Environmental Health Perspectives
Vol. 57, pp. 141-146, 1984

Results of Testing Fifteen Glycol Ethers in a Short-Term *in Vivo* Reproductive Toxicity Assay

by Ronald L. Schuler,* Bryan D. Hardin,* Richard W. Niemeier,* Gary Booth,† Keith Hazelden,‡ Vincent Piccirillo** and Kirby Smith§

Fifteen glycol ethers were investigated for their potential to cause adverse reproductive toxic effects using an *in vivo* mouse screening bioassay. Pregnant mice were orally dosed once per day on days 7 through 14 of gestation at concentrations causing 0 to 41% maternal mortality. Reproductive endpoints included pup survival *in utero* (percent of live litters/pregnant survivors), pup perinatal and postnatal survival (number of live pups per litter, number of dead pups per litter, and pup survival to 2.5 days of age), and pup body weight statistics (weight at birth and weight at 2.5 days of age).

The study was conducted in two phases: a dose range-finding phase using nonpregnant female mice, and a definitive reproductive phase using time-mated mice. The range-finding phase sought to identify, for each chemical, the maternal LD_{10} as the target dose. However, based upon reproductive phase results, such an exact dose was impractical to achieve. Thus, a range from the LD_5 to the LD_{20} was considered a sufficient challenge dose that would not affect results due to high mortality, i.e., greater than the LD_{20}.

Glycol ethers were assigned to groups having different priorities for further testing based upon whether a sufficient challenge dose was administered and the degree of effects recorded for each chemical. These groups and chemicals are: (a) very high priority, triethylene glycol dimethyl ether (triEGdiME); (b) high priority, ethylene glycol (EG), ethylene glycol monomethyl ether (EGME), ethylene glycol monoethyl ether (EGEE), ethylene glycol diethyl ether (EGdiEE), and diethylene glycol monomethyl ether (diEGME); (c) middle to high priority, ethylene glycol dimethyl ether (EGdiME) and diethylene glycol dimethyl ether (diEGdiME); (d) middle priority, ethylene glycol monobutyl ether (EGBE), diethylene glycol (diEG), diethylene glycol diethyl ether (diEGdiEE) and triethylene glycol (triEG); (e) low priority, diethylene glycol monoethyl ether (diEGEE) and diethylene glycol dibutyl ether (diEGdiBE). Diethylene glycol monobutyl ether (diEGBE) was not administered at a sufficient challenge dose and should be repeated.

NIOSH does not regard these results as appropriate for labeling a compound as safe or unsafe. Instead they are suggestive, when considered along with other information on each chemical, of the urgency with which these chemicals should be considered for more detailed conventional testing.

Introduction

Conventional reproductive testing is expensive, involves complex scheduling, and requires the commitment of highly trained personnel. These intricate requirements, coupled with the existence of a large number of compounds that lack reproductive toxicity information, have created an urgent need for rapid, inexpensive methods of screening chemicals for reproductive toxicity. With this in mind, the National Institute for Occupational Safety and Health (NIOSH), in conjunction with the National Toxicology Program (NTP) in 1981 began to evaluate an *in vivo* screening test developed by Chernoff and Kavlock (*1*). For this test, pregnant mice are treated during organogenesis with high doses of the test chemicals. Females are then allowed to deliver their litters and the number of live-born pups, their birth weight, and growth and survival to 2 to 3 days of age are monitored. While the test is not appropriate for labeling a compound as safe

*Department of Health and Human Services, U. S. Public Health Service, Centers for Disease Control, National Institute for Occupational Safety and Health, Division of Biomedical and Behavioral Science, Robert A. Taft Laboratories, 4676 Columbia Parkway, Cincinnati, OH 45226.

†Minority Enterprise Service Associates, 1156 South Street, Suite 105, Orem, UT 84057.

‡Inveresk Research International Ltd., Edinburgh EH21 7UB, Scotland.

**Borriston Laboratories, Inc., 5050 Beech Place, Temple Hills, MD 20748.

§Bioassay Systems Corporation, 225 Wildwood Avenue, Woburn, MA 01801.

Table 1. Glycol ethers investigated.

Glycol	Formula		Purity, %	Contractors[a]
	Structural	Empirical		
Ethylene glycol (EG)	HO-Et-OH	$C_2O_2H_6$	99+	Inveresk
Ethylene glycol monomethyl ether (EGME)	Me-O-Et-OH	$C_3O_2H_8$	99	Bioassay
Ethylene glycol dimethyl ether (EGdiME)	Me-O-Et-O-Me	$C_4O_2H_{10}$	99+	MESA
Ethylene glycol monoethyl ether (EGEE)	Et-O-Et-OH	$C_4O_2H_{10}$	99	Bioassay
Ethylene glycol diethyl ether (EGdiEE)	Et-O-Et-O-Et	$C_6O_2H_{14}$	95	Borriston
Ethylene glycol monobutyl ether (EGBE)	Bu-O-Et-OH	$C_6O_2H_{14}$	99	Bioassay
Diethylene glycol (diEG)	HO-Et-O-Et-OH	$C_4O_3H_{10}$	97	Inveresk
Diethylene glycol monomethyl ether (diEGME)	Me-O-Et-O-Et-OH	$C_5O_3H_{12}$	99	Bioassay
Diethylene glycol dimethyl ether (diEGdiME)	Me-O-Et-O-Et-O-Me	$C_6O_3H_{14}$	99	MESA
Diethylene glycol monoethyl ether (diEGEE)	Et-O-Et-O-Et-OH	$C_6O_3H_{14}$	99+	Borriston
Diethylene glycol diethyl ether (diEGdiEE)	Et-O-Et-O-Et-O-Et	$C_8O_3H_{18}$	98+	MESA
Diethylene glycol monobutyl ether (diEGBE)	Bu-O-Et-O-Et-OH	$C_8O_3H_{18}$	99+	Borriston
Diethylene glycol dibutyl ether (diEGdiBE)	Bu-O-Et-O-Et-O-Bu	$C_{12}O_3H_{26}$	99+	Inveresk
Triethylene glycol (triEG)	HO-Et-O-Et-O-Et-OH	$C_6O_4H_{14}$	99	Borriston
Triethylene glycol dimethyl ether (triEGdiME)	Me-O-Et-O-Et-O-Et-O-Me	$C_8O_4H_{18}$	99	MESA

[a]Biossay = Bioassay Systems Corporation, 225 Wildwood Avenue, Woburn, MA 01801; Borriston = Borriston Laboratories, Incorporated, 5050 Beech Place, Temple Hills, MD 20748; Inveresk = Inveresk Research International Limited, Edinburgh EH21 7UB, Scotland; MESA = Minority Enterprise Service Associates, 1156 South State, Orem, UT 84057.

or unsafe, it may serve to generate data useful in establishing priorities for conventional testing. It may also be useful for rapidly surveying structure-activity relationships. As part of the NTP evaluation of potential reproductive toxins, four contracts were awarded by NIOSH under which a total of 30 chemicals were tested. Fifteen of the chemicals were glycols or glycol ethers and the results of those tests are summarized here. Of these 15, three contractors tested 4 chemicals each and one contractor tested the remaining 3 (see Table 1). None were tested in more than one laboratory.

Methods

All contractors used CD-1 mice purchased from Charles River Breeding Laboratories, Inc. (Wilmington, MA) throughout these studies. Chemicals were evaluated in two phases: a preliminary dose-finding study in nonpregnant mice followed by the reproductive phase using time-mated females. In both phases chemicals were evaluated in blocks of two to four chemicals with a shared concurrent vehicle control group. Some blocks included only glycols, others included other chemicals. Only data on glycols are reported here. Chemicals were provided to contractors by NIOSH and were tested in blind, with the chemicals identified by an arbitrary code number. Table 1 summarizes the glycols tested and their abbreviations, structural formulas, chemical purity and the laboratories that performed the investigations. diEGdiBE was administered in corn oil due to its insolubility in water. Distilled water served as the vehicle for all other glycols tested. Dosage was by oral gavage in all instances.

The dose range-finding study was conducted at 5 dose levels using ten mice, 6 to 8 weeks old, per treated or control group (except for diEGBE and diEGdiEE where the mice were 60 to 80 days old*). Upon receipt, mice were weighed and marked for individual identification, then formally randomized to treatment groups. Mice were group-housed, five per cage, throughout the range-finding study. Standard laboratory rodent chow and untreated tap water were available *ad libitum*. Bedding of a type known not to induce microsomal enzymes was changed as needed or at least once per week. Oral doses were administered once daily for 8 consecutive days using a constant dose volume of 10 mL/kg body weight. Body weights were recorded on days 1 and 8 of the dosing period and on days 4 and 8 of an 8-day post-dosing observation period. Group mean or individual body weights taken on the first day of dosing were used to calculate treatment volumes over the entire 8-day dosing period. Survivors were sacrificed immediately following the last weighing on the 8th post-dosing day. All mice that died before that time were necropsied for evidence of dosing error as a cause of death. Based on the results of these dose-finding studies, the estimated LD_{10} dose was selected for the reproductive phase.

Reproductive studies were conducted in time-mated CD-1 mice, 6 to 8 weeks of age, orally dosed on days 7 to 14 of gestation (day 1 of gestation is the day on which a copulatory plug is observed). Mice were received on or before day 5 of gestation. On day 5 they were weighed and marked for individual identification, then formally randomized to treatment or control groups of 50 mice each. Test chemicals were administered at a single dose in a constant volume of 10 mL/kg body weight. Maternal

*Because of the demand placed upon the single animal supplier by all four contractors, the initial requirement to use 60- to 80-day-old mice was changed. This change required the use of the more readily available 6- to 8-week-old mice.

body weights were taken on day 7 of gestation immediately before dosing, on day 18 of gestation, and on day 3 postpartum. The weight of the animal on gestation day 7 was used to calculate the dosage for the entire period. All mice were housed individually throughout the reproductive study. Food, water and bedding were provided as in the range-finding studies except bedding was not changed after gestation day 18.

Females were observed with minimal disturbances twice daily beginning on day 18 of gestation. As soon as possible after litters were delivered (within 12 hr), the number of live and stillborn pups was recorded. Maternal body weight was recorded and all live pups were weighed together. Pups and their dams were then returned to nest boxes and were left undisturbed until 48 hr after the initial weighing, at which time the number of live pups, their total weight, and maternal body weight were again recorded.

Details of the statistical analyses varied from one contractor to another, but generally the procedures were similar. Body weight data were analyzed by analysis of variance. The proportion of surviving pregnant mice that gave birth to viable litters (one or more live-born pups) was evaluated by the Fisher-Irwin exact test. Numbers of live and stillborn pups and percent survival to 2.5 days of age were analyzed by analysis of variance and the Student's t-test.

Results

Tables 2 and 3 present the findings of the postnatal screen of the 15 glycol ethers. Because these chemicals were investigated by four independent laboratories at different times and in some cases concurrently with other chemicals, seven control groups were used (some controls served more than one chemical). Control values were generally consistent across these seven groups. There was only one maternal death in all control groups and that was a result of a gavage error. Reproductive success in the controls ranged from 91 to 100% of all pregnant survivors. The average litter size ranged from 9 to 11 pups per litter. The percent pup postnatal survival (to 2.5 days postpartum) ranged from 98 to 100%. The average pup weight gain over days 1 to 3 postpartum ranged from 0.4 g to 1.1 g, and the average pup birth weight ranged from 1.6 g to 1.7 g.

Nine of fifteen glycols tested affected the viable litter index. Pregnant mice treated with EGME, EGEE, EGdiME, diEGdiME, and triEGdiME produced no viable litters. Mice treated with EG, EGBE, EGdiEE

Table 2. Glycol ether results: maternal mortality and pregnancy success.

Block	Glycol	Dose		Maternal mortality (%)[a]	Viable litters (%)[b]
		mmole/kg	mg/kg		
A	Control			0/50 (0)	31/32 (97)
	EGME	18.4	1400	7/49 (14)	0/30* (0)
	EGEE	40.1	3605	5/50 (10)	0/32* (0)
	EGBE	10.0	1180	10/50 (20)	24/31* (77)
	diEGME	33.3	4000	5/50 (10)	5/32* (16)
B	Control			0/49 (0)	30/31 (97)
	diEGBE	3.1	500	0/50 (0)	36/37 (97)
C	Control			0/50 (0)	42/42 (100)
	EGdiEE	25.0	2955	5/50 (10)	4/35* (11)
	diEGEE	41.0	5500	7/50 (14)	32/33 (97)
	triEG[c]	75.1	11270	2/50 (4)	36/36 (100)
D	Control			0/50 (0)	29/29 (100)
	EG[c]	178.9	11090	5/50 (10)	15/37* (41)
	diEG[c]	105.5	11180	2/50 (4)	33/36 (92)
E	Control[d]			0/50 (0)	45/45 (100)
	diEGdiBE[d]	9.2	2000	4/50 (8)	38/40 (95)
F	Control			0/50 (0)	41/45 (91)
	diEGdiEE	18.5	3000	0/40 (0)	35/41 (85)
G	Control			0/50 (0)	42/43 (98)
	EGdiME	22.2	2000	13/50 (26)	0/34* (0)
	diEGdiME	22.4	3000	20/49 (41)	0/27* (0)
	triEGdiME	19.7	3500	2/50 (4)	0/37* (0)

[a]Treatment-related deaths/number on test (percent mortality).
[b]Litters with one or more live-born pups/number of pregnant survivors (percent of pregnancies).
[c]Administered without dilution in volume of 10 mL/kg.
[d]Corn oil used as the vehicle; all other groups used distilled water vehicle.
*Differs significantly ($p < 0.05$) from concurrent control by Fisher's exact test.

Table 3. Neonatal observations.

Block	Glycol	Dose mmole/kg	Dose mg/kg	No. live pups per litter at birth	No. dead pups per litter at birth	Pup postnatal survival (%)	Pup weight gain over days 1–3 post partum, g	Pup birth weight, g
A	Control			10	0.1	100	0.4	1.6
	EGME	18.4	1400	No litters	—	—	—	—
	EGEE	40.1	3605	No litters	—	—	—	—
	EGBE	10.0	1180	10	0.2	95	0.4	1.5
	diEGME	33.3	4000	3*	0.6	31*	0.5	1.4
B	Control			10	0	99	1.1	1.6
	diEGBE	3.1	500	10	0	99	1.1	1.6
C	Control			10	0	99	0.9	1.6
	EGdiEE	25.0	2955	1‡	2‡	45‡	0.6‡	1.3‡
	diEGEE	41.0	5500	10	0	98	0.9	1.5†
	triEG	75.1	11270	9	0	99	1.0	1.5†
D	Control			9	0.1	100	0.7	1.7
	EG	178.9	11090	2†	1.5†	40†	0.2†	1.4†
	diEG	105.5	11180	10	0.2	97	0.6†	1.6
E	Control			11	0	100	0.6	1.7
	diEGdiBE	9.2	2000	11	0.2†	100	0.6	1.7
F	Control			10	0.1	98	0.5	1.6
	diEGdiEE	18.5	3000	10	0.4*	97	0.5	1.5*
G	Control			10	0.3	98	0.7	1.6
	EGdiME	22.2	2000	No litters	—	—	—	—
	diEGdiME	22.4	3000	No litters	—	—	—	—
	triEGdiME	19.7	3500	No litters	—	—	—	—

*Significantly different ($p < 0.05$) from concurrent control by analysis of variance.
‡Not tested statistically due to small sample size.
†Significantly different ($p < 0.05$) from concurrent control by Student's t-test.

and diEGME showed a significant reduction ($p < 0.05$) in viable litters produced (41, 77, 11, and 16 percent viable litters produced, respectively). The remaining glycols and glycol ethers produced no effect on that reproductive index at the concentrations administered.

Postnatal observations varied widely in those groups with viable litters. EG and EGdiEE reduced the number of live pups per litter, increased the number of dead pups per litter, reduced pup survival, reduced pup birth weight and reduced pup weight gain over days 1 to 3 postpartum. EGdiEE data were not analyzed statistically because of the small sample size. diEGME significantly reduced ($p < 0.05$) the number of live pups per litter and pup survival over days 1 to 3 postpartum. diEGdiEE significantly increased ($p < 0.05$) the number of dead pups per litter and significantly reduced ($p < 0.05$) pup birth weight. diEGdiBE increased ($p < 0.05$) the number of dead pups per litter. diEG reduced ($p < 0.05$) pup weight gain over day 1 to 3 postpartum and triEG and diEGEE reduced ($p < 0.05$) mean pup birth weight.

Discussion

Because it is our intent to use this bioassay to screen chemicals for their potential to cause reproductive toxicity in pregnant females, it is necessary to employ clearly toxic doses. If a chemical is evaluated as a low priority, one wants to be relatively confident that it was tested at a sufficiently severe challenge level. Clear maternal toxicity does not mean that reproductive toxicity follows. diEG and triEG produced 4% maternal mortality; diEGdiBE produced 8% mortality; and diEGEE produced 14% mortality. None of these showed strong evidence of reproductive toxicity. In fact, diEGEE treatment did not adversely affect any of the reproductive indices.

As noted, the estimated maternal LD_{10} was chosen as the challenge dose to be used for the reproductive studies. In practice, mortality will vary somewhat, and a response in the LD_{5-20} range was considered acceptable in the reproductive phase. If reproductive effects are noted in the presence of more than 20% maternal mortality, the test probably should be repeated at a lower dose. Conversely, if there is no reproductive toxicity and less than 5% maternal mortality, the test probably should be repeated at a higher dose. This LD_{5-20} range, however, is only a tentative suggestion and further experience with this test may suggest other criteria for judging the appropriateness of the challenge dose.

The six end points examined for determining the

priority of chemicals for further testing can be condensed into three levels of consideration. Most important is pup survival *in utero*, i.e., percent viable litters delivered by pregnant survivors. Of second importance is pup perinatal and postnatal survival, i.e., the number of live and dead pups per litter at birth, and pup survival over days 1 to 3 post partum. Final consideration is given to pup body weight end points, i.e., pup weight gain over days 1 to 3 and pup weight at birth.

Chemicals were assigned to groups having different priorities for further testing, based upon whether a sufficient dose was administered (the maternal LD_{520}) and the degree of effects recorded for each chemical. triEGdiME therefore has a very high priority for further testing because the administered dose of 4% maternal mortality was less than the LD_{5-20}, and the results were profound, i.e., no viable litters delivered. Other chemicals deserving high priority include EG, EGME, EGEE, EGdiEE, and diEGME in that all were tested within the range of 5 to 20% maternal mortality and all showed a drastic reduction of viable litters. A middle to high level priority group would include EGdiME and diEGdiME because both produced no viable litters but they received a dose greater than the LD_{5-20} which could have influenced the results due to maternal toxicity effects. A middle level priority group would include EGBE, diEG, diEGdiEE and triEG. EGBE significantly reduced viable litters with no other effects when dosed at the upper limit of the range of acceptable mortality. diEG, diEGdiEE and triEG mice received less than the LD_{5-20} dose but still produced some lesser effects: reduced pup weight gain for diEG; reduced pup weight gain and decreased number of live pups per litter for triEG; and an increased number of dead pups per litter plus a reduced pup birth weight for diEGdiEE. A low priority group would include diEGEE and diEGdiBE because the LD_{5-20} dose was achieved and only lesser effects were seen, i.e., a reduced pup birth weight for diEGEE and an increased number of dead pups per litter for diEGdiBE. diEGBE mice did not receive a maternally toxic dose and no effects were found, thus diEGBE should be repeated until an LD_{5-20} dose is achieved.

It is important to note that, for the purposes of this screen, comparisons among chemicals are based upon maternal mortality, i.e., doses less than, greater than, or within the LD_{5-20} range. Comparisons as to the potential exposure hazard are not made. For example, although EG is designated to a higher priority group than EGBE, it may be that an individual is more likely to receive an 1180 mg/kg dose of EGBE (LD_{20}) than he is to receive an 11,090 mg/kg dose of EG (LD_{10}). Thus EGBE may be more of a potential hazard than EG.

Previous investigations have shown several of the glycol ethers assessed in the current work to be teratogenic in traditional teratology test systems. EGME (designated in our high priority group) induced skeletal anomalies in the offspring of mice receiving, by oral gavage, as low as 31 mg/kg/day over days 7 through 14 of gestation (*2*). Gross (external) anomalies and the incidence of embryonic death were greatly increased in the offspring of mice receiving 250 mg/kg/day. In an inhalation study, 200 ppm EGME for 7 hr/day on gestation days 7 through 15 caused complete embryonic death in rats (*3*). Reduced fetal weights, skeletal and cardiovascular defects, as well as increased embryonic death occurred at both 50 and 100 ppm.

EGEE, also in the high priority group, induced skeletal anomalies, increased embryonic death, and decreased pup weight in offspring of rats treated by oral gavage on days 1 through 21 of gestation (*4*). Doses ranged from 12 to 327 mg/kg/day. Inhalation of 160 ppm EGEE for 7 hr/day on days 1 through 18 of gestation increased embryonic death and skeletal anomalies in rabbits (*5*). At 615 ppm complete embryonic death occurred. Offspring of rats receiving a 1.0 mL or 2.0 mL dermal application of EGEE on days 7 through 16 of gestation showed greatly increased embryonic deaths, and cardiovascular and skeletal anomalies (*2*). Offspring of rats receiving 100 ppm of EGEE for 7 hr/day on days 7 through 13 or 14 through 20 of gestation showed altered behavioral patterns and altered brain neurochemical concentrations (*7*).

EGdiME, placed in our middle to high level priority group, administered to pregnant mice by oral gavage on days 7 through 10 of gestation caused increased embryonic death at concentrations of 250, 350, and 490 mg/kg/day (*8*). Skeletal and external anomalies occurred in the 490 mg/kg group. EGBE, in our middle priority group, caused no apparent adverse effect on the offspring of rats exposed to 200 ppm EGBE for 7 hr/day on gestation days 7 through 15 (*3*). diEGEE, in our low priority group, caused no adverse effect on the offspring of rats exposed to 100 ppm for 7 hr/day on days 7 through 15 of gestation (*3*).

Some general statements can be made regarding structure–activity relationships. All mice receiving glycol ethers having terminal methyl groups, i.e., EGME, EGdiME, diEGME, diEGdiME and triEGdiME produced few viable litters (0, 0, 16, 0, and 0%, respectively). Only EGEE and EGdiEE having terminal ethyl groups produced similar results (0 and 11% viable litters, respectively). The remaining ethyl ethers (diEGEE and diEGdiEE), the butyl ethers (EGBE, diEGBE, diEGdiBE), and the glycol ethers with terminal hydroxy groups (EG, diEG and triEG) did not produce such profound fetotoxicity. Maternal toxicity of the glycols was sharply increased by the addition of an alkyl group. EGBE was more toxic than EGME which was more toxic than EGEE. All three showed greater toxicity than EG. The diEG mono-and diEGdi-alkyl ethers were more toxic than diEG, and triEGdiME was more toxic than triEG. The methyl ethers were generally more toxic than the ethyl or butyl ethers with the exception of EGBE.

We would caution again that neither NIOSH nor the NTP regards these results as definitive. Instead, they

are suggestive, when considered along with other information on each chemical, of the urgency with which these chemicals should be considered for more detailed conventional testing. From the current available information on the glycol ethers, a correlation can be seen between the known positive teratogens (EGME, EGEE, and EGdiME) and their results in this *in vivo* screen where these compounds were designated either in a high priority or middle to high priority group. Also, EGBE and diEGEE, which showed no reproductive toxicity in conventional tests, were given a lower priority ranking (middle or low group) following testing in this screen.

The authors wish to express their appreciation to Sandra Clark (NIOSH) for the excellent typing of this manuscript.

REFERENCES

1. Chernoff, N., and Kavlock, R. J. An *in vivo* teratology screen utilizing pregnant mice. J. Toxicol. Environ. Health 10: 541–550 (1982).
2. Nagano, K., Nakayama, E., Oobayashi, H., Yamada, T., Adachi, H., Nishizawa, T., Ozawa, H., Nakaichi, M., Okuda, H., Minami, K., and Yamazaki, K. Embryotoxic effects of ethylene glycol monomethyl ether in mice. Toxicology 20: 335–343 (1981).
3. Nelson, B. K., Setzer, J. V., Brightwell, W. S., Mathinos, P. R., Kuczuk, M. H., Weaver, T. E., and Goad, P. T. Comparative inhalation teratogenicity of four glycol ether solvents and an amino derivative in rats. Environ. Health Perspect. 57: 261–272 (1984).
4. Stenger, E. G., Aeppli, L., Muller, D., Peheim, E., and Thomann, P. The toxicology of ethylene glycol monoethyl ether. Arzneim. Forsch. 21: 880–885 (1971).
5. Andrew, F. D., Buschbom, R. L., Cannon, W. C., Miller, R. A., Montgomery, L. F., Phelps, D. W., and Sikov, M. R. Teratologic assessment of ethylbenzene and 2-ethoxyethanol. NIOSH contract report. Battelle Pacific Northwest Laboratory, Richland, WA, 1981.
6. Hardin, B. D., Niemeier, R. W., Kuczuk, M. H., Mathinos, P. R., and Weaver, T. E. Teratogenicity of 2-ethoxyethanol by dermal application. Drug Chem. Toxicol. 5(3): 277–294 (1982).
7. Nelson, B. K., Brightwell, W. S., Setzer, J. V., Taylor, B. J., Hornung, R. W., and O'Donohue, T. L. Ethoxyethanol behavioral teratology in rats. Neurotoxicology 2: 231–249 (1981).
8. Uermura, K. The teratogenic effects of ethylene glycol dimethyl ether on the mouse. Acta Obstet. Gynaec. Japan 32(1): 113–121 (1980).