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ORIGINAL

December 1, 1994



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Office of Pollution Prevention and Toxics
U. S. Environmental Protection Agency
401 M Street, SW
Washington, DC 20460
ATTN: 8(e) Coordinator

Contains No CBI

Dear Sir or Madam:

Subject: Report submitted in accordance with the U. S. Environmental Protection Agency Statement of Interpretation and Enforcement Policy; Notification of Substantial Risk-Section 8(e) TSCA.

The following information is submitted in accordance with the above statement. The submission pertains to 3,5-bis(1,1-dimethylethyl)-4-hydroxybenzoic acid (CAS# 1421-49-4) and is being submitted because of central nervous system signs observed in animals during an acute oral toxicity test.

We do not believe the information in this report reasonably supports the conclusion that the substance presents a substantial risk. It is, however, being submitted to enable the Agency to draw its own conclusions.

Groups of five male rats and five female rats were administered a single dose of the test compound by gavage at a dose level of 2000 mg/kg body weight. At this dose level, one female and four males died prior to study termination. Two additional dose groups, each consisting of five males, were administered single oral doses of 1000 or 500 mg/kg of the test material. No deaths were observed at the 1000 or 500 mg/kg dose levels.

Tremors were observed in all animals in all dose groups on the day of dosing. No other abnormal clinical signs were observed in the 500 mg/kg dose group. Abnormal clinical signs in the 1000 mg/kg dose group were limited to diarrhea in a single male and reduced amount of feces in a second male on the day following dosing. At the high dose level (2000 mg/kg), additional abnormal clinical signs included hypothermia, staggering (only on the day of dosing), polyuria, slight to severe weakness, diarrhea, dehydration, and convulsions prior to death. All animals in all dose groups that survived to scheduled necropsy gained weight. The major treatment-related change noted at necropsy was hemorrhage in the glandular gastric mucosa.

*R. Hays Bell, Ph.D., Vice-President and Director, Corporate Health, Safety, and Environment
Eastman Kodak Company, Rochester, NY 14652-6256*



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12/30/94

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In addition to the acute oral toxicity study, we have enclosed a copy of an acute dermal irritation study in rabbits. No dermal irritation was evident when a single topical dose of 0.5 grams was left in contact with the skin under an occlusive wrap for four hours.

The test material is a low-volume, site-limited intermediate used in the synthesis of another chemical. Unreacted test material is not expected to be present in the final chemical. We are not aware of any adverse health problems associated with the manufacture or use of the test material. The original health hazard evaluation of this intermediate resulted in a "Health Hazards Unknown" rating. This rating is accompanied by a statement to employees to "Avoid all contact". We will continue to handle the material in the same manner based on the new toxicology data. Employees are required to wear white, uncoated Tyvek® suits, dust masks, and impervious gloves when working with the dry material.

The new toxicity information will be incorporated into the Material Safety Data Sheet (MSDS). A copy of the revised MSDS will be forwarded to the Agency upon completion. We are currently evaluating the need for further testing.

Please contact me if additional information is required.

Sincerely,



R. Hays Bell
(716) 722-5036

RHB:JAF

Enc.

STUDY TITLE

3,5-DI-TERT-BUTYL-4-HYDROXYBENZOIC ACID
ACUTE DERMAL IRRITATION STUDY IN THE RABBIT

HAEL NUMBER: 94-0047 KAN: 109629
CAS REGISTRY NUMBER: 1421-49-4

FINAL REPORT

AUTHOR

Contains No CBI

Kenneth P. Shepard, B.S.

PERFORMING LABORATORY

Toxicological Sciences Laboratory
Corporate Health and Environment Laboratories
Eastman Kodak Company
1100 Ridgeway Avenue
B-320 Kodak Park
Rochester, New York 14652-6272
USA

LABORATORY PROJECT ID

HAEL Number: 94-0047

STUDY SPONSOR

Eastman Kodak Company

STUDY COMPLETION DATE

July 28, 1994

QUALITY ASSURANCE INSPECTION STATEMENT
(21 CFR 58.35(B)(7), 40 CFR 792.35(B)(7), AND 40 CFR 160.35(B)(7))

STUDY: 94-0047-1 STUDY DIRECTOR: SHEPARD, K.P.
ACCESSION NUMBER: 109629

PAGE 1
07/25/94

STUDY TYPE: ACUTE DERMAL IRRITATION TEST

Mr. L. James
(AUDITOR, QUALITY ASSURANCE UNIT)

7/25/94
DATE

TO THE BEST OF MY KNOWLEDGE, THIS FINAL REPORT ACCURATELY DESCRIBES
THE METHODS AND STANDARD OPERATING PROCEDURES, AND THE REPORTED
RESULTS ACCURATELY REFLECT THE RAW DATA. THIS STUDY WAS INSPECTED
BY 1 OR MORE PERSONS OF THE QUALITY ASSURANCE UNIT OF HAEI, EASTMAN
KODAK COMPANY ROCHESTER, N.Y. AND WRITTEN STATUS REPORTS WERE
SUBMITTED ON THE FOLLOWING DATES:

INSPECTION DATES	PHASE(S) INSPECTED	STATUS REPORT DATES
-----	-----	-----
06/28/94	PROTOCOL APPENDIX SUBMISSION	
06/30/94	CLINICAL SIGNS AT 48 HRS.	07/25/94
07/25/94	FINAL REPORT REVIEW	07/25/94

COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The study described by this report was conducted in compliance with the following Good Laboratory Practice Standards:

Annex 2 of the Organization for Economic Cooperation and Development
Guidelines for Testing of Chemicals C(81)30 (Final).



Kenneth P. Shepard, B.S.
Study Director

7/28/94

Month/Day/Year

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ABSTRACT

3,5-DI-TERT-BUTYL-4-HYDROXYBENZOIC ACID

ACUTE DERMAL IRRITATION STUDY IN THE RABBIT

**HAEL NUMBER: 94-0047 KAN: 109629
CAS REGISTRY NUMBER: 1421-49-4**

A dermal irritation study was conducted by administering single topical doses of 0.5 gram of the test material to rabbits. The test material was left in contact with the skin under an occlusive wrap for four hours. No signs of irritation were evident at any time during the 72-hour observation period. Based on the lack of an irritant response, the test material requires no skin irritation classification as defined in the 18th Adaptation on the EC Classification, Packaging, and Labelling of Dangerous Substances.

PERFORMING LABORATORY

Toxicological Sciences Laboratory
Corporate Health and Environment Laboratories
Eastman Kodak Company
1100 Ridgeway Avenue
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Rochester, New York 14652-6272
USA

SPONSOR

Eastman Kodak Company

STUDY DATES

Study Initiation: June 28, 1994
Experiment Initiation: June 28, 1994
Experiment Completion: July 1, 1994
Study Completion: July 28, 1994

STUDY DIRECTOR

Kenneth P. Shepard, B.S.

OTHER KEY PERSONNEL

Len Sakal, B.S., Study Technician
John W. Mosher, B.S., Principal Investigator
Milan S. Vlaovic, D.V.M., Ph.D., Laboratory Animal Medicine

PURPOSE/OBJECTIVE

The purpose of the study was to determine the potential of the test material to cause primary irritation of mammalian skin.

TEST SUBSTANCE

Test Material Name: 3,5-Di-tert-butyl-4-hydroxybenzoic acid
CAS Registry Number: 1421-49-4
HAEL Laboratory Number: 94-0047
KAN: 109629
CIN: Not available
SRID or Lot I.D. Number: BB2673-133C
Physical State and Appearance: Light yellow solid
Received at Performing Laboratory: June 3, 1994
Composition: Refer to composition information included in the notification when applicable.

TEST SYSTEM

Species: Rabbit
Strain: Hra:(NZW)SPF
Source: Hazleton Research Laboratories, Denver, PA, USA
No. of Animals: 3
Sex: Not Determined
Body Weight Range at Dosing (grams): 2664 - 3085
Age: Young Adults (At least three months old)

HUSBANDRY AND ENVIRONMENTAL CONDITIONS

Housing

All animals were individually housed in suspended, stainless-steel, mesh cages.

HUSBANDRY AND ENVIRONMENTAL CONDITIONS, Cont.

Environmental Conditions

A photoperiod of 12 hours light from 6 a.m. to 6 p.m. was maintained. Room temperature was maintained at 65-67°F. Relative humidity was maintained at 70-71%.

Diet and Water

Agway® ProLab™ High Fiber Rabbit Diet certified pellets and water (Monroe County (NY) Water Authority) were available ad libitum. No known contaminants which would interfere with the outcome of the study were expected to be present in feed or water from these sources. Analyses of feed and quarterly analyses of water are maintained on file within the testing laboratory.

Isolation

Rabbits were isolated and monitored for at least five days after arrival and before release to the testing facility.

Animal Identification

All rabbits were identified by cage numbers and uniquely-numbered, metal ear tags.

TEST PROCEDURES AND CONDITIONS

Test Procedure Guideline

OECD Guideline for Testing of Chemicals: Guideline 404, Dated 17 July, 1992; (Annex V, test B.4).

Dose Level

0.5 gram/animal

TEST PROCEDURES AND CONDITIONS, Cont.

Identification Numbers of Animals Used

28, 29, and 30

Dosing Regimen

The hair was removed from an area of the dorsal skin with an electric clipper. A single dose of the material was placed in contact with the skin using a fiber pad and an occlusive wrap to hold the test material in place for four hours. At the end of the exposure period, the application site was rinsed with running water.

Control Substance

No control substance was used. Adjacent areas of untreated skin of each animal served as control sites for the test areas.

Vehicle

No vehicle was used. The test material was administered as a solid moistened thoroughly with water.

Clinical Observations

The site of application was examined at 1, 24, 48, and 72 hours after removal of the occlusive patch. Observations included estimation of erythema, edema, necrosis, eschar formation, scarring, erosion, and staining caused by the material as well as general systemic effects.

Necropsy

No necropsies were conducted at the conclusion of the 72-hour observation period.

RESULTS

Clinical Observations

Graded as described in OECD Guideline 404 (Annex V test B.4) (erythema, edema)

ANIMAL NUMBER	DOSE (gram)	RESPONSE AT THE SITE OF APPLICATION			
		1 HOUR	24 HOURS	48 HOURS	72 HOURS
28	0.5	0,0	0,0	0,0	0,0
29	0.5	0,0	0,0	0,0	0,0
30	0.5	0,0	0,0	0,0	0,0

Description of Serious Lesions and Irritation Other Than Erythema and Edema

No irritant response or serious lesion was noted during the 72-hour observation period.

Toxic Effects Other Than Irritation

No toxic effects were noted during the study.

DATA ANALYSIS

Not applicable

DISCUSSION AND INTERPRETATION

Since no signs of irritation were evident at any time during the study, the test material was not considered a dermal irritant.

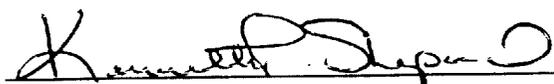
CONCLUSION

Based on the lack of an irritant response, the test material requires no skin irritation classification as defined in the 18th Adaptation on the EC Classification, Packaging, and Labelling of Dangerous Substances.

DATA STORAGE

All test results presented in this report are supported by raw data which are maintained in the archives of the Corporate Health and Environment Laboratories, Eastman Kodak Company.

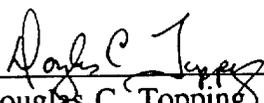
SIGNATURE PAGE



Kenneth P. Shepard, B.S.
Study Director

7/28/94

Month/Day/Year



Douglas C. Topping, Ph.D.
Unit Director, Mammalian Toxicology Section

Jul 25, 1994

Month/Day/Year



John L. O'Donoghue, V.M.D., Ph.D.
Director, Corporate Health and Environment Laboratories

7/27/94

Month/Day/Year

STUDY TITLE

3,5-DI-TERT-BUTYL-4-HYDROXYBENZOIC ACID

ACUTE ORAL TOXICITY STUDY IN THE RAT

HAEL NUMBER: 94-0047 KAN: 109629

CAS REGISTRY NUMBER: 1421-49-4

FINAL REPORT

Contains No CR!

AUTHOR

Kenneth P. Shepard, B.S.

PERFORMING LABORATORY

Toxicological Sciences Laboratory
Corporate Health and Environment Laboratories
Eastman Kodak Company
1100 Ridgeway Avenue
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Rochester, New York 14652-6272
USA

LABORATORY PROJECT ID

HAEL Number: 94-0047

STUDY SPONSOR

Eastman Kodak Company

STUDY COMPLETION DATE

November 14, 1994

QUALITY ASSURANCE INSPECTION STATEMENT

[21 CFR 58.35(B)(7), 40 CFR 792.35(B)(7), and 40 CFR 160.35(B)(7)]

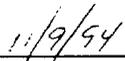
STUDY: 94-0047-1 STUDY DIRECTOR: SHEPARD, K.P.
ACCESSION NUMBER: 109629

PAGE 1
11/09/94

STUDY TYPE: ACUTE ORAL TOXICITY



(AUDITOR, QUALITY ASSURANCE UNIT)



DATE

TO THE BEST OF MY KNOWLEDGE, THIS FINAL REPORT ACCURATELY DESCRIBES
THE METHODS AND STANDARD OPERATING PROCEDURES, AND THE REPORTED
RESULTS ACCURATELY REFLECT THE RAW DATA. THIS STUDY WAS INSPECTED
BY 1 OR MORE PERSONS OF THE QUALITY ASSURANCE UNIT OF Hael, EASTMAN
KODAK COMPANY ROCHESTER, N.Y. AND WRITTEN STATUS REPORTS WERE
SUBMITTED ON THE FOLLOWING DATES:

INSPECTION DATES	PHASE(S) INSPECTED	STATUS REPORT DATES
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07/27/94	PROTOCOL APPENDIX/AMENDMENT SUBMISSION	
07/29/94	CLINICAL SIGNS AT 48 HRS.	11/09/94
08/01/94	PROTOCOL APPENDIX/AMENDMENT SUBMISSION REPEAT - LOWER DOSES IN MALES ONLY	
08/04/94	CLINICAL SIGNS AT 72 HRS. MALE RATS ONLY	11/09/94
09/20/94	GROSS PATHOLOGY PATHOLOGY REPORT	09/20/94
11/09/94	FINAL REPORT REVIEW	11/09/94

COMPLIANCE WITH GOOD LABORATORY PRACTICE STANDARDS

The study described by this report was conducted in compliance with the following Good Laboratory Practice Standards:

Annex 2 of the Organization for Economic Cooperation and Development
Guidelines for Testing of Chemicals C(81)30 (Final).



Kenneth P. Shepard, B.S.
Study Director

11 / 14 / 94
Month/Day/Year

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ABSTRACT

3,5-DI-TERT-BUTYL-4-HYDROXYBENZOIC ACID

ACUTE ORAL TOXICITY STUDY IN THE RAT

HAEL NUMBER: 94-0047 KAN: 109629

CAS REGISTRY NUMBER: 1421-49-4

An acute oral toxicity study was conducted in rats with the test material administered by gavage. Initially, a single oral dose of 2000 mg/kg of the test material was administered to a group of five males and five females. Four males and a single female died after exposure to the test material. Therefore, two additional dose groups were added to the study with each group consisting of five males. Each male was administered either a single oral dose of 1000 or 500 mg/kg of the test material. No other mortality was observed during the study.

For all animals in all dose groups, tremors were noted on the day of dosing. At the 500 mg/kg dose level, no other abnormal clinical signs were evident. At the 1000 mg/kg dose level, additional abnormal clinical signs were limited to diarrhea from a single male and a reduced amount of feces for a second male on the day following dosing. No other abnormal clinical signs were noted for this dose group during the study. At the 2000 mg/kg dose group, additional abnormal clinical signs included hypothermia, staggering, and polyuria. The staggering was noted only on the day of dosing. Other abnormal signs noted during the study included slight to severe weakness, diarrhea, convulsions prior to death, inguinal hair wet with urine, dehydration, urine and/or fecal staining of the inguinal hair, and staining (urine) of the abdominal hair. No other abnormal clinical signs were noted at this dose level during the study. All animals in all dose groups which survived to scheduled necropsy gained weight. The major treatment-related change noted at necropsy was hemorrhage in the glandular gastric mucosa.

The hemorrhage in the glandular gastric mucosa provided evidence that the test material was a gastric irritant. The acute oral LD₅₀ for this test material was calculated to be 1414 mg/kg for male rats and was greater than 2000 mg/kg for female rats. Based on the male mortality data, the test material was classified as slightly toxic in rats according to the criteria set forth by Hodge and Sterner (1949) and classified as harmful if swallowed as defined in the 18th Adaptation on the EC Classification, Packaging, and Labelling of Dangerous Substances.

PERFORMING LABORATORY

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1100 Ridgeway Avenue
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USA

SPONSOR

Eastman Kodak Company

STUDY DATES

Study Initiation: July 27, 1994
Experiment Initiation: July 27, 1994
Experiment Completion: September 20, 1994
Study Completion: November 14, 1994

STUDY DIRECTOR

Kenneth P. Shepard, B.S.

OTHER KEY PERSONNEL

Leonard Sakal, B.S., Study Technician
John W. Mosher, B.S., Principal Investigator
Milan S. Vlaovic, D.V.M., Ph.D., Pathologist, Laboratory Animal Medicine

PURPOSE/OBJECTIVE

The purpose of the study was to determine the estimated oral LD₅₀ of the test material in male and female rats and the clinical signs of toxicity associated with an oral dose.

TEST SUBSTANCE

Test Material Name: 3,5-Di-tert-butyl-4-hydroxybenzoic acid
CAS Registry Number: 1421-49-4
HAEL Laboratory Number: 94-0047
KAN: 109629
CIN: Not available
SRID or Lot I.D. Number: BB2673-133C
Physical State and Appearance: Light yellow solid
Received at Performing Laboratory: June 3, 1994
Composition: Refer to composition information included in the notification when applicable.

TEST SYSTEM

Species: Rat
Strain: CD®(SD)BR VAF/Plus®
Source: Charles River Laboratories, Kingston, NY, USA
Sex: Male and Female
Number of Animals: 2000 mg/kg = five of each sex
500 and 1000 mg/kg = five males
Body Weight Range at Dosing (grams):
2000 mg/kg: Males = 257 - 274 Females = 198 - 208
500 and 1000 mg/kg: Males = 172 - 196
Age at Study Initiation: Males = 6-9 weeks Females = 9-10 weeks

HUSBANDRY AND ENVIRONMENTAL CONDITIONS

Housing

All animals were individually housed in suspended, stainless-steel, mesh cages.

HUSBANDRY AND ENVIRONMENTAL CONDITIONS, Cont.

Environmental Conditions

A photoperiod of 12 hours light from 6 a.m. to 6 p.m. was maintained. Room temperature was maintained at 69-72 °F. Relative humidity was maintained at 47-56%.

Diet and Water

Agway® Prolab™ Animal Diet - RMH 3000 (certified) pellets and water (Monroe County (NY) Water Authority) were available ad libitum. No known contaminants which would interfere with the outcome of the study were expected to be present in feed or water from these sources. Analyses of feed and results of quarterly analyses of water are maintained on file within the testing laboratory.

Isolation

Animals were isolated and monitored for at least five days after arrival and before release to the testing facility.

Animal Identification

All animals were identified by cage numbers and uniquely-numbered, metal ear tags.

TEST PROCEDURES AND CONDITIONS

Test Procedure Guideline

OECD Guideline for Testing of Chemicals: Guideline 401 (Annex V, test B.1).

Randomization

A clinical examination was performed on each animal to ensure that only healthy animals were utilized. The procedure for including animals in the study was to randomly select and assign animals from the same shipment to the study. Randomization was done by computer-generated lists using the Automated Animal Toxicology System. After assignment of animals to the study, the body weights were determined to ensure that individual body weights did not exceed 20% of the mean weight for each sex.

TEST PROCEDURES AND CONDITIONS, Cont.

Identification Numbers of Animals Used

<u>Dose level</u>	<u>Males</u>	<u>Females</u>
500 mg/kg	301-305	-----
1000 mg/kg	306-310	-----
2000 mg/kg	281-285	286-290

Dose Level

Single doses of 2000 mg/kg were administered to five males and five females. In addition, single doses of 1000 or 500 mg/kg were administered to two groups of five males. Variability in test volumes was minimized by adjusting the concentration to ensure a constant volume at all dose levels.

Dosing Regimen

A single dose of the test material was administered by gavage to animals that had been fasted overnight.

Control Substance

No control substance was used.

Vehicle

The test material was administered as a 5%, 10%, or 20% suspension in the vehicle. The vehicle was a 0.5% aqueous suspension of guar gum (Jaguar®), Control Number: F-10-88-592-10.

Clinical Observations

Animals were observed three times on the day of dosing (Day 0), and once each day thereafter for the duration of the experiment (a total of 14 calendar days). Observations included, but were not limited to, changes in the skin; fur; feces; urine; eyes; mucous membranes; respiratory, circulatory, autonomic, and central nervous systems; somatomotor activity; and behavior pattern.

TEST PROCEDURES AND CONDITIONS, Cont.

Body Weight Determinations

Body weights were collected on Days 0 (prior to treatment), 7, and 14.

Necropsy

Animals that died during the study were necropsied as soon as possible. Surviving animals were necropsied at the completion of the 14-day observation period.

RESULTS

Initially, a limit dose of 2000 mg/kg was administered to a group of five male and five female rats. Based on the mortality rate for male rats at the limit dose, additional dose levels of 500 and 1000 mg/kg, administered to males only, were added to the study.

Mortality

For male rats, mortality was 0% at 500 mg/kg, 0% at 1000 mg/kg, and 80% at 2000 mg/kg. For the females, mortality was 20% at 2000 mg/kg.

MORTALITY TABLE

DOSE (mg/kg)	NUMBER OF RATS EXPOSED (Male, Female)	NUMBER OF DEATHS (Male, Female)	TIME OF DEATH
500	5,0	0,--	-----
1000	5,0	0,--	-----
2000	5,5	4,1	Day 2

RESULTS, Cont.

Clinical Observations

For the five males (Rats 301-305) assigned to the 500 mg/kg dose group, tremors were noted on the day of dosing. This observation was noted for three males one hour after dosing and for all males at two and four hours after dosing. The five male rats appeared clinically normal on the day following dosing to termination of the 14-day observation period, and all gained weight during the study. No other abnormal clinical signs were evident for this dose group.

At the 1000 mg/kg dose level, tremors were noted for the five males (Rats 306-310) at two and four hours after administration of the test material. On the day following dosing, diarrhea was observed from a single male (Rat 307) and a reduced amount of feces was noted for a second male (Rat 308). At this time, the three remaining males appeared clinically normal. By Day 2 of the study, all animals appeared clinically normal. No other abnormal clinical signs were noted for this dose group during the study. All five male rats gained weight during the observation period.

After administration of a dose of 2000 mg/kg of the test material, abnormal clinical signs noted for the five males (Rats 281-285) and five females (Rats 286-290) on the day of dosing included tremors, hypothermia, staggering, and polyuria. The tremors and staggering were noted only on the day of dosing. On the day following dosing, hypothermia and polyuria were again noted for all animals. Additional abnormal clinical signs noted on the day after dosing included severe weakness for all males, slight weakness for a single female (Rat 286), moderate weakness for four females (Rats 287-290), diarrhea for three females (Rats 287, 288, and 290), convulsions for two males (Rats 282 and 283), and inguinal hair wet with urine for all five males and five females. The two males with convulsions (Rats 282 and 283) along with two other males (Rats 281 and 284) and a single female (Rat 289) died prior to clinical examinations on the following day (Day 2 of the study). Abnormal clinical signs observed on Day 2 for the remaining male (Rat 285) and four females (Rats 286, 287, 288, and 290) included slight weakness for two females (Rats 287 and 290), diarrhea for the single male and two females (Rats 287 and 290), hypothermia for one female (Rat 287), polyuria for the one male and two of the females (Rats 286 and 287), inguinal hair wet with urine and dehydration for the single male and three females (Rats 287, 288, and 290), and fecal staining of the inguinal hair for the remaining male. At the time of clinical examinations on Day 3, polyuria and staining (urine and fecal) of the inguinal hair were noted for the single male. At this examination, one female (Rat 288) appeared clinically normal; polyuria was noted for one of the three remaining females (Rat 286); slight weakness, dehydration, and inguinal and

RESULTS, Cont.

Clinical Observations, Cont.

abdominal hair stained with urine were noted for two females (Rats 287 and 290). By Day 4 of the study, an additional female (Rat 290) appeared clinically normal. Abnormal clinical signs noted at this time for the remaining male and two females (Rats 286 and 287) included polyuria for all animals and the abdominal hair of a single female (Rat 287) was stained with urine. At the Day 5 examinations, the single male and three of the four surviving females (Rats 286, 288, and 290) appeared clinically normal. Staining (urine) of the inguinal hair was still present for the remaining female (Rat 287). This female appeared clinically normal on Day 6 of the study. No other abnormal clinical signs were noted at this dose level during the study. All animals which survived to scheduled necropsy gained weight.

TABLE OF CLINICAL OBSERVATIONS
 (500 mg/kg and 1000 mg/kg)

DOSE (mg/kg)	CLINICAL SIGNS	TIME	NUMBER OF ANIMALS AFFECTED
500	Tremors	Day 0	5/5 Males
500	Appeared Clinically Normal	Days 1-14	5/5 Males
1000	Tremors	Day 0	5/5 Males
1000	Diarrhea	Day 1	1/5 Males
1000	Reduced Amount of Feces	Day 1	1/5 Males
1000	Appeared Clinically Normal	Days 1-14 Days 2-14	3/5 Males 5/5 Males

RESULTS, Cont.

TABLE OF CLINICAL OBSERVATIONS, Cont.
 (2000 mg/kg)

DOSE (mg/kg)	CLINICAL SIGNS	TIME	NUMBER OF ANIMALS AFFECTED
2000	Tremors and Staggering	Day 0	5/5 Males, 5/5 Females
2000	Hypothermia	Days 0-1 Day 2	5/5 Males, 5/5 Females 1/5 Females
2000	Polyuria	Days 0-1 Days 2-4 Days 2&4	5/5 Males, 5/5 Females 1/1 Males, 1/4 Females 1/4 Females
2000	Slight Weakness Moderate Weakness Severe Weakness	Day 1 Days 2-3 Day 1 Day 1	1/5 Females 2/5 Females 4/5 Females 5/5 Males
2000	Inguinal Hair Wet with Urine	Day 1 Day 2	5/5 Males, 5/5 Females 1/1 Males, 3/4 Females
2000	Convulsions Prior to Death	Day 1	2/5 Males
2000	Death	Day 2	4/5 Males, 1/5 Females
2000	Diarrhea	Day 1 Days 1-2	1/4 Females 1/1 Males, 2/4 Females
2000	Dehydration	Day 2 Day 3	1/1 Males, 3/4 Females 2/4 Females
2000	Fecal Staining of the Inguinal Hair	Days 2-3	1/1 Males
2000	Urine Staining of the Inguinal Hair Urine Staining of the Abdominal Hair	Day 3 Day 3 Days 3-5	1/1 Males, 2/4 Females 1/4 Females 1/4 Females
2000	Appeared Clinically Normal	Days 3-14 Days 4-14 Days 5-14 Days 6-14	1/4 Females 1/4 Females 1/1 Males, 1/4 Females 1/4 Females

RESULTS, Cont.

Body Weights

All animals which survived to termination of the study gained weight.

Individual Body Weights

TABLE OF INDIVIDUAL BODY WEIGHTS - MALES

DOSE (mg/kg)	ANIMAL NUMBER	INDIVIDUAL BODY WEIGHTS (grams)		
		DAY 0	DAY 7	DAY 14 or (Terminal)
500	301	177	271	333
500	302	173	260	324
500	303	183	282	342
500	304	189	288	361
500	305	172	258	322
1000	306	194	294	363
1000	307	196	289	356
1000	308	193	274	344
1000	309	195	292	352
1000	310	172	255	325
2000	281	258	Died Day 2	(216)
2000	282	263	Died Day 2	(236)
2000	283	257	Died Day 2	(223)
2000	284	274	Died Day 2	(246)
2000	285	265	312	372

RESULTS, Cont.

Individual Body Weights, Cont.

TABLE OF INDIVIDUAL BODY WEIGHTS - FEMALES

DOSE (mg/kg)	ANIMAL NUMBER	INDIVIDUAL BODY WEIGHTS (grams)		
		DAY 0	DAY 7	DAY 14 or (Terminal)
2000	286	198	235	249
2000	287	208	256	263
2000	288	208	247	272
2000	289	208	Died Day 2	(171)
2000	290	206	256	276

Necropsy and Histopathology Findings

Treatment-related changes at necropsy were noted only for animals which died after exposure to the test material. These changes included minimal to minor hemorrhage in the glandular gastric mucosa, the presence of urine stain on the inguinal hair, and red discolored urine in the urinary bladder of a single animal. A record of the incidence and severity of all gross abnormalities is presented in computer-generated tables which are included in the appended pathology report.

DATA ANALYSIS

The LD₅₀ results were as follows:

LD₅₀ IN MALE RATS: 1414 mg/kg (95% C.I. = 960 to 2084 mg/kg)
LD₅₀ IN FEMALE RATS: > 2000 mg/kg (95% C.I. = No Range Calculable)

No dose/mortality curve was constructed since graphs become statistically useful only with the use of large numbers of animals and dose groups.

DISCUSSION AND INTERPRETATION

Initially, a single oral dose of 2000 mg/kg of the test material was administered to a group of five males and five females. Four males and a single female died on Day 2 of the study. Therefore, two additional dose groups were added to the study with each group consisting of five males. Each male was administered either a single oral dose of 1000 or 500 mg/kg of the test material. No other mortality was observed during the study. The major abnormal clinical signs were noted at the 2000 mg/kg dose level and were either transient or observed prior to death. The test material was a gastric irritant, as evidenced at necropsy by hemorrhage in the glandular gastric mucosa. The cause for red discolored urine in the urinary bladder at necropsy was not determined. Based on these observations and the oral LD₅₀, the test material appears to be slightly toxic by the oral route to male and female rats.

CONCLUSION

The acute oral LD₅₀ for this test material was calculated to be 1414 mg/kg for male rats and was greater than 2000 mg/kg for female rats. Based on the male mortality data, the test material was classified as slightly toxic in rats according to the criteria set forth by Hodge and Sterner (1949) and classified as harmful if swallowed as defined in the 18th Adaptation on the EC Classification, Packaging, and Labelling of Dangerous Substances.

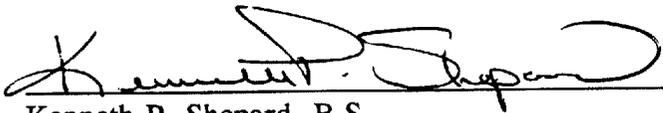
DATA STORAGE

All test results presented in this report are supported by raw data which are maintained in the archives of the Corporate Health and Environment Laboratories, Eastman Kodak Company.

REFERENCES

- Hodge, H.C. and Sterner, J.H. (1949). Tabulation of toxicity classes. *Am. Indust. Hyg. Quart.*, 10:93-96.
- Weil, C.S. (1952). Tables of convenient calculations of medium-effective dose (LD₅₀ or ED₅₀) and instructions in their use. *Biometrics*, 8:249-263.

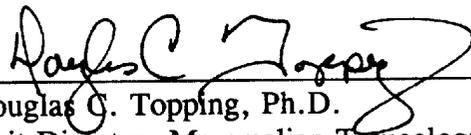
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Kenneth P. Shepard, B.S.
Study Director

11/14/94

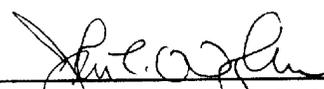
Month/Day/Year



Douglas C. Topping, Ph.D.
Unit Director, Mammalian Toxicology Section

11/11/94

Month/Day/Year



John L. O'Donoghue, V.M.D., Ph.D.
Director, Corporate Health and Environment Laboratories

11/14/94

Month/Day/Year

APPENDIX

Study No. 94-0047
Acc. No. 109629

PATHOLOGY REPORT

Compound: 3,5-Di-tert-butyl-4-hydroxybenzoic acid

Male rats given 2000, 1000, or 500 mg/kg of the test material by gavage and female rats given 2000 mg/kg of the test material by gavage, as part of an acute oral toxicity study, were necropsied. Necropsy lesions are listed in computer-generated tables.

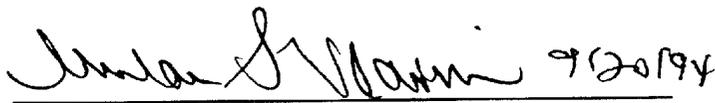
GROSS PATHOLOGY

Male Rats - 2000 mg/kg dose group: Treatment-related changes in four rats, which died on Day 2, included minimal to minor hemorrhage in the glandular gastric mucosa (3/4) and presence of urine stain on the inguinal hair (4/4). A possible treatment-related change consisted of red discolored urine in the urinary bladder (1/4). The carcasses of four rats showed minor to moderate autolysis. No treatment-related changes were observed in the remaining rat, which survived the 14-day observation period.

Male Rats - 1000 and 500 mg/kg dose groups: No treatment-related changes were observed in either group. All rats from both groups survived the 14-day observation period.

Female Rats - 2000 mg/kg dose group: Treatment-related changes in a single rat, which died on Day 2, consisted of urine stain on the inguinal hair. No signs of organ toxicity were observed. The carcass of a single rat showed moderate autolysis. No treatment-related changes were observed in the remaining four rats, which survived the 14-day observation period.

Comments: The test material was a gastric irritant, as evidenced by hemorrhage in the glandular gastric mucosa. The cause for red discolored urine in the urinary bladder of a single rat was not determined.


Milan S. Vlaovic, D.V.M., Ph.D.

MSV:dap
09/16/94

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 940047A0

COMPOUND # 94-0047
SOFTWARE VERS # 3.0
ACCESSION NUMBER 109629

GROUP	500.000	1000.000	2000.000
	MG/KG M	MG/KG M	MG/KG M
TRACHEA	5	5	5
LUNGS	5	5	5
THYMUS	5	5	5
HEMORRHAGE	0	0	4
HEART	5	5	5
ESOPHAGUS	5	5	5
STOMACH	5	5	5
STOMACH, GLANDULAR HEMORRHAGE	0	0	3
DUODENUM	5	5	5
JEJUNUM	5	5	5
ILEUM	5	5	5
CECUM	5	5	5
COLON	5	5	5
RECTUM	5	5	5
LIVER	5	5	5
KIDNEYS	5	5	5
RIGHT KIDNEY HYDRONEPHROSIS	1	0	0
URINARY BLADDER	5	5	5
URINE DISCOLORATION, RED	0	0	1
PITUITARY GLAND	5	5	5
ADRENALS	5	5	5
PANCREAS, NOS	5	5	5
THYROID GLANDS	5	5	5
PARATHYROID GLANDS	5	5	5
SPLEEN	5	5	5
MESENTERIC LYMPH NODES	5	5	5
BONE MARROW	5	5	5
BRAIN	5	5	5
EYES	5	5	5
SALIVARY GLANDS	5	5	5
ADIPOSE TISSUE	5	5	5

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
THE NUMBER OF TISSUES WITH EACH ABNORMALITY

REVIEWED BY:

John M. ...

DATE:

9-14-91

ACCEPTED BY:

... ..

DATE:

9/15/91

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 940047A0

COMPOUND # 94-0047
 SOFTWARE VERS # 3.0
 ACCESSION NUMBER 109629

GROUP	500.000	1000.000	2000.000
	MG/KG M	MG/KG M	MG/KG M
SKIN, NOS	5	5	5
HAIR	5	5	5
HAIR OF INGUINAL REGION			
HAIRCOAT-DRY URINE STAIN	0	0	3
HAIRCOAT-WET BY URINE	0	0	1
ACCESSORY SEX ORGANS (MALE)	5	5	5
EPIDIDYMIDES	5	5	5
TESTES	5	5	5
BODY AS A WHOLE, NOS	0	0	4
AUTOLYSIS	0	0	4

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
 THE NUMBER OF TISSUES WITH EACH ABNORMALITY

REVIEWED BY: John M. Mather DATE: 9-14-40 ACCEPTED BY: Andrew J. V. V. V. DATE: 9/15/40

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 940047A0

COMPOUND # 94-0047
SOFTWARE VERS # 3.0
ACCESSION NUMBER 109629

ANIMAL #	500.000 MG/KG GROUP - M				
	301	302	303	304	305
DAYS ON TEST	14	14	14	14	14
TRACHEA	X	X	X	X	X
LUNGS	X	X	X	X	X
THYMUS	X	X	X	X	X
HEART	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X
STOMACH	X	X	X	X	X
DUODENUM	X	X	X	X	X
JEJUNUM	X	X	X	X	X
ILEUM	X	X	X	X	X
CECUM	X	X	X	X	X
COLON	X	X	X	X	X
RECTUM	X	X	X	X	X
LIVER	X	X	X	X	X
KIDNEYS	X	X		X	X
RIGHT KIDNEY HYDRONEPHROSIS			1		
URINARY BLADDER	X	X	X	X	X
PITUITARY GLAND	X	X	X	X	X
ADRENALS	X	X	X	X	X
PANCREAS, NOS	X	X	X	X	X
THYROID GLANDS	X	X	X	X	X
PARATHYROID GLANDS	X	X	X	X	X
SPLEEN	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X
BONE MARROW	X	X	X	X	X
BRAIN	X	X	X	X	X
EYES	X	X	X	X	X
SALIVARY GLANDS	X	X	X	X	X
ADIPOSE TISSUE	X	X	X	X	X
SKIN, NOS	X	X	X	X	X
HAIR	X	X	X	X	X
ACCESSORY SEX ORGANS (MALE)	X	X	X	X	X
EPIDIDYMIDES	X	X	X	X	X
TESTES	X	X	X	X	X

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE
P-PRESENT, A-ABSENT, * -SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

REVIEWED BY: John M. Moker DATE: 9-14-91 ACCEPTED BY: Janet J. V. V. V. DATE: 9/15/91

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 940047A0

COMPOUND # 94-0047
SOFTWARE VERS # 3.0
ACCESSION NUMBER 109629

ANIMAL #	1000.000 MG/KG				
	GROUP - M				
	306	307	308	309	310
DAYS ON TEST	14	14	14	14	14
TRACHEA	X	X	X	X	X
LUNGS	X	X	X	X	X
THYMUS	X	X	X	X	X
HEART	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X
STOMACH	X	X	X	X	X
DUODENUM	X	X	X	X	X
JEJUNUM	X	X	X	X	X
ILEUM	X	X	X	X	X
CECUM	X	X	X	X	X
COLON	X	X	X	X	X
RECTUM	X	X	X	X	X
LIVER	X	X	X	X	X
KIDNEYS	X	X	X	X	X
URINARY BLADDER	X	X	X	X	X
PITUITARY GLAND	X	X	X	X	X
ADRENALS	X	X	X	X	X
PANCREAS, NOS	X	X	X	X	X
THYROID GLANDS	X	X	X	X	X
PARATHYROID GLANDS	X	X	X	X	X
SPLEEN	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X
BONE MARROW	X	X	X	X	X
BRAIN	X	X	X	X	X
EYES	X	X	X	X	X
SALIVARY GLANDS	X	X	X	X	X
ADIPOSE TISSUE	X	X	X	X	X
SKIN, NOS	X	X	X	X	X
HAIR	X	X	X	X	X
ACCESSORY SEX ORGANS (MALE)	X	X	X	X	X
EPIDIDYMIDES	X	X	X	X	X
TESTES	X	X	X	X	X

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE
P-PRESENT, A-ABSENT, *SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

REVIEWED BY: John Mosher DATE: 9-14-94 ACCEPTED BY: William J. Blawie DATE: 9-15-94

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 940047A0

COMPOUND # 94-0047
SOFTWARE VERS # 3.0
ACCESSION NUMBER 109629

ANIMAL #	2000.000 MG/KG				
	GROUP - M				
	281	282	283	284	285
DAYS ON TEST	2	2	2	2	14
TRACHEA	X	X	X	X	X
LUNGS	X	X	X	X	X
THYMUS HEMORRHAGE	2	3	3	2	X
HEART	X	X	X	X	X
ESOPHAGUS	X	X	X	X	X
STOMACH STOMACH, GLANDULAR HEMORRHAGE				X	X
DUODENUM	1	2	2		
JEJUNUM	X	X	X	X	X
ILEUM	X	X	X	X	X
CECUM	X	X	X	X	X
COLON	X	X	X	X	X
RECTUM	X	X	X	X	X
LIVER	X	X	X	X	X
KIDNEYS	X	X	X	X	X
URINARY BLADDER URINE DISCOLORATION, RED	X		X	X	X
		P			
PITUITARY GLAND	X	X	X	X	X
ADRENALS	X	X	X	X	X
PANCREAS, NOS	X	X	X	X	X
THYROID GLANDS	X	X	X	X	X
PARATHYROID GLANDS	X	X	X	X	X
SPLEEN	X	X	X	X	X
MESENTERIC LYMPH NODES	X	X	X	X	X
BONE MARROW	X	X	X	X	X
BRAIN	X	X	X	X	X
EYES	X	X	X	X	X
SALIVARY GLANDS	X	X	X	X	X
ADIPOSE TISSUE	X	X	X	X	X
SKIN, NOS	X	X	X	X	X
HAIR					X
HAIR OF INGUINAL REGION HAIRCOAT-DRY URINE STAIN HAIRCOAT-WET BY URINE	P	P	P	P	
ACCESSORY SEX ORGANS (MALE)	X	X	X	X	X
EPIDIDYMIDES	X	X	X	X	X
TESTES	X	X	X	X	X
BODY AS A WHOLE, NOS AUTOLYSIS	2	3	3	3	

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE
P-PRESENT, A-ABSENT, *SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

REVIEWED BY: John M. Miller DATE: 9-14-94 ACCEPTED BY: Charles J. V. Brown DATE: 9/15/94

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 940047A0

COMPOUND # 94-0047
 SOFTWARE VERS # 3.0
 ACCESSION NUMBER 109629

GROUP	500.000	1000.000	2000.000
	MG/KG F	MG/KG F	MG/KG F
TRACHEA	0	0	5
LUNGS	0	0	5
THYMUS	0	0	5
HEART	0	0	5
ESOPHAGUS	0	0	5
STOMACH	0	0	5
DUODENUM	0	0	5
JEJUNUM	0	0	5
ILEUM	0	0	5
CECUM	0	0	5
COLON	0	0	5
RECTUM	0	0	5
LIVER	0	0	5
KIDNEYS	0	0	5
URINARY BLADDER	0	0	5
PITUITARY GLAND	0	0	5
ADRENALS	0	0	5
PANCREAS, NOS	0	0	5
THYROID GLANDS	0	0	5
PARATHYROID GLANDS	0	0	5
SPLEEN	0	0	5
MESENTERIC LYMPH NODES	0	0	5
BONE MARROW	0	0	5
BRAIN	0	0	5
EYES	0	0	5
SALIVARY GLANDS	0	0	5
ADIPOSE TISSUE	0	0	5
SKIN, NOS	0	0	5
HAIR	0	0	5
HAIR OF INGUINAL REGION			
HAIRCOAT-WET BY URINE	0	0	1

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS,
 THE NUMBER OF TISSUES WITH EACH ABNORMALITY

REVIEWED BY: John Mosher DATE: 9-14-94 ACCEPTED BY: Janet S. Heavin DATE: 9/15/94

SUMMARY GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 940047A0

COMPOUND # 94-0047
 SOFTWARE VERS # 3.0
 ACCESSION NUMBER 109629

GROUP	500.000	1000.000	2000.000
	MG/KG F	MG/KG F	MG/KG F
FALLOPIAN TUBES	0	0	5
VAGINA	0	0	5
UTERUS	0	0	5
HYDROMETRA	0	0	1
OVARIES	0	0	5
CERVIX UTERI	0	0	5
BODY AS A WHOLE, NOS	0	0	1
AUTOLYSIS	0	0	1

NUMBERS REPRESENT NUMBER OF TISSUES EXAMINED, OR IN THE CASE OF ABNORMAL FINDINGS, THE NUMBER OF TISSUES WITH EACH ABNORMALITY

REVIEWED BY: John Mosher DATE: 9.14.94 ACCEPTED BY: Donald V. Lanni DATE: 9/15/94

INDIVIDUAL ANIMAL GROSS PATHOLOGY INCIDENCE TABLE

EXPERIMENT # 940047A0

COMPOUND # 94-0047
SOFTWARE VERS # 3.0
ACCESSION NUMBER 109629

ANIMAL #	2000.000 MG/KG					GROUP - F
	286	287	288	289	290	
DAYS ON TEST	14	14	14	2	14	
TRACHEA	X	X	X	X	X	
LUNGS	X	X	X	X	X	
THYMUS	X	X	X	X	X	
HEART	X	X	X	X	X	
ESOPHAGUS	X	X	X	X	X	
STOMACH	X	X	X	X	X	
DUODENUM	X	X	X	X	X	
JEJUNUM	X	X	X	X	X	
ILEUM	X	X	X	X	X	
CECUM	X	X	X	X	X	
COLON	X	X	X	X	X	
RECTUM	X	X	X	X	X	
LIVER	X	X	X	X	X	
KIDNEYS	X	X	X	X	X	
URINARY BLADDER	X	X	X	X	X	
PITUITARY GLAND	X	X	X	X	X	
ADRENALS	X	X	X	X	X	
PANCREAS, NOS	X	X	X	X	X	
THYROID GLANDS	X	X	X	X	X	
PARATHYROID GLANDS	X	X	X	X	X	
SPLEEN	X	X	X	X	X	
MESENTERIC LYMPH NODES	X	X	X	X	X	
BONE MARROW	X	X	X	X	X	
BRAIN	X	X	X	X	X	
EYES	X	X	X	X	X	
SALIVARY GLANDS	X	X	X	X	X	
ADIPOSE TISSUE	X	X	X	X	X	
SKIN, NOS	X	X	X	X	X	
HAIR	X	X	X		X	
HAIR OF INGUINAL REGION						
HAIRCOAT-WET BY URINE				P		
FALLOPIAN TUBES	X	X	X	X	X	
VAGINA	X	X	X	X	X	
UTERUS	X	X		X	X	
HYDROMETRA			2			
OVARIES	X	X	X	X	X	
CERVIX UTERI	X	X	X	X	X	
BODY AS A WHOLE, NOS						
AUTOLYSIS				3		

KEY: N-NORMAL AND TISSUE COLLECTED FOR HISTOPATHOLOGY, 1-MINIMAL, 2-MINOR, 3-MODERATE, 4-SEVERE
P-PRESENT, A-ABSENT, *--SEE COMMENT REPORT (FORM #2), X-NORMAL BUT NOT COLLECTED

REVIEWED BY: John M. Moker DATE: 9-14-90 ACCEPTED BY: Anton J. Vecchi DATE: 9/15/94