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DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service



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March 8, 1999

National Institutes of Health  
National Institute of  
Environmental Health Sciences  
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Dear Dr. Document Control Office:

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 Anthraquinone (CAS No. 84-65-1) 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](mailto:cdm@niehs.nih.gov).

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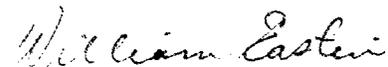
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Hard copies of documents such as NTP Technical Reports, short-term Toxicity Reports, and the Report on Carcinogens are available from the Environmental Health Information Service (EHIS). You can contact EHIS by phone at (919) 541-3841, by fax at (919)541-0273,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

Sincerely,



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

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

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CHAIRPERSON'S REPORT  
PATHOLOGY WORKING GROUP REVIEW  
ANTHRAQUINONE (C88036)  
A CHRONIC DOSED FEED STUDY IN  
B6C3F1 MICE CONDUCTED AT  
BATTELLE-COLUMBUS

Date of Pathology Working Group Review: September 17, 1998

Participants: Robert Maronpot, D.V.M.; NIEHS  
Ronald Herbert, D.V.M., Ph.D.; NIEHS  
Abraham Nyska, D.V.M.; NIEHS  
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Sabine Rehm, D.V.M.; Smithkline Beecham  
Nobuyuki Izumisawa, D.V.M., Ph.D.;  
Yamanouchi, USA (Observer)  
Michael Ryan, D.V.M., Ph.D.; Battelle-Columbus  
(Study Pathologist)  
Elias Gaillard, D.V.M., M.S.; EPL  
(QA Pathologist)  
John Curtis Seely, D.V.M.; PATHCO  
(PWG Chairperson)

STUDY DESIGN

Male and female B6C3F1 mice were exposed to Anthraquinone by dosed feed at concentrations of 0, 833, 2500, and 7500 ppm for up to 105 weeks. The control animals received only the undosed NIH-07 Open Formula meal feed. Feed was provided ad libitum up to study termination. Table 1 summarizes the animal disposition for the study.



TABLE 1  
Male Mice

Dose (PPM)	0	833	2500	7500
Animals in Study	50	50	50	50
Moribund Sacrifice	3	3	3	8
Natural Deaths	2	6	4	19
Terminal Sacrifice	45	41	43	23

Female Mice

Dose (PPM)	0	833	2500	7500
Animals in Study	50	50	50	50
Moribund Sacrifice	6	3	4	2
Natural Deaths	9	5	8	5
Terminal Sacrifice	35	42	35	42
Other	0	0	3	1

#### SUMMARY

Administration of Anthraquinone by dosed feed, under the conditions of this study, was associated with the following histopathologic lesions:

1. The apparent dose-related increased incidence of hepatocellular proliferative lesions including single to multiple hepatocellular adenomas and hepatocellular carcinomas in the livers of treated male and female animals. The incidence of eosinophilic foci were also slightly increased in the treated males and females. In addition, the increased incidence of single to multiple hepatoblastomas was also dose-related in the treated males. One hepatoblastoma was confirmed in a high-dose female.

A 09



The following potential target organs and/or specific organ diagnoses were reviewed by the QAP from all control and treated mice as directed by NTP.

Male Mice

Liver  
Spleen  
Thyroid Gland  
Urinary Bladder  
Transitional Epithelium

Female Mice

Liver  
Spleen  
Thyroid Gland  
Urinary Bladder  
Transitional Epithelium

Male Mice

Islets, Pancreatic - Hyperplasia  
Tooth - Malformation  
All Tumors in All Organs

Female Mice

Liver - Lymphoma Malignant  
Lymph Nodes (All) - Lymphoma Malignant  
Spleen - Lymphoma Malignant  
Thymus - Lymphoma Malignant  
All Tumors in All Organs  
Stomach, Forestomach - Hyperplasia  
Stomach, Forestomach, Epithelium - Hyperplasia  
Skin - Fibrosarcoma

The PWG Chairperson selected a set of 107 slides for review by the PWG. These slides included representative examples of potential treatment-related lesions, lesions for which there was a difference of opinion between the SP and QAP and lesions selected because of general interest (see Chairperson's PWG Worksheets). All slides were examined by each participant without knowledge of the dose group or



diagnoses rendered by the SP and QAP. Final diagnoses for the lesions presented were determined by the consensus of the PWG participants.

## PWG RESULTS

### Liver

Treatment-related non-neoplastic and neoplastic lesions were diagnosed by the SP in the liver. As noted in the study report, hepatic masses were frequently a cause of death especially in the large number of unscheduled deaths seen in the 7500 ppm males.

Centrilobular hepatocellular hypertrophy was confirmed during the PWG review. A similar dose-related increase in centrilobular hypertrophy had been previously confirmed in the subchronic mouse anthraquinone study. This lesion was characterized by increased hepatocellular size and decreased sinusoidal width in centrilobular regions. Both cytoplasm and nuclei appeared larger. The cytoplasm often had a finely vacuolated appearance. The severity of this change was determined by the increased cellular size and how far the change extended from central regions of the hepatic lobules.

The PWG also confirmed two additional non-neoplastic lesions identified by the QAP as potential treatment-related lesions. The incidence of focal fatty degeneration, as noted by the QAP, was greater in the 7500 ppm females compared to



the control female group. Fatty degeneration was characterized by the presence of large, clear vacuoles within hepatocytes. There did not appear to be any strong lobular preference in the location of the affected hepatocytes.

Another lesion which was confirmed by the PWG was termed Hepatocyte - Cystic Degeneration by the QAP to denote clusters of two or more hepatocytes which were distended by erythrocytes. The nuclei of these hepatocytes were often eccentrically displaced by the erythrocytes. Based upon the QA review, this lesion was elevated in the treated males compared to the control males. It was not observed in the females. Considerable discussion ensued concerning the terminology for this change. All participants agreed that this change was distinctly different from "Spongiosis Hepatis" or telangiectasis commonly described in the rat and occasionally the mouse. Several PWG participants suggested that this lesion represented hepatocellular erythrophagocytosis. As the QAP noted, this lesion had been reported from at least one NTP study viz. NTP Technical Report 414. A few participants recalled that this lesion might have been reported with other hepatocarcinogens.

Subsequent to the PWG the NTP pathologists rediscussed the appropriate terminology for what was termed "cystic degeneration" by the QA pathologist. Based upon the



deliberation, it was decided that the diagnostic term "cystic degeneration" would be best reserved for the lesion typically associated with cystic degeneration (sometimes referred to as spongiosis hepatis) and that this change noted in this particular study should be called "hepatocytic erythrophagocytosis". This reversal of the QA pathologist's diagnosis was made to better reflect the actual change present and to permit the future retrospective recovery of this finding in the NTP data base.

The PWG also confirmed a number of proliferative lesions within the liver. Anthraquinone appeared to be a strong hepatocarcinogen producing an increased number of eosinophilic foci, hepatocellular adenomas, hepatocellular carcinomas and hepatoblastomas. There was a dose-related increase in the multiplicity of these tumors as well. The neoplastic response was greater in the males. Only one hepatoblastoma was confirmed in a high-dose female (#379). One hepatocholangiocarcinoma was confirmed in a low dose male (#038). The increased presence of hepatocellular necrosis in this study was mainly associated with the increased incidence of hepatocellular neoplasms.

The criteria used to diagnose the proliferative hepatic lesions are presented in Table 2.



**TABLE 2**  
Proliferative Hepatocellular Lesions

Foci of Cellular Alteration

- \* Localized lesions ranging from barely perceptible alterations in arrangement of hepatic plates to discrete lesions.
- \* Tintorial variation from surrounding hepatic parenchyma; subclassified as basophilic, eosinophilic, clear, vacuolated, or mixed cell.
- \* Foci vary in size: usually less than one hepatic lobule to up to several lobules in diameter.
- \* Round to oval; but sometimes irregular in shape.
- \* May have some cellular pleomorphism but generally maintain lobular architecture.
- \* Hepatic plates merge imperceptibly with surrounding hepatocytes.
- \* Little to no compression.

Hepatocellular Adenoma

- \* Typically are well-circumscribed occupying an area greater than one lobule.
- \* Distinct compression of adjacent parenchymal.
- \* Hepatocytes resemble those found in the various foci.
- \* Adenomas usually have an absence of normal lobular architecture.
- \* Show altered growth patterns and hepatic plates impinge at right angles to adjacent liver.
- \* Central veins and portal tracts are not readily apparent.
- \* Cells may occur in irregular plates one to three cells thick.
- \* Cellular atypia and mitotic figures may be observed.

Hepatocellular Carcinoma

- \* Generally, larger neoplasms than adenomas.
- \* Not always well-demarcated.
- \* Abnormal growth patterns and cellular atypia.
- \* Trabecular, glandular and solid pattern types.
- \* Where trabeculae are thick, the central cells tend to be necrotic. Trabeculae are generally three or more cells thick.



- \* Glandular (pseudo-glandular) forms are characterized by a dilated central clear space (bile canaliculus) surrounded by neoplastic hepatocytes that are generally a single layer thick.
- \* Metastasis to the lung may be observed
- \* May be noted to arise within adenomas.

#### Hepatoblastoma

- \* Hepatoblastoma is often found within or closely adjacent to hepatocellular adenoma or carcinoma. By NTP convention, in these cases only the hepatoblastoma is diagnosed (adenoma or carcinoma are not diagnosed separately).
- \* Generally a well-demarcated, expansive neoplasm. Local invasion may be seen in the more malignant tumors.
- \* The tumor is often an irregular mass with blood-filled cystic spaces.
- \* Necrosis and hemorrhage are often present in larger neoplasms.
- \* Cells are generally small but may vary in size. Nuclei appear irregular and hyperchromatic and most cells contain scant basophilic cytoplasm (similar to hepatoblasts of fetal liver). The unmistakable presence of hepatoblastoma cells, no matter how discrete, are enough to make the diagnosis of hepatoblastoma.
- \* Cells are often arranged in rows or rosettes around blood-filled vascular spaces lined by flattened epithelium.
- \* Occasionally, osteoid tissue formation may be observed.
- \* Mitotic figures tend to be numerous.
- \* May metastasize, primarily to lungs.

#### Hepatocholangiocarcinoma

- \* Comprised of neoplastic elements from both hepatocytes and biliary epithelium.
- \* Both cell types may be well-to-poorly differentiated.
- \* Neoplastic hepatocellular and ductular may share same basement membrane.
- \* One or the other or both lineages may metastasize, particularly to the lung.



Hepatocellular foci, adenoma and carcinoma are believed to represent a spectrum of changes that comprise neoplastic development in the liver. Hepatoblastoma is a rare neoplasm in mice and the spontaneous incidence in B6C3F1 mice has been reported to be less than 1%. Because of their almost exclusive occurrence within existing hepatocellular carcinomas and occasionally hepatocellular adenomas, hepatoblastomas in the mouse are speculated to be a rare undifferentiated variant of hepatocellular neoplasms but their origin is still unclear. Occasionally, hepatoblastomas may be encountered as separate neoplasms not located within existing hepatocellular carcinomas. This may reflect intrahepatic metastasis of a primary hepatoblastoma located elsewhere in the same liver. The likelihood of encountering hepatoblastomas appear to be greater in studies where there is a high incidence of hepatocellular carcinomas. At the present time, the NTP groups hepatoblastomas with hepatocellular adenomas and hepatocellular carcinomas for purposes of hazard identification.

One of the most difficult areas in the definitive diagnosis of hepatocellular proliferative lesions is the distinction between large foci and hepatocellular adenomas. The ultimate diagnosis rests upon the use of a combination of criteria of which cytomorphologic features, compression, and



growth pattern are all important in foci from adenomas. Use of size criterion for distinguishing foci from adenomas is discouraged.

While diagnosis of foci is straight forward with practically unanimous agreement among pathologists, classification of foci of cellular alteration into subtypes is subjective. Variable staining recipes and ingredients between laboratories influence the tinctorial appearance of foci in standard hematoxylin and eosin-stained sections and, thus, their classification as basophilic or eosinophilic. Mixed cell foci are less common than other types of foci in control B6C.F1 mice. They are comprised of two or more of any of the cell types described above in varying proportions. For instance, when the proportions of comprising cell types in foci are half-and-half (in case of two different phenotypes) or one third (33%) for each (in case of three different phenotypes), they are referred to as mixed cell foci. NTP recommendations are that foci of cellular alteration be classified by the predominant cell type. As a guideline, NTP recommends that any foci with 80% or greater of a given cell type be subclassified by that predominant cell type. The data analysis for foci of cellular alteration should include the individual subtypes as well as all subtypes lumped together.



The origin of hepatocholangiocarcinomas was also discussed during the PWG. Currently, these neoplasms should probably be considered as one tumor as opposed to two "collision tumors" until further investigation is conducted.

The original statistical analysis of primary tumors in the liver, including hepatocellular adenoma, carcinoma and hepatoblastoma, was statistically significant in the mid- and high-dose males and in all three treated female groups.

#### Urinary Bladder

Representative examples of male and female urinary bladders were reviewed during the PWG to confirm the presence of intracytoplasmic, eosinophilic granules within the lining transitional epithelial cells. These granular inclusions were also noted in the bladder urothelium of mice in the subchronic study and were diagnosed as cytoplasmic alteration. During the QA review, the presence and slight dose-related increased severity of the granular inclusions was confirmed. Granular inclusions were identified from all treatment groups of both sexes but not in controls.

The intracytoplasmic eosinophilic granules tended to be multiple, small and variably sized. For the most part, affected cells were luminal cells. Granules were not observed in deeper or basilar cells. Similar granules were not observed in the transitional epithelium lining the renal



pelvis. The granules were PAS-positive suggesting some proteinaceous component. Neither hyperplasia nor necrosis were associated with the presence of the granules.

The etiology of this change was unclear. One possibility might involve a unique pinocytosed metabolite or reaction product (lysosomal complex) within the cytoplasm. Another possibility might be some form of cytoplasmic degenerative process. This latter possibility is supported by the fact that apparently similar eosinophilic inclusions representing cytoplasmic degradative products have been reported in response to injury (Alden and Frith, 1991). Ultrastructural examination of the granules may help in their identification.

Subsequent to the PWG, NTP pathologists elected to change the diagnoses of "cytoplasmic alteration" to "cytoplasmic inclusions". This was decided for three reasons: (1) the diagnosis "cytoplasmic inclusions" more accurately reflects the change observed, (2) "cytoplasmic alteration" or the synonymous term "cytologic alteration" is typically used as an umbrella term to reflect a constellation of changes that would be impractical to document and grade separately, and (3) future retrieval of this lesion will be facilitated by the more specific diagnostic terminology.



Thyroid Gland

The PWG also examined a number of slides representing follicular cell hyperplasia and/or adenoma because of the reported increased incidence of follicular cell hyperplasia in treated male and female animals.

Follicular cell hyperplasia was characterized as a focal to multifocal change consisting of enlarged follicles lined by increased numbers of follicular epithelial cells. Because of the increased cellularity, simple papillary infoldings were present in the more severe cases. The epithelial cells tended to be slightly hypertrophied but otherwise uniform in appearance. Several cases of follicular cell hyperplasia appeared to be more diffuse in nature, but these were the exception.

Several follicular cell adenomas and carcinomas were also confirmed by the PWG. The criteria for these neoplasms are presented in Table 3.

TABLE 3  
Follicular Cell Adenoma and Carcinoma

Follicular Cell Adenoma

- \* Discrete and well-demarcated mass; generally not encapsulated.
- \* Compression of adjacent tissue.
- \* Growth pattern that varies from normal (complex papillary or follicular).
- \* Cells tend to be well-differentiated, but characterized by cytoplasmic and nuclear pleomorphism.
- \* No invasion of capsule.



Follicular Cell Carcinoma

- \* Poorly defined mass without well-demarcated boundaries.
- \* Varied growth patterns occasionally associated with hemorrhage, necrosis and a scirrhous reaction.
- \* Cellular morphology may exhibit pleomorphism, atypia or anaplasia.
- \* Invasion of capsule, or metastases.

The number of follicular cell adenomas and/or carcinomas did not appear to be statistically significant in any of the exposed male or female groups. In addition, the number of adenomas in any one of the exposed groups was within the male and female historical control range as reported in the 1997 B6C3F1 NTP database for feed studies. The two confirmed carcinomas in the 7500 ppm female group was outside the normal range. Therefore, although not statistically significant, the follicular cell neoplasms may be biologically significant with regard to the increased presence of follicular cell hyperplasia in these groups.

The mechanism of follicular cell hyperplasia in the exposed animals was not totally clear; however, known cytochrome P-450 inducers such as anthraquinone could affect the negative-feedback process involving reduced circulating levels of T3/T4 and the release of thyroid-stimulating



hormone (TSH). This mechanism has been reported for a wide range of chemicals which have caused follicular cell hypertrophy, hyperplasia and neoplasia in the rodent thyroid gland (Alison, Capen and Prentice, 1991).

#### MISCELLANEOUS

A number of lesions were examined by the PWG to either confirm their incidence or because a discrepancy existed. In most instances, these lesions represented unusual or diagnostically challenging lesions/neoplasms which were either diagnosed once or only in a few instances.

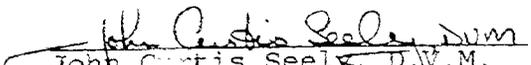
Three renal tubule adenomas were confirmed by the PWG. Two of these were in mid dose males and the other in a low dose male. All three renal tubule adenomas were characterized by a solid nodular growth pattern which was well-demarcated from the adjacent renal parenchyma. The neoplasms were expansive but not locally invasive. The tumor cells were pleomorphic in morphology. Dose-related increase in renal tubule hyperplasia was not noted in the study. Additionally, the incidence of these tumors did not appear to be statistically significant.

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QUALITY OF HISTOTECHNIQUE

The overall quality of the slides as determined by the  
Histotechnique Quality Assessment was good.

  
John Curtis Seely, D.V.M.  
Diplomate, American College  
of Veterinary Pathologists

November 9, 1998  
Date



REFERENCES

Alden, CL and Frith, CH (1991). Urinary System.  
In: Handbook of Toxicologic Pathology. Haschek, WM and  
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Alison, RH, Capen, CC, and Prentice, DE (1994). Neoplastic  
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22: 179-186.

TO: Experimental Test: 86036-04  
Study Type: CHRONIC  
Route: POSED FEED

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

Report: PEIRPT03  
Date: 12/11/98  
Time: 08:53:17

2 YEAR CHRONIC MICE

Facility: Battelle Columbus Laboratory

Chemical CAS #: 84-65-1

Lock Date: 07/01/97

Cage Range: All

Reasons For Removal: All

Removal Date Range: All

Treatment Groups: Include All

Report: PEIRPT03  
Date: 12/11/98  
Time: 08:53:17

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

NTP Experiment-Test: 88036-04  
Study Type: CHRONIC  
Route: DOSED FEED

	0 PPM	833 PPM	2500 PPM	7500 PPM
863F1 MICE FEMALE				
DISPOSITION SUMMARY				
Animals Initially In Study	50	50	50	50
Early Deaths				
Natural Death	9	5	8	5
Moribund Sacrifice	6	3	4	2
Accidentally Killed			3	
Survivors				
Terminal Sacrifice	35	42	35	42
Missing				1
Animals Examined Microscopically	50	50	50	49

ALIMENTARY SYSTEM

Esophagus	(50)	(49)	(50)	(49)
Inflammation, Chronic	1 (2%)			
Intestinal Smell, Duodenum	(50)	(50)	(50)	(48)
Ulcer	1 (2%)		1 (2%)	
Liver	(49)	(50)	(50)	(49)
Basophilic Focus	1 (2%)	1 (2%)	1 (2%)	3 (6%)
Clear Cell Focus	4 (8%)	1 (2%)	1 (2%)	3 (6%)
Degeneration, Diffuse, Fatty	1 (2%)	1 (2%)	1 (2%)	
Degeneration, Fatty, Focal	2 (4%)	3 (6%)	1 (2%)	9 (18%)
Eosinophilic Focus	6 (12%)	15 (30%)	11 (22%)	22 (45%)
Fatty Change, Focal	5 (10%)	2 (4%)	1 (2%)	3 (6%)
Hematopoietic Cell Proliferation	1 (2%)	1 (2%)	3 (6%)	1 (2%)
Infiltration Cellular, Lymphocyte				3 (6%)
Mineralization, Focal				1 (2%)
Mixed Cell Focus	4 (8%)	2 (4%)	2 (4%)	3 (6%)
Necrosis, Focal	5 (10%)	3 (6%)	1 (2%)	2 (4%)
Tension Fibrosis	1 (2%)			1 (2%)
Bile Duct, Cyst	3 (6%)	2 (4%)	2 (4%)	1 (2%)
Bile Duct, Hyperplasia				
Centrilobular, Atrophy	1 (2%)			1 (2%)
Centrilobular, Degeneration, Fatty	1 (2%)			
Centrilobular, Hypertrophy	1 (2%)	27 (54%)	22 (44%)	39 (80%)
Hepatocyte, Erythrophagocytosis				
Steatosis, Inflammation, Chronic	1 (2%)			
Mesothery	(6)	(4)	(6)	(7)
Inflammation, Chronic	1 (17%)		1 (17%)	
Inflammation, Chronic Active				
Artery, Thrombosis	1 (17%)			
Fat, Necrosis	4 (67%)	3 (75%)	2 (33%)	7 (100%)
Lymphatic, Angiectasis			1 (17%)	
Pancreas	(50)	(50)	(50)	(49)
Hyperplasia, Focal		2 (4%)		

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

Report: PEIRPT03  
 Date: 12/11/98  
 Time: 08:53:17

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

NTP Experimental Test: 08016-04  
 Study Type: CHRONIC  
 Route: Dosed Feed

0 PPM	833 PPM	2500 PPM	7500 PPM
<b>ALIMENTARY SYSTEM - CONT</b>			
Inflammation, Chronic	1 (2%)	2 (4%)	1 (2%)
Atrophy, Allogly	2 (4%)	1 (2%)	1 (2%)
Cyst	(50)	(50)	(49)
Stomach, forestomach			
Inflammation, Suppurative			
Ulcer	4 (8%)	1 (2%)	2 (4%)
Epithelium, Hyperplasia, Focal	1 (2%)	1 (2%)	1 (2%)
Serosa, Inflammation, Chronic	(50)	(50)	(49)
Stomach, Glandular	1 (2%)	1 (2%)	
Ulcer			
Epithelium, Hyperplasia			
Epithelium, Hyperplasia, Focal	1 (2%)		1 (2%)
Serosa, Inflammation, Chronic	(1)		
Teeth			
Periodontal Tissue, Inflammation, Granulomatous	1 (100%)		
<b>CARDIOVASCULAR SYSTEM</b>			
Blood Vessel	(50)	(49)	(49)
Aorta, Mineralization	2 (4%)	1 (2%)	
Heart	(50)	(50)	(49)
Thrombosis			
Myocardium, Degeneration	2 (4%)	1 (2%)	1 (2%)
Myocardium, Mineralization	2 (4%)		
Valve, Inflammation			
<b>ENDOCRINE (SMEN)</b>			
Adrenal Cortex	(50)	(50)	(49)
Hyperplasia, Focal	1 (2%)	1 (2%)	2 (4%)
Necrosis			
Adrenal Medulla	(50)	(49)	(49)
Hyperplasia, Focal			
Islets, Pancreatic	(50)	(50)	(49)
Hyperplasia	5 (12%)	10 (23%)	14 (29%)
Pituitary Gland	(47)	(48)	(46)
Adipogenesis	2 (4%)	1 (2%)	
Atrophy			
Cyst			
Pancreas, Hyperplasia, Focal	8 (17%)	12 (23%)	1 (2%)
Thyroid Gland	(45)	(40)	(48)
Inflammation, Acute, Focal	1 (2%)		
Follicle, Cyst	2 (4%)	1 (2%)	
Follicular Cell, Hyperplasia	10 (22%)	14 (29%)	15 (31%)

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

Report: PEIRPT03  
Date: 12/11/98  
Time: 08:53:17

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

NTP Experiment-Test: 88036-04  
Study Type: CHRONIC  
Route: DOSED FEED

B6C3F1 MICE FEMALE      0 PPM      833 PPM      2500 PPM      7500 PPM

GENERAL BODY SYSTEM

Peritoneum (1) (100%)  
Necrosis 1 (100%)

GENITAL SYSTEM

Ovary (45) (49) (49)  
Aniectasis 3 (7%) 4 (8%) 2 (4%)  
Cyst 1 (2%) 7 (14%) 5 (10%)  
Granulosa Cell, Hyperplasia (50) (50) (47)  
Uterus 1 (2%) 1 (2%)  
Angiectasis 2 (4%) 1 (2%)  
Inflammation, Chronic 1 (2%) 1 (2%)  
Inflammation, Suppurative 1 (2%) 2.3 (46%) 39 (80%)  
Thrombosis 35 (70%)  
Endometrium, Hyperplasia, Cystic (1) (100%)  
Vagina 1 (100%)  
Hemorrhage

HEMATOPOIETIC SYSTEM

Bone Marrow (50) (50) (49)  
Myeloid Cell, Hyperplasia (5) (4) (4)  
Lymph Node 1 (50%) 1 (25%)  
Lambert, Ectasia (48) (48) (49)  
Lumbar, Hemorrhage 1 (20%)  
Mediastinal, Inflammation, Chronic (46) (48) (48)  
Lymph Node, Mandibular 1 (2%)  
Hyperplasia, Lymphoid (50) (49) (48)  
Inflammation, Suppurative (48) (48) (48)  
Lymph Node, Mesenteric (45) (49) (48)  
Spleen 9 (20%) 17 (35%) 26 (54%)  
Hematopoietic Cell Proliferation 1 (2%)  
Pigmentation 1 (2%)  
Capsule, Inflammation, Chronic 8 (18%) 5 (10%) 6 (13%)  
Lymphoid Follicle, Hyperplasia (44) (47) (44)  
Thymus 1 (2%)  
Hyperplasia, Lymphoid

a. Number of animals examined macroscopically at site and number of animals with lesion

Report: PEIRP03  
Date: 12/11/93  
Time: 08:51:17

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

APP Experiment: 04036-04  
Study Code: 04036-04  
Group: 04036-04

ANATOMIC SITE	DOSE (PPM)			
	0 PPM	833 PPM	2500 PPM	7500 PPM
<b>RESPIRATORY SYSTEM</b>				
Respiratory Tract	(48)	(48)	(48)	(49)
Inflammation, Suppurative	1 (2%)			
Edema	(50)	(50)	(50)	(49)
Focal			1 (2%)	
<b>MUSCULOSKELETAL SYSTEM</b>				
Bone	(50)	(50)	(50)	(49)
Osteoporosis	2 (4%)	2 (4%)	1 (2%)	3 (6%)
Osteoarthritis	(3)	(2)	(2)	(1)
Skeletal Muscle				
Degeneration, Acute	1 (3%)			
Inflammation, Chronic	1 (3%)			
<b>HELVETIA 7:1EM</b>				
Brain	(50)	(50)	(50)	(49)
Basal Ganglia				
Hydrocephalus			1 (2%)	
Hypothalamus, Compression		1 (2%)	1 (2%)	1 (2%)
Hypothalamus, Degeneration				
Hypothalamus, Necrosis		1 (2%)		
Hypothalamic Nerve	(2)		(1)	
Axon, Degeneration	2 (100%)			
Spinal Cord	(2)		(1)	
Spinal Nerve, Degeneration	1 (5%)			
<b>RESPIRATORY SYSTEM</b>				
Lung	(50)	(50)	(50)	(49)
Congestion			2 (4%)	
Basal Epithelial Cell Proliferation				1 (2%)
Basal Ganglia				
Bronchiolitis, Chronic, Focal	1 (2%)			
Inflammation, Chronic			1 (2%)	
Fibrosis, Diffuse			2 (4%)	
Bronchus, Foreign Body	1 (2%)			
Interstitial Inflammation, Chronic, Focal	1 (2%)			1 (2%)
Infectious, Microabscess				
Perivascular, Edema	(50)	(50)	1 (2%)	(49)
Inflammation, Suppurative	2 (4%)			

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