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Attn: Section 8(e), Coordinator

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Dear Sir:

In May, 1987, submitted a TSCA Section 8(e) notification on the toxicity of clarified slurry oil (CAS 64741-62-4) and the relationship between subchronic and developmental toxicity and chemical composition. Supplemental submissions to this 8(e) have been made for several other refinery streams, further describing the relationship between stream composition and toxicity, usually in the form of interim (preliminary) reports for subchronic dermal studies. At this time we are submitting a final report for another of these studies. The test article, with CAS number, is given below. We believe the effects seen in this study are due largely to polycyclic aromatic compounds in agreement with conclusions reported in our previous submissions.

The interim submission made for this study reported maternal toxicity based on decreased food consumption, net body weight gain, decreased thymus and liver weights and increased liver weight. In utero death (resorptions) and decreased fetal weights were also reported. The current submission adds data from visceral and skeletal evaluations. No significant incidences of malformations or variations were observed. Skeletal evaluations showed statistically significant signs of growth retardation at the lowest dose tested; the response, however, was not dose related.

<u>Study #</u>	<u>CAS #</u>	<u>Test Article</u>
64168	64741-81-7	Heavy Coker Gas Oil (Joliet)

This study was carried out at

Confidentiality is being claimed for company identifiers and names of company employees. All pages containing this information have been stamped "Confidential". Two copies of this notification are being submitted; the confidential information has been circled in one copy and excised from the other. The latter copy is intended for the EPA's public file. The substantiation for this claim is attached.

Sincerely,

SUMMARY

Heavy Coker Gas Oil (JHCGO) was applied once daily via dermal application to groups of presumed-pregnant rats at doses of 0, 8, 30, 125, or 250 mg/kg/day. All animals were dosed on gestation days 0-19; cesarean sections were performed on gestation day 20.

Maternal toxicity was observed at all dose levels. The effects noted were decreased thymus weights (both absolute and relative) and increased liver weights (relative). Numerous clinical signs of maternal toxicity were also observed at 30 mg/kg and above. They included red vaginal discharge, paleness, emaciation, and moribundity (250 mg/kg). With the exception of the clinical observations, a dose-related response was demonstrated for all maternal parameters evaluated. Consequently, adverse effects observed at lower dose levels were considered biologically significant in the few cases where statistical significance was not achieved. Application of JHCGO also resulted in skin irritation which ranged from slight (8 mg/kg) to severe (250 mg/kg). The serum chemistry data shows that there is a significant difference in the serum analysis of pregnant rats exposed to JHCGO at 125 and 250 mg/kg/day from control pregnant rats. Statistically significant differences were found between the untreated and treated animals for hematology parameters.

Developmental toxicity was observed at 30 mg/kg and above. In utero death (resorption) was significantly increased and fetal weights significantly decreased at 125 and 250 mg/kg. The incidence of resorption was also increased at 30 mg/kg and, although not statistically significant, is considered to be biologically significant. The fetal skeletal evaluations showed statistically significant signs of growth retardation at 8 mg/kg/day; the response, however, was not dose related.

In summary, these data indicate that the No-Observed-Adverse-Effect-Level for JHCGO for maternal toxicity is less than 8 mg/kg and for developmental toxicity is 8 mg/kg.

1.0 INTRODUCTION

A developmental toxicity study was conducted at _____ in which _____ Heavy Coker Gas Oil (HCGO) was applied to the skin of pregnant Sprague-Dawley rats. HCGO, a refinery stream produced by thermal cracking of vacuum residuum, was applied dermally since production and processing of this material can result in repeated human skin contact. The primary objectives of this study were to evaluate the effects of dermal HCGO exposure on female rats during gestation and to determine if such exposure adversely affects fetal viability and development. Selection of dose levels was based on the results of a subchronic toxicity study using this material (Study No. 64165 [1]). Sprague-Dawley rats were chosen as species and strain because 1) they have been widely used throughout industry for non-clinical studies of teratogenic and/or reproductive toxic potential, 2) data obtained on them can be compared with a bank of historical control data, and 3) there are no non-animal alternative test procedures that will accomplish the objectives of this study.

In order to obtain a more complete profile of maternal toxicity, the following procedures were also performed: maternal necropsy, weighing of the liver and thymus, serum chemistry analysis, hematology analysis, micronucleus analysis, and DNA adduct analysis (fetal liver samples were also collected for DNA adduct analysis). The micronucleus and DNA adduct analyses were performed under separate protocols and will be issued as separate reports by the Genetic Toxicology group (Study Nos. 64169 and 64170, respectively).

2.0 METHODOLOGY

2.1 Experimental Design

Presumed-pregnant rats were distributed into five experimental groups with dose levels of 0, 8, 30, 125, and 250 mg/kg/day. JHCGO was administered daily to each female throughout gestation (days 0-19). The dosing regimen is summarized below:

Summary of Experimental Design

GROUP	DOSE LEVEL (mg/kg/day)	MATERIAL	DAYS OF ADMINISTRATION*
Group 1	0	Sham Control	0-19
Group 2	8	JHCGO	0-19
Group 3	30	JHCGO	0-19
Group 4	125	JHCGO	0-19
Group 5	250	JHCGO	0-19

* Designation as gestation day 0 followed detection of a vaginal plug (*in situ* or expelled) and spermatozoa in the vaginal lavage fluid.

All animals were monitored throughout the study until sacrifice for 1) changes in appearance, behavior, and excretory function, and 2) signs of ill-health, mortality, and abortion. A pre-partum investigation on a variety of maternal and fetal parameters was undertaken to assess the influence of JHCGO on reproductive performance and development of offspring. The inclusive dates for specific study activities were as follows:

Acclimation Period: December 17, 1991 to January 6, 1992
 Mating Period: January 6-17, 1992
 Gestational Period: January 7 to February 6, 1992
 Cesarean Section: January 27 to February 6, 1992
 Experimental Termination Date: September 1, 1994

2.2 Animal Data

One hundred female Sprague-Dawley rats [VAF/Plus Crl:CD(SD)BR; 7 weeks old] were obtained from Charles River Breeding Laboratories, Kingston, New York (the breeder males were received in July of 1991 from the same supplier and location). The females were acclimated to the test facility for three weeks before the breeding period was initiated. Each female was individually identified by a numbered metal ear tag on gestation day 0.

Animals were individually housed in suspended, stainless steel cages, 10" long x 7" high x 7" wide, with wire mesh bottoms and fronts. Absorbent material in the dropping pans was changed daily. Clean cages were supplied approximately every two weeks. Animals were housed in air-conditioned rooms which averaged 69-70°F (low of 69° F, high of 73° F), 42-64% relative humidity (low of 14%, high of 79%) and 12-hour light-dark cycles. On a number of occasions the humidity fell outside of the acceptable range of 40-70%. These deviations did not affect the results of this study. Purina Certified Lab Chow (#5002) meal was provided ad libitum. Well water, also available ad libitum, was delivered by an Edstrom Automatic Watering System. The system was set to flush the room distribution lines daily at high pressure to minimize water stagnation and bacterial growth. No contaminant was considered to be present in animal feed or water at a level sufficient to interfere with this study.

2.3 Mating Period

During the mating period, nulliparous female rats were placed with male rats in a ratio of 1:1 and observed daily for evidence of having engaged in breeding activity. Each morning during the period of cohabitation, the drop-pan papers under the animal cages were checked for the presence of expelled vaginal sperm plugs; additionally, each female rat was examined for the presence of in situ vaginal sperm plugs. Vaginal lavage fluid was obtained from each female which exhibited a vaginal plug in situ or on the drop-pan papers, and was examined for the presence of spermatozoa. Females that were positive for sperm plug as well as for spermatozoa were considered to be at day 0 of presumed gestation and were placed in individual housing units. The cohabitation period was continued until 75 presumed-pregnant female rats were obtained. Female rats which showed no evidence of breeding activity, and the male rats used for breeding, were returned to the general rat population in the facility.

2.4 Assignment to Experimental Groups

Presumed-pregnant female rats were distributed among the experimental groups using a computer-generated table of random numbers for a stratified sample size of five. This procedure was continued each morning during the cohabitation period until each group contained fifteen presumed-pregnant females.

2.5 Material to be Administered

Test Material: Heavy Coker Gas Oil (from the refinery)
Identification: CRU #86181
Density: 0.94 g/ml
Expiration Date: 04-01-92

2.6 Test Material Administration/Control

2.6.1 JHCGO Dermal Administration (Groups 2-5)

The test material was administered to pregnant females in Groups 2-5 via dermal application on gestation days 9-19. This interval spans the entire period of embryogenesis. The dorsal trunk of each animal was clipped on gestation day 0 using Oster electrical clippers with #40 blades prior to dosing. Hair was clipped once weekly thereafter. The amount of test material to be applied to each animal was calculated using the most recently recorded body weight for that animal, the dose level, and the density of the test material. The exposure sites were not covered but the animals wore cardboard "Elizabethian" collars to minimize the ingestion of the test substance. Collars were fitted on gestation day 0 and replaced as necessary. JHCGO was applied once daily to the clipped, intact, nonoccluded, dorsal surface of the rat at a dose level of 8, 30, 125, or 250 mg/kg body weight/day. The test material was measured using a 10 μ l syringe (with gradations of 0.2 μ l) for Groups 2 and 3 (towards the end of the study, a 50 μ l syringe was used for Group 3 since the doses began to exceed 10 μ l), a 50 μ l syringe (gradations of 1.0 μ l) for Group 4, and a 100 μ l syringe (gradations of 1.0 μ l) for Group 5. During dispensing, the test material was spread evenly on the dorsal skin of the rat using the tip of the syringe.

2.6.2 Sham Control (Group 1)

Presumed-pregnant rats were clipped and collared as above (Section 2.6.1). The dorsal skin of each rat was stroked with the tip of a 1.00 μ l syringe, but no test material was applied.

2.7 Observations During Gestation

2.7.1 Clinical Observations

On weekdays, animals were checked for morbidity and mortality twice daily. On weekends, they were checked once, as soon as practical each day. In addition each presumed pregnant female was observed at least once a day throughout gestation until sacrifice for signs of pathosis, abortion, premature delivery and/or death. All unusual findings were recorded.

2.7.2 Body Weights and Food Consumption

The body weight of each female was measured to the nearest 0.1 gram on days 0, 3, 6, 10, 13, 16, and 20 of gestation. Similarly, the amount of food consumed by

each animal was calculated for gestation day intervals 0-3, 3-6, 6-10, 10-13, 13-16, and 16-20. Stainless-steel feeders, identified individually by female rat number, were weighed on the first and last day of the specified interval. Feeders were weighed before noon. Since rats feed mainly at night, more definite control of the weighing time is unnecessary. When a rat spilled nonrecoverable amounts of food, the "consumption data" for that animal were excluded from data calculations for that collection interval.

2.8 Female Necropsy

Each female rat was sacrificed by over-exposure to diethyl ether on its 20th day of presumed gestation. The abdominal cavity was exposed and blood collected for hematology and serum chemistry analysis (see section 2.8.3 & 2.8.4). The reproductive organs were examined grossly for evidence of pathosis. Following removal of the uterus and ovaries, the carcass was given to the Pathology Group for macroscopic examination of the remaining organs. The thymus and liver of each pregnant female were weighed (to the nearest 0.001 gram), and the weights recorded by a member of the Pathology Group. Only the livers of pregnant females were preserved in 10% neutral buffered formalin.

2.8.1. Uterine/Ovarian Examination

The ovaries and uterus of each rat were excised and examined grossly. The number of corpora lutea (a measure of the number of eggs ovulated) per ovary of each pregnant female was counted and recorded. The ovaries of nonpregnant females were grossly examined and then discarded. All remarkable findings were recorded. The weight of the intact uterus was measured to the nearest tenth of a gram and recorded. The uterine contents of each pregnant rat were exposed, and the number and location of all implantations (early/late resorptions and live/dead fetuses) were recorded. The uterus of each female rat that appeared non-gravid was pressed between two glass slides, examined grossly for evidence of implantation, and then discarded. The uteri and ovaries (except those given to the Genetic Toxicology group for DNA analysis) of pregnant females were discarded following data collection.

2.8.2 Fetal Evaluations

Each live fetus was stripped of its surrounding extra-embryonic membranes, and its umbilical cord was clamped flush with the abdominal wall. The cord was then severed distal to the clamp. Each fetus was gendered, weighed to the nearest tenth of a gram, and grossly examined for external anomalies. The following definitions/terminology were used in describing fetal findings [2]:

Malformation: Permanent structural deviation which generally is incompatible with, or severely detrimental to normal postnatal survival or development. Additionally absence of a structure which should have been present, as well as deviations in tail development, are also classified as malformations.

Variation: A variation is a divergence beyond the usual range of structural constitution. It has an indeterminate effect on health and generally has no effect on survival.

Incidental: An incidental finding is generally an accidental event, e.g., accidentally the tip of the tail was cut off.

After gross evaluation, fetuses were submerged in cold water until no response to stimuli was evident. Fetuses in each litter (except one litter in Group 2 for which all fetuses were inadvertently prepared for skeletal exam) were then equally distributed into two groups, and preparation began for either soft tissue or skeletal evaluations.

2.8.3 Hematology

Blood samples were collected from abdominal aorta of each assumed pregnant female for clinical chemistry and hematology analyses. One tube containing EDTA as an anticoagulant was filled with whole blood from each animal. Hematology analysis was performed using an Oriño ELT-8/ds. Uncolotted samples were analyzed on the same calendar day that they were collected for:

hematocrit (HCT)	red blood cell (RBC) count
hemoglobin (HGB)	white blood cell (WBC) count
platelet count (PLT)	

Mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and mean corpuscular hemoglobin concentration (MCHC) were calculated. A thin smear of blood was made for determination of red blood cell morphology, nucleated RBCs and white blood cell differentials [seven components including segmented neutrophils (SEG) and lymphocytes (LYM)]. A detailed description of the procedures employed is available in the Document Archives [Study 64168HA (3)].

2.8.4 Serum Chemistry

Whole blood from each dam was allowed to clot for approximately thirty minutes, and centrifuged to obtain the serum. Samples were analyzed for the following biochemical parameters using a Centrifchem or sodium/potassium analyzer:

sorbitol dehydrogenase (SDH)	cholesterol	glucose
alanine aminotransferase (ALT)	triglycerides	uric acid
aspartate aminotransferase (AST)	total protein	potassium
alkaline phosphatase (ALKP)	albumin (A)	calcium
inorganic phosphorus	bilirubin, total	chloride
urea nitrogen (BUN)	creatinine	sodium
lactate dehydrogenase		

Globulin (G) and A/G ratio were calculated. A detailed description of the procedures employed is available in the Document Archives [Study 64168CA (4)].

2.9 Data Analysis

Data were collected, processed, and analyzed using the Reproduction module of the Grosse Data Acquisition/Reporting System. Maternal biophase data, cesarean section data, and fetal data were evaluated statistically by analysis of variance followed by group comparisons using Fisher's Exact or Dunnett's Test.

Thymus and liver weights were collected, processed, and analyzed using the Pathology module of the Grosse Data Acquisition/Reporting System. The data were statistically evaluated using analysis of variance and Tukey's Test.

Serum chemistry and hematology data were collected, processed and analyzed using "CLINPATH" (Grosse System). A description of the statistical analysis performed on the hematology and serum chemistry can be found in the reports on said topics [3,4] which are available in the document Archives.

For all statistical analyses, differences between control and treated groups were considered to be statistically significant if the probability of the difference being due to chance was less than 5% ($p < 0.05$).

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3.0 RESULTS

ALL DATA TABLES ARE LOCATED FOLLOWING THE CONCLUSIONS SECTION.

3.1 Clinical Observations

Incidental observations reported during gestation are presented in Table 1. The red nasal exudate and chromodacryorrhea noted in control and treated groups are common in animals that are collared and/or stressed. Scratches were observed on the backs of four animals. Three of these were noted at the time of the first clipping and probably occurred during mating activity. Scratches appeared on one female in Group 5 during the latter part of gestation. She was probably scratching in response to the irritation of the treated skin; this case of "scratches" is identified as a separate observation in Table 1. Several females developed neck lesions in spite of the protective soft rubber tubing that lined the inner surface of the cardboard collar.

JHCGO-related observations reported during gestation are also included in Table 1. Skin irritation was present in all groups exposed to JHCGO. The irritation ranged from slight at 8 mg/kg (erythema and flaking) to severe at 125 and 250 mg/kg (thickening of the skin, fissuring of the skin, and open sores). Clinical signs of maternal toxicity were evident and, in some cases, severe at 125 and 250 mg/kg. Red vaginal discharge was observed at 30 mg/kg and above; the incidence increased with increasing dose level. In all cases, the discharge could be attributed to resorption of offspring. Several females at the 125 and 250 mg/kg dose levels became pale and their skin became cool to the touch following the onset of the red vaginal discharge. One female in the high dose group (250 mg/kg) was sacrificed moribund on gestation day 16. She had no stool, was emaciated and cool to the touch, and had severe vaginal bleeding (red vaginal discharge). Uterine examination revealed 20 implantation sites, all of which were resorbed. Another female in this group exhibited decreased activity and labored breathing on gestation day 17. Individual clinical observations are presented in Appendix 6.1.

3.2 Body Weights and Food Consumption

Mean body weights, mean body weight changes, and mean uterine and net body weights are presented in Tables 2, 3, and 4, respectively. In general, the mean body weights of all groups treated with JHCGO were significantly lower than the mean weights of the control group throughout most of gestation (Table 2). It should be noted that on gestation day 0 there were no significant differences

among the mean body weights for the groups. Individual body weights, body weight change, and uterine weight and net maternal body weight change are presented in Appendices 6.2, 6.3, and 6.4 respectively.

Overall mean body weight gain (gestation days 0-20) decreased with increasing dose level. Mean body weight gains were significantly reduced at 30, 125, and 250 mg/kg. At 30 mg/kg, the significance was apparent when overall body weight gain was calculated. The decrease in body weight gain was more severe at the 125 and 250 mg/kg dose levels and achieved statistical significance for nearly all intervals measured (Table 3). Although not statistically significant, body weight gain was also reduced throughout the gestational period at 8 mg/kg.

Net body weight gain was significantly reduced at 125 and 250 mg/kg (Table 4). Statistical significance was not achieved for the mean net body weight changes at 8 and 30 mg/kg, however both were reduced compared to the control mean value.

Mean daily food consumption values during gestation are presented in Table 5. Food consumption was significantly decreased in all groups treated with JHCGO during many of the intervals evaluated. The number of intervals during which food consumption was significantly reduced, as well as the amount of reduction, increased with increasing dose level. Individual food consumption data are presented in Appendix 6.5.

3.3 Observations at Cesarean Section

3.3.1 Maternal Necropsy Findings

There were no remarkable maternal necropsy findings. Individual maternal necropsy findings are presented in Appendix 6.6. Individual macroscopic examination results from Pathology group are presented in Appendix 6.7.

3.3.2 Organ Weights

Mean maternal liver and thymus weights are shown in Table 6. The mean absolute liver weight for the high-dose group (250 mg/kg) was significantly reduced. Under normal conditions, liver weight increases during pregnancy. When animals resorb their litters, as was the case for animals exposed to 250 mg/kg, the liver returns to the smaller size which is normal for a non-pregnant female. Calculation of relative weights (Table 6) shows that the mean relative liver weights were significantly increased at 125 and 250 mg/kg. Absolute thymus weights were significantly reduced at 30 mg/kg and above. Relative thymus weights decreased with increasing dose level, but statistical significance

was achieved only at 125 and 250 mg/kg. Individual liver and thymus weights are presented in Appendix 6.8.

3.3.3 Reproductive/Developmental Evaluations

A summary of the reproductive data is presented in Table 7. Viable litter size was significantly reduced at 125 and 250 mg/kg. Both mean number and percent resorptions were significantly increased at these same dose levels as was the number of dams with resorptions. Overall, resorption increased with increasing dose level. The increase at 30 mg/kg is considered to be biologically significant since approximately one-half of the females in this group had between 14 and 39 percent fetal resorption (the mean for the control group was 4.9 percent resorption). The biological significance of the increase in percent resorption for the 8 mg/kg group is uncertain.

The statistical significance achieved at 30 mg/kg for the number of male and female fetuses is not considered to be biologically significant and can be attributed to the unusually high number of males and low number of females in the control group. The individual Cesarean section data is presented in Appendix 6.9. The individual fetal status and uterine location are presented in Appendix 7.0.

Fetal body weights, a parameter of body growth and development, were significantly decreased for all viable fetuses at the 125 and 250 mg/kg dose levels (Table 8). Individual fetal body weights are presented in Appendix 7.1.

Gross external fetal examinations indicated isolated incidences of variations and malformations at 8, 30, and 125 mg/kg (Table 9). Kinked tail was noted in two fetuses: one in the 8 mg/kg dose group and one in the 125 mg/kg dose group. One fetus (30 mg/kg) had gastroschisis (protrusion of the intestines through a fissure in the abdominal wall). These scattered findings did not appear to be related to test material administration. Summary of fetal external evaluations are presented in Table 9 and individual external evaluations are presented in Appendix 7.2.

Fetal skeletal evaluations showed a statistically significant increase in incompletely ossified or unossified sternbrae at dose level of 8 mg/kg/day. This indicates significant growth retardation at 8 mg/kg. The summary of skeletal evaluations is presented in Table 10, and individual skeletal evaluations are presented in Appendix 7.3. The fetal visceral evaluations showed isolated incidences of variations and malformations. These scattered findings did not appear to be related to test material administration. The summary of visceral evaluations is presented in Table 11, and individual visceral evaluations are presented in Appendix 7.4.

3.4 Hematology

Statistically significant differences ($p < 0.05$, Tukey's multiple comparison test) were found between the untreated and treated animals for RBC, HGB, MCV, HCT, MCH, PLT, segmented neutrophils, lymphocytes and monocytes. A linear relationship (>99% confidence level, Pearson's correlation coefficient) was found between the dose and blood level for all of the above except segmented neutrophils, lymphocytes, and monocytes. When the historical hematology reference values are taken into consideration, the dose response curves for all the affected parameters fell outside the normal range as defined by the 10th and 90th percentiles of the historical data. Mean hematology values are presented in Table 12. A more detailed description of the hematology results, including the RBC morphology data, can be found in the Document Archives [Study No. 64168HA (3)].

3.5 Serum Chemistry

A summary of serum chemistry values is presented in Table 13. Statistically significant differences were found between the untreated and treated animals for glucose, urea nitrogen, creatinine, triglycerides, total protein, bilirubin, albumin, sodium, inorganic phosphorus, calcium, sorbitol dehydrogenase, and chloride. A linear relationship (>99% confidence level, Pearson's correlation coefficient) was found between the dose and blood level for all the above components except bilirubin. The dose response curves for all the above except creatinine fell above the normal range as defined by the 10th and 90th percentiles of the historical data. The levels of serum glucose, triglycerides, albumin and A/G ratio are noticeably different between non-pregnant and pregnant rats on gestation day 20. Serum data indicates that with the exception of A/G ratio, the above serum components in rats treated at 125 and 250 mg/kg/day are comparable with the normal range of non-pregnant animals. A more detailed description of the serum chemistry results can be found in the Document Archives [Study No. 64168CA (4)].

4.0 DISCUSSION AND CONCLUSIONS

Daily application of JHCGO on the skin of pregnant rats during gestation resulted in maternal toxicity at all dose levels. Evidence of maternal toxicity included numerous clinical signs, decreased food consumption and net body weight gain, decreased thymus weights, and increased liver weights. Although statistical significance was not always achieved at the lower dose levels, (e.g., relative liver and thymus weights at 8 and 30 mg/kg), a clear dose-response relationship exists for all maternal parameters evaluated. Application of JHCGO to the skin also resulted in skin irritation which ranged from slight (8 mg/kg) to severe (250 mg/kg).

Fetal development was adversely affected by JHCGO administration. The number and percent resorptions were significantly increased and live litter size significantly decreased at 125 and 250 mg/kg. The increase in in utero death (resorption) at 30 mg/kg is considered to be biologically significant. The percent resorption was also increased at the lowest dose level (8 mg/kg), however, the increase was due to two females with 24 and 25 percent resorption, respectively. These two females may have been more sensitive to the effects of JHCGO administration.

External evaluations of fetuses revealed a significant decrease in fetal weights at 125 and 250 mg/kg as well as apparently isolated incidences of malformation and variation at 8, 30, and 125 mg/kg. With regard to the incidence of malformation/variation, the total number of affected fetuses per group were two, one, and two, respectively; there is no evidence of a dose response. Due to this low incidence of seemingly unrelated observations and the lack of a dose response, the observed external anomalies cannot be positively correlated with JHCGO exposure. Although fetal skeletal evaluations showed statistically significant growth retardation at 8 mg/kg, the response was not dose related. Fetal visceral evaluations showed few malformations and variations. The number of responses was low and there was no evidence of dose response. These findings suggest that the observed visceral anomalies are not treatment related.

Hematology data and serum chemistry data showed statistically significant differences between the untreated and treated animals for most of the parameters involved. When historical data was taken into consideration the dose response curves fell outside the normal range for all the components except creatinine. A review of the serum data indicates that with the exception of the albumin/globulin ratio, the serum components in rats treated 125 and 250 mg/kg/day are comparable with the normal range of non-pregnant animals. The results are in agreement with a high degree of resorptions observed in these treated groups.

In conclusion, the data suggest that daily dermal administration of JHCGC throughout gestation produces maternal toxicity at an exposure level of 8 mg/kg/day and developmental toxicity at exposure levels greater than 8 mg/kg.