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In compliance with the National Toxicology Program's (NTP) mission to keep our colleagues informed of the current NTP findings during on-going studies, a copy of the Pathology Working Group (PWG) report and the Summary Pathology Tables for the chronic dosed feed studies on Emodin (CAS No. 518-82-1) are enclosed for your review.

The NTP assembles a Pathology Working Group to review every study and to resolve any differences between the study laboratory and quality assessment pathology evaluations. Please note that the PWG conclusion of the study results is based solely on the pathology for this study and may not reflect final NTP conclusions. In determining final conclusions, the NTP assesses a broad array of information that includes other results from this study and historical control data.

All study data are subject to an NTP retrospective audit and the interpretation may be modified based on the findings. The technical report for this study is currently being prepared for presentation to the NTP Board of Scientific Counselors' Technical Reports Review Subcommittee with an anticipated peer-review date of May 1999.

The Summary Pathology Tables along with a wide variety of NTP information are also available in electronic format on the world-wide web. For example, the NTP Annual Plan, abstracts of NTP Reports, study data, and the status of all NTP studies may be viewed electronically with access to the internet and a Web browser such as Netscape Navigator or Internet Explorer.

To locate the NTP home page, use the URL http://ntp-server.niehs.nih.gov/. The NTP individual animal and summary pathology tables, survival tables, and survival and growth curves may be accessed from the NTP homepage selecting "Testing Information and Study Results" and then choosing "Data of Completed Studies." Comments on the usefulness of this site and suggestions for improvement are encouraged.

Please contact Central Data Management (CDM) at (919)541-3419 if you have any questions. You may also fax your requests for information to CDM at (919)541-3687 or send them via e-mail to cdm@niehs.nih.gov.

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Hard copies of documents such as NTP Technical Reports, short-term Toxicity Reports, and the Report on Carcinogens are available from the Environmental Health Information Service (EHIS). You can contact EHIS by phone at (919) 541-3841, by fax at (919)541-0273, or by e-mail at ehis@niehs.nih.gov.

Sincerely,

William Eastin

William Eastin, Ph.D.
Head, Information Systems & Central Files
Environmental Toxicology Program

Encls: Rats & Mice, PWG, Pathology Summary Tables
cc: Dr. J. Bucher
Dr. R. Irwin
Central Data Management

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PATHOLOGY QUALITY ASSESSMENT AND PATHOLOGY WORKING GROUP

REPORT OF

CHRONIC TOXICITY/CARCINOGENICITY STUDY OF EMODIN ADMINISTERED BY DOSED FEED TO B6C3F1 MICE

TDMS Number: 05211-06
Southern Research Institute Study ID: A09-CRM-2

Prepared for

National Toxicology Program
National Institute of Environmental Health Sciences
Research Triangle Park, NC 27709

Prepared by

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PATHOLOGY WORKING GROUP (PWG) REPORT

CHRONIC TOXICITY/CARCINOGENICITY STUDY OF EMODIN ADMINISTERED BY DOSED FEED TO B6C3F1 MICE

TDMS Number: 05211-06
Southern Research Institute Study ID: A09-CRM-2

INTRODUCTION

Emodin was nominated for carcinogenicity testing by the National Toxicology Program because of the known mutagenicity of its metabolite 2-hydroxyemodin (2-OH-EM) and other anthraquinones. Doses for the chronic study were selected based on the results of repeated-dose and subchronic studies. The in-life phase of this study was conducted by Southern Research Institute, Birmingham, AL. The histopathologic evaluation of the microscopic sections was conducted by Dr. D Farnell of Southern Research Institute. Dr. Cynthia Shackelford of Experimental Pathology Laboratories, Inc. (EPL) served as the Quality Assessment pathologist (QAP).

Pathology Associates International (PAI) was tasked with preparing a pathology working group (PWG) for this study. Dr. Mark Butt of PAI performed these tasks. The PWG was held on September 10, 1998 at the NIEHS facilities at Research Triangle Park, NC. Participants at the PWG were: Drs. Mark Butt (PAI, Chairperson), Joel Mahler, Abraham Nyska, Ronald Herbert (all of NIEHS), Cynthia Shackelford (EPL) and Richard Miller (NCSU).

CONFLICT STATEMENT

The PWG Chairperson has had no involvement in the generation or previous evaluation of data in this study. Further, he has no relevant connection with the originating laboratory.

CONDUCT OF THE PWG

Before the PWG, the chairperson reviewed the study report prepared by the testing facility, all TDMS generated pathology tables and all documents supplied by the QAP. Tissues to be examined by the PWG chairperson were those examined by the QAP pathologist as prescribed by the NTP. Subsets of slides were selected by the PWG chairperson for review by the full PWG and are listed by individual species later in this report.

STUDY DESIGN

Mice (60/sex) were assigned to three treated groups (160, 312, and 625 ppm for males; 312, 625, and 1250 ppm for females) and one untreated group (0 ppm). A scheduled interim sacrifice of 10 mice/sex/dose group was conducted at 12 months (to evaluate the effect of emodin on the weights and pathology of the liver and kidney) and terminal sacrifices were conducted after 105 weeks of treatment.

METHODS

The study pathologist (SP) evaluated all protocol tissues from all mice.

The Quality Assessment pathologist (QAP) reviewed the following:
-kidney, males and females, all animals
-all tumors, males and females, all animals
-liver, "Lymphoma, Malignant", males
-lung, "Alveolar/Bronchiolar Hyperplasia", males
-spleen, "Lymphoma, Malignant", males
-thymus, "Lymphoma, Malignant", males
-thyroid gland, follicular cell, "Hyperplasia", males
-thyroid gland, "Adenoma, Multiple", males
-pituitary gland, "Carcinoma", females
-thyroid gland, Adenoma, Multiple", females.

Slides from all of these tissues/organs/diagnoses were assembled into the slide set presented for review by the PWG Chairperson. The QAP provided Slide Review Work Sheets to the PWG Chairperson. Those work sheets listed, by CID number order, potential target organs, neoplasms, and nontumor pathology which were examined by the QAP. Entries under reviewing pathologist's comments indicated a disagreement with the study pathologist's diagnosis. Additionally, all data from the Slide Review Work Sheets were provided to the PWG Chairperson electronically on disk. During his review, the PWG Chairperson entered his findings directly into the Pathology Quality Assurance System, PWG Module.

During the PWG Chairperson's review, selected slides were assembled by Dot Group into a PWG slide set. These slides were then reviewed by the full PWG. The consensus of the PWG members for these selected slides/findings is provided in Appendix 1 to this report.

RESULTS

Clinical Signs (from a review of the study report)
There were no biologically significant differences in the incidence of clinical observations. Female mice did have a decreased number of grossly observed tissue masses in the 625 and 1250 dose groups (0 and 1 masses, respectively) as compared to the 0 and 312 ppm groups (6 and 5 masses, respectively). The biologic significance of this difference and its relationship to treatment was not apparent.

Mortality (from a review of the study report)

Emodin had no effect on survival of mice of either sex.

Body Weights (from a review of the study report)

Emodin had no effect on body weights of mice of either sex.

Food Consumption(from a review of the study report)

Emodin had no effect on body weights of mice of either sex.

Pathology
The only target organ for Emodin (at both sacrifices) was the kidney. The incidence of all other nonneoplastic and neoplastic lesions seen in Emodin-treated mice was not statistically different from controls and such lesions were considered to be incidental or related to normal aging of the mouse. Specific lesions, particularly the decrease of lymphoma in the high dose male mice, are discussed below.

Interim Sacrifice
Compound related lesions were increased incidence and/or severity of nephropathy in the male and female mice in the high dose groups and pigment deposition in all male treatment groups (160, 312 and 625 ppm) and the female 625 and 1250 ppm treatment groups. Pigment deposition was increased in a dose-related manner in both sexes. Male mice generally had more pigment than female mice.

Pigment was generally found within tubules in the corticomedullary junction area. The pigment was generally brown to brown/red and occasionally pigment granules were found within epithelial cells of affected tubules. Pigment deposition was similar to that seen in the subchronic study with emodin. The pigment was presumed to be emodin or one or more metabolic products of emodin. The SP and QAP noted a correlation between the presence of pigment deposition in individual nephrons and the lesions of nephropathy in the same nephrons. The nephropathy had the general characteristics of the age-related change seen in untreated B6C3F1 mice. The PWG reviewed slides of the kidney from male and female interim sacrifice mice and verified the findings of the SP and QAP. Additionally, the PWG reviewed special stains (bile stain, PAS stain and Prussian Blue stain) from a high dose male with pigment. The special stains were negative with respect to further characterization of the pigment.

Terminal (2-year) Sacrifice
Emodin related microscopic changes were limited to the kidney in the males and females. At the terminal sacrifice, pigment was observed in all female as well as all male emodin treated groups. There was an increased severity of nephropathy in the high dose males. There was an increased incidence of nephropathy in all emodin treated female groups with an associated increased severity of nephropathy in at least the 625 and 1250 ppm female dose groups. The PWG reviewed selected slides from males and females in the 2-year term sacrifice group and generally verified the findings of the SP and QAP. The character of the pigment was similar to that previously described in the Interim Sacrifice section.

There were no statistically different incidences of neoplastic lesions seen in the emodin-treated mice. One unusual finding, however, was the decreased incidence of "Lymphoma, Malignant" in the high dose males. The reviews by the QAP, PWG Chairperson and PWG verified the decreased incidence of "Lymphoma, Malignant" in the high dose males except that one male in the high dose group not diagnosed with "Lymphoma, Malignant" by the SP was diagnosed with "Lymphoma, Malignant" by the PWG. The exact relationship of this decreased incidence of "Lymphoma, Malignant" to the feeding of emodin was not determined. Emodin has been shown to have immunosuppressive effects (1) and a structurally similar compound (1-amino-2,4-Dibromoanthraquinone) has been associated with a decreased incidence of mononuclear cell leukemia in the Fischer rat (2).

The SP and QAP also noted a decreased incidence of alveolar/bronchiolar carcinoma in the high dose males in comparison to the other groups. At the PWG, 3/7 control and 4/6 alveolar/bronchiolar carcinomas (diagnosed by the SP) selected for review by the PWG Chairperson were considered to be adenomas. Although this change in diagnosis for several animals in both the control and high dose groups had no significant effect on the apparent overall decreased incidence of carcinomas in the high dose males, the PWG members felt that this decrease in alveolar/bronchiolar carcinomas in the high dose males had no relationship to the feeding of Emodin.

Other slide sets (dot groups) evaluated by the PWG were assembled by the PWG Chairperson to reconcile differences between the SP and RP concerning selected lesions in the thyroid gland and various neoplasms, most notably differences concerning hepatocellular carcinoma versus adenoma. Concerning thyroid lesions, in several animals the SP had diagnosed "Follicular cell, Adenoma" whereas the QAP had diagnosed "Follicular cell, Hyperplasia". In general, the PWG was in agreement with the QAP (reviewing pathologist) that the lesions were more compatible with "Follicular cell, Hyperplasia". In general, numerous hepatocellular carcinomas diagnosed by the SP were determined by the PWG (and QAP) to be adenomas or in some cases foci. These changes in diagnosis had no effect on the overall evaluation of the effects of emodin.

Miscellaneous

In the review of the study materials and documentation, the PWG Chairperson noted the followed items.

The study report by the testing facility made no mention of the special stains performed on selected animals from the interim sacrifice.

The title of the table on page 25 of the Quality Assessment Report (volume I of VII) should have read "Incidence of Selected Lung Lesions in Male Mice" not "Incidence of Selected Renal Lesions in Male Mice".

For animal #409 (625 ppm female), slides 22, 23 and 24 are mislabeled on the paper label. The paper labels incorrectly had the animal number as "404".

SUMMARY

Emodin was administered in dosed feed for two years to B6C3F1 mice of both sexes at dose levels of 160, 312, and 625 ppm for males and 312, 625, and 1250 ppm for females. An interim sacrifice was performed at 12 months to evaluate the effect of emodin on the weights and pathology of the liver and kidney.

The general assessments of the PWG, regarding the effects of emodin, generally agreed with the assessments provided by the study pathologist in the study report and the quality assessment pathologist in the quality assessment report.

The only target organ for emodin in this study was the kidney. Pigment in renal tubules (and occasionally within renal tubular epithelial cells) believed to be emodin or a metabolite was a treatment related effect in all male and female emodin treated groups at the two year sacrifice and in all male and the mid and high dose females at the interim sacrifice. Increased incidence and/or severity of nephropathy, possibly directly related to the presence of pigment, was associated with the feeding of emodin in all male groups and the mid and high dose females at the two year sacrifice and in the high dose male and female groups at the interim sacrifice.

There were no statistically different incidences of neoplastic lesions between the control and emodin treated groups in either sex. A decreased incidence of "Lymphoma, Malignant" in the high dose males (two year sacrifice) was considered to have a possible relationship to the feeding of emodin.

Mark T. Butt — 10/11/98

Mark T. Butt, DVM — Date
Diplomate, American College of Veterinary Pathologists
PWG Chairperson

References

1) Huang H, Chang J, Tung S, Wu R, Foegh M, Chu S. Immunosuppressive effect of emodin, a free radical generator. Eur J Pharm 211 (1992) 359-364.
2) Elwell M, Dunnick J, Hailey J, Haseman J. chemicals associated with decreased in the incidence of mononuclear cell leukemia in the Fischer rat. Tox Path (1996) 24: 238-245.

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PATHOLOGY WORKING GROUP
CHAIRPERSON'S REPORT

27-WEEK AND 53-WEEK INTERIM SACRIFICE AND
2-YEAR CHRONIC STUDY OF
EMODIN (C62408)
ADMINISTERED BY DOSED FEED TO F344 RATS

Prepared by:

Micheal P. Jokinen, DVM
Pathology Working Group Chairperson

Pathology Associates International
4915D Prospect Drive
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Submitted to:

National Toxicology Program/NIEHS
Research Triangle Park, NC

November 20, 1998

The pathologist performing this review, Dr. Micheal P. Jokinen, has had no involvement with any laboratory or organization concerned with this study other than NTP, and has not been involved in the origination or any previous review of data from this study.

PATHOLOGY WORKING GROUP CHAIRPERSON'S REPORT

27-Week and 53-Week Interim Sacrifice and 2-Year Chronic Study of
Emodin in F344 Rats

Participants: Drs. M. Jokinen (PAI - PWG Chairperson), R. Hailey (NIEHS), R. Miller (NCSU), A. Nyska (NIEHS), C. Shackelford, EPL (QA-Pathologist), R. Sills (NIEHS)

Date: October 15, 1998
Site: NIEHS, Research Triangle Park, NC

The PWG was convened to evaluate selected slides from F344 rats administered emodin by dosed feed for 27 weeks, 53 weeks, or two years The doses and numbers of animals examined microscopically per group were as follows:

	27-Week		53-Week		2-Year	
Dose	M	F	M	F	M	F
0 ppm	10	10	5	5	50	50
280 ppm	10	10	5	5	50	50
830 ppm	10	10	5	5	50	50
2500 ppm	10	10	5	5	50	50

The study was conducted at Southern Research Institute. The Study Pathologist (SP) was Dr. J. Heath. The Quality Assessment Pathologist (QAP) was Dr. C. Shackelford of EPL.

A number of organs were reviewed by the QAP for potential treatment-related effects; the QAP reviewed these organs in all for animals for all diagnoses, neoplastic and nonneoplastic. Organs reviewed for all diagnoses were as follows:

27-Week and 53-Week Interim Sacrifice Studies

Male Rats	Female Rats
Kidney	Kidney

2-Year Study

Male Rats	Female Rats
Kidney	Kidney
Liver	Liver
Spleen	Spleen

In addition, all males in the 2-year study were examined for Islets, Pancreatic - Hyperplasia; Prostate, Epithelium - Hyperplasia; and Bone Marrow - Hyperplasia;

and all females in all groups were examined for Bone Marrow - Hyperplasia; and Uterus - Hyperplasia, Cystic. Furthermore, slides of certain organs were examined when a specific diagnosis was listed as present. For males these included Lymph Node, Mesenteric - Ectasia; and Mesentery, Fat - Necrosis; for females these included Lymph Node, Mandibular - Ectasia.

In addition to the above, the QAP reviewed all tumor diagnoses in all animals (except Testis - Interstitial Cell Adenoma).

SUMMARY OF REVIEW FINDINGS

A slight increase in the incidence of **Prostate - Adenoma** was observed in the 2500 ppm male group as compared with control males.

Increased incidences and/or severities of **Kidney, Renal Tubule - Hyaline Droplets** and **Kidney, Renal Tubule - Pigment** were observed in treated males and females in the 27-week and 53-week interim sacrifices, and the 2-year study.

Incidences of **Leukemia, Mononuclear Cell** were lower in the 2500 ppm male and female groups as compared with the control and other dosed groups.

Incidences of proliferative lesions of the **Islets, Pancreatic** including **Hyperplasia, Adenoma**, and **Carcinoma** were lower in treated groups of males as compared with control males.

CONDUCT OF THE PWG

Prior to the PWG, the PWG Chairperson reviewed the pathology tables, the SP's narrative, the Pathology Data Review, the Quality Assessment Report, and microslides of tissues selected for QA review. The PWG Chair then selected slides for review by the PWG, including representative examples of lesions, and lesions for which there was a difference in diagnosis among the SP, QAP, and PWG Chair.

RESULTS OF THE PWG REVIEW

Prostate

The SP had diagnosed a higher incidence of **Prostate, Epithelium - Hyperplasia** in the 2500 ppm males than in the other treated male groups or in control males. The QAP added several additional diagnosis of hyperplasia, primarily in the control group, with the result that the incidence of hyperplasia as diagnosed by the QAP was greater in the control group than in the 2500 ppm group. However, the QAP also considered a number of the lesions diagnosed

as hyperplasia by the SP to represent **Prostate - Adenoma** so that the incidence of adenoma as diagnosed by the QAP was greater in the 2500 ppm group than in the control group. With few exceptions the PWG Chair concurred with the QAP's findings. The additional hyperplasias diagnosed by the QAP generally were of minimal severity. In addition, the QAP diagnosed **Carcinoma** in nearly equal numbers of animals in the control and each of the treated groups. The PWG examined representative examples of hyperplasias, as well as all of the lesions that had been diagnosed as a neoplasm (adenoma or carcinoma). Prior to examining the prostatic lesions, the PWG discussed the diagnostic criteria used for these lesions included in the Pathology of the Fischer Rat.

Microscopically, hyperplasias were small to moderate sized lesions, consisting of nodular foci composed of multiple layers of glandular epithelium, which often formed small gland-like structures, that projected into the glandular lumens. More severe hyperplasias filled much or nearly all of the glandular lumen. Adenomas were larger lesions that filled and, generally, distended the glandular lumens; larger adenomas extended into adjacent lumens. The PWG noted that all the adenomas occurred within the ventral prostate. The PWG also noted some prostates contained hyperplasia that occurred secondary to inflammation, and was of the opinion that this represented reactive hyperplasia that was part of the inflammation and did not warrant a separate diagnosis; this was consistent with the diagnostic criteria in the Pathology of the Fischer Rat, and is in accordance with the recommendation of Bosland (1992). The location of the hyperplasias and adenomas within the ventral prostate and the microscopic appearance of these lesions was consistent with the descriptions in the Pathology of the Fischer Rat, and findings reported by Bosland (1987, 1992). Bosland (1987) states that naturally occurring adenomas of the dorsolateral prostate have not been reported.

The lesions diagnosed as Carcinoma by the QAP were located in the dorsolateral prostate and sometimes were bilateral. All had a similar microscopic appearance and consisted of local areas of dense fibrous tissue containing multiple variably-sized glands, many of which were dilated and filled with what appeared to be mucus. Some of the glands were partially to completely lined by tall basophilic epithelial cells.

The PWG concurred with the diagnoses of hyperplasia and with nearly all of the diagnoses of adenoma. However, the PWG was of the opinion that the lesions in the dorsolateral prostate diagnosed as Carcinoma by the QAP represented **Fibrosis** of the prostate with secondary hyperplasia of epithelium within the glands that had been encompassed by the fibrous tissue. The PWG was of this opinion due to the fact that no atypical architecture or definite evidence of invasion were seen within any of the lesions. Bosland (1987) states that carcinomas of the dorsolateral prostate "are invasive in nature and clear-cut invasion of the capsule and other signs of infiltrative behavior are conclusive for carcinoma". The origin of these lesions was unclear, but some of the PWG

members suggested they may have represented old areas of inflammation that had healed by fibrosis. Presumably glands had been trapped by the fibrous tissue causing secondary changes in the epithelium and resulting in the glands filling with mucus and undergoing dilatation. Although hyperplastic epithelium was present within some of these lesions it was not diagnosed separately as it was considered to be a reaction secondary to the fibrous change. Since the PWG members had not encountered lesions such as these previously and it was desired to determine their nature accurately, following the PWG Dr. Robert Maronpot of NIEHS, who has specialized knowledge of prostatic lesions, was asked to evaluate these lesions. Dr. Maronpot agreed with the PWG consensus that all of these lesions represented fibrosis and were not neoplasms.

The PWG confirmed there was a slight increase in the incidence of prostatic adenoma in the 2500 ppm group as compared with the control group. The significance of this was uncertain. The incidence of adenoma fell outside the historical control range for NTP feed studies (range 0/50-2/50, 0-4%; mean 0.22%). However, the PWG members noted that the lesions in this study were in the ventral prostate, the site at which prostate neoplasms commonly arise in rats. There was concern as to whether the present NTP historical control database accurately reflected the incidence of neoplasms in the rat prostate. As a post-PWG action item, it was recommended that the prostates from a number of NTP studies be examined to determine the way in which they were sectioned and to see whether the ventral prostate was included in the prostate sections.

Kidney

The SP had diagnosed increased in[illegible]ces and/or severities of **Renal Tubule - Cytoplasmic Alteration** and **Rena[illegible]ule - Pigment** in treated groups of males and females in the 27-week, 53-week, and 2-year studies. The SP had found no differences in the incidences and or severities of **Nephropathy** between control and treated males and females at the 27-week, 53-week, or 2-year studies. The QAP confirmed the presence of the changes reported by the SP, and in general there was good agreement between the SP and QAP. However, the QAP recommended use of the terminology **Renal Tubule - Hyaline Droplets** instead of the SP's terminology of Cytoplasmic Alteration. In addition, in the 2-year study the QAP added several additional diagnoses of minimal Pigment in the control males and females and in the 280 ppm male group, and minimal Nephropathy in the control and treated female groups. The incidences and severities of Nephropathy in females, as diagnosed by the QAP, were similar in the control and treated groups. With few exceptions the PWG Chair concurred with the QAP.

The PWG examined representative examples from the 27-week, 53-week, and 2-year study, and concurred with the SP's diagnosis of Pigment, but preferred the QAP's terminology of Hyaline Droplets, and recommended all of the SP's diagnoses of Cytoplasmic Alteration be changed to Hyaline Droplets for the

following reasons: (1) the change diagnosed as Cytoplasmic Alteration by the SP morphologically was consistent with that of Hyaline Droplets, and (2) a similar change had been seen in treated rats from the 13-week subchronic study and the PWG for that study had preferred the term Hyaline Droplets, so use of this term in the chronic study would make the terminology consistent between the subchronic and chronic studies.

Microscopically, Pigment consisted of granular brown pigment within the cytoplasm of epithelial cells from cortical tubules adjacent to the cortico-medullary junction. Hyaline Droplets consisted of variably-sized, homogeneous, eosinophilic to brown droplets within the cytoplasm of epithelial cells within proximal tubules. Pigment and Hyaline Droplets similar to those seen in treated animals were also seen in control animals, but were of very minimal severity in controls as compared with treated animals, in which the severity generally was mild to moderate. The PWG members noted that the hyaline droplets in males generally were eosinophilic with smaller numbers of brown droplets, while those in females commonly were brown with smaller numbers of eosinophilic droplets.

The PWG Chair was directed to review the kidneys from treated male and female rats from the 13-week subchronic study to determine if the hyaline droplets present in that study were the same as those seen in the chronic study. The PWG Chair observed that the droplets were morphologically the same in both studies, except that the droplets in females in the subchronic study were mainly eosinophilic as compared with the chronic study in which they were commonly brown. This indicated that the number of brown droplets in females increased with increasing duration of the study.

The nature of the pigment and the hyaline droplets was uncertain. Special stains, including a bile stain, a PAS stain, and a Prussian Blue stain for iron had been performed on selected control and 2500 ppm males and females from the 27-week and 53-week studies. The bile stains were negative. The hyaline droplets stained positive with the PAS stain. Fine granules of Prussian Blue positive material were scattered with tubular epithelial cells, but these had no relationship to either the pigment granules or the hyaline droplets. The pigment granules did not stain with any of the three stains. The hyaline droplets were not considered to represent alpha-2U-microglobulin for the following reasons: (1) alpha-2U-microglobulin is not seen in any appreciable levels in females and hyaline droplets were prominent in the females (2) alpha-2U-microglobulin levels are usually low in aged males thus one would not expect prominent hyaline droplets as was seen in the males at the end of this study and (3) there was no effect on the incidence and severity of nephropathy in treated animals.

As mentioned previously, small amounts of pigment and hyaline droplets, similar to those seen in treated animals, were present in control animals. This finding led to the speculation that the increase in pigmentation and hyaline droplets in treated animals may have represented an excessive accumulation of naturally

occurring substances in the kidneys of treated animals. The PWG suggested that selected control and high dose kidneys be stained with the Mallory-Heidenhain stain for protein and a stain for lipofuscin to attempt to identify further the nature of the pigment and hyaline droplets.

The SP had diagnosed a greater incidence of **Kidney - Inflammation, Chronic** in the 2500 ppm male group as compared with the other treated male groups and the control males. Microscopically, this change consisted of scattered focal aggregates of mononuclear inflammatory cells, mainly lymphocytes with some plasma cells and macrophages. This type of infiltrate is a common component of chronic nephropathy and generally is considered part of the nephropathy and not diagnosed separately. Since there was no difference in the incidences or severities of nephropathy among the control and treated male groups, the greater incidence of Inflammation, Chronic in the 2500 ppm dose group is of no apparent biological significance.

Mononuclear Cell Leukemia

Incidences of Mononuclear Cell Leukemia in the spleen, liver, and bone marrow were lower in the 2500 ppm male and female groups than in the other treated groups or respective controls. As there was very good agreement among the SP, QAP, and PWG Chair concerning the diagnoses of Mononuclear Cell Leukemia, no examples were reviewed by the PWG. The PWG did review a few cases in which there was disagreement concerning the presence of Leukemia. Emodin has been reported to have potential anti-neoplastic activities, and the lower incidences of Mononuclear Cell Leukemia may be a reflection of this.

Pancreatic Islets

The SP had diagnosed lower incidences of proliferative lesions of the pancreatic islets (hyperplasia, adenoma, carcinoma) in treated groups of males as compared with control males. These findings were confirmed by the QA/PWG review. The incidence of **Islets, Pancreatic - Hyperplasia** was greater in the control group than in any of the treated groups. The combined incidence of **Islets, Pancreatic - Adenoma** and **Islets, Pancreatic - Carcinoma** were similar in the control and 280 ppm groups, and were greater than in the other two treated groups. However, the incidence of Carcinoma was greater in the control group than in the 280 ppm group. The PWG reviewed examples of Hyperplasia, Adenoma, and Carcinoma and confirmed the diagnoses. The PWG also reviewed one lesion which was borderline between Adenoma and Carcinoma. Microscopically, the lesions in this study had the typical appearance described for these lesions in F344 rats. The PWG discussed the significance of this finding. One possibility was that it represented an anti-neoplastic effect of emodin. However, the PWG members noted the incidences of neoplasms in the control and 280 ppm groups appeared high and questioned whether the negative trend in islet cell neoplasms was due to a high control incidence. The historical

control incidence for combined islet cell adenoma and carcinoma from NTP two year feeding studies is: range 0/50-5/50 (0-10%), mean 4.35%. Thus, the combined incidence in the controls is at the high end of the control range.

Spleen

The SP had diagnosed a somewhat greater incidence of **Hematopoietic Cell Proliferation** in 2500 ppm males, and marginally greater incidences of **Pigment** in the 830 and 2500 ppm male groups as compared with controls. In addition, the SP had diagnosed substantially greater incidences of **Hematopoietic Cell Proliferation** and **Pigment** in the 830 and 2500 ppm dose groups of females as compared with controls. Moreover, the SP diagnosed lower incidences of **Fibrosis** in the 830 and 2500 ppm male dose groups as compared with control males. The QAP confirmed the SP's findings. The PWG Chair noted that a small amount of pigment and hematopoietic cell proliferation was present in all spleens as a normal background change and that the SP diagnosed these changes when they appeared to exceed this background level. The PWG Chair further noted that a number of spleens of control females in which no diagnosis had been made contained a similar degree of pigment and/or hematopoietic cell proliferation as was present in 2500 ppm females in which these changes had been diagnosed. Using for reference representative spleens from 2500 ppm females in which pigment and hematopoietic cell proliferation had been diagnosed by the SP and confirmed by the QAP, the PWG Chair examined all spleens from females in which no diagnosis had been made and added diagnoses of one or both of these changes in each of the groups, but primarily in controls. The incidences of these changes as diagnosed by the PWG Chair maintained the positive trend for both of these changes in treated groups of females but the trend was not as strong as previously.

The PWG examined representative examples of spleens in which the SP had diagnosed pigment and hematopoietic cell proliferation as well as a number of spleens in which these changes had been diagnosed by the PWG Chair. The PWG was given the reference spleens used by the PWG Chair while examining the spleens. In each case the PWG confirmed the presence of pigment and hematopoietic cell proliferation and recommended that the additional diagnoses made by the PWG Chair be added to the pathology findings. The PWG members noted that the hematopoietic cell proliferation included both erythroid and myeloid cells, although it appeared that erythroid cells were predominant.

Special stains, PAS stain and Prussian Blue stain for iron, had been performed on representative spleens from control and 2500 ppm males and females to aid in identification of the pigment. The staining results were similar in the control and 2500 ppm dose spleens. The pigment stained strongly with the Prussian Blue stain and to a lesser degree with the PAS stain. The PWG opinion was that the pigment consisted primarily of hemosiderin with some, presumably, lipofuscin present and that the pigment was the same in the control and 2500 ppm

spleens. The PWG noted that the pigment in the spleen was different from that in the kidney, and was of the opinion that the pigment in the spleen was not related to the test compound.

The PWG discussed the significance of the increased incidences of pigment and hematopoietic cell proliferation in treated groups of males and females. The PWG members noted that the degree of pigment and hematopoietic cell proliferation was relatively mild. It was also noted that the incidences of Mononuclear Cell Leukemia were greater in the control and lower dose groups of males and females than in the 2500 ppm groups; thus, it is possible that the differences in incidence may have been due in part to the fact that the Leukemia obscured the presence of these changes in more animals in the control and lower dose groups than in the 2500 ppm dose groups. The PWG members were not convinced that these splenic changes represented significant treatment effects, in light of the facts that the changes were relatively mild, they occurred primarily in one sex (females), and that the incidences of these changes may have been affected by the differences in the incidences of Leukemia.

The decreased incidence of **Fibrosis** in the 2500 ppm male dose group was considered secondary to the lower incidence of Mononuclear Cell Leukemia in this group, as fibrosis of the spleen is a common sequel to Leukemia. The incidence of Fibrosis in the 830 ppm male dose group was also lower than in controls although the incidences of Leukemia in these two groups were similar. Fibrosis of the spleen generally occurs in advanced cases of Leukemia in which large amounts of leukemic infiltrate have caused significant damage to the spleen. It is possible that some of the cases of Leukemia in the 830 ppm group were not advanced to the point that they caused sufficient damage to the spleen to produce fibrosis. In order to determine if this were true, however, it would be necessary to stage the leukemias.

Bone Marrow

The SP had diagnosed a greater incidence of **Bone Marrow - Hyperplasia** in the 2500 ppm dose group of males, but not in females. The PWG examined some representative examples of bone marrow hyperplasia and confirmed its presence, and also examined a few bone marrows in which there was a difference of opinion concerning the presence of hyperplasia. The PWG members noted that the incidence of Mononuclear Cell Leukemia in the bone marrow was lower in the 2500 ppm male group than in the control and other treated male groups. The PWG was of the opinion that the greater incidence of hyperplasia in the 2500 ppm group may have been due, at least in part, to the fact that the presence of Leukemia in the bone marrow in other dose groups may have obscured the presence of hyperplasia. The PWG members also recommended that the PWG Chair examine the pathology findings in each of the 2500 ppm males with bone marrow hyperplasia to see if hyperplasia in the spleen were also present, and if any lesion, such as a large neoplasm, were

present which could cause an inflammatory response and induce hyperplasia. Of the 10 animals with bone marrow hyperplasia, six had neoplasms (three skin neoplasms, two preputial gland carcinomas, and a cholangiocarcinoma). One of the males with a preputial gland carcinoma also had a mesothelioma and hematopoietic cell proliferation in the spleen. Of the remaining four animals, one had fat necrosis and one had inflammation of the kidney and large intestine, and both of these also had hematopoietic cell proliferation in the spleen; the last two animals had bone marrow hyperplasia without accompanying hematopoietic cell proliferation in the spleen or any neoplastic or inflammatory lesions. Based upon these findings it seems unlikely that the higher incidence of bone marrow hyperplasia in the 2500 ppm male dose group represents a treatment related effect.

Mandibular and Mesenteric Lymph Nodes

The SP had diagnosed somewhat greater incidences of **Ectasia** in the mandibular lymph node in the 830 and 2500 ppm female groups, and in the mesenteric lymph node in the 2500 ppm male dose group as compared with respective controls. The PWG evaluated a representative example and confirmed the presence of the change. Ectasia was a slight change consisting of multiple, small, clear, cyst-like spaces within the lymph nodes. The PWG questioned the significance of this change. The QAP noted that not all of the mandibular and mesenteric lymph nodes had been reviewed by the QAP, but only those in which Ectasia had been diagnosed. The PWG noted that the Ectasia in this study was of slight severity and that ectasia of lymph nodes occurs as a normal background change. The PWG was of the opinion that the higher incidences of Ectasia in the mesenteric and mandibular lymph nodes did not represent a treatment effect and were not biologically significant.

The SP had also noted the presence of yellow/brown **Pigment** within the mandibular nodes of the females, and diagnosed a somewhat greater incidence in the 2500 ppm group than in the other female groups. Special stains, a PAS stain and a Prussian Blue stain for iron, were performed on selected mandibular lymph nodes from the control and 2500 ppm dose groups. Staining results were similar between the control and 2500 ppm group animals. The pigment stained with both the Prussian Blue stain and with the PAS stain; there appeared to be a somewhat greater degree of PAS staining than Prussian Blue staining. The PWG opinion was that the pigment consisted of hemosiderin and, presumbly, lipofuscin, and was not related to the test material.

Uterus

The SP diagnosed somewhat greater incidences of **Uterus - Hyperplasia, Cystic** in treated groups of females than in controls; the SP had diagnosed this change in only one control animal. The SP's findings were confirmed by the QAP and PWG Chair. The PWG reviewed some examples and confirmed the

presence of the change, which was a slight change consisting of one to few cystically dilated uterine glands. The PWG noted this was a common background change in the uterus of F344 rats, and questioned whether the incidence in the control group of this study (1/50) was low and suggested it be compared with the incidence of this change in the control groups of other studies. Since historical control data are not maintained for nonneoplastic lesions from NTP studies, the PWG Chair was furnished with the control incidences of this lesion from a number of NTP two year studies in order to determine an average control incidence. The PWG Chair picked 20 studies, containing a total of 1000 animals. The range of this lesion from these 20 studies was 0/50-13/50 (0-26%), mean 7.3%. The incidences of this change as diagnosed by the SP fall within the control range of this change determined from selected NTP two year studies. Thus, it does not appear the higher incidences of Cystic Hyperplasia in treated groups represents a treatment related effect.

Liver

The SP had diagnosed higher incidences of **Angiectasis** in the 2500 ppm dose groups of males and females than in controls. The SP had also diagnosed higher incidences of **Eosinophilic Focus** in 2500 ppm males and females, and a higher incidence of Clear Cell Focus in 2500 ppm males as compared with controls. The higher incidences of these changes in the 2500 ppm dose groups were considered to be related to the lower incidences of Mononuclear Cell Leukemia in the livers in these groups. Since the presence of leukemic infiltrate can obscure the presence of these other changes, the lower incidence of Leukemia in these groups allowed these changes to be detected in more animals than in the controls, which had higher incidences of Leukemia.

The SP had diagnosed higher incidences of **Liver, Bile Duct - Hyperplasia** in treated groups of males as compared with control males, and in the 2500 ppm female group as compared with the control and lower dose female groups. This was presumably secondary to the lower incidences of Mononuclear Cell Leukemia in treated groups, as bile duct hyperplasia commonly occurs secondary to liver damage caused by the presence of Leukemia. The incidences of Leukemia in the control and the 280 and 830 ppm dose groups were similar to that in control males, although the incidences of bile duct hyperplasia were lower in these two groups. As with the spleen, it was possible the leukemias in these groups were not advanced to the point that they caused sufficient liver damage to produce bile duct hyperplasia. In order to determine if this were true, however, it would be necessary to stage the leukemias

Mesentery

The SP had diagnosed greater incidences of **Mesentery, Fat - Necrosis** in the 830 and 2500 ppm dose groups of males as compared with the control and 280 ppm groups. All of these were observed grossly, and their presence was

confirmed by the QA/PWG review. These lesions consist of nodular aggregates of necrotic fat, often mixed with inflammatory cells, and are a normal background finding in F344 rats. The greater incidences of these lesions in the two higher dose groups of males does not appear to be biologically significant.

Miscellaneous

The SP diagnosed **Nose - Squamous Cell Carcinoma** in two 2500 ppm males. The PWG examined both noses and agreed that squamous cell carcinoma was present. However, there was a question as to whether these neoplasms in the nose may have represented extensions of squamous cell carcinomas that had arisen within the oral cavity. It was recommended the residual wet tissues from these animals be examined to determine if it was possible that these neoplasms had arisen within the oral cavity. This was done, additional slides were made, and the nasal cavity was confirmed as the site of origin for both of these neoplasms.

The SP diagnosed **Zymbal's Gland - Carcinoma** in three 2500 ppm females (animal numbers 447, 449, and 463). The QAP and PWG Chair concurred with the SP's diagnoses. In addition, the SP had diagnosed **Skin - Squamous Cell Carcinoma** in three 2500 ppm males; the QAP agreed with one of these diagnoses (in animal number 195) but considered one of the other neoplasms (in animal number 211) to be **Skin - Squamous Cell Papilloma** and the third (in animal number 238) to be **Skin - Basal Cell Carcinoma**. The PWG Chair agreed with the QAP's diagnoses. Since these neoplasms had not been shown to the PWG the slides were forwarded to NIEHS where they were reviewed by Drs. Hailey, Nyska, and Sills, who confirmed with the diagnoses of Zymbal's gland carcinoma in the females and also confirmed the QAP's diagnoses in the skin of the males.

A number of animals had two or more mammary gland fibroadenomas; generally there were trace gross lesions corresponding to these fibroadenomas. The SP had diagnosed these as Mammary Gland - Fibroadenoma. The QAP and PWG Chair agreed with the SP that multiple fibroadenomas were present; however, the PWG Chair changed these diagnoses to **Mammary Gland - Fibroadenoma, multiple**, which is the preferred NTP terminology. Since this was only a minor change in terminology and there was no difference in opinion as to the presence of the fibroadenomas, it was not considered necessary to show these slides to the PWG.

Post-PWG Action Items

1) Stain representative kidneys from control and high dose (2500 ppm) animals with Mallory-Heidenhain stain for protein and with a stain for lipofuscin.

B 09

2) Examine prostate sections from other NTP studies to determine how commonly ventral prostate is included in the sections.

3) Examine oral cavity from two 2500 ppm males with squamous cell carcinoma in the nose to determine if these neoplasms could have arisen in the oral cavity. This was done and the nasal cavity was confirmed as the site of origin for both of these neoplasms.

Micheal P. Jokinen, DVM
PWG Chairperson

11/20/98
Date

References:

Boorman, G., Elwell, M.R., and K. Mitsumori. Male Accessory Sex Gland, Penis, and Scrotum. In. Pathology of the Fischer Rat. G.A. Boorman, S.L. Eustis, M.R. Elwell, C.A. Montgomery, Jr., and W.F. MacKenzie (eds.), Academic Press, San Diego, 1990.

Bosland, M. Adenoma, Prostate, Rat. In: Monographs on Pathology of Laboratory Animals. Genital System. T.C. Jones, U. Mohr, and R.D. Hunt (eds.), Springer-Verlag, Berlin Heidelberg, 1987.

Bosland, M. Lesions in the Male Accessory Sex Gland and Penis. In. Pathobiology of the Aging Rat. Vol. 1. Blood and Lymphoid, Respiratory, Urinary, Cardiovascular, and Reproductive Systems. U. Mohr, D.L. Dungworth and C.C. Capen (eds.), ILSI Press, Washington, D.C., 1992.

NATIONAL TOXICOLOGY PROGRAM
TR-493 Emodin
CAS# 518-82-1

Pathology Tables - Rats

P03 - Incidence Rates of Non-Neoplastic Lesions - 2 year Study

P03 - Incidence Rates of Non-Neoplastic Lesions - 27 Week Sacrifice

P05 - Incidence Rates of Neoplasms by Anatomic Site (systemic lesions abridged) - 2 year Study

P05 - Incidence Rates of Neoplasms by Anatomic Site (systemic lesions abridged) - 27 Week Sacrifice

P08 - Statistical Analysis of Primary Tumors - 2 year Study

Pathology Tables - Mice

P03 - Incidence Rates of Non-Neoplastic Lesions - 2 year Study

P03 - Incidence Rates of Non-Neoplastic Lesions - 53 Week Sacrifice

P05 - Incidence Rates of Neoplasms by Anatomic Site (systemic lesions abridged) - 2 year Study

P05 - Incidence Rates of Neoplasms by Anatomic Site (systemic lesions abridged) - 53 Week Sacrifice

P08 - Statistical Analysis of Primary Tumors - 2 year Study

Pathology Tables - Rats Special 53 Week Study

P03 - Incidence Rates of Non-Neoplastic Lesions

P05 - Incidence Rates of Neoplasms by Anatomic Site (systemic lesions abridged)

TP Experiment-Test: 05211-05
Study Type: CHRONIC
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN

Report: PEIRPT03
Date: 01/08/99
Time: 11:20:43

2 YEAR CHRONIC RATS

Facility: Southern Research Institute

Chemical CAS #: 518-82-1

Lock Date: 07/30/97

Cage Range: All

Reasons For Removal: 25019 Moribund Sacrifice 25020 Natural Death
25021 Terminal Sacrifice

Removal Date Range: All

Treatment Groups: Include All

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 05211-05
Study Type: CHRONIC
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN

Report: PEIRPT03
Date: 01/08/99
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FISCHER 344 RATS FEMALE	0 PPM	280 PPM	830 PPM	2500 PPM
DISPOSITION SUMMARY				
Animals Initially In Study	60	60	60	60
Early Deaths				
Moribund Sacrifice	12	8	11	15
Natural Death	5	3	4	1
Survivors				
Terminal Sacrifice	33	39	35	34
Animals Examined Microscopically	50	50	50	50
ALIMENTARY SYSTEM				
Intestine Large, Cecum	(49)	(50)	(49)	(50)
Edema			1 (2%)	
Hemorrhage			1 (2%)	
Inflammation, Acute			1 (2%)	
Intestine Small, Duodenum	(48)	(50)	(49)	(50)
Epithelium, Hyperplasia			1 (2%)	
Liver	(49)	(50)	(50)	(50)
Angiectasis			2 (4%)	4 (8%)
Basophilic Focus	39 (80%)	44 (88%)	41 (82%)	45 (90%)
Clear Cell Focus	2 (4%)	10 (20%)	4 (8%)	11 (22%)
Eosinophilic Focus	18 (37%)	10 (20%)	18 (36%)	27 (54%)
Hematopoietic Cell Proliferation	2 (4%)		2 (4%)	2 (4%)
Hemorrhage	1 (2%)		1 (2%)	
Hepatodiaphragmatic Nodule	3 (6%)	9 (18%)	7 (14%)	7 (14%)
Infiltration Cellular, Mixed Cell	15 (31%)	12 (24%)	9 (18%)	11 (22%)
Mixed Cell Focus	4 (8%)	5 (10%)	6 (12%)	1 (2%)
Necrosis, Focal	4 (8%)	4 (8%)	3 (6%)	
Bile Duct, Hyperplasia	1 (2%)		4 (8%)	1 (2%)
Centrilobular, Necrosis		1 (2%)		1 (2%)
Hepatocyte, Vacuolization Cytoplasmic	3 (6%)	2 (4%)	2 (4%)	2 (4%)
Kupffer Cell, Pigmentation	2 (4%)	2 (4%)	3 (6%)	1 (2%)
Mesentery	(1)	(6)	(1)	(6)
Accessory Spleen		2 (33%)		2 (33%)
Fat, Necrosis	1 (100%)	4 (67%)	1 (100%)	5 (83%)
Pancreas	(49)	(50)	(49)	(50)
Atrophy	13 (27%)	15 (30%)	18 (37%)	13 (26%)
Metaplasia, Hepatocyte	1 (2%)			
Salivary Glands	(49)	(50)	(50)	(50)
Atrophy	1 (2%)		1 (2%)	2 (4%)
Stomach, Forestomach	(49)	(50)	(50)	(50)
Edema	1 (2%)	1 (2%)	1 (2%)	
Erosion			1 (2%)	
Perforation			1 (2%)	
Epithelium, Hyperplasia	1 (2%)			

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 05211-05
Study Type: CHRONIC
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN

Report: PEIRPT03
Date: 01/08/99
Time: 11:20:43

FISCHER 344 RATS FEMALE	0 PPM	280 PPM	830 PPM	2500 PPM
ALIMENTARY SYSTEM - CONT				
Stomach, Glandular	(49)	(50)	(50)	(50)
Edema			1 (2%)	
Erosion		1 (2%)	1 (2%)	1 (2%)
Tongue		(1)		
Epithelium, Hyperplasia		1 (100%)		
CARDIOVASCULAR SYSTEM				
Heart	(49)	(50)	(50)	(50)
Cardiomyopathy	22 (45%)	16 (32%)	17 (34%)	16 (32%)
Inflammation, Chronic Active		1 (2%)		
ENDOCRINE SYSTEM				
Adrenal Cortex	(49)	(50)	(50)	(50)
Accessory Adrenal Cortical Nodule	6 (12%)	4 (8%)	7 (14%)	10 (20%)
Atrophy				2 (4%)
Degeneration, Fatty	12 (24%)	9 (18%)	14 (28%)	10 (20%)
Hemorrhage	1 (2%)	1 (2%)		
Hyperplasia, Diffuse	1 (2%)			
Hyperplasia, Focal	3 (6%)	3 (6%)	8 (16%)	7 (14%)
Hypertrophy	1 (2%)			
Hypertrophy, Focal	12 (24%)	7 (14%)	12 (24%)	10 (20%)
Necrosis		2 (4%)		
Adrenal Medulla	(47)	(50)	(50)	(50)
Hyperplasia	2 (4%)	2 (4%)	2 (4%)	3 (6%)
Islets, Pancreatic	(49)	(50)	(49)	(50)
Hyperplasia		1 (2%)		
Pituitary Gland	(49)	(50)	(49)	(49)
Pars Distalis, Angiectasis	9 (18%)	10 (20%)	6 (12%)	5 (10%)
Pars Distalis, Cyst	22 (45%)	11 (22%)	13 (27%)	16 (33%)
Pars Distalis, Hyperplasia, Focal	13 (27%)	10 (20%)	3 (6%)	5 (10%)
Pars Intermedia, Cyst		1 (2%)		
Thyroid Gland	(49)	(50)	(50)	(50)
Ultimobranchial Cyst	1 (2%)		1 (2%)	
C-Cell, Hyperplasia	21 (43%)	9 (18%)	11 (22%)	12 (24%)
Follicle, Cyst	1 (2%)	1 (2%)	2 (4%)	2 (4%)
GENERAL BODY SYSTEM				
None				

a Number of animals examined microscopically at site and number of animals with lesion

NTP Experiment-Test: 05211-05
Study Type: CHRONIC
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
EMODIN

Report: PEIRPT03
Date: 01/08/99
Time: 11:20:43

FISCHER 344 RATS FEMALE	0 PPM	280 PPM	830 PPM	2500 PPM
GENITAL SYSTEM				
Clitoral Gland	(49)	(50)	(49)	(49)
Cyst	1 (2%)		4 (8%)	1 (2%)
Hyperplasia	3 (6%)	2 (4%)	6 (12%)	3 (6%)
Inflammation, Chronic	5 (10%)	5 (10%)	6 (12%)	5 (10%)
Ovary	(49)	(50)	(50)	(50)
Cyst	10 (20%)	6 (12%)	6 (12%)	7 (14%)
Uterus	(49)	(50)	(50)	(50)
Angiectasis		1 (2%)		
Hydrometra	5 (10%)	3 (6%)	5 (10%)	6 (12%)
Hyperplasia, Cystic	1 (2%)	5 (10%)	4 (8%)	7 (14%)
Inflammation, Chronic	1 (2%)		1 (2%)	2 (4%)
HEMATOPOIETIC SYSTEM				
Bone Marrow	(49)	(50)	(50)	(50)
Hyperplasia	5 (10%)	3 (6%)	4 (8%)	6 (12%)
Infiltration Cellular, Histiocyte		2 (4%)	4 (8%)	2 (4%)
Lymph Node	(5)	(3)	(4)	(3)
Mediastinal, Hemorrhage			2 (50%)	1 (33%)
Mediastinal, Hyperplasia, Lymphoid			1 (25%)	1 (33%)
Mediastinal, Pigmentation	1 (20%)	1 (33%)	1 (25%)	
Pancreatic, Hematopoietic Cell Proliferation			1 (25%)	
Pancreatic, Hemorrhage			1 (25%)	
Lymph Node, Mandibular	(49)	(50)	(50)	(50)
Ectasia	1 (2%)	2 (4%)	6 (12%)	6 (12%)
Hemorrhage	2 (4%)	4 (8%)	4 (8%)	4 (8%)
Hyperplasia, Lymphoid	1 (2%)		2 (4%)	1 (2%)
Pigmentation	18 (37%)	19 (38%)	21 (42%)	25 (50%)
Lymph Node, Mesenteric	(49)	(50)	(49)	(50)
Hemorrhage	2 (4%)	5 (10%)	2 (4%)	4 (8%)
Pigmentation	2 (4%)	2 (4%)		2 (4%)
Spleen	(50)	(50)	(50)	(50)
Angiectasis				1 (2%)
Depletion Cellular		1 (2%)		
Developmental Malformation				1 (2%)
Fibrosis				2 (4%)
Hematopoietic Cell Proliferation	27 (54%)	24 (48%)	31 (62%)	40 (80%)
Hemorrhage	1 (2%)		1 (2%)	
Hyperplasia, Histiocytic			1 (2%)	
Necrosis	1 (2%)	1 (2%)		
Pigmentation	30 (60%)	30 (60%)	35 (70%)	43 (86%)
Thymus	(47)	(49)	(49)	(50)
Cyst				1 (2%)

a Number of animals examined microscopically at site and number of animals with lesion