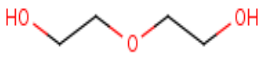
WORKPLACE ENVIRONMENTAL EXPOSURE LEVEL®

OARS WEEL

Diethylene Glycol (2016)

I. IDENTIFICATION[1,5]

Chemical Name: 2,2'-Oxybisethanol
Synonyms: DEG; Diethylene Glycol; Ethylene Diglycol; 2,2' Oxydiethanol; 2-(2-Hydroxyethoxy) Ethanol; 2,2'-Dihydroxydiethyl Ether
CAS Number: 111-46-6
Molecular Formula: $C_4H1_0O_3$
Structural Formula:



II. CHEMICAL AND PHYSICAL PROPERTIES[1-5]

Physical State and Appearance: Colorless viscous liquid
Odor Description: No data available
Odor Threshold: No data available
Molecular Weight: 106.12
Conversion Factors: 1 mg/m^3 = approx. 0.227 ppm; 1 ppm = approx. 4.403 mg/m^3
Density: 1.119 g/mL at 20°C (68°F)
Boiling Point: 245°C (473°F) at 760 mmHg
Melting Point: -6.5°C (-20.3°F)
Vapor Pressure: 0.01 mmHg at 20°C (68°F), 1 mmHg at 92°C
Saturated Vapor Conc: 13 ppm at 20°C (68°F)
Flash Point: 138°C (280°F) (Pensky-Martens closed cup)
Flammability Limits in Air (by volume):
Lower explosive limit: 1.7%;
Upper explosive limit: 10.6%
Autoignition Temperature: 229°C (444°F)
Vapor Density (Air = 1): 3.66
Reactivity and Incompatibilities: Hygroscopic
Solubility: Completely soluble in water at 20°C, soluble in alcohol, ether and acetone; insoluble in benzene and carbon tetrachloride.

III. USES[2,5]

Antifreeze solutions; solvent; additive in printing inks, adhesives, brake fluids, lubricants, cosmetics; paper and textile manufacturing; lacquer industry; for industrial drying of gases; monomer for polyester resins and polyester polyols.

IV. ANIMAL TOXICOLOGY DATA

A. Acute Toxicity and Irritancy

1. Lethality Data

Species	Route	LD_{50} (g/kg)
Mouse	Oral	13.30-28.23[6-8]
Rat	Oral	16.56-30.21[6-11]
Guinea Pigs	Oral	8.68-14.00[6,8,9]
Dog	Oral	11.19[6]
Rabbit	Oral	2.69-4.92[6,8]
Rabbit	Dermal	12.5-13.3[11,17]

Oral (gavage) administration of 15 ml/kg DEG (16.76 g/kg) to 30 male Wistar rats was lethal to 20 animals within 5 days.[12,13]

2. Eye Irritation

Undiluted DEG (volume not specified) instilled into the conjunctival sac of rabbits, dogs, and cats produced no visible irritation reactions and had no effect on pupillary reaction or corneal reflexes.[7] Instillation of 0.5 ml DEG into the conjunctival sac of the rabbit produced little or no irritation.[18] Instillation of 0.1 ml DEG into the eyes of rabbits produced minor to moderate conjunctival irritation but no corneal injury or iritis. No ocular irritation was observed in any rabbit after 24 hrs. Overall, DEG is minimally irritating to the eyes.[19]

3. Skin Absorption

No data available.

4. Skin Irritation

Application of undiluted DEG to the clipped, uncovered abdomen of 5 rabbits produced no signs of erythema, edema, or necrosis within 24 hrs (grade 1/10).[11] In studies with rats and guinea pigs, 2-hr applications of 25 ml/kg DEG produced no signs of irritancy in either species.[7]

5. Skin Sensitization

Diethylene glycol was not a dermal sensitizer in a guinea pig maximization test.[20] In a human repeat insult patch test involving 397 human volunteer subjects, no sensitization response was noted.[21]

6. Acute Inhalation Toxicity

Groups of six rats exposed for 8 hrs to an essentially saturated atmosphere generated at approximately 170°C and a fog generated at about 70°C caused no deaths.[14] Male and female Aplk:AP_fSD (Wistar-derived) rats were exposed to 5,080 mg/m^3 diethylene glycol aerosol (MMAD = 2.83 μm, GSD = 2.05) for 4 hrs.[15] No animals died during the course of the study. No deaths were reported in rats exposed to a saturated vapor of diethylene glycol for 6 hrs.[16]

7. Other

Male Swiss Webster mice were exposed by inhalation to 1,900 to 11,300 mg/m^3 DEG in an upper airway sensory irritation study. Diethylene glycol produced respiratory depression but did not produce responses that would be considered typical of a "pure upper airway sensory irritant." [22]

B. Subacute Toxicity

1. Inhalation Toxicity

Male and female Aplk:AP_fSD (Wistar-derived) rats were exposed nose-only to 0, 530, 3,000 or 5,060 mg/m^3 DEG aerosol, 6 hrs/day, 5 days/week for a total of nine exposure days. The mean mass aerodynamic diameters (MMADs) for the low, mid, and high exposure groups were: 2.76 ± 0.31 (GSD = 1.93 ± 0.18), 3.20 ± 0.28 (GSD = 1.97 ± 0.19), and 3.34 ± 0.27 (GSD = 2.03 ± 0.16) μm for low, mid, and high dose groups, respectively. At 5,060 mg/m^3, there were minor changes in hematological and clinical chemistry parameters (alanine aminotransferase, aspartate aminotransferase, alkaline phosphatase activity, and hemoglobin, hematocrit, red blood cell and platelet counts). The author stated that the changes noted above would normally be considered of no toxicological significance, but thought they were significant because "toxicologically significant effects in these parameters by other routes and at higher doses suggests that the small changes seen here may progress with longer duration inhalation exposure". The lowest observed effect level (LOEL) and the no observed effect level (NOEL) for this study were considered to be 5,060 and 3,000 mg/m^3, respectively. [23]

2. Oral Toxicity

Groups of five Sherman rats of each sex were fed diets containing 0, 11, 46, 180, or 850 mg/kg/day DEG for 32 days. Exposure to 850 mg/kg/day DEG in the diet resulted in degenerative changes in the kidney tubules and significantly increased relative kidney weights. The NOEL for this study is 180 mg/kg/day. [24]

C. Subchronic Toxicity

1. Inhalation Toxicity

No data available.

2. Oral Toxicity

Groups of five Sherman rats of each sex were fed diets containing 9 or 36 mg/kg/day DEG for 90 days. Control groups of 10 rats of each sex were included. No adverse effects were noted in the DEG-fed rats. Thus, the NOEL for this study is 36 mg/kg/day. [24]

A single group of eight adult female Sprague-Dawley rats was exposed daily to 0 or 200 mg/kg body weight DEG in drinking water for 90 days. In a preliminary acute range-finding study conducted as part of this study, single oral (gavage) doses of 700, 2,000, or 8,000 mg/kg DEG were shown to produce dose-related changes in renal function, as measured by several urinalysis parameters. A single (gavage) dose of 200 mg/kg DEG produced no changes. Oral (drinking water) exposure to 200 mg/kg/day DEG for 90 days resulted in no significant effects on body weight or relative kidney weight versus the control groups.[25]

Male DDY mice (15 in each group) were exposed to 1%, 5%, and 10% DEG (2,000, 10,000, and 20,000 mg/kg/day) in drinking water for up to 6 months. Interim sacrifices of 3-4 mice/dose group were made after 1 and 3 months of oral exposure. At the 10% DEG exposure level, about half the mice had died within 3 months of exposure via drinking water. Treatment-related changes in body weight gains were noted in the mid- and high-dose mice. At the 10% DEG exposure level, the average body weight progressively declined from the start of the experiment through 1 and 3 months. At the 5% DEG level, 1 month of exposure did not result in a significant difference in body weight gain compared with the control and 1% DEG groups; however, average body weight gain declined after 3 or 6 months of exposure. Histological changes to the livers of DEG-exposed mice occurred in a treatment-related manner, including abnormalities in cell nuclei, proliferation of smooth

endoplasmic reticulum, partial necrosis of parenchyma, and changes in fat storage cells.[26]

Groups of 20 NMRI female mice each received drinking water containing 0%, 0.03%, 0.3%, or 3% (equivalent to 0, 60, 600, or 6,000 mg/kg/day) DEG. At 1 week post-exposure, the mice were immunized with tetanus toxoid, vaccinia virus, and human erythrocytes. After 4 months of DEG exposure, the mice were infected intraperitoneally (i.p.) with group A β-haemolytic streptococci. Using the hemagglutination inhibition test, no significant change in vaccinia antibodies was detected after 3.5 months of DEG exposure. A statistically significant reduction in tetanus antibodies was determined by the more sensitive ELISA assay method at the 0.3% and 3% DEG exposure levels. Late reaction to human erythrocytes determined after 2 months exposure was not affected by DEG exposure. Although resistance to *Streptococcus pyrogenes* was significantly decreased vs. the control in the 0.3% DEG group, no significant differences were noted between the control and the 3% DEG group for this parameter. Blood coagulation time was determined in all groups after 14 weeks of exposure to DEG. Inhibition of blood coagulation was significantly increased in a dose-dependent manner relative to the untreated control group. It was not determined whether the inhibition of blood coagulation was plasmatic or thombocytic in nature. The authors set the NOEL at <0.03% DEG, based on the blood coagulation effect.[27]

Groups of 5 rats (7-8 weeks old) were administered drinking water containing DEG at concentrations of 0.125%, 0.25%, 0.5%, 1%, 2% or 4% for 9 weeks. At the highest level, 3 out of 5 rats died within 9 days on test. No mortalities were observed at the lower DEG concentrations; however, body weight gains during the 9-week exposure period were less than half that of the controls at the 0.25%, 0.5%, 1% and 2%, 1% DEG exposure levels. Histological examination (H&E stain) of the sections of the liver, kidney, heart, and lung of treated animals revealed slight changes (unspecified) in the heart at the 0.5%, 1% and 2% DEG exposure levels. The NOEL established in this study was 0.125% (approx. 175 mg/kg/day) DEG.[28]

3. Dermal Toxicity

A group of five female rabbits was exposed daily to 0.5 cc of a mixture of equal parts of DEG and propylene glycol (PG) for a total of 100 days. The test substance was applied to a 100 cm^2-shaved area on the flank of each rabbit. The application sites were covered with a dressing after each application. Small skin biopsies were obtained from each animal every 10 days. A shaved and untreated area of skin on the same animal served as the control. No measures of dermal absorption or systemic toxicity were done. Repeated dermal exposure to the DEG/PG mixture resulted in slight histological effects (thickened stratum granulosum and proliferation in the stratum basale).[29]

D. Chronic Toxicity/Carcinogenicity

1. Inhalation Toxicity

An aerosol-vapor mixture produced by heating DEG in a petri dish at 30°C-35°C was used to expose groups of 16 female mice (mixed strains) via inhalation for 2 hr/day for a period of 7 months. The concentration of DEG inhaled by the mice was reported as 4-5 mg/m^3 (0.92 ppm); however, there was no information presented on how the actual exposure level was determined. A control group composed of 20 female mice was included in the study. The treated animals exhibited bronchitis and interstitial pneumonia. Ten of 12 treated mice developed a tumor within 2.5 to 11 months after the end of the inhalation exposure. Adenocarcinomas of the mammary glands were observed in 7 treated mice. No tumors were observed in the control group.[34]

2. Oral Toxicity

Groups of 10 albino-inbred rats (6 male, 4 female) were fed diets containing DEG at concentrations of 0, 1.71, or 3.42% for a period of 2 years. There were no differences in growth or food consumption noted between the control and DEG-exposed rats. All rats were sacrificed at the conclusion of the study (24 months). Pathological examination of the DEG-exposed rats revealed that 3 males had bladder stones, and slight kidney and liver damage relative to controls. [30]

Groups of male Osborne-Mendel rats (12 per dose) were fed diets containing 0, 1, 2, or 4% DEG for 2 years. Analysis of weight changes during the first 26 weeks of the study showed that weight gain during this period was significantly reduced at all DEG exposure levels. After the first year of the test, the growth of rats fed the 4% DEG diets was significantly reduced relative to the control group. There were no significant differences in food consumption at any treatment level. Mortality in rats fed the 4% DEG diet was significantly higher than the control group, with all rats dead before the end of the study (most dying during the last 12 months), compared with 7/12 control deaths. The incidence of bladder stones and bladder tumors increased with DEG exposure level, with 0, 0, 6, and 5 bladder tumors observed in the control, 1, 2, and 4% DEG groups, respectively. Bladder stones were observed in 0, 2, 7, and 11 rats in the control, 1, 2, and 4% DEG groups, respectively. In all but one case, bladder stones were present

when bladder tumors were observed, suggesting that chronic irritation was a factor in production of bladder tumors. The severity and incidence of signs of kidney damage (hydronephrosis, hydroureter, focal tubular atrophy, hyalin cast formation, glomerular atrophy) increased in a treatment-related manner, with gross kidney lesions observed in 1/12. 3/12 and 8/12 of the rats in the low-, mid-, and high-dose groups, respectively. Liver damage observed histologically also increased with the level of DEG exposure.[31]

A two-year study in which groups of 20 rats (both sexes) of various ages were fed diets containing 0, 2, or 4% DEG (containing 0.031% ethylene glycol) was conducted. Rats were either just weaned, 2-months old, or 12-months old at the initiation of the exposure. The dietary concentration of DEG was adjusted for the food consumption and body weight of each group. For a 4% diet, the dosage in weanlings was 5,400 mg/kg/day for the first 28 days, approximately 3,700 mg/kg/day during the next two-week period, gradually declined to about 2,000 mg/kg/day over the next three months, and remained at that level for the rest of the study. A study average of 2,300 mg/kg/day for weanlings fed 4% in the diet was calculated from data provided by the authors. None of the 12-month-old male rats included in the study survived, whereas all the females in that group survived to termination of the study. Although weanling rats developed more bladder stones than the other groups, the difference was insignificant. The yearling rats developed their bladder stones somewhat earlier. The yearling rats fed 4% DEG in their diet had the highest stone formation (8 out of 20 rats) and had the only bladder tumor in this dose group; the rat with the bladder tumor also had bladder stones. No bladder stones or tumors were observed in rats of any age in the control or in the 2% DEG groups. The bladder tumors associated with the stones were considered to be the result of mechanical irritation, and DEG was not considered to be a primary rat carcinogen. The lowest observed adverse effect level (LOAEL) and no observed adverse effect level (NOAEL) for this study were dietary concentrations of 4% and 2%, respectively.[32]

Male and female F344 rats were given 0, 1.25 or 2.5% DEG (97% purity) in drinking water for two years. The data were insufficient to calculate mg/kg/day. The body weights of the DEG-treated male rats tended to be less than those of the controls. There were no significant differences between treated and controls in the hematology and clinical chemistry results, final body weights or organ weights, and incidence of tumors. The NOAEL for this study was 2.5% DEG in drinking water. [33]

It cannot be ruled out that the older studies which showed a significant increase in bladder stones and bladder tumors may have been influenced by the presence of ethylene glycol as an impurity. The more recent studies [32, 33] with high purity diethylene glycol either reported very few bladder stones and tumors at high dietary levels (4%) or none at all.

E. Reproductive/Developmental Toxicity

When DEG was administered in drinking water to rats (exposure duration and group size not specified) of both sexes at a concentration of 0.5%, pregnancy did not occur. Smaller and fewer litters were reported in groups of females exposed via drinking water to 0.25% or 0.5% DEG when mated with untreated males.[28]

Groups of 10 rats of each sex were given daily doses by oral gavage with 1 ml/100 g body weight of a 20% aqueous solution of DEG (approx. 2 ml/kg/day) for 8 weeks. A control group of 10 rats of each sex was given daily doses by oral gavage with 1 ml/100 g body weight distilled water. Five of the treated females were dosed with DEG until parturition, the other 5 until the pups were weaned. Oral exposure to DEG did not impair reproduction. Rats in the control and test group became pregnant at the same time, litter sizes were comparable, and the DEG-treated pups exhibited growth, development and onset of sexual maturation comparable to that of the control group. [35]

In another reproductive toxicity study, groups of 30 Sprague-Dawley rats of each sex received DEG in drinking water at target doses of 0, 150, 500, or 1,500 mg/kg/day prior to, during, and after mating.[36] Half of the pregnant females were killed on gestation day (g.d.) 20 and the fetuses were examined for skeletal and visceral malformations. Exposure of males to 500 or 1,500 mg/kg/day DEG reduced weight gain in the first week of exposure. Relative kidney weights in males of the P and F_1 generation were increased in males exposed at 1,500 mg/kg/day. There were no significant differences in either the reproductive or developmental parameters between the DEG-treated groups and the control group.

In another small study, groups of 6 pregnant Wistar rats each were fed diets containing 0%, 0.2%, 1%, or 5% DEG on g.d. 0-20 and for 7 weeks following parturition.[37] There were no effects attributable to DEG exposure noted among any of the reproductive indices measured. However, pup body weight gain in both sexes at the 5% DEG exposure level was significantly depressed relative to the control from the fifth to the seventh week after birth.

The reproductive toxicity of DEG was studied in CD-1 mice using a protocol for reproductive assessment by continuous breeding (RACB).[38] In the continuous breeding phase of the study, DEG was administered in the drinking water to groups of 20 mice of each sex (40 of each sex in the control group) at 0.35%, 1.75%, or 3.5% w/w. These treatment levels were selected following an initial dose range-finding study. Mice were exposed for 7 days prior to mating, 98 days during cohabitation of breeding pairs, and a further 23 days after segregation of each pair. The mice given 1.75% or 3.5% w/w DEG consumed significantly more drinking water than did the controls. On the basis of water consumption and body weight data, the 0%, 0.35%, 1.75%, and 3.5% DEG concentrations in drinking water were equivalent to average daily intakes of 0, 610, 3,060, or 6,130 mg/kg/day, respectively. There was no mortality attributable to DEG exposure.

At the 6,130 mg/kg/day level of DEG exposure, significant decreases in the number of litters produced per pair, number of live pups per litter, proportion of pups born alive, and pup weights were observed. A significant dose-related trend for reduced pup weights was observed, with average weights of 1.61, 1.62, 3.57, and 1.46 g in the control-, low-, mid-, and high-dose groups, respectively. Exposure to the highest DEG level also resulted in a significant increase in the cumulative days to litter and fewer breeding pairs were able to produce litters (82%, 76%, and 59% of the 6,130 mg/kg breeding pairs were able to produce third, fourth or fifth litters, as compared with 97%-100% in the control group). Craniofacial malformations such as exencephaly and cleft palate were observed in 34/114 of the live born pups (7/14 of these died on postnatal day 2) and 38/19 of the stillborn pups of the final litter of the high-dose group.[38]

In the crossover phase (only one sex exposed to DEG prior to mating) of the study, no significant effects on the fertility of males exposed at 6130 mg/kg/day were observed. When control males were bred with high dose females, pup weights were significantly reduced relative to the control group. The 6,130 mg/kg/day also produced a significant reduction in the mean body weight of female mice relative to control females at necropsy. Maternal (F0) toxicity (7% decrease in body weight).was noted for this dose group. The F1 generation, at the high dose of 6,130 mg/kg/day, had decreased body weights at birth and exhibited poor postnatal survival. [38]

The final litters from mice in the continuous breeding phase of the study were reared and at approximately 74 days were paired with non-siblings from the same dosage level to evaluate reproductive and developmental toxicity in the next generation. Because of the significant incidence of fetotoxicity and malformations observed at the highest dose level in the continuous breeding phase, the mid-dose level (3,060 mg/kg/day) was used to evaluate fertility and reproduction in the F_1 generation. At birth, there was no significant difference between the weights of control and mid-dose F_1 pups. However, by weaning (postnatal day 23) the mean body weights of the mid-dose F_1 pups were significantly depressed relative to the control group. Body weight depression relative to the control group remained significant three weeks after the F, mice were mated. Other signs of toxicity observed in these F1 mice included increased relative liver weights. There were no significant differences between the mid-dose and the control groups for any of the mating, fertility, or reproductive parameters measured in the F_1 generation. The LOAEL and NOAEL for this study are 6,130 and 3,060 mg/kg/day, respectively. [38]

Groups of 12-14 pregnant Wistar rats were fed diets containing 0%, 0.2%, 1%, or 5% DEG on g.d. 0-20.[37] There was no evidence of maternal toxicity at any of the DEG treatment levels, and mean body weight gains among dams in all groups were comparable. There were no significant differences between the control and DEG-treated groups in the mean number of implants, resorptions, dead fetuses, live fetuses, sex ratio, external anomalies, or fetal body weight. The incidence of cervical rib was significantly elevated in the 5% DEG group (7/86) compared with the control (0/80). No other skeletal or visceral effects attributable to DEG exposure were noted.

Time-pregnant CD rats were dosed by oral gavage with 0, 1,118, 4,472 or 8,944 mg/kg on gestational days 6-15. In the high-dose females, there were reduced body weight gain, reduced food consumption, increased water consumption, increased liver and kidney weights, and histopathological changes in the kidney. The mid-dose females exhibited only increased water consumption. There were no treatment-related effects on corpora lutea or implantations. Fetal body weights were reduced in the high-dose animals. Total or individual external or visceral variations were similar between treated and control groups; however, individual skeletal variations were significantly increased in the mid- and high- dose groups. The pattern of delayed ossification was considered consistent with reduced fetal body weight. Malformations were similar between treated and control groups. The maternal and developmental NOELs for this study were considered to be 1,118 mg/kg/day.[39,40]

In another rat teratology study, DEG was administered by oral gavage on gestational days 1 to 19 at doses of 1/5 or 1/50 of the oral LD_{50} (specific doses not specified) to groups of 15 and 11

pregnant rats, respectively.[41] A second part of the same study involved whole body inhalation exposure of groups of 7-12 pregnant rats on gestational days 1 to 19 for 4 hr/day at 10.5, 46, or 328 mg/m^3. Maternal toxicity was not reported for either the oral or inhalation exposures. Both studies included appropriate controls. When orally administered, DEG significantly affected the incidence of both pre- and post-implantation loss, with combined embryo losses of 10.5%, 13.4%, 22.4%, and 23.1% in the historical control, control, low-dose, and high-dose groups, respectively. The fecundity index of rats treated at high-dose was reported as 3.67 vs. 8.85 in the control. Pup body and placenta weight was reduced relative to the control at both oral doses. External anomalies such as exencephaly and phocomelia were observed in 18.5% of the fetuses from the 1/5 LD_{50} DEG dose group. Visceral and skeletal effects at the same oral dosage included hydrocephaly, hydronephrosis, hydroureter, haematomas, and delayed ossification of several bones. Other effects noted in the 1/5 LD_{50} DEG dose group were anophthalmia, micropthalmia, and cataracts. The incidence of anomalous fetuses at the high-dose, low-dose, and control was approximately 50%, 30%, and 5%, respectively.

Pre- and post-implantation loss was less significant by inhalation than in the oral study. The incidence of implantation loss was 18.3% at 328 mg/m^3 vs. 13.2% in the control. Approximately 60% of the embryos in the 328 mg/m^3 DEG exposure group displayed signs of retarded development on g.d. 20; however, none of the exposure levels in the inhalation study resulted in any significant increase in anomalous fetuses compared with the control group. The author attributed developmental toxicity of DEG differences in the oral and inhalations studies to differences in toxicokinetics and toxicodynamics.

Time-pregnant CD-1 mice were dosed by oral gavage with 0, 559, 2,795, or 11,180 mg/kg/day during g.d. 6-15. In the high-dose females, there was mortality, clinical signs, and increased water consumption; only increased water consumption was observed in the mid-dose females. Fetal body weights were significantly reduced in the high-dose animals. There were no increases in variations or malformations between treated and control animals. The maternal and developmental NOELs were 559 and 2,795 mg/kg/day, respectively.[40,42]

In another mouse teratology study**,** oral doses of 0, 1250, 5000, or 10,000 mg/kg DEG were administered by gavage to groups (26-31/group) of timed pregnant Swiss (CD-1) mice on g.d. 6-15. No significant effects were noted on maternal body weight gain at any treatment level. Maternal food consumption in the high-dose group was decreased from g.d. 6-12 while water intake in the mid- and high-dose groups was significantly increased during and following treatment. Mean maternal kidney weight was significantly increased in the high- and mid-dose groups, and renal lesions were observed in 3/28 high-dose mice. The only significant developmental effect noted among the fetuses was a reduction in fetal body weight in the high-dose group. The authors set the developmental toxicity NOEL at 5,000 mg/kg/day and the maternal toxicity NOEL at 1,250 mg/kg.[43]

DEG was also assessed using the Chernoff-Kavlock teratogenicity screening assay, in which 50 pregnant CD-1 mice were orally (gavage) dosed with 11,180 mg/kg DEG on gestational days 7-14. Maternal body weight was determined on gestational day 7, and was used for dose calculations for the entire dosing period. Live and stillborn pups were counted within 12 h of parturition. Live pup weight was determined on post-partum days 1 and 3. Maternal mortality in the DEG group was 4/50 vs. 0/50 in the control. Litter viability was 33/36 in the DEG group vs. 29/29 in the control. Although there was no significant difference in pup birth weight between control and DEG-exposed groups, pup weight gain from g.d. 1-3 was significantly reduced in the DEG-treated group (0.6 g vs. 0.7 g, controls). [44,45] These data are reported twice by two different groups of authors. One group reported the minimal difference in 3-day pup growth as evidence of developmental toxicity, whereas the second group did not claim this. It is generally considered that the difference in three-day growth does not constitute evidence of a developmental effect.

Groups of 15 pregnant Himalayan rabbits were administered oral (gavage) doses of 0, 100, 400, or 1000 mg/kg DEG on g.d. 7-19. No maternal toxicity was observed at any of the DEG doses administered. The fetal and litter incidence of skeletal, soft tissue, and external anomalies or variations were comparable to those of the control and/or historical control groups. The authors set the maternal and developmental toxicity NOELs at ›1,000 mg/kg.[46]

In summary, DEG has produced developmental toxicity at high (often maternally toxic) doses in rats and mice, but not in rabbits.

F. Genotoxicity/Mutagenicity

1. In Vitro

DEG was not mutagenic in the Ames assay, with or without S-9 activation, using *Salmonella* tester strains TA98, TA100, TA1535, TA1537, and TA1538.[5,47,48] No mutagenic effects

were seen when *E.coli* were treated with DEG in a SOS-chromotest.[49]

2. In vivo

DEG was also tested for genotoxicity in the Chinese hamster ovary (CHO) chromosome aberration assay.[5,57] No evidence of clastogenic or cytotoxic effects were observed with or without S-9 activation. DEG was also negative in the CHO/HGPRT mutation test and sister chromatid exchange assay.[5,51]

G. Metabolism/Pharmacokinetics

An *in vivo* disposition study was conducted in rats with ^{14}C-DEG following a single oral gavage dose (50 or 5,000 mg/kg), intravenous injection, or 0.3, 1.0 and 3.0% DEG in drinking water for three days. Oral doses of DEG were well absorbed and were primarily (~80%) excreted in urine within 24 hours of administration (>50% of the dose being excreted in the first 6 hrs after dosing). Accumulation of DEG and/or its metabolites in tissues were minimal. Saturation of metabolism occurred at higher dose levels and resulted in greater excretion of the parent compound in urine. Greater than half of the dose was excreted unchanged, and 10-30% of the dose was excreted as 2-(hydroxyl)ethoxyacetic acid (HEAA). Only trace amounts of oxalic acid were detected in the urine.[16] An *in vivo* disposition study was also conducted in dogs with ^{14}C-diethylene glycol following a single oral gavage dose of 50 mg/kg. The metabolic profile was similar that from the rat study[52], with about 30% of the dose being converted to HEAA.[52]

Absorption of [^{14}C]-DEG (50 mg/12 cm^2) from the shaved skin of rats was slow and steady. Approximately 3% of the applied dose was absorbed per day and excreted in the urine over a 72-hr period. 9.1 ± 1.5% of the dose was recovered in excreta, and 0.9 ± 0.3% was recovered in tissues.[52]

Male Wistar Furth rats were given 1.1 g [^{14}C]-DEG/kg by oral gavage or by intravenous injection. No [^{14}C]-oxalate was detected in urine. In orally dosed rats, 43 ± 7 % of the dose was recovered in urine within 6 hr (79.5% DEG, 20.5% HEAA). In rats given an intravenous injection, 35 ± 5% of the dose (80.3% DEG, 19.7% HEAA) was recovered in the urine after 6 hr, and 46% of the dose was recovered after 12 hours. Pyrazole, an alcohol dehydrogenase inhibitor, decreased the amount of HEAA in the urine at 6 hr post dosing by about 91%.[53]

Male Sprague-Dawley rats were given a single oral dose of 1, 5, or 10 ml [^{14}C]-DEG/kg. The elimination half-lives were 6, 6, and 10 hr, respectively. Urinary [^{14}C] elimination was zero-order for the first 9 and 18 hr following oral doses of 5 and 10 ml of ^{14}C-DEG/kg, respectively. [^{14}C]-DEG elimination kinetics changed into first-order 6, 9, and 18 hr after oral doses of 1, 5, and 10 ml/kg, with a half-life of 3 hr. The urinary concentrations of non-metabolized DEG and its metabolite HEAA in the urine of rats dosed with DEG were 61-68% and 16-31%, respectively. The metabolism of DEG in the rat was accompanied by a change in urinary pH, suggesting metabolic acidosis. [54]

Oral doses of 1, 5, and 10 ml [^{14}C]-DEG/kg were rapidly absorbed into the blood of male Sprague-Dawley rats, with calculated half-lives of 21 $\pm$ 4 min and 11 $\pm$ 6 min for the 1 and 5 ml/kg doses, respectively. Maximum [^{14}C] plasma concentrations were determined after 25 to 120 min after dosing. [^{14}C]-DEG was rapidly distributed from the blood into the organs and tissues in the order expected from blood flow. The relative volume of distribution was determined to be 298 ml, indicating distribution over the whole body. 73-96% of [^{14}C] activity in blood was excreted with the urine and 0.7-2.2% with the feces. From the cumulative urinary excretion kinetics, half-lives of 6 hrs were determined for doses of 5 ml/kg, and 10 hrs for a 10 ml/kg dose. Rats dosed with 10 mg [^{14}C]-DEG/kg excreted 0.003% of the administered dose as oxalate.[55]

Male Wistar rats were treated by oral gavage with water, 2 g/kg DEG (low dose), 10 g/kg DEG (high dose), or 10 g/kg DEG + fomepizole (an alcohol dehydrogenase inhibitor), and blood and urine were collected over 48 h. After administration of the low and high doses of DEG, HEAA was the primary metabolite in the urine, with only minor amounts of urinary diglycolic acid (DGA). Small amounts of ethylene glycol (EG), but not oxalate or glycolate, were observed in the urine. Treatment with fomepizole blocked the formation of HEAA and DGA and the development of metabolic acidosis and the kidney and liver toxicity. Thus, it was concluded that the metabolites of DEG, not DEG itself nor the formation of EG from DEG, are responsible for its target organ toxicity.[56]

Some of the earlier pharmacokinetic/metabolism studies had suggested that EG might be primary metabolite of DEG based on the presence of two-carbon metabolites in those studies, and that oxalic acid accounted for DEG toxicity. The possibility of contamination of DEG with EG in these earlier studies has been proposed since DEG is produced on an industrial scale by the reaction of EG with ethylene oxide.[62] Further evidence that DEG does not undergo ether cleavage to become two EG molecules is that oxalate crystals, a hallmark of EG poisoning, are not found in the urine or kidney tissue of DEG-intoxicated patients.[57-59]

V. HUMAN USE AND EXPERIENCE

A mass poisoning occurred in 1937 with the medication "elixir of sulphanilamide" which contained 72% DEG. 96 deaths were attributed to ingestion of the medication. Deaths occurred at an average of 9 days after ingestion of DEG. Symptoms included dizziness, headaches, and vomiting, followed by polyuria, oliguria, and finally anuria. Prior to death, coma, tremors, and convulsions were observed in some patients. An additional 200 adults and 48 children survived repeated ingestion of the medication. Children survivors (up to age 14) ingested an average dose of 44.2 ml (equal to 32 ml DEG). Adult survivors (persons over age 15) ingested an average of 83.7 ml (equal to 60 ml DEG). Among those who died, autopsies revealed that the principal signs of intoxication were in the kidneys and liver (cortical necroses, nephrosis with severe vacuolization of the tubular epithelium, liver congestion, and fatty degeneration).[60]

An outbreak of acute renal failure among children in Haiti in 1996 was investigated to determine etiology and institute control measures. Diethylene glycol-contaminated glycerin was used in acetaminophen syrup. Anuria or severe oliguria was commonly reported, with a median of 6 days from first dose to onset. Other toxic effects were hepatitis, pancreatitis, and severe neurological manifestations. 85 of 87 renal failure patients remaining in hospitals in Haiti died. Among 32 renal failure patients for whom a maximum ingested dose could be estimated, the median estimate was 1.34 ml/kg (range 0.22-4.42 ml/kg). Well-children (no renal failure) included 17 children with estimated ingestion of 0.05-2.48 ml DEG/kg.[61]

Seven children died following treatment with sedative mixtures containing DEG. The symptoms of intoxication were similar to those seen in the previous poisoning with "elixir of sulphonilamide." No information concerning the amount of DEG ingested by these patients was reported.[62]

In a retrospective epidemiological study, 90 workers (56 male, 34 female, aged 20-49) who had occupational contact with DEG for periods of 1-9 years showed no increased cancer risk.[63]

The toxic dose of DEG in humans has been estimated to be about 0.2 g/kg and a lethal dose about 1–1.5 g/kg.[59,61]

VI. RATIONALE

Inhalation exposure to DEG is likely to occur by aerosols rather than by vapor because of its low vapor pressure, and would be limited to industrial operations in which DEG is heated or where fogs or mists are generated. DEG is quite stable chemically, and does not present a flammability hazard, except at high temperatures, or where an aerosol is involved.

Acute lethality studies in rodents indicate that DEG has a low acute toxicity by the oral, inhalation and dermal routes of exposure. The acute toxic effects of DEG in laboratory animals and humans following oral exposure can include metabolic acidosis and kidney/liver toxicity. It is minimally irritating to the skin and eye, and does not appear to be an upper respiratory tract irritant at high aerosol exposures. DEG is not a skin sensitizer.

Repeated oral exposure to high doses of DEG induces kidney and liver toxicity in laboratory animals. Bladder stones and bladder tumors have been observed in some dietary studies, however, it cannot be ruled out that these findings may have been influenced by the presence of EG as an impurity. DEG has been shown to be negative in a variety of *in vitro* genotoxicity tests. Repeated-dose toxicity studies on DEG by the inhalation route are limited. A nine-day inhalation study showed minor changes in some hematology and clinical chemistry parameters in rats exposed to an aerosol concentration of 5,060 mg/m^3 (but not at 3,000 mg/m^3), but the biological significance of these changes are unclear. No adverse histopathological effects were noted. One study reported that an aerosol-vapor mixture of 4-5 mg/m^3 (0.92 ppm) DEG for 2 hours/day for 7 months induced bronchitis, pneumonia, and adenocarcarcinomas of the mammary gland.[34] These findings are difficult to interpret because of inadequate documentation of the methods and results, and that the effects occurred at substantially lower concentrations than those used in multiple oral toxicity studies. Without confirmation the findings in this study are considered of questionable value.

DEG has been shown to induce reproductive and developmental toxicity at high (often maternally toxic) doses in rats and mice; no developmental effects were seen in rabbits dosed orally with DEG.

The adverse effects observed in both laboratory animals and humans from oral exposures to DEG are unlikely to occur in the occupational environment because of the very high aerosol exposures needed to achieve a comparable dose level and that it is not readily absorbed through the skin. Some hazard from repeated prolonged inhalation may exist in operations involving heated material or where aerosols are generated. This situation may be avoided using reasonable industrial hygiene control.

A WEEL guide of 10 mg/m^3 (respirable) is recommended to provide adequate protection from all known toxicological hazards of DEG, and is consistent with good hygiene practices.

VII. RECOMMENDED WEEL GUIDE

8-hr time-weighted average (TWA): 10 mg/m^3 (respirable)

This WEEL value was originally established in 1985 and updated in 1999. No significant new literature was identified since the last revision (1999) that supports a change to the recommended WEEL value.

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