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Chemical Category			
HEAVY COKER GAS OIL; SYNTOWER BOTTOMS; COKER LIGHT GAS OIL;*			

SUPP

OFFICE OF TOXIC SUBSTANCES
CODING FORM FOR GLOBAL INDEXING

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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 final reports for four of these studies. The test articles, with CAS numbers, are given below. We believe the effects seen in these studies are due largely to polycyclic aromatic compounds in agreement with conclusions reported in our previous submissions.

In agreement with the interim submissions, the most prominent findings in the reports being submitted at this time include mortality, decreased body weight, alterations in serum chemistry and hematology, liver necrosis, and histopathologic changes in spleen, thymus, lymph nodes and bone marrow. Changes in other organs were seen for one or two materials. The streams for which one or more of these effects were observed are listed below. Visbreaker Residue was the least toxic of the four materials; no treatment related histopathological effects were seen for this material.

<u>Study #</u>	<u>CAS #</u>	<u>Test Article</u>
50391	64741-81-7	Heavy Coker Gas Oil
62710	64741-62-4	Syntower Bottoms
61996	64741-82-8	Coker Light Gas Oil
64002	64741-80-6	Visbreaker Residue

SUMMARY

Heavy Coker Gas Oil from refinery (HCGO-P, CRU #83366) was administered 5 days/week for no more than 14 weeks to the skin of groups of 10 male and 10 female Charles River CD(SD) rats at doses of 30, 125, 500, and 2000 mg/kg/day. The rats were fitted with cardboard "Elizabethan" collars to minimize the ingestion of the test material, which was applied neat and left uncovered on the skin. A similar group of rats served as controls; they were treated the same as the test animals except that no material was applied to their skin.

At the site of application, HCGO-P produced moderate to severe effects to the skin. Moderate erythema and edema occurred, accompanied by thickening and cracking of the epidermis with some open sores on the skin. Animals exposed to HCGO-P exhibited numerous signs of systemic toxicity, which increased in severity with increasing dose. Mortality was observed at doses of 125 mg/kg/day or greater; 10% of those dosed at 125 mg/kg/day died, and none treated at 500 or 2000 mg/kg/day survived the entire 14 weeks of study. Decreased body weight resulted from doses of 30 mg/kg/day or greater. Anemia resulted from doses of 125 mg/kg/day or greater. Serum chemistry parameters affected included aspartate aminotransferase, alkaline phosphatase, sorbitol dehydrogenase, total protein, albumin, and urea nitrogen. Sperm morphology was not adversely affected by exposure to HCGO-P.

HCGO-P applied dermally to rats caused microscopic skin changes that are consistent with irritation at the lowest dose administered. At the next higher doses, HCGO-P caused skin ulcers. The red blood cell phagocytosis in the lymph nodes, the reduced number of lymphocytes in the thymus, the cysts and fibrous foci in the spleen, and fibrosis and necrosis of the liver are considered to be treatment-related and were observed, in some cases, at 30 mg/kg/day. The weight changes in the thymus, liver, spleen and adrenals are also considered to be treatment-related.

Toxic effects were seen at all doses of HCGO-P administered; a No-Observed-Effect-Level was not found.

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1.0 INTRODUCTION

Heavy Coker Gas Oil (CAS #64741-81-7) from refinery (HCGO-P) is a petroleum residual fuel which is derived from the thermal rearrangement of heavy hydrocarbons in a unit called a coker. HCGO-P contains about 52% polycyclic aromatic compounds (PACs), including about 9% materials which are 3-ring or greater. Some of these PACs contain nitrogen (N-PAC) or sulfur (S-PAC).

The industrial use of petroleum residuals may result in repeated and prolonged human contact. This study was conducted to assess the potential toxic response from such dermal exposure. The dose levels were chosen based on data obtained in thirteen-week studies previously conducted in this laboratory using other refinery streams. The study was conducted in Sprague-Dawley rats because of the large amount of relevant background literature in this strain, and because rats have been a good model for predicting toxicological effects in humans.

This study was initiated at

on June 28, 1985. Administration of the test material occurred between July 25, 1985 and November 4, 1985. Necropsies were completed on November 5, 1985. When initiated, the duration of exposure was designed for 13 weeks. The exposure period was extended to 14 weeks to accommodate scheduling conflicts of staff.

2.0 MATERIALS AND METHODS

2.1 Experimental Design

A summary of the experimental design is presented in Table 1. All treatments were scheduled to be performed daily, five days per week, for fourteen weeks; exceptions are noted in the RESULTS (Section 3.0). The material was applied via dermal application.

Table 1: Summary of Experimental Design

Group	Treatment	Dose (mg/kg/day)	Treated	Number of Animals	
				Lab. Studies	Necropsy
1	Control	0	10M, 10F	All	All
2	HCGO-P	30	10M, 10F	All	All
3	HCGO-P	125	10M, 10F	All	All
4	HCGO-P	500	10M, 10F	All	All
5	HCGO-P	2000	10M, 10F	All	All

2.2 Animal and Animal Husbandry Data

Sixty-three male and sixty-five female Sprague-Dawley derived rats (crl:COBS CD[SD]BR) were received from Charles River, Lakeview, NJ. The animals were born and raised in a virus-free colony until twenty-seven days of age when they were shipped in crates designed to prevent virus contamination. They were acclimated to the laboratory for nine days before allocation into treatment groups. During the acclimation, the health of each animal was checked daily. No animals died during acclimation and none was removed because of poor health. At the end of the acclimation period, 100 healthy animals were assigned to treatment groups using a TOXSYS program ("ANIALLOC") that provided all groups with essentially identical body weight distributions. After assignment to treatment groups, each animal was identified by a uniquely-numbered ear tag.

After allocation, the animals were transferred to isolation units within Room 322; air was supplied to the room outside the isolation units, exhausted through each isolation unit, and observed for an additional week before dosing was initiated. The animals were housed individually in suspended, stainless steel cages, 10" long x 7" wide, with wire mesh bottoms and fronts. Absorbent material in the dropping pans was changed at least three times each week. Clean cages were supplied at least once every two weeks. The animals were housed in an air-conditioned room; the temperature and relative humidity were monitored continuously. Except for 3 periods of less than 2 hours each, the humidity was maintained between 48% and 60%; during the brief excursions, the maximum humidity was 82%. The temperature was maintained between 68 and 72° F except for one 7-hour period when the minimum temperature was 66° F. The room was provided with 12-hour light-dark phases.

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Prior to initiation of the study, as well as during the study, the animals were fed Purina Certified Lab Chow #5002 in pellet form, ad libitum, except for periods of deprivation required for hematology/serum chemistry studies and necropsy. Well water, also provided 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 the feed or water at levels sufficient to interfere with this study.

2.3 Material to be Administered

HCGO-P was supplied by CRU (Chemical Repository Unit).

Test material: Heavy Coker Gas Oil
Identification: CRU No. 83366
Stability: Three years at room temperature
Expiration Date: December, 1987

2.4 Test Material Administration/Control

Using Oster electric clippers with #40 blades, the hair was clipped (shaved) from the dorsal trunk of each animal approximately 24 hours before the start of dosing. Hair was reclipped as necessary, but at least once per week. Care was taken to avoid abrasion of the skin during removal of the hair. The animals were approximately 43 days of age at the initiation of dosing. They were dosed each weekday by application of the test material to their shaved backs. The animals in Groups 2 and 3 received HCGO-P 5 days/week for 14 weeks at daily doses of 30 and 125 mg/kg/day, respectively. (NOTE: The duration of the exposure period was extended from 13 to 14 weeks to accommodate the schedule of the the Study Pathologist at the time the study was conducted.) Because of the toxic effects which occurred at the higher dose levels, the animals in Group 4 received HCGO-P 5 days/week for 10 weeks at daily doses of 500 mg/kg/day, while the animals in Group 5 received HCGO-P 5 days/week for 2 weeks at daily doses of 2000 mg/kg/day. Each animal in Groups 2, 3, 4, and 5 received an amount of HCGO-P that was calculated from its most recent body weight and the dose for that group. The test material was measured by volume in a syringe that allowed accuracy within 10% of the calculated volume. HCGO-P was applied evenly over the backs of the animals, starting at the scapula and proceeding posteriorly along the spine, avoiding areas of skin with severe cracking of the skin or open sores. The site of application was not covered, but the animals wore cardboard "Elizabethan" collars to minimize ingestion of the test substance. These

collars are lined with latex tubing to minimize the development of irritation or lesions. Collars were fitted on the rats several days prior to the initiation of dosing so that the rats were used to them when the first dose was administered. During the week, if an animal was found to be without a collar, a new collar was applied prior to the next dosing. Each Saturday, the collars were removed and the backs of the rats were wiped off with gauze to remove as much residual test substance as possible. This was done to minimize oral ingestion while allowing any areas affected by the collars a two-day period to recover. Collars were replaced on Monday morning prior to or at the time of test material application. The untreated control animals were handled in the same manner as the other test animals except that no material was applied to their skin. Treated animals were dosed through the day prior to their scheduled sacrifice.

2.5 Observations During the Study

2.5.1 Clinical Observations and Skin Irritation

On weekdays, animals were checked for morbidity and mortality twice daily, at least seven hours apart. On weekends and holidays, they were checked once, as soon as practical each day. Any exceptions to this are noted in the study file. Each animal was also observed daily during the course of the study for normal and abnormal clinical signs. All findings were recorded. The parameters observed included appearance, behavior, excretory function, and discharges. Effects of the test material on the skin at the site of application were scored weekly. Erythema and edema were evaluated using the Draize scales. The skin was also examined and scored for chronic deterioration: flaking, thickening, stiffening, cracking, and sloughing. The scale used for scoring skin irritation is presented in Table 2. On days when scoring was not performed, no comment was made on the condition of the skin.

Table 2: Scale for Scoring Skin Irritation

ERYTHEMA*

- 0 = Normal
- 1 = Barely perceptible
- 2 = Well defined
- 3 = Moderate
- 4 = Severe (bee: red) to slight eschar

EDEMA*

- 0 = Normal
- 1 = Barely perceptible
- 2 = Edges of area well defined
- 3 = Area raised by approximately 1 mm
- 4 = Area raised by more than 1 mm or edema extends beyond area of exposure

CHRONIC DETERIORATION OF THE SKIN (CDS)

- 0 = Normal
- 1 = Desquamation (flaking of skin)
- 2 = Feels thickened and/or stiff; feels leathery
- 3 = Visibly thickened and/or stiffened; visibly leathery
- 4 = Cracks and fissures; almost no pliability
- 5 = Dermis is exposed (sloughing of crust; ulceration; open sores) or scar tissue is present.

* Draize, J.H., Woodward, G. and Calvery, H.O. (1944). Methods for the study of irritation and toxicity of substances applied topically to the skin and mucous membranes. *J. Pharmacol Exp. Therap.*, 82: 377-390.

2.5.2 Body Weights

During the acclimation period, the animals were weighed the day after receipt and 7 days thereafter (the latter for allocation into experimental groups). Animals allocated into experimental groups were weighed immediately before the initiation of dosing and approximately weekly thereafter. The body weight of each animal was measured and recorded to the nearest tenth of a gram using Beckman's TOXSYS computer system.

2.5.3 Hematology

During Weeks 5, 9, 13 and 15, blood samples were collected from all surviving animals in the study. Blood was collected from the males the first day and females the second day. The afternoon before blood collections, food was removed from the cage of each rat scheduled. Toxicology technicians anesthetized the rats with diethyl ether and collected blood samples from the orbital sinus. Food was returned after the bleed was completed.

One Microtainer tube containing EDTA as an anticoagulant was filled with approximately 400 ml of whole blood from each animal. Hematology analyses were performed by the Pathology Group using an Ortho ELT 8. Unclotted samples were analyzed on the same calendar day that they were collected for:

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

Mean corpuscular volume (MCV), mean corpuscular hemoglobin concentration (MCHC), and mean corpuscular hemoglobin (MCH) were calculated. During blood collection, a thin smear of fresh blood was made by a member of the Pathology Group for determination of RBC morphology and WBC differentials.

2.5.4 Serum Chemistry

Blood samples were collected as described in Section 2.5.3, except that no sample was obtained Week 15. During Weeks 5, 9, and 13, approximately 600 ml of whole blood was collected from each animal in two Microtainer tubes, allowed to clot for approximately thirty minutes, and centrifuged to obtain the serum. Samples were analyzed for the following biochemical parameters by a member of the Biochemical Toxicology Section using a Centrifichem 600 or flame photometer:

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

Globulin (G) and A/G ratio were calculated. A detailed description of the procedures employed is available in the Document Archives [Study 50391CA (1)]

2.5.5 Pathology

Any animals which were found dead during the study were necropsied as soon as possible. After 2, 10, and 14 weeks of treatment, the surviving animals from Groups 5, 4, and 1-3, respectively, were anesthetized with carbon dioxide gas and necropsied. Animals from Groups 1-3, but not from Groups 4 & 5, were fasted overnight and exsanguinated in an order that rotated through the treatment groups and sexes. Each

animal was necropsied, under the supervision of a pathologist, immediately after sacrifice. Each animal received its last dose the day before it was sacrificed. All necropsies were performed according to approved Standard Operating Procedures.

From all animals sacrificed as scheduled, the following organs (when present) were weighed to the nearest milligram:

adrenals	heart	ovaries	testes
brain	kidneys	prostate	thymus
epididymides	liver	spleen	uterus
thyroid/parathyroid (weighed after fixation)			

The following tissues (when present) were removed from each animal and preserved in 10% neutral buffered formalin:

adrenals	brain	epididymides	esophagus
femur	Hardarian Glands	head (entire)	heart and aorta
kidneys	lacrimal glands	lungs and bronchi	lymph nodes
ovaries	pancreas	pituitary	salivary glands
spleen	testes	thymus	tongue
trachea	treated skin	urinary bladder	vagina
gross lesions			
bone and marrow (sternum, rib)		eyes & optic nerves	
uterus (cervix, corpus and horns)		mammary gland (with skin)	
prostate and seminal vesicles		skeletal muscle and sciatic nerve	
spinal cord (cervical, thoracic)		stomach (glandular and squamous)	
thyroid and parathyroid			
large intestine (cecum, colon, and rectum)			
small intestine (duodenum, jejunum and ileum)			
liver (part of median and right lateral lobes)			

The following tissues (when present) from all animals were processed for microscopic examination according to Standard Operating Procedures:

adrenals (both)	brain	epididymides	heart
kidneys	lung (left lobe)	ovaries (both)	pancreas
salivary gland	spleen	testes (both)	thymus
seminal vesicles	thyroid	liver (2 lobes)	stomach
urinary bladder	gross lesions	marrow (sternum)	prostate
bone (sternum & rib)		uterus (body and both horns)	
skeletal muscle (thigh)		large intestine (colon)	
small intestine (duodenum)		sciatic nerve	
eyes & optic nerves (left)		treated skin (2 sections)	

Sections for examination were stained with hematoxylin and eosin. Microscopic examination was performed by a pathologist. A detailed description of the procedures employed is available in the Document Archives [Study 50391P (2)].

2.5.6 Sperm Evaluations

The effect of treatment with HCGO-P on the morphology of sperm was assessed by comparing the frequency of abnormal sperm from the cauda epididymis from five control males and five males treated at 125 mg/kg/day (Group 3), the highest dose group surviving to the end of the study. Each epididymis was minced, diluted with 40 ml of distilled water, strained through a 70 mm mesh, stained with eosin Y, and examined microscopically. One-thousand sperm from each animal were examined. A detailed description of the procedures employed is available in the Document Archives [Study 50391M (3)].

2.6 In Vivo Skin Penetration

The extent of skin penetration by HCGO-P in vivo was determined by the Biochemical Toxicology Section. Six rats of each sex not assigned to treatment groups were dosed like the animals on study; for the first 8 doses, they received 2000 mg/kg/day, followed by a 3-day rest period, and at least 11 additional weeks of dosing at 125 mg/kg/day. An additional six rats of each sex were kept which did not receive any HCGO-P. A plastic ring with an inside area of 1.3 cm² was attached securely to the back of each rat with an adhesive. The test material, spiked with radioactive markers, was applied to completely cover the skin inside the ring. To prevent the rats from removing the test material, a wire mesh cover was attached to the ring. Each rat was placed in a separate metabolism cage; urine and fecal samples were collected once daily. Four days after application of the test material, tissues and organs were removed from the rats for determination of the levels of radioactivity. Radioactivity was measured by liquid scintillation counting. From the results of the experiment, the extent of in vivo percutaneous absorption of HCGO-P can be determined in treated and previously untreated rats. A detailed description of the procedures employed is available in the Document Archives [Study 50391A (4)].

2.7 Data Handling and Storage

Body weights, clinical signs, skin irritation scores, dose calculations, and evidence of dosing were recorded and maintained using the TOXSYS Computer System. Necropsy (gross) observations, organ weights, sperm evaluations, mortality, and animal husbandry data were recorded by hand. Serum chemistry data, hematology data and organ weight data were analyzed using SAS procedures. Subsequently, organ weight data and necropsy observations were entered into the Grosse System and analyzed as

described below. Sperm evaluations were processed and analyzed using Lotus 1-2-3 [3]. Microscopic observations were recorded and maintained using PATHDATA SYSTEM [2]. All raw data and original study documents (i.e., test request, protocol, amendments, compound receipt, and dispensing records, etc.) will be stored in the Document Archives. Wet tissue samples, sperm morphology, and hematology slides will be stored in the Specimen Archives.

Quantitative data (body weight, serum chemistry, hematology, and organ weight data) were analyzed by parametric methods: analysis of variance (ANOVA) and associated F-test, followed by Dunnett's test (body weights) and Tukey's Multiple Comparison Test (serum chemistry, hematology and organ weight data), provided that there was statistical significance in ANOVA. Differences between control and treated groups were considered statistically significant only if the probability of the differences being due to chance was less than 5% ($p < 0.05$).

3.0 RESULTS

ALL DATA TABLES ARE LOCATED FOLLOWING THE CONCLUSIONS SECTION

3.1 Clinical Observations and Skin Irritation

After 2 weeks of treatment with HCGO-P at 2000 mg/kg/day, the rats were in poor health, and were terminated as a group, rather than waiting for each rat to die, in order to examine the organs for toxic effects without secondary complications. Two females treated at 500 mg/kg/day were sacrificed in a moribund condition during Week 9; because of the general poor health condition and severe skin effects, the remaining rats treated with HCGO-P at 500 mg/kg/day were terminated after 10 weeks of treatment. One female treated at 125 mg/kg/day was found dead during Week 9 and one male treated at 125 mg/kg/day was found dead during Week 11. No rats treated at 30 mg/kg/day and none of the controls died.

Dry dark exudate around the eyes (chromodacryorrhea) and nose was observed with about the same frequency and of the same severity in the treated and control rats; this was attributed to the restriction of preening activity by the collars. This was groomed off during each weekend when the collars were removed. In a few animals, sores developed on the skin where the collar rubbed.

The application of HCGO-P to the skin of rats caused moderate erythema, moderate edema, and thickening, cracking of the skin with sloughing of the epidermis in some of the high-dose animals. Since the lower doses covered smaller areas, the local effects became less obvious at lower doses. To some extent the skin appeared to adapt to the repeated insult from HCGO-P; by the end of the study the degree of irritation decreased to about one-third its value at the beginning. Mean skin irritation scores are presented in Table 3 Individual skin scores are presented in Appendix 7.2.

3.2 Body Weight (Table 4, Appendix 7.1)

In general, HCGO-P-exposed animals weighed significantly less than control animals. The effect on body weight became more pronounced with increasing dose. Mean body weight data are presented in Table 4. Individual body weights are presented in Appendix 7.1

3.3 Hematology (Table 5, Appendix 7.3)

Hematologic evaluations revealed an anemia, observed first at 5 weeks in the rats treated at 500 mg/kg/day. By Week 9, those treated at 125 mg/kg/day were also affected. Hematocrit, hemoglobin concentration, and the number of red blood cells appeared equally affected. Although the values of these three red blood cell parameters for the rats dosed at 30 mg/kg/day were not statistically different from the values of the control rats, they were lower than those of the controls at the termination of the study. In addition, rats treated at 125 or 500 mg/kg/day had reduced platelet counts. The rats treated at 500 mg/kg/day had an increased number of segmented white blood cells with a decrease in lymphocytes. Mean hematology values are presented in Table 5. Individual hematology values are presented in Appendix 7.3.

3.4 Serum Chemistry (Table 6)

Serum analyses indicate that liver and kidney may be target organs. After 9 weeks of treatment at 500 mg/kg/day, males and females had abnormal values for aspartate transaminase, alkaline phosphatase, sorbitol dehydrogenase, albumin, and total protein; urea nitrogen was also increased, particularly in females. Similar changes in several of these parameters, although generally not statistically significant, occurred in the rats treated at 125 mg/kg/day. After 13 weeks of treatment, serum data were available only for those dosed at 30 and 125 mg/kg/day. Sorbitol dehydrogenase, aspartate aminotransferase, and urea nitrogen were the only parameters clearly affected. Mean serum chemistry values of select parameters are presented in Table 6. A detailed report of clinical chemistry findings can be found in the Document Archives [1].

3.5 Pathology

A detailed report of pathology findings can be found in the Document Archives [2].

3.5.1 Organ Weights (Table 7a & 7b - Absolute; Table 8a & 8b - Relative)

Relative liver and spleen weights were significantly increased in male rats exposed to 125 mg/kg/day. A significant decrease in absolute and relative thymus weight was observed in male and female rats dosed at 125 mg/kg/day. A significant increase was also observed in absolute and relative adrenal and liver weights of female rats at this same dose level.

3.5.2 Observations at Necropsy (Table 9)

Select gross observations made at necropsy are summarized in Table 9. In general, treated skin showed numerous changes including discoloration, scabbing, evidence of dryness, and ulceration. Enlarged and/or red axillary, brachial, cervical, inguinal, mediastinal, mesenteric, pancreatic, and thymic lymph nodes were seen. Of these, the axillary lymph nodes were most affected. Abnormal areas, cyst, discolored and enlarged spleen, and small thymus were also observed in rats administered HCGO-P. Effects on the liver were minimal.

3.5.3 Histopathology (Table 10)

Select histopathological findings are summarized in Table 10. In general, the major target organs appeared to be spleen, bone marrow, liver and thymus. Fibrosis of bone marrow suggests probable dysfunction of hematopoiesis. The other organs evaluated, such as the kidneys, lungs, brain, and heart, showed non-treatment age-related changes.

3.6 Sperm Morphology (Table 11)

There were no differences between the males treated at 125 mg/kg/day and the control males in the type or frequency of abnormal sperm observed. These data suggest that dermal administration of HCGO does not have an adverse effect on rat spermatogenesis. A detailed description of the sperm morphology results can be found in the Document Archives [3].

3.7 In Vivo Skin Penetration

The dermal bioavailability of the carbazole-like components in HCGO-P was found to be approximately 66% in both the untreated and treated male rats. In contrast, a statistically significant increase in the skin permeation of these HCGO-P components was observed in treated female rats (80% bioavailability) in comparison with the untreated rats (60% bioavailability). The dermally observed HCGO-P was predominantly eliminated in the urine, with <2% of the absorbed dose remaining in body tissues at 96 hr post dose. A detailed description of the percutaneous absorption results can be found in the Document Archives [4].

4.0 CONCLUSIONS

Heavy Coker Gas Oil from _____ refinery was administered to the skin of rats at doses of 30, 125, 500, and 2000 mg/kg/day. The rats were fitted with cardboard "elizabethan" collars to minimize the ingestion of the test material, which was applied neat and left uncovered on the skin. A similar group of rats served as controls, they were treated the same as the test animals except that no material was applied to their skin.

At the site of application, HCGO-P produced moderate to severe effects to the skin. Moderate erythema and edema occurred, accompanied by thickening and cracking of the epidermis with some open sores on the skin. In general, these effects were observed at all dose levels. Microscopic examination revealed skin ulcers at dose levels in excess of 30 mg/kg/day. In addition, many degenerative, chronic inflammatory changes were seen at all levels of exposure. Male rats appeared more susceptible to the skin changes produced by HCGO-P than female rats.

Animals exposed to HCGO-P exhibited numerous signs of systemic toxicity, which increased in severity with increasing dose. Mortality was observed at doses of 125 mg/kg/day or greater; 10% of those dosed at 125 mg/kg/day died, and none treated at 500 or 2000 mg/kg/day survived the entire 14 weeks of study. Decreased body weight resulted from doses of 30 mg/kg/day or greater. Alterations in hematologic and serum chemistry parameters occurred primarily at doses greater than 30 mg/kg/day. The clinical chemistry results suggest that HCGO-P can adversely effect hematopoiesis, and kidney and liver function. Results of microscopic examination of tissues were supportive of most of the clinical findings. The red blood cell phagocytosis in the lymph nodes, the reduced number of lymphocytes in the thymus, the cysts and fibrous foci in the spleen, and fibrosis and necrosis of the liver are considered to be treatment-related and were observed, in some cases, at 30 mg/kg/day. Microscopic examination of the kidneys revealed no adverse effects. The weight changes in the thymus, liver, spleen and adrenals are also considered to be treatment-related.

Toxic effects were seen at all doses of HCGO-P administered. Although a No-Observed-Effect-Level was not found, the effects observed at 30 mg/kg/day were minimal.