UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

SEP - 3 1998

MEMORANDUM

Subject: **Glycolic Acid**

From: S. L. Malish, Toxicologist, RASSB/AD S. L. Malish 9/1/98

To: Robert B. Brennis, Product Manager, Team 32

Thru: Winston Dang, Team Leader, Team One,
Risk Assessment and Science Support Branch (RASSB)
Antimicrobials Division (AD)

and

Norman Cook, Chief, RASSB/AD Norman J. Cook 09/03/98

TASK:

DP BARCODE:	D247673	SUBMISSION:	S545623
P.C. CODE:	101	CASE TYPE:	Registration
EPA Reg ID:	71654-R		

ACTION REQUESTED: Review toxicology data [(§ 83-3) Developmental Toxicity/Rat] to support registration of the product.

CONCLUSION: The study is classified as **Acceptable** and satisfies the data requirements for [§ 83-3] Developmental Toxicity study in the rat. The Executive summary is noted below. The Data evaluation report is attached.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44589501), Glycolic acid (99.6% a.i.) was administered by oral gavage to groups of 25 pregnant Crl:CD®BR rats at doses of 0, 75, 150, 300, or 600 mg/kg/day on gestation days (GD) 7 through 21,

inclusive. On GD 22, all dams were sacrificed and all fetuses were weighed and examined for external malformation/variations. The fetuses from approximately one half of each litter were decapitated and examined for visceral abnormalities including renal development. All fetuses were stained for skeletal evaluation.

All animals survived to terminal sacrifice. At the 600 mg/kg/day, high dose, there was a significant trend ($p \leq 0.05$) for the number of animals affected by abnormal gait or mobility (5/25), irregular respiration (2/25), lethargy (2/25), and lung noise (8/25) compared with 0/25 in the 0 mg/kg/day group. One animal in the 75 mg/kg/day group had an abnormal gait. No clinical signs were observed in the 150 mg/kg/day group. Lung noise was also heard in two dams from the 300 mg/kg/day group and was considered treatment-related. High dose dams had significantly ($p \leq 0.05$; 95% of control) lower absolute and adjusted body weights as compared to the controls on GD 22. Body weight gains by the high dose group were significantly ($p \leq 0.05$) less than the control group for the intervals of GD 7-9, 17-19, 19-21, 21-22, and 7-22 (dosing interval). After GD 17, body weight gains by the 600 mg/kg/day group were 67-80% of the control group level. Body weights and body weight gains of the 75, 150, and 300 mg/kg/day groups were similar to the control group throughout gestation. Food consumption was unaffected by treatment and maternal gross necropsy was unremarkable.

Therefore, the maternal toxicity LOEL is 300 mg/kg/day based on clinical signs of toxicity (lung noise) and the maternal toxicity NOEL is 150 mg/kg/day.

Fetal body weights in the high dose group were significantly ($p \leq 0.05$) less [13%] than the controls. No differences were observed between the treated and control groups for number of corpora lutea/dam, implantations/dam, pre or post implantation loss, resorptions/dam, fetuses/litter, or fetal sex ratios.

No treatment related external or visceral malformations/variations were observed in any fetus. The litter incidence rates for all skeletal malformations/variations in the 0, 75, 150, 300, and 600 mg/kg/day groups were 7/25, 4/25, 3/23, 4/23, and 17/23 ($p \leq 0.01$), respectively. Significantly ($p \leq 0.05$) increased incidences of sternebra anomalies occurred in the 600 mg/kg/day group and included fused (3/23), nonfused (5/23), and misaligned (11/23) sternebra compared with 0/25, 1/25, or 1/25 control litters, respectively. In the 300 and 600 mg/kg/day groups, fused ribs occurred in 2/23 and 9/23 ($p \leq 0.05$) litters, respectively, and fused vertebra occurred in 2/23 and 6/23 ($p \leq 0.05$) litters,

2

respectively, compared with 0/25 controls. The incidences of fused ribs and vertebra in the 300 mg/kg/day litters are considered treatment related because the same malformation occurred in the high dose group but not in the controls.

Therefore, the developmental toxicity LOEL is 300 mg/kg/day based on skeletal malformations (fused ribs and fused vertebrae) and the developmental toxicity NOEL is 150 mg/kg/day.

This study is classified as (§ 83-3) **Acceptable** and satisfies the requirements for a developmental toxicity study in rats. Historical control data would be helpful in determining the biological significance of the fetal malformations observed in the 300 mg/kg/day group.

Reviewed by: Steven L. Malish, Ph.D., Toxicologist, S.L. Malish 8/27/98
Team 1, RASSB/Antimicrobials Branch (7510 W)
Secondary Reviewer: Winston Dang, Ph.D., Team 1 Leader, 9/2/98
RASSB/Antimicrobials Branch (7510 W)

DATA EVALUATION RECORD

STUDY TYPE: Developmental Toxicity/Rat
OPPTS 870.3700 [§ 83-3]

DP BARCODE: D247673
P.C. CODE: 101
EPA Reg ID: 71654-R

SUBMISSION CODE: S545623
CASE TYPE: Registration

TEST MATERIAL: Glycolic Acid (99.6% a.i.)

SYNONYMS: Hydroxyacetic acid

CITATION: Munley, S.M. Developmental Toxicity Study of Glycolic Acid in Rats. E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE 19714. Medical Research Project No. 10492-001. Lab Report No. 191-96. June 20, 1996. MRID 44589501. Unpublished.

SPONSOR: DuPont Specialty Chemicals, E.I. du Pont de Nemours and Company

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 44589501), Glycolic acid (99.6% a.i.) was administered by oral gavage to groups of 25 pregnant Crl:CD®BR rats at doses of 0, 75, 150, 300, or 600 mg/kg/day on gestation days (GD) 7 through 21, inclusive. On GD 22, all dams were sacrificed and all fetuses were weighed and examined for external malformation/variations. The fetuses from approximately one half of each litter were decapitated and examined for visceral abnormalities including renal development. All fetuses were stained for skeletal evaluation.

All animals survived to terminal sacrifice. At the 600 mg/kg/day, high dose, there was a significant trend ($p \leq 0.05$) for the number of animals affected by abnormal gait or mobility (5/25), irregular respiration (2/25), lethargy (2/25), and lung noise (8/25) compared with 0/25 in the 0 mg/kg/day group. One animal in

the 75 mg/kg/day group had an abnormal gait. No clinical signs were observed in the 150 mg/kg/day group. Lung noise was also heard in two dams from the 300 mg/kg/day group and was considered treatment-related. High dose dams had significantly ($p \leq 0.05$; 95% of control) lower absolute and adjusted body weights as compared to the controls on GD 22. Body weight gains by the high dose group were significantly ($p \leq 0.05$) less than the control group for the intervals of GD 7-9, 17-19, 19-21, 21-22, and 7-22 (dosing interval). After GD 17, body weight gains by the 600 mg/kg/day group were 67-80% of the control group level. Body weights and body weight gains of the 75, 150, and 300 mg/kg/day groups were similar to the control group throughout gestation. Food consumption was unaffected by treatment and maternal gross necropsy was unremarkable.

Therefore, the maternal toxicity LOEL is 300 mg/kg/day based on clinical signs of toxicity (lung noise) and the maternal toxicity NOEL is 150 mg/kg/day.

Fetal body weights in the high dose group were significantly ($p \leq 0.05$) less [13%] than the controls. No differences were observed between the treated and control groups for number of corpora lutea/dam, implantations/dam, pre or post implantation loss, resorptions/dam, fetuses/litter, or fetal sex ratios.

No treatment related external or visceral malformations/variations were observed in any fetus. The litter incidence rates for all skeletal malformations/variations in the 0, 75, 150, 300, and 600 mg/kg/day groups were 7/25, 4/25, 3/23, 4/23, and 17/23 ($p \leq 0.01$), respectively. Significantly ($p \leq 0.05$) increased incidences of sternebra anomalies occurred in the 600 mg/kg/day group and included fused (3/23), nonfused (5/23), and misaligned (11/23) sternebra compared with 0/25, 1/25, or 1/25 control litters, respectively. In the 300 and 600 mg/kg/day groups, fused ribs occurred in 2/23 and 9/23 ($p \leq 0.05$) litters, respectively, and fused vertebra occurred in 2/23 and 6/23 ($p \leq 0.05$) litters, respectively, compared with 0/25 controls. The incidences of fused ribs and vertebra in the 300 mg/kg/day litters are considered treatment related because the same malformation occurred in the high dose group but not in the controls.

Therefore, the developmental toxicity LOEL is 300 mg/kg/day based on skeletal malformations (fused ribs and fused vertebrae) and the developmental toxicity NOEL is 150 mg/kg/day.

This study is classified as (§ 83-3) **Acceptable** and satisfies the requirements for a developmental toxicity study in rats.

5

Historical control data would be helpful in determining the biological significance of the fetal malformations observed in the 300 mg/kg/day group.

COMPLIANCE: Signed and dated Quality Assurance, Good Laboratory Practice, Data Confidentiality, and Flagging statements were included.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test material: Glycolic acid

Description:	Crystalline
Lot No.:	4100199
Purity:	99.6% a.i.
Stability:	Stable according to analyses
CAS No.:	79-14-1
Formula:	$HOCH_2COOH$

2. Vehicle

Deionized water was used as the vehicle and negative control.

3. Test animals

Species:	Rat	
Strain:	Crl:CD®BR	
Source:	Charles River Laboratories, Inc., Raleigh, North Carolina	
Age:	Approx. 63 days;	
Weight:	192-267 g	
Acclimation:	≥6 days	
Housing:	Females were individually housed in suspended, wire mesh, stainless steel cages.	
Diet:	Purina® Certified Rodent Chow® #5002 (meal form) and tap water were available *ad libitum*.	
Environmental:	Temperature:	23±1°C
	Humidity:	50±10%
	Air changes:	not stated
	Photoperiod:	12 hours light/dark

6

B. PROCEDURES AND STUDY DESIGN

This study was designed to assess the developmental toxicity of glycolic acid when administered by gavage to rats on gestation days 7 through 21, inclusive.

1. In life dates

Start: October 16, 1995; end: December 4, 1995

2. Mating

Female rats were cohabited with males of the same strain and source at a ratio of 1:1 for breeding. Copulation was confirmed by the presence of a copulatory plug in the vagina or on the cageboard. The day copulation was confirmed was designated as gestation day (GD) 1.

3. Animal assignment and dose selection are presented in Table 1. Bred females were ranked by their body weights on GD 1 and randomly assigned to control or experimental groups.

TABLE 1. Animal assignment^

Group number	Test group	Dose (mg/kg/day)	Number assigned
1	Control	0	25
2	Low Dose	75	25
3	Mid Dose 1	150	25
4	Mid Dose 2	300	25
5	High Dose	600	25

^Data taken from text table, p. 13, MRID 44589501.

4. Dose selection rationale

Doses were selected based on the results of a pilot developmental toxicity study in rats with a 70% technical solution of the test article. Groups of 8 rats were administered 0, 125, 250, 500, or 1000 mg/kg/day on GD 7-21. At the high dose, maternal toxicity consisted of mortality and reduced body

7

weights, weight changes, and food consumption. Clinical signs of toxicity at 1000 mg/kg/day included abnormal gait/mobility, lung noise, salivation, and stained and wet fur. At 500 mg/kg/day, there was reduced body weight gain and similar, but less severe, clinical signs of toxicity. Developmental toxicity at 1000 mg/kg/day included increased fetal mortality and an increased incidence of malformations (not described). Decreased fetal body weights and an increase in fetal variations (not described) were observed in the 500 and 1000 mg/kg/day groups. The maternal and developmental toxicity NOEL was 250 mg/kg/day.

Based on the results of the pilot study, dose levels of 0, 75, 150, 300, and 600 mg/kg/day were chosen for the main study.

5. Dosing

All doses were administered in a volume of 10 mL/kg of body weight/day. Dosing was based on the most recently recorded body weight.

6. Dose solution preparation and analysis

Solutions of the test material in deionized water were prepared weekly during the study and stored in the refrigerator. The method of dosing solution preparation was not described in the report. Samples of each dosing solution were taken three times during the study. The first sample was analyzed for concentration and stability, the other samples were analyzed for concentration. Stability was measured following storage in the refrigerator for 7 days. Homogeneity of the dosing solutions was not measured.

Absence of test article was confirmed in the vehicle. Concentrations of the four dosing solutions ranged from 97.5% to 103% of nominal. Following one week of storage in the refrigerator, concentrations of the dosing solutions were 93-100% of their initial measured concentrations. The analytical results showed that the test article was stable in the vehicle and the variation between nominal and actual dosage to the animals was acceptable.

C. OBSERVATIONS

1. Maternal observations and evaluations

The animals were checked daily for clinical signs of toxicity, as well as for mortality and morbidity. Clinical signs were also recorded twice daily during the dosing interval. Maternal body weights were recorded on GD 1 and 7-22. Food was weighed on GD 1, 3, 5, 7, 9, 11, 13, 15, 17, 19, 21, and 22. Dams were sacrificed on GD 22 by carbon dioxide asphyxiation and subjected to gross necropsy. Gravid uteri were weighed. Ovaries were examined for number of corpora lutea and uteri were examined for numbers of live and dead fetuses and resorptions. Uteri of apparently nonpregnant animals were stained with ammonium sulfide to detect early resorptions.

2. Fetal evaluations

Live fetuses were weighed, sexed, and examined for external malformations/ variations. To identify stunted fetuses, the maximum stunted weight (MSW) was calculated for each litter; a fetus weighing less than or equal to the MSW was considered stunted. The first live fetus and thereafter every other fetus in each litter was decapitated and examined for visceral malformations/variations. Retarded renal development was classified using the schema of Woo and Hoar. The heads were fixed in Bouin's solution and examined. The remaining fetuses were euthanized by an intraperitoneal injection or an oral dose of sodium pentobarbital. The processed for skeletal examination.

D. DATA ANALYSIS

1. Statistical analysis

Sequential trend testing was applied to the data for each parameter. For litter parameters, the proportion of affected fetuses per litter or the litter mean was the experimental unit for statistical evaluation. The level of significance was $p<0.05$. Maternal body weight, weight changes, and food consumption data were analyzed by a linear contrast of means from the Analysis of

9

Variance (ANOVA). The numbers of live and dead fetuses, resorptions, implantations, and corpora lutea and the incidence of fetal malformations/ variations were analyzed by Jonckheere's test. Incidence rates for pregnancy, clinical observations, maternal mortality, total resorptions, and early deliveries were analyzed by the Cochran-Armitage test. Fetal body weights (covariates litter size, sex ratio) and sex ratios (covariate litter size) were analyzed by linear contrast of least square means from ANCOVA.

2. Historical control data were not provided to allow comparison with current controls.

II. RESULTS

A. MATERNAL TOXICITY

1. Mortality and clinical signs

All animals survived to terminal sacrifice. Treatment related clinical signs of toxicity are listed in Table 2. At the high dose, there was a significant trend ($p \leq 0.05$) for the number of animals affected by abnormal gait or mobility, irregular respiration, lethargy, and lung noise. Lung noise was also heard in two dams from the 300 mg/kg/day group. Irregular respiration was observed simultaneously with lung noise in the high dose dams.

TABLE 2: Incidence rates of clinical signs of toxicity in rats given glycolic acid Days 7 to 21^

Observation	0 mg/kg/day	75 mg/kg/day	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
Abnormal gait or mobility	0/25	1/25	0/25	0/25	5/25*
Irregular respiration	0/25	0/25	0/25	0/25	2/25*
Lethargy	0/25	0/25	0/25	0/25	2/25*
Lung noise	0/25	0/25	0/25	2/25	8/25*

^Data taken from Table 3, p. 28, MRID 44589501.
*Significant trend (Cochran-Armitage test); $p \leq 0.05$.

10

2. Body weight

Selected maternal body weights and body weight changes during gestation are listed in Table 3. High dose dams had significantly ($p \leq 0.05$) lower absolute and adjusted body weights as compared to the controls on GD 22. The final absolute and adjusted body weights of the 600 mg/kg/day group were both 95% of the control group level. Body weight gains by the high-dose group were significantly ($p \leq 0.05$) greater than the control group during GD 1-7 and significantly ($p \leq 0.05$) less than the control group for the intervals of GD 7-9, 17-19, 19-21, 21-22, and 7-22 (dosing interval). After GD 17, body weight gains by the 600 mg/kg/day group were 67-80% of the control group level.

Body weights and body weight gains of the 75, 150, and 300 mg/kg/day groups were similar to the control group throughout gestation.

TABLE 3. Selected maternal body weights and body weight changes (g)^

Day of gestation	0 mg/kg/day	75 mg/kg/day	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
1	241.3	241.1	241.6	239.2	241.7
7	274.4	275.6	277.3	275.4	279.8
9	281.9	283.6	286.9	284.2	278.8
15	313.3	317.3	321.0	315.9	312.4
19	355.9	359.1	363.5	355.2	347.7
22	409.0	413.7	419.8	410.6	387.6* (95)
Wt. change GD 7-22	134.7	138.1	142.5	135.2	107.8* (80)
Adjusted body weight, GD 22[a]	316.0	321.2	328.2	316.9	301.2* (95)

^Data taken from Table 1 and Appendix D, pp. 26 and 69-79, respectively, MRID 44589501.
[a]Adjusted body weight = final body weight - gravid uterine weight.
Significant trend:*$p \leq 0.05$; numbers in parentheses are per cent of control.

3. Food consumption

Food consumption was comparable between the 75, 150, and 300 mg/kg/day groups and the control group throughout the study. The 600 mg/kg/day high dose group had significantly ($p \leq 0.05$; 81% of control) lower

11

food consumption than the controls during GD 21-22 and significantly ($p \leq 0.05$; 108% of control) greater food consumption than the controls during GD 1-7.

4. Gross pathology

No treatment-related abnormalities were noted in any dam at necropsy.

5. Cesarean section data

Data collected at cesarean section are summarized in Table 4. Fetal body weights in the high dose group were significantly ($p \leq 0.05$) less (13%) than the controls. No differences were observed between the treated and control groups for number of corpora lutea/dam, implantations/dam, pre- or post implantation loss, resorptions/ dam, fetuses/litter, or fetal sex ratios. One dam in the 150 mg/kg/day group delivered early on GD 21.

TABLE 4. Cesarean section observations^

Observation	0 mg/kg/ day	75 mg/kg/day	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
No. Animals Assigned	25	25	25	25	25
No. Pregnant	25	25	24	23	23
Pregnancy Rate (%)	100	100	96	92	92
Maternal Mortality	0	0	0	0	0
Delivered early/aborted	0	0	1	0	0
Total Corpora Lutea[a]	408	408	364	400	391
Corpora Lutea/Dam	16.3	16.3	15.8	17.4	17.0
Total Implantation[a]	384	374	338	352	366
Implantation/Dam	15.4	15.0	14.7	15.3	15.9
Preimplantation loss (%)[a]	6	8	7	12	6
Postimplantation loss(%)[a]	5	5	5	4	4
Total Live Fetuses[a]	366	354	321	339	352
Live Fetuses/litter	14.6	14.2	14.0	14.7	15.3
Mean Fetal Weight (g)	5.02	5.20	5.17	5.05	4.38*
Sex Ratio (% Male)	44	49	50	50	48
Total Resorptions/dam	0.7	0.8	0.7	0.6	0.6
Early resorptions/dam	0.7	0.8	0.7	0.6	0.6
Late resorptions/dam	0.0	0.0	0.1	0.0	0.0
Total Dead Fetuses	0	0	0	0	0
Dams with allresorptions	0	0	0	0	0

^Data extracted from Table 4 and Appendix H, pp. 29 and 131-135, respectively, MRID 44589501.
Significant trend (Linear contrast of least square means from ANCOVA), *$p \leq 0.05$.
[a]Calculated by reviewer.

B. DEVELOPMENTAL TOXICITY

The number of litters examined in the 0, 75, 150, 300, and 600 mg/kg/day groups was 25, 25, 23, 23, and 23, respectively. The incidence rate of fetuses(litters) with treatment-related malformations/variations was 17(7), 9(7), 16(5), 16(6), and 98(18) ($p \leq 0.01$), respectively. Statistical significance was calculated by the reviewer using Fisher's Exact test. The most prominent effects at 300 and 600 mg/kg/day were malformations/variations of the skeleton.

1. External examination

Selected external malformations/variations are listed in Table 5. Singular occurrences are not shown on the table, but are included in the group totals. At the high dose, three fetuses from one litter were observed with clubbed foot and two fetuses from two litters had gastroschisis.

2. Visceral examination

The total number of fetuses(litters) examined for visceral malformations/ variations was 187(25), 182(25), 168(23), 176(23), and 183(23) in the 0, 75, 150, 300, and 600 mg/kg/day groups, respectively. A septal defect in the heart was observed in two fetuses from two control litters, in one fetus in each of the 75 and 150 mg/kg/day groups, and in three fetuses from one litter in the 600 mg/kg/day group. A distended brain was seen in 0(0), 1(1), 2(2), 2(1), and 5(1) fetuses (litters) from the 0, 75, 150, 300, and 600 mg/kg/day groups, respectively.

3. Skeletal examination

Selected skeletal malformations/variations are listed in Table 5. Singular occurrences are not shown on the table, but are included in the group totals. Treatment related skeletal anomalies occurred in the ribs, sternebrae, and vertebrae of fetuses in the high-dose litters and in the ribs and vertebrae of the 300 mg/kg/day litters.

TABLE 5. Incidence rates of selected malformations/variations^

	0 mg/kg/day	75 mg/kg/day	150 mg/kg/day	300 mg/kg/day	600 mg/kg/day
No. examined (external and skeletal)	366 (25)[a]	354 (25)	321 (23)	339 (23)	352 (23)
External					
No. affected[b]	0 (0)	1 (1)	1 (1)	1 (1)	6 (3)
Gastroschisis	0 (0)	1 (1)	0 (0)	0 (0)	2 (2)
Clubbed foot	0 (0)	0 (0)	0 (0)	0 (0)	3 (1)
Skeletal					
No. affected[b]	15 (7)	6 (4)	14 (3)	14 (5)	95 (18)++
Rib - absent - fused	0 (0) 0 (0)	0 (0) 0 (0)	0 (0) 0 (0)	0 (0) 2 (2)	3 (3)* 9 (9)*
Sternebra - fused - nonfused - misaligned - retarded ossification	 0 (0) 1 (1) 1 (1) 14 (6)	 0 (0) 0 (0) 1 (1) 4 (2)	 0 (0) 0 (0) 0 (0) 13 (2)	 0 (0) 1 (1) 1 (1) 12 (3)	 3 (3)* 6 (5)* 17 (11)* 60 (14)*
Vertebra - fused - hemi	 0 (0) 0 (0)	 0 (0) 1 (1)	 0 (0) 0 (0)	 2 (2) 1 (1)	 6 (6)* 8 (8)*

^Data taken from Tables 5 and 6 and Appendix J, pp. 31-34, 35-39, and 140-243, respectively, MRID 44589501.
[a]Fetuses (litters)
[b]Number affected includes singular occurrences within groups that are not shown on the table.
*Significant trend (Jonckheere's test); $p \leq 0.05$.
++Significantly different from control; $p \leq 0.01$; calculated by reviewer using Fisher's Exact test.

III. DISCUSSION

A. INVESTIGATORS' CONCLUSIONS

The study author concluded that both maternal and developmental toxicity were observed at 300 and 600 mg/kg/day. At the high dose, there was a significant reduction in maternal weight changes, and clinical signs of toxicity included abnormal gait/ staggering, lung noise, irregular respiration, and lethargy. Lung noise was also heard in two dams in the 300 mg/kg/day group and was attributed to treatment.

Developmental toxicity in fetuses from the 600 mg/kg/day dams consisted of significantly reduced fetal body weights and significantly increased incidences of skeletal malformations such as fused and absent ribs, fused and hemi vertebrae, and abnormally fused and non fused sternebrae. Also at the high dose, there was an increased incidence of skeletal variations including misaligned and incompletely ossified sternebra and incompletely ossified vertebra. A slight, although not statistically significant, increase in the incidences of fused ribs and fused vertebra occurred in the 300 mg/kg/day group; the incidences for both of these findings was 2 fetuses from 2 litters. The maternal and developmental toxicity NOEL were 150 mg/kg/day.

B. REVIEWER'S DISCUSSION

1. MATERNAL TOXICITY

Clear indications of maternal toxicity were observed in the 600 mg/kg/day dams. Significantly increased incidences of clinical signs of toxicity at the high dose included abnormal gait, irregular respiration, lung noise, and lethargy. Irregular respiration was a concurrent finding with lung noise in two of the high dose dams but not in the 300 mg/kg/day group, possibly due to the severity of the effects at the higher dose. Although lung noise was observed in only two of 25 animals in the 300 mg/kg/day group, the incidence is considered treatment related at this dose because it appears to be dose related and the controls were unaffected. Also, the incidence of lung noise was significantly increased in the range finding study at doses of 500 and 1000 mg/kg/day.

The high-dose group had a significantly greater body weight gain for GD 1-7 which was followed by a significant decrease for GD 7-9. The initial increase was most likely due to the increase in food consumption by the high-dose dams for the GD 1-7 interval and the subsequent decrease was probably compensatory. Therefore, the lower body weight gain by the high-dose group at the beginning of the dosing interval is not considered treatment related. On the other hand, decreased maternal body weight gains by the high-dose

group after GD 17 are considered treatment-related. The reduced body weight gains by this group during the last week of treatment resulted in significantly lower weight gains for the entire dosing interval and lower final absolute body weights as compared to the control group.

Therefore, the maternal toxicity LOEL is 300 mg/kg/day based on clinical signs of toxicity (lung noise) and the maternal toxicity NOEL is 150 mg/kg/day.

2. DEVELOPMENTAL TOXICITY

a. Deaths/resorptions

Maternal treatment with glycolic acid did not result in fetal deaths or in an increase in resorptions.

b. Altered growth

Mean fetal body weights from high dose dams were significantly less than the controls. Because the effect on maternal body weight gains occurred later in the dosing interval, and hence later in gestation, maternal toxicity is likely to have contributed to the reduced growth of the fetuses.

c. Developmental variations

An increase in the incidence of reduced ossification of the sternebrae in litters from the high-dose group correlated with the lower fetal body weights.

d. Malformations

The incidence rate of malformations of the skeletal system was increased in the 300 and 600 mg/kg/day litters. Significant increases occurred for the number of high dose litters containing fetuses with rib, sternebrae, and vertebrae anomalies. A low incidence, although not statistically significant, of fused ribs and fused vertebrae was also observed at 300 mg/kg/day. Although historical control data for the testing facility were not provided in the report, the reviewer compared the incidence rates of fused rib and fused vertebra in the current study to Charles River historical control data for Crl:CD®(SD)BR rats (Charles River Laboratories,

1996). For the years 1992-1994, fused rib was seen in only 3 fetuses from 2 litters out of a total of 14,364 fetuses from 2,094 litters. Fused vertebra was not listed and, therefore, assumed to have not been observed at all. Because of the apparent rarity of fused rib and fused vertebra, and because these were seen in the current study in the high-dose group but not in the controls, these effects in the 300 mg/kg/day litters are considered treatment-related.

Therefore, the developmental toxicity LOEL is 300 mg/kg/day based on skeletal malformations (fused ribs and fused vertebrae); developmental toxicity NOEL is 150 mg/kg/day.

C. STUDY DEFICIENCIES

No major deficiencies were identified in the conduct of this study. Historical control data would have been helpful in establishing a more definitive developmental toxicity NOEL.

D. CORE CLASSIFICATION

This study is classified as **Acceptable** and satisfies the requirements for a (§ 83-3) Developmental Toxicity study in rats.