred for rats. Relative testes weights of rabbits in the 100 ppm group also tended to be lower than for controls on the average. Body weights and relative liver weights of rabbits were not statistically significantly altered by the EGME exposures, although the body weights of rabbits in the 300 ppm group tended on the average to be lower than controls.

Histopathologic observations for rats in the 300 ppm EGME group included: bilateral, severe to moderate degeneration of the testicular germinal epithelium; reduced numbers of spermatogonia; increased degenerating spermatogonia; slight reduction in prostatic secretory material; and decreased thymic cortical lymphocytes. There were no treatment-related histopathologic observations in rats exposed to 100 ppm or 30 ppm EGME.

### Table 2. Hematologic analyses for rats exposed to EGME.

| Sex | EGME, ppm | RBC | Hgb | PCV | WBC | Platlets |
|-----|-----------|-----|-----|-----|-----|----------|
| Male | 0         | 8.69 ± 0.68 | 17.3 ± 1.0 | 52.1 ± 2.8 | 13.7 ± 5.0 | 1381 ± 140 |
|     | 30        | 8.70 ± 0.52 | 16.4 ± 0.6 | 49.4 ± 2.3 | 10.5 ± 2.4 | 1316 ± 179 |
|     | 100       | 8.83 ± 0.20 | 16.8 ± 0.5 | 50.9 ± 1.8 | 11.8 ± 2.5 | 1338 ± 127 |
|     | 300       | 8.48 ± 0.52 | 15.5 ± 1.2 | 46.5 ± 3.6 | 8.6 ± 2.8* | 953 ± 120 |
| Female | 0      | 7.86 ± 0.38 | 16.1 ± 0.6 | 48.8 ± 1.9 | 9.6 ± 2.8 | 1317 ± 156 |
|       | 30       | 8.12 ± 0.50 | 16.3 ± 0.6 | 49.9 ± 2.0 | 8.3 ± 1.9 | 1402 ± 132 |
|       | 100      | 8.14 ± 0.15 | 16.2 ± 0.4 | 49.0 ± 1.3 | 9.0 ± 2.4 | 1345 ± 125 |
|       | 300      | 7.66 ± 0.38 | 14.7 ± 0.6 | 44.6 ± 1.9* | 4.5 ± 1.8* | 1166 ± 148* |

*Statistically significant deviation from control group mean using Dunnett's test.

### Table 3. Hematologic analyses for rabbits exposed to EGME.

| Sex | EGME, ppm | RBC | Hgb | PCV | WBC | Platlets |
|-----|-----------|-----|-----|-----|-----|----------|
| Male | 0         | 5.98 ± 0.37 | 14.6 ± 0.9 | 42.8 ± 2.7 | 8.5 ± 1.6 | 759 ± 153 |
|     | 30        | 5.89 ± 0.24 | 14.3 ± 0.6 | 41.9 ± 1.5 | 9.9 ± 1.3 | 732 ± 103 |
|     | 100       | 5.48 ± 0.24 | 13.4 ± 0.5 | 39.0 ± 1.7 | 8.7 ± 1.5 | 702 ± 88 |
|     | 300       | 4.02 ± 0.73* | 9.6 ± 1.6* | 28.1 ± 5.0* | 4.1 ± 0.9* | 469 ± 187* |
| Female | 0       | 5.39 ± 0.49 | 12.7 ± 1.6 | 37.8 ± 2.4 | 7.7 ± 2.7 | 787 ± 103 |
|       | 30       | 5.60 ± 0.25 | 12.8 ± 0.3 | 38.5 ± 1.5 | 6.8 ± 1.1 | 883 ± 255 |
|       | 100      | 4.86 ± 0.52 | 11.5 ± 0.9 | 34.3 ± 2.9 | 8.3 ± 2.6 | 924 ± 409 |
|       | 300      | 3.54 ± 0.31* | 8.5 ± 0.8* | 25.0 ± 2.2* | 3.5 ± 1.2* | 687 ± 236 |

*Statistically significant deviation from control group mean using Dunnett's test.

### Table 4. Terminal body weights and organ weights of rats exposed to EGME.

| Sex | EGME, ppm | Body wt, g | Liver, g/100 | Thymus, g/100 | Testes, g/100 |
|-----|-----------|------------|--------------|---------------|---------------|
| Male | 0         | 487 ± 53   | 2.47 ± 0.23  | 0.07 ± 0.01   | 0.71 ± 0.13   |
|     | 30        | 465 ± 53   | 2.48 ± 0.13  | 0.08 ± 0.02   | 0.62 ± 0.17   |
|     | 100       | 501 ± 30   | 2.36 ± 0.17  | 0.07 ± 0.01   | 0.71 ± 0.05   |
|     | 300       | 432 ± 31*  | 2.31 ± 0.08  | 0.04 ± 0.01*  | 0.33 ± 0.08*  |
| Female | 0       | 277 ± 23   | 2.61 ± 0.10  | 0.14 ± 0.03   |               |
|       | 30       | 264 ± 28   | 2.68 ± 0.11  | 0.13 ± 0.02   |               |
|       | 100      | 247 ± 21   | 2.62 ± 0.17  | 0.13 ± 0.03   |               |
|       | 300      | 229 ± 20*  | 2.68 ± 0.23  | 0.06 ± 0.01*  |               |

*Statistically significant deviation from control group mean using Dunnett's test.
TOXICITY AND METABOLISM OF EGME AND PGME

There was bilateral, severe degeneration of testicular germinal epithelium, as well as lymphoid tissue atrophy and decreased liver glycogen in rabbits in the 300 ppm group. Similar but less severe testicular changes were found in three of five rabbits exposed to 100 ppm EGME, and slight degenerative changes were found in one of five rabbits in the 30 ppm group. A follow-up study (Chemical Manufacturers Association, unpublished data) with larger numbers of animals resulted in no testicular effects in rabbits exposed to 3, 10 or 30 ppm EGME vapors for 13 weeks. Hence, 30 ppm is a virtual no-adverse-effect level for testicular effects in rabbits.

Although histopathologic effects on the bone marrow were not apparent in rats or rabbits exposed to EGME for 13-weeks, a marked decrease in bone marrow cellularity was found in animals exposed to 1000 ppm for 2 weeks (Table 5). Hence, the observed hematologic changes were presumably the result of a primary effect on bone marrow.

### Table 5. Terminal body weights and organ weights of rabbits exposed to EGME.

| Sex | EGME, ppm | Body wt, g | Liver, g/100 | Thymus, g/100 | Testes, g/100 |
|-----|-----------|------------|--------------|---------------|--------------|
| Male | 0         | 4193 ± 528 | 2.38 ± 0.30  | 0.16 ± 0.03   | 0.14 ± 0.03  |
|     | 30        | 4255 ± 288 | 2.44 ± 0.47  | 0.16 ± 0.02   | 0.13 ± 0.04  |
|     | 100       | 4036 ± 539 | 2.25 ± 0.35  | 0.14 ± 0.02   | 0.10 ± 0.03  |
|     | 300       | 3745 ± 369 | 2.57 ± 0.30  | 0.09 ± 0.03   | 0.04 ± 0.01  |
| Female | 0       | 4511 ± 676 | 2.32 ± 0.33  | 0.18 ± 0.06   |              |
|       | 30        | 4798 ± 455 | 2.57 ± 0.15  | 0.17 ± 0.04   |              |
|       | 100       | 3910 ± 410 | 2.20 ± 0.58  | 0.16 ± 0.01   |              |
|       | 300       | 3945 ± 218 | 2.45 ± 0.77  | 0.09 ± 0.01   |              |

*Statistically significant deviation from control group mean using Dunnett's test.

### Table 6. Hematology analyses for rats exposed to PGME.

| Sex | PGME, ppm | RBC | Hgb | PCV | WBC | Platlets |
|-----|-----------|-----|-----|-----|-----|----------|
| Male | 0         | 8.51 ± 0.32 | 16.7 ± 0.7 | 45.9 ± 1.6 | 7.7 ± 0.6 | 892 ± 42 |
|     | 300       | 8.37 ± 0.31 | 16.7 ± 0.6 | 45.2 ± 2.0 | 7.5 ± 0.8 | 866 ± 62 |
|     | 1000      | 8.37 ± 0.19 | 16.4 ± 0.4 | 44.9 ± 1.1 | 7.2 ± 1.1 | 845 ± 77 |
|     | 3000      | 8.43 ± 0.33 | 16.3 ± 0.6 | 45.2 ± 1.6 | 7.5 ± 0.5 | 937 ± 51 |
| Female | 0       | 7.75 ± 0.19 | 16.1 ± 0.3 | 44.8 ± 1.0 | 6.3 ± 0.6 | 913 ± 71 |
|       | 300       | 7.63 ± 0.28 | 15.9 ± 0.6 | 44.1 ± 1.5 | 7.4 ± 1.3 | 930 ± 76 |
|       | 1000      | 7.72 ± 0.13 | 16.0 ± 0.3 | 44.4 ± 0.7 | 6.6 ± 0.9 | 965 ± 28 |
|       | 3000      | 7.93 ± 0.17 | 15.9 ± 0.4 | 44.5 ± 1.2 | 5.1 ± 0.5 | 975 ± 42 |

*Statistically significant deviation from control group mean using Dunnett's test.

### Table 7. Hematology analyses for rabbits exposed to PGME.

| Sex | PGME, ppm | RBC | Hgb | PCV | WBC | Platlets |
|-----|-----------|-----|-----|-----|-----|----------|
| Male | 0         | 6.62 ± 0.35 | 14.1 ± 0.9 | 45.9 ± 3.1 | 8.5 ± 1.2 | 359 ± 33 |
|     | 300       | 6.54 ± 0.34 | 14.1 ± 0.8 | 46.5 ± 2.5 | 9.6 ± 1.8 | 400 ± 76 |
|     | 1000      | 6.00 ± 0.58 | 13.8 ± 1.0 | 45.0 ± 3.3 | 8.2 ± 1.3 | 415 ± 52 |
|     | 3000      | 6.48 ± 0.23 | 14.4 ± 0.5 | 47.8 ± 1.5 | 8.2 ± 1.7 | 412 ± 61 |
| Female | 0       | 5.96 ± 0.37 | 13.4 ± 0.6 | 43.9 ± 2.0 | 8.1 ± 1.7 | 299 ± 94 |
|       | 300       | 6.29 ± 0.30 | 14.0 ± 0.4 | 46.2 ± 1.6 | 8.0 ± 1.8 | 345 ± 63 |
|       | 1000      | 5.56 ± 0.34 | 12.9 ± 0.6 | 42.0 ± 2.2 | 7.9 ± 2.2 | 355 ± 68 |
|       | 3000      | 5.79 ± 0.28 | 13.4 ± 0.5 | 43.1 ± 1.5 | 7.6 ± 2.7 | 279 ± 79 |

### PGME Subchronic Vapor Inhalation Study

There were no mortalities of rats prior to scheduled sacrifice. One male rabbit in the 3000 ppm group was sacrificed after 9 weeks of study after being accidentally injured while weighing.

Rats and rabbits in the 3000 ppm group appeared to be sedated, particularly during the first few days of exposure. Rats were hypothermic following the first few exposures; these sedative effects were no longer apparent after approximately the first 2 weeks of exposure.

There were no treatment-related hematologic changes in male or female rats (Table 6). White cell counts of female rats in the 300 ppm group were higher than controls, while white cell counts of females in the 3000 ppm group were lower than controls. These apparent differences in white cell counts were thought to be sporadic occurrences unrelated to exposure in view of the absence of a dose-response relationship.
Table 8. Terminal body weight and organ weights of rats exposed to PGME.

| Sex  | PGME, ppm | Body wt, g | Liver, g/100 | Thymus, g/100 | Testes, g/100 |
|------|------------|------------|--------------|---------------|---------------|
| Male | 0          | 301 ± 13   | 2.54 ± 0.11  | 0.08 ± 0.01   | 1.03 ± 0.04   |
|     | 300        | 295 ± 8    | 2.48 ± 0.08  | 0.08 ± 0.02   | 1.04 ± 0.05   |
|     | 1000       | 296 ± 14   | 2.50 ± 0.08  | 0.09 ± 0.01   | 1.05 ± 0.09   |
|     | 3000       | 295 ± 12   | 2.70 ± 0.20  | 0.07 ± 0.01   | 1.06 ± 0.05   |
| Female | 0         | 165 ± 10   | 2.45 ± 0.15  | 0.13 ± 0.03   |               |
|       | 300        | 169 ± 9    | 2.48 ± 0.17  | 0.14 ± 0.03   |               |
|       | 1000       | 169 ± 8    | 2.53 ± 0.09  | 0.13 ± 0.02   |               |
|       | 3000       | 167 ± 5    | 2.65 ± 0.07  | 0.12 ± 0.01   |               |

*Statistically significant deviation from control group mean using Dunnett’s test.

Table 9. Terminal body weight and organ weights of rabbits exposed to PGME.

| Sex  | PGME, ppm | Body wt, g | Liver, g/100 | Testes, g/100 |
|------|------------|------------|--------------|---------------|
| Male | 0          | 4180 ± 609 | 2.50 ± 0.43  | 0.13 ± 0.02   |
|     | 300        | 4088 ± 451 | 2.18 ± 0.53  | 0.16 ± 0.03   |
|     | 1000       | 4252 ± 483 | 2.70 ± 0.61  | 0.15 ± 0.03   |
|     | 3000       | 3913 ± 161 | 2.64 ± 0.48  | 0.14 ± 0.02   |
| Female | 0        | 4678 ± 375 | 2.50 ± 0.34  |               |
|       | 300        | 4606 ± 316 | 2.60 ± 0.30  |               |
|       | 1000       | 4674 ± 322 | 2.54 ± 0.57  |               |
|       | 3000       | 4612 ± 626 | 2.62 ± 0.34  |               |

There were no hematologic changes in male or female rabbits exposed to 300, 1000 or 3000 ppm PGME vapors (Table 7).

In sharp contrast to EGME, terminal body weights, thymus weights and testes weights of rats were not altered by exposure to PGME (Table 8). Liver weights of rats in the 3000 ppm group were higher than controls. However, there were no associated gross pathologic changes or degenerative histopathologic changes in livers of these animals.

Likewise, the terminal body weights, liver weights and testes weights of rabbits were not altered by exposure to PGME concentrations as high as 3000 ppm (Table 9). Thymus weights of rabbits in the PGME study were not measured.

Histopathologic examinations revealed indications of hepatocellular swelling, but no degenerative changes, in livers of female rats in the 3000 ppm group. Otherwise, there were no gross or histopathologic changes in either male or female rats or rabbits exposed to 300, 1000 or 3000 ppm PGME.

Comparative Metabolism of EGME and PGME

Male Fischer 344 rats, approximately 200 to 225 g, were used for the metabolism studies. Three rats were used per dose; each animal was given a single dose of radiolabeled EGME or PGME by gavage. 14C-labeled as well as 13C-labeled EGME and PGME were utilized. EGME was labeled on either the 1 or 2 carbon; PGME was labeled on the 1 carbon.

The animals were given a dose of approximately 1 mmole/kg or 8.7 mmole/kg of EGME or PGME. For the mass balance studies, each rat was given approximately 10 μCi of 14C-labeled EGME or PGME. Additional groups of rats were given the high dose and approximately 100 μCi as well as 13C-labeled EGME or PGME in order to facilitate isolation and identification of urine metabolites.

Immediately after dosing, each animal was placed in a Roth-type metabolism cage for collection and analysis of expired air and excreta. Urine was collected at daily intervals at 12 hr intervals after dosing. Air from the metabolism cages was passed through charcoal and CO₂ traps; the charcoal traps were changed at 12-hr intervals. The CO₂ traps were changed at 4 hr intervals for 12 hr and thereafter at 12-hr intervals. Feces were collected at 24 hr intervals after dosing.

14C in urine, on charcoal and as 14CO₂ in expired air was quantitated by liquid scintillation spectrometry. 14C in feces, tissues, and carcass were quantitated by liquid scintillation spectrometry following combustion of samples with a biological material oxidizer. Urine samples were fractionated via an ion exclusion chromatography system using AMINEX 50W × 4 (20–30 μm) cation exchange resin (BIO-RAD Laboratories, Richmond, CA). Radioactivity in successive 0.5-mL fractions from the chromatography system were quantitated by either liquid scintillation spectrometry or by use of an in-line radioactivity detector. After fractionation of urine samples, metabolites in urine were identified by chemical ionization gas chromatography–mass spectrometry utilizing a radio-gas detector.

After giving the low dose of [14C] EGME, 54.3% of the 14C was recovered in urine within 48 hr (Table 10). About 12% of the administered radioactivity was eliminated as 14CO₂ in expired air. Only 2.7% of the 14C was excreted in feces, and recovery of 14C from charcoal traps was minimal. Approximately 18% remained in the carcass when animals were sacrificed 48 hr after dosing.

Elimination of the high dose (3.7 mmole/kg) of EGME was essentially the same as for the low dose (Table 10). Urine was the major route of elimination of 14C; 63.2% was excreted in urine within 48 hr after dosing. Again about 12% was eliminated as 14CO₂. Recovery from charcoal was minimal, and only 2.6% was excreted in feces; 12.6% remained in carcass after 48 hr.

In contrast, elimination of 14C from animals given 1 mmole/kg [14C] PGME, on the other hand, was
Table 10. Percent recovery during a 48-hr period after dosing.

| Recovery, %* | EGME 1 mmol/kg | 8.7 mmol/kg | PGME 1 mmol/kg | 8.7 mmol/kg |
|--------------|----------------|-------------|----------------|-------------|
| Urine        | 54.3 ± 5.0     | 63.2 ± 3.9  | 11.2 ± 0.5     | 24.8 ± 2.0  |
| Feces        | 2.7 ± 1.1      | 2.6 ± 0.9   | 0.9 ± 0.1      | 0.7 ± 0.2   |
| Charcoal     | 0.4 ± 0.1      | 0.3 ± 0.9   | 3.0 ± 0.2      | 6.9 ± 0.5   |
| CO₂          | 11.8 ± 2.6     | 11.9 ± 2.0  | 63.0 ± 1.0     | 56.5 ± 2.6  |
| Carcass      | 18.3 ± 3.0     | 12.6 ± 1.1  | 9.2 ± 0.8      | 6.3 ± 0.7   |
| Skin         | 3.5 ± 0.4      | 3.6 ± 0.2   | 1.7 ± 0.1      | 1.7 ± 0.6   |
| Wash         | 3.8 ± 0.3      | 1.2 ± 0.3   | 2.8 ± 0.1      | 0.6 ± 0.2   |
| Total        | 94.8 ± 6.7     | 95.4 ± 0.7  | 91.8 ± 2.0     | 98.4 ± 1.3  |

*Numbers are mean ± SD values for n = 3 animals.

Table 11. Distribution of radioactivity 48 hr after giving ¹⁴C-EGME.

| Tissue/blood | % of dose |
|--------------|-----------|
| Body         | 0.19      | 9.60 ± 0.8 |
| Liver        | 0.66      | 1.57 ± 0.3 |
| Kidney       | 0.35      | 0.20 ± 0.0 |
| Blood        | 1.00      | 0.67 ± 0.2 |
| Testes       | 0.19      | 0.13 ± 0.0 |
| Fat          | 0.05      |           |
| Thymus       | 0.30      | 0.02 ± 0.0 |
| Spleen       | 0.29      | 0.03 ± 0.0 |

Table 12. Distribution of radioactivity 48 hr after giving ¹⁴C-PGME.

| Tissue/blood | % of dose |
|--------------|-----------|
| Body         | 0.36      | 3.91 ± 0.13 |
| Liver        | 2.33      | 1.40 ± 0.02 |
| Kidney       | 1.11      | 0.14 ± 0.06 |
| Blood        | 1.00      | 0.10 ± 0.02 |
| Testes       | 0.34      | 0.08 ± 0.06 |
| Fat          | 0.09      |           |
| Thymus       | 1.19      | 0.02 ± 0.0 |
| Spleen       | 1.12      | 0.03 ± 0.0 |

primarily via ¹⁴CO₂ (Table 10). A total of 63% of the dose was eliminated as ¹⁴CO₂ within 48 hr after dosing; 33% of the dose was eliminated during the first 4 hr and another 24% during the 4 to 8 hr interval. Hence, the low dose of PGME was very rapidly and extensively metabolized. Excretion of ¹⁴C in urine of animals given the low dose of PGME amounted to only 11.2% of the dose. Excretion in feces was minimal, and only about 3% was recovered from charcoal traps; 9.2% remained in the carcass after 48 hr.

For the high dose of PGME, 56.5% of the administered dose was eliminated as ¹⁴CO₂ in 48 hr (Table 10). In urine, 24.8% of the administered ¹⁴C was excreted in 48 hr. Excretion in feces was minimal, but almost 7% of the high dose was recovered from charcoal. Only about 6% of the high dose of PGME remained in the carcass after 48 hr. The percentage in urine was twice as great, and the total percentage eliminated as ¹⁴CO₂ was slightly less after giving the high dose than after giving the low dose. Also, the percentage remaining in carcass was slightly less after giving the high dose than after giving the low dose.

Of the radioactivity remaining in the various tissues 48 hr after giving 8.7 mmole/kg of [¹⁴C] EGME, the blood had the greatest quantity per gram of tissue (Table 11). The conspicuous target organs of EGME, e.g., testes, thymus and spleen had lesser amounts of ¹⁴C than did the blood, and thus exhibited no apparent tendency to accumulate the labeled test material or its metabolites.

The liver had the greatest amount of ¹⁴C per gram of tissue 48 hr after giving the high dose of PGME (Table 12). This observation is consistent with the fact that absolute and relative liver weights are elevated in male rats exposed to high concentrations of PGME. However, in view of the fact that the liver weight increases have not been associated with gross or histopathologic treatment-related changes, the significance of the high concentration of ¹⁴C in the liver is unknown.

Fractionation of urine collected during the first 12 hr after giving 8.7 mmole/kg [¹⁴C] EGME revealed only two distinct peaks of radioactivity (Fig. 1). Peak B, the

![Image of radioactivity per ion exclusion chromatography fractions](image-url)
FIGURE 2. Radioactivity per ion exclusion chromatography fractions for urine from male rats given an oral dose of [14C] PGME. Peak A represented 22%, Peak B 46%, Peak C 20%, and Peak D 12% of the radioactivity in urine.

The largest of the two peaks, accounted for approximately 95% of the [14C] in the urine. This peak was identified by GC-MS as methoxyacetic acid. Since 50 to 60% of the administered [14C] is eliminated in urine, oxidation of EGME to methoxyacetic acid represents the major route of biotransformation of EGME. Peak A, a minor peak accounting for less than 5% of the activity in urine, has not been conclusively identified.

Fractionation of urine collected during the first 12 hr after giving the high dose of PGME revealed four distinct peaks of radioactivity (Fig. 2). Peak A had about 22% of the [14C] in urine, and was identified by FAB mass spectrometry as a sulfate conjugate of PGME. The largest of the peaks, Peak B, accounted for 46% of the [14C] in the urine and was identified as a glucuronide conjugate of PGME. Peak C had 19 to 20% of the [14C] and was identified by GC–MS as 1,2-propanediol (propylene glycol). However, the amount in urine is probably only a small portion of the propylene glycol actually formed in vivo from PGME, since propylene glycol itself is known to be rapidly and extensively metabolized, with only a small percentage being excreted unchanged in urine (5). In fact, propylene glycol is probably one of the intermediates for the large fraction of the dose of PGME which is ultimately eliminated as [14C] CO2. Peak D was identified by GC–MS as the parent compound (PGME), and represented 12% of the radioactivity in urine.

Hence, the types of urine metabolites for EGME and PGME indicate that the two chemicals are biotransformed via totally different routes (Fig. 3). EGME is primarily oxidized to methoxyacetic acid, presumably via the alcohol dehydrogenase pathway. About 50 to 60% of the dose of EGME is excreted in urine as methoxyacetic acid. Approximately 10 to 20% of a dose of EGME is much more extensively metabolized and excreted as [14C] CO2 in the expired air.

PGME, on the other hand, is not a substrate for alcohol dehydrogenase and instead apparently undergoes O-demethylation to form propylene glycol, which in turn is more extensively metabolized to CO2 and excreted in expired air or eliminated unchanged in urine. Although the parent compound (PGME) and its sulfate and glucuronide conjugates as well as propylene glycol are all present in urine, only about 10 to 20% of the dose of PGME is eliminated via urine while 50 to 60% is eliminated as [14C] CO2.

Summary

Recent studies have shown that there are pronounced differences in the toxicologic properties and potency of EGME and PGME. EGME has a broad spectrum of toxicity in adult laboratory animals, including bone marrow effects with concomitant hematologic changes, testicular effects which may culminate in infertility in males, and lymphoid tissue atrophy. The tissues that are conspicuously affected by EGME are those in which there are high rates of cell division. However, not all rapidly proliferating tissues are affected by EGME, e.g., the intestinal epithelium. Therefore, factors other than cell division are obviously important with regard to the observed target organ specificity of EGME. Although rabbits appear to be more sensitive than either rats or mice with regard to certain effects, all three species respond to EGME in qualitatively the same manner.

In sharp contrast, exposure to high concentrations of PGME results in central nervous system depression and compensatory liver weight changes in laboratory
animals. The pronounced differences in the toxicologic properties of EGME and PGME are believed to be due to differences in routes of metabolism and types of metabolites. Ethylene-series glycol ethers are primary alcohols which are apparently metabolized via ADH in the same manner as ethanol. The adverse effects of EGME probably are due to its primary metabolite methoxyacetic acid rather than the parent compound, since methoxyacetic acid has the same spectrum of toxicity as EGME in male rats (6). Propylene-series glycol ethers are predominantly secondary alcohols, and are biotransformed via microsomal enzymes to metabolites such as propylene glycol which are relatively innocuous.

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