



Contains No CBI

F41-1100-1396

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

National Institutes of Health
National Institute of
Environmental Health Sciences
P. O. Box 12233
Research Triangle Park, NC 27709

November 08, 2000

Document Control Office (7407)
Attn: TSCA Section FYI
East Tower Room G99
Ofc. of Pollution Prevention & Toxics
401 M St. SW
Washington, DC 20460-0001

RECEIVED
OPPT/CBIC
2000 NOV 14 PM 12:01

Dear Document Control Office:

In compliance with the National Toxicology Program's (NTP) mission to keep our colleagues informed of the current NTP findings during ongoing studies, a copy of the Pathology Working Group (PWG) report and the Summary Pathology Tables for the chronic Dosed Feed study on P-NITROTOLUENE (99-99-0) 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.

The Summary Pathology Tables contain the Incidence Rates of Neoplastic and Non-neoplastic Lesion data and the Statistical Analysis of Primary Tumors data pertaining to the laboratory animals. All study data are subject to an NTP retrospective audit and the interpretation may be modified based on the findings.

A wide variety of NTP information is 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. To view this information requires access to the internet and a Web browser such as Netscape Navigator or Internet Explorer. To access the NTP home page, use the URL <http://ntp-server.niehs.nih.gov>. Comments on the usefulness of this site and suggestions for improvement are encouraged.

RECEIVED
OPPT/NCIC
2000 NOV 16 PM 12:19

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.



FYI-00-001396

MF 41192



84010000305

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

Encls: PWG Report and Pathology Summary Tables for Rats & Mice
cc: Central Data Management

A 05



Pathology Associates International

A Company of Science Applications International Corporation

KWG-CT-111



99-99-0
C62537D

**PATHOLOGY WORKING GROUP
CHAIRPERSON'S REPORT**

**2-YEAR CHRONIC STUDY OF
p-NITROTOLUENE (C62537D)
ADMINISTERED BY DOSED FEED TO B6C3F1 MICE**

Prepared by:

**Micheal P. Jokinen, DVM
Pathology Working Group Chairperson**

**Pathology Associates International
4915D Prospectus Drive
Durham, NC 27713**

Submitted to:

**National Toxicology Program/NIEHS
Research Triangle Park, NC**

October 12, 1999

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

2-Year Chronic Study of p-Nitrotoluene in B6C3F1 Mice

Participants: Drs. M. Jokinen (PAI - PWG Chairperson), S. Ching (SVC Assoc.), S. Hayashi (NIEHS), R. Herbert (NIEHS), J. Mahler (NIEHS), G. Marrs (EPL- QA Pathologist), and A. Nyska (NIEHS).

Date: September 23, 1999
Site: NIEHS, Research Triangle Park, NC

The PWG was convened to evaluate selected slides from B6C3F1 mice administered p-Nitrotoluene by dosed feed for two years. The doses and numbers of animals examined microscopically per group were as follows:

<u>Dose</u>	<u>M</u>	<u>F</u>
0ppm	50	50
1250ppm	50	50
2500ppm	50	50
5000ppm	50	50

The study was conducted at Southern Research Institute. The Study Pathologist (SP) was Dr. D. Farnell and the Quality Assessment Pathologist (QAP) was Dr. G. Marrs of EPL.

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

<u>Male Mice</u>	<u>Female Mice</u>
Liver	Liver
Lung	Lung

In addition, thyroid glands were reviewed from all males or all females for the presence of Thyroid Gland - Degeneration, Cystic, Focal.

SUMMARY OF REVIEW FINDINGS

Combined incidences of Lung - Alveolar/Bronchiolar Adenoma; Alveolar/Bronchiolar Adenoma, Multiple; Alveolar/Bronchiolar Carcinoma; and Alveolar/Bronchiolar Carcinoma, Multiple were increased in all treated groups of males as compared with control males.

Lung, Alveolar Epithelium – Bronchiolization was present in each of the treated groups of males and females, but not in male and female controls. The incidence and severity increased with increasing dose.

Slight Liver – Syncytial Alteration, Focal was present in numerous animals in all treated male groups, but was present in only a very few control males and was not present in any control or treated females.

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

Lung

The SP had diagnosed higher combined incidences of Lung – **Alveolar/Bronchiolar Adenoma; Alveolar/Bronchiolar Adenoma, Multiple; Alveolar/Bronchiolar Carcinoma; and Alveolar/Bronchiolar Carcinoma, Multiple** in the treated male groups as compared with control males. Incidences of lung tumors diagnosed by the SP in females was similar across groups. Incidences of Lung, Alveolar Epithelium – **Hyperplasia** were very low and similar across groups of males and females. These findings were confirmed by the QA/PWG review. There was very good agreement among the SP, QAP, and PWG Chair concerning the diagnoses of lung neoplasms. The PWG reviewed all diagnosed alveolar/bronchiolar neoplasms in control and high dose males and confirmed the SP's findings. The PWG also reviewed a few lungs in the low and mid-dose male groups in which either the QAP or PWG Chair had a difference of opinion with the SP's diagnoses.

Microscopically, the hyperplasias and neoplasms had the typical appearance of these lesions seen in B6C3F1 mice. Hyperplasias were focal lesions consisting of clusters of alveoli lined by cuboidal epithelial cells, instead of the normal squamous epithelium. Normal alveolar architecture was maintained in hyperplasias. Adenomas were discrete nodular lesions which generally displaced adjacent normal parenchyma. Adenomas were composed of cuboidal to round or polygonal cells, with moderate amounts of eosinophilic cytoplasm, that formed papillary or alveolar structures, or solid clusters that filled alveolar spaces, or a combination of these. Carcinomas were nodular, generally large, masses, some of which contained areas of infiltration of the surrounding normal

A 08

A 09

parenchyma. Carcinomas consisted of pleomorphic, round to cuboidal to tall columnar cells, which formed papillary or tubular structures, or solid sheets of cells, or a combination of these. Carcinomas were distinguished by cellular atypia, infiltrative growth, and the tendency to form multiple cell layers or larger solid cellular areas.

In addition, the QAP noted a change in numerous lungs in treated groups of males and females which the SP had not diagnosed. The QAP designated this change as **Lung, Alveolar Epithelium – Bronchiolization**. Microscopically, bronchiolization was characterized by extension of cuboidal epithelium from terminal bronchioles to the adjacent alveolar ducts and alveoli, which are normally lined by simple squamous epithelium. The incidence and average severity increased with increasing dose. The PWG Chair confirmed the QAP's findings, and added a few additional diagnoses. The PWG reviewed two examples of bronchiolization from each of the treated groups of males and females and in each case confirmed the presence of the change. The PWG also examined the slides in which the PWG Chair had diagnosed additional cases of bronchiolization, and confirmed the PWG Chair's findings. It was noted that the incidences and average severities of bronchiolization were similar in high dose males and females, and that the incidences of bronchiolization in low and mid-dose females were greater than they were in males. However, there was no increase in lung neoplasms in treated females, suggesting there was no relationship between bronchiolization and the occurrence of lung neoplasms.

Liver

The SP had diagnosed moderately to markedly greater incidences of **Liver, Hepatocyte – Syncytial Alteration, Focal** in all treated groups of males, as compared with control males. The incidence and average severity was greatest in the high dose group. This change was not observed in any of the females. No treatment effect on the incidences of liver tumors was observed in males or females. The SP's findings were confirmed by the QA/PWG review. The PWG examined two examples of syncytial alteration from each of the treated male groups and in each case confirmed the presence of the change.

Microscopically, syncytial alteration was a very slight change, diagnosed by the SP as being of minimal to mild severity, consisting of one to several scattered hepatocytes with an increased amount of cytoplasm which contained, usually, four to six nuclei. The PWG members noted the change was very slight in all livers examined. The QAP and PWG Chair commented that careful examination of the liver at moderate magnification was often necessary to detect the presence of the syncytial alteration; in some cases only one or two syncytia were observed in a liver section, and even in the most severe cases generally only approximately 10 to 12 syncytia were observed. As the incidences of liver

neoplasms was similar across the male groups, the syncytial alteration was apparently not a potential preneoplastic lesion.

The SP had diagnosed relatively similar incidences of **Liver – Infiltration Cellular, Mixed Cell**, a minimal to moderate change consisting of few to several scattered, small, focal clusters of mixed inflammatory cells, in control and treated groups of males and females. The QAP basically confirmed the SP's findings and added a few additional diagnoses, principally in the low dose female group. The incidences as diagnosed by the QAP were essentially the same across the control and treated groups of males and females, with no indication of a treatment effect. The PWG Chair confirmed the QAP's findings. Mixed cell infiltrate is a common background finding in the livers of B6C3F1 mice.

In addition, the SP had diagnosed **Liver, Hepatocyte – Necrosis, Focal** in a number of livers in treated and control groups of males and females. The QAP noticed that in a few livers the change consisted of one or more discrete foci of hepatocyte coagulative necrosis, and concurred with the diagnosis. In most cases, however, the change diagnosed as focal hepatocyte necrosis by the SP was characterized by the presence of one to few necrotic hepatocytes or degenerate appearing hepatocytes with brightly eosinophilic cytoplasm adjacent to the clusters of mixed cell infiltrate. These necrotic or degenerate cells are seen commonly adjacent to these clusters of mixed cells and are not diagnosed separately. Consequently, the QAP recommended deleting the diagnoses of focal necrosis except in those cases in which one or more discrete foci of necrosis were seen. The PWG Chair concurred with the QAP's findings. The PWG examined some examples of necrotic or degenerate cells adjacent to mixed cell infiltrate in control and high dose males and females, and agreed with the QAP that the change should not be diagnosed. Consequently, the PWG recommended deleting the diagnoses of focal necrosis as indicated by the QAP.

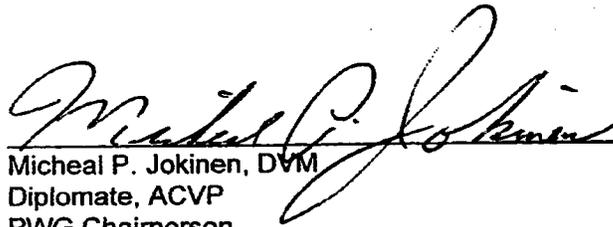
Thyroid Gland

The SP had diagnosed slightly increased incidences of **Thyroid Gland – Degeneration, Cystic, Focal** in the mid- and high dose groups of males, and in the mid-dose females, as compared with respective controls. The QAP agreed with the SP's diagnoses and added some additional diagnoses such that the incidences were similar in control and treated groups of males, while the incidences in the low and mid-dose female groups were somewhat higher than in the control and high dose female groups. The PWG Chair confirmed the QAP's findings, and added a few more diagnoses of cystic degeneration. The PWG examined some representative examples of the change that had been diagnosed by the SP and confirmed by the QAP and PWG Chair, as well as the additional diagnoses made by the PWG Chair. In each case the PWG agreed with the presence of the change.

Microscopically, focal cystic degeneration consisted of one to few variably sized thyroid follicles that were filled with pale staining colloid. Occasionally the affected follicles were located in a cluster separated by incomplete interfollicular connective tissue septa such that the follicles were confluent. The PWG considered this to be a normal change in the thyroid gland of B6C3F1 mice, and did not consider it to have any biological or toxicological significance.

POST-PWG ACTION ITEMS

There were no post-PWG action items.

 10/12/99
Michael P. Jokinen, DVM Date
Diplomate, ACVP
PWG Chairperson

A 11



Pathology Associates International
A Company of Science Applications International Corporation



PWG CHR
99-99-0

**PATHOLOGY WORKING GROUP
CHAIRPERSON'S REPORT**

**2-YEAR CHRONIC STUDY OF
p-NITROTOLUENE (C62537D)
ADMINISTERED BY DOSED FEED TO F344 RATS**

DEC

Prepared by:

**Micheal P. Jokinen, DVM
Pathology Working Group Chairperson**

**Pathology Associates International
4915D Prospectus Drive
Durham, NC 27713**

Submitted to:

**National Toxicology Program/NIEHS
Research Triangle Park, NC**

December 27, 1999

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

2-Year Chronic Study of p-Nitrotoluene in F344 Rats

Participants: Drs. M. Jokinen (PAI - PWG Chairperson), R. Herbert (NIEHS), J. Mahler (NIEHS), G. Marrs (EPL- QA Pathologist), G. Parker (ILS -Observer), C. Shackelford (EPL), and J. Seely (Pathco)

Date: November 18, 1999
Site: NIEHS, Research Triangle Park, NC

The PWG was convened to evaluate selected slides from F344 rats administered p-Nitrotoluene by dosed feed for two years. The doses and numbers of animals examined microscopically per group were as follows:

Dose	M	F
0ppm	50	50
1250ppm	50	50
2500ppm	50	50
5000ppm	50	50

The study was conducted at Southern Research Institute. The Study Pathologist (SP) was Dr. J. Heath and the Quality Assessment Pathologist (QAP) was Dr. G. Marrs of EPL.

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

Male Rats

Liver
Kidneys
Spleen
Testes

Female Rats

Liver
Kidneys
Spleen
Uterus
Mammary Gland

In addition, the QAP reviewed selected organs from all males or all females for the presence of specific lesions. These are listed below.

Male Rats

Lung -- Infiltration Cellular, Histiocyte
Lung, Alveolar Epithelium -- Hyperplasia
Lymph Node, Mandibular -- Pigmentation
Mammary Gland -- Hyperplasia
Preputial Gland -- Inflammation
Prostate -- Hyperplasia, and Inflammation

Female Rats

Bone - Osteopetrosis

Thyroid, C-Cell - Hyperplasia, and Adenoma

The QAP also reviewed all diagnosed neoplasms in all tissues in all animals.

Due to the large number of organs and diagnoses reviewed by the QAP, the PWG Chair was directed to review all findings in the liver, kidney, testes, and to review only disagreements between the SP and QAP diagnoses in the spleen, uterus, mammary gland, lung, mandibular lymph node, preputial gland, prostate, bone, and thyroid C-cell. Furthermore, since a high incidence of clitoral gland neoplasms had been diagnosed in the 2500ppm female group and the clitoral gland had not been chosen for a complete QA review (i.e., the QAP reviewed only the diagnosed neoplasms), the PWG Chair was directed to review all clitoral glands for the presence of proliferative lesions. The PWG Chair also reviewed all diagnosed neoplasms in all animals. For mononuclear cell leukemia, the liver and, usually, the spleen were reviewed to confirm the presence of leukemia, unless leukemia also occurred in other tissues selected for review. For lymphoma, only selected tissues were reviewed to confirm the presence of lymphoma unless lymphoma also occurred in other tissues selected for review.

SUMMARY OF REVIEW FINDINGS

The incidences of **Mononuclear Cell Leukemia** were decreased in all treated groups of males and in the 2500 and 5000ppm groups of females.

The incidences and severities of **Kidney, Renal Tubule - Hyaline Droplets** and **Kidney, Renal Tubule - Pigmentation** were increased in treated groups of males and females. The incidences and severities of **Kidney - Mineralization** and the incidences of **Kidney, Renal Tubule - Hyperplasia, Oncocytic** were increased in treated groups of females. The incidence of **Kidney - Nephropathy** was decreased in the 5000ppm male group.

The incidences and/or severities of **Spleen - Hematopoietic Cell Proliferation** and **Spleen - Pigmentation** were increased in treated groups of males and females.

The severities of **Liver - Infiltration Cellular, Mixed Cell** were increased in all groups of treated females. The incidences of **Liver - Basophilic Focus, Liver - Mixed Cell Focus, and Liver - Eosinophilic Focus** were greater in the 5000 ppm than in the control and lower dose groups, while the severities of **Liver, Bile Duct - Hyperplasia** were decreased in treated groups of males; these findings were presumably secondary to the decrease in mononuclear cell leukemia.

Incidences of **Testes, Interstitial Cell - Adenoma; Testes, Interstitial Cell - Hyperplasia; and Testes, Germinal Epithelium - Atrophy** were increased and

incidences of **Testes, Interstitial Cell, Bilateral - Adenoma** were decreased in the 1250 and 5000ppm male groups.

The incidences of **Uterus, Endometrium - Hyperplasia, Cystic** were increased in the 2500 and 5000ppm female groups.

The incidence of **Mammary Gland - Hyperplasia** was decreased in the 5000ppm female group.

The incidence of **Prostate - Inflammation, Chronic** was decreased in the 5000ppm male group, and the incidences of **Prostate - Hyperplasia** were decreased in the 2500 and 5000ppm male groups.

The incidences of **Femur - Osteopetrosis** were decreased in the treated groups of females.

The incidences of **Thyroid Gland, C-Cell - Hyperplasia** were decreased in 2500 and 5000ppm female groups.

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

Mononuclear Cell Leukemia

The SP had diagnosed lower incidences of mononuclear cell leukemia in all treated groups of males and females as compared with controls. These findings were confirmed by the QA/PWG review. Since there was excellent agreement among the SP, QAP, and PWG Chair, the PWG elected not to review any examples, but did review one disagreement in diagnosis.

Kidney

The SP diagnosed increased incidences and severities of **Kidney, Renal Tubule - Cytoplasmic Alteration** and **Kidney, Renal Tubule - Pigmentation** in all treated groups of males and females. The SP's findings were confirmed by the QA/PWG review. Microscopically, the change diagnosed as cytoplasmic alteration consisted of one to few variably sized homogeneous eosinophilic to golden brown to brown droplets within the proximal tubular epithelium.

The droplets were generally most easily detected in the outer portion of the cortex. Pigmentation was generally seen in kidneys containing the droplets, and consisted of multiple, small, irregular, brown granules within the proximal tubular epithelium. This pigmentation was distinct from the dark, granular pigmentation commonly seen as a background change in tubular epithelium at the corticomedullary junction. Pigmentation at the corticomedullary junction was seen in animals in this study but was not diagnosed. According to the SP's narrative, the SP had diagnosed the severity of the droplets and pigmentation based upon the number of tubules containing the change. The PWG Chair observed in each of the groups that a few kidneys contained slight droplets and/or pigmentation but no diagnosis had been made. It appeared that the SP had set a threshold level and if the severity of the changes fell below this level, they were not diagnosed. Since the SP appeared to have been consistent in this, it did not appear that diagnosing these cases of slight droplets or pigmentation would have affected the study findings. The QAP had made numerous changes in the SP's findings concerning droplets and pigmentation, nearly all of which were concerned with the severity of the lesions. The PWG Chair was of the opinion that changing the SP's diagnoses would not add substantially to the study findings and usually concurred with the SP.

The PWG reviewed examples of the droplets and pigmentation and agreed that the changes were present, but considered the SP's terminology of cytoplasmic alteration to be inappropriate, and preferred to use instead the morphologically accurate terminology of **Kidney, Renal Tubule - Hyaline Droplets**. In addition, the terminology Hyaline Droplets had been used for a similar change seen in the kidneys of males in the 13-week study with this chemical, and use of this terminology in the 2-year study would make the terminology consistent between the two studies. Consequently, the PWG recommended that all of the SP's diagnoses of Cytoplasmic Alteration be changed to Hyaline Droplets.

The SP had also diagnosed greater incidences and severities of **Kidney - Mineralization** in treated groups of females and lower incidences of **Kidney - Nephropathy** in treated groups of males, as compared with respective controls. The QAP added a number of diagnoses of mineralization, generally of minimal severity, to each of the groups. The PWG Chair generally agreed with the QAP's findings. The QAP's findings confirmed the increases in incidences and average severities of mineralization in treated female groups. The QAP also added a number of additional diagnoses of nephropathy, generally of minimal severity, to each of the male and female groups. The QAP's findings indicated a lower incidence of nephropathy occurred only in the 5000ppm male group. The PWG Chair confirmed the QAP's findings. The PWG examined representative examples and confirmed the presence of mineralization and nephropathy.

Microscopically the mineral consisted of irregular crystalline basophilic concretions within the renal pelvis or, less commonly, within the renal papilla. According to the SP's narrative, the severity of mineralization was diagnosed

based upon the approximate total area in square microns occupied by the mineral.

The SP had diagnosed **Kidney, Renal Tubule - Degeneration** in a few animals in the 5000ppm male group and in each of the treated female groups. The QAP considered this change to represent **Kidney, Renal Tubule - Hyperplasia, Oncocytic**. The PWG Chair concurred with the QAP. Representative examples of the change were shown to the PWG, which concurred with the QAP's diagnosis of oncocytic hyperplasia. Microscopically, the change consisted of small foci composed of a few large cells with abundant, granular eosinophilic cytoplasm.

Spleen

The SP had diagnosed higher incidences and/or severities of **Spleen - Hematopoietic Cell Proliferation** and **Spleen - Pigmentation** in treated groups of males and females. The pigment was golden-brown, granular material that stained positive for iron and was considered to be hemosiderin. The QAP added a few diagnoses of each of these changes to each of the control and treated groups of males and females; the PWG Chair generally agreed with the QAP. The QAP's findings confirmed the SP's findings. It was noted by the PWG Chair that a slight degree of pigmentation and hematopoietic cell proliferation was seen in spleens in which no diagnosis had been made. Apparently the SP considered this to be normal background and diagnosed the changes when they were increased over this background level. The severities of hematopoietic cell proliferation and pigmentation in the spleen were based on the degree of increase above the background level in the controls. The PWG reviewed a representative spleen from each of the treated groups, using control spleens containing the normal background level for reference, and confirmed the presence of the changes in each spleen from a treated animal.

Liver

The SP had diagnosed increased incidences and severities of **Liver - Infiltration Cellular, Mixed Cell** in treated female groups as compared with control females. The QAP added a few additional diagnoses in each of the groups, primarily in the control and lower dose groups, but confirmed the SP's findings. The PWG Chair observed minimal mixed cell infiltrate in a number of livers in the control, low and mid-dose groups that had not been diagnosed previously, and added these diagnoses. The PWG reviewed representative examples of mixed cell infiltrate diagnosed by the SP and those added by the PWG Chair and confirmed the presence of the change in each case. Based upon these findings, the PWG recommended adding all of the additional diagnoses made by the PWG Chair. The incidences, as diagnosed by the PWG Chair, were similar across the control and treated groups; however, the increase in severity of the change in treated groups was confirmed.

B 03.

Mixed cell infiltrate is a commonly occurring spontaneous lesion in the livers of F344 rats and the microscopic appearance of the lesion in control and treated rats from this study was typical of that seen with this lesion in F344 rats. Microscopically, mixed cell infiltrate consisted of aggregates of macrophages mixed with varying numbers of lymphocytes and neutrophils. Severity of the lesion was graded based upon the number and size of the aggregates, with minimal lesions consisting of a few very small scattered aggregates, while marked lesions consisted of numerous large aggregates.

The incidences of Liver - Basophilic Focus, Liver - Clear Cell Focus, and Liver - Eosinophilic Focus in 5000 ppm males were greater than in the control and lower dose groups. In addition, the severity of Liver, Bile Duct - Hyperplasia was lower in the 2500 and 5000ppm male groups as compared with the control and 1250ppm male groups. These findings may have been related to the lower incidences of mononuclear cell leukemia in treated males, since leukemic infiltrate in the liver can obscure the presence of foci of cellular alteration, and can increase the severity of bile duct hyperplasia.

Testes

The incidences of Testes, Bilateral, Interstitial Cell - Adenoma (interstitial cell adenoma in both testes) were decreased in the 1250 and 5000ppm male groups, while the incidences of Testes, Interstitial Cell - Adenoma (interstitial cell adenoma in one testis) in these same groups were increased, as compared with the control and 2500ppm male groups. Since hyperplasia, unilateral adenoma, and bilateral adenoma of this cell type are believed to represent a biologic continuum of proliferative change, the interpretation of these findings was that treatment was associated with delayed development of proliferative lesions of the interstitial cells.

In addition, the incidences of Testes, Germinal Epithelium - Atrophy were considerably greater in the 5000ppm group, and to a lesser extent in the 1250ppm dose group, as compared with the control and 2500ppm groups. The SP did not diagnose atrophy in a testis containing an interstitial cell adenoma (since atrophy commonly occurs secondary to the presence of the tumor), thus the increased incidence of atrophy was considered to be due at least in part to the decreased incidence of bilateral adenoma. However, moderate to marked bilateral atrophy was seen in most animals in the 5000ppm group, which indicated the increase in atrophy may have been a direct treatment effect.

Microscopically, interstitial cell hyperplasias and adenomas had the typical microscopic appearance of these lesions in F344 rats. Lesions up to approximately the size of the diameter of a normal seminiferous tubule were diagnosed as hyperplasias, and larger lesions were diagnosed as adenomas. Germinal epithelial atrophy consisted of loss of part or all of the seminiferous epithelial cells from most or all seminiferous tubules, leaving tubules lined with Sertoli cells.

The PWG examined representative examples of interstitial cell hyperplasia and adenoma, and germinal epithelial atrophy, and confirmed the diagnoses. The PWG also reviewed a few lesions for which there had been a difference in diagnosis between the SP and QAP and the PWG Chair.

Uterus

The SP had diagnosed higher incidences of **Uterus – Hydrometra** in the 5000ppm female group, and **Uterus – Hyperplasia, Cystic** in the 2500 and 5000ppm female groups as compared with the control and 1250ppm female groups. In many cases the SP had diagnosed both changes in the same uterus. Microscopically, the change diagnosed by the SP as hydrometra consisted of dilatation of the entire uterine lumen, while the change diagnosed as cystic hyperplasia consisted of one or more cystic areas within the endometrium. The QAP confirmed the SP's findings, but considered the two different diagnoses to refer to different degrees of severity of cystic endometrial hyperplasia, rather than being two separate lesions. Consequently, the QAP suggested combining the two diagnoses under the NTP preferred term of **Uterus, Endometrium – Hyperplasia, Cystic**. The PWG Chair concurred with the QAP. The PWG reviewed representative examples of the lesions diagnosed by the SP as hydrometra or cystic hyperplasia, agreed with the QAP that these represented endometrial cystic hyperplasia, and recommended that the QAP's findings be adopted. The QAP's findings indicated greater incidences of cystic endometrial hyperplasia in the 2500 and 5000ppm female groups.

Prostate

The SP had diagnosed lower incidences of **Prostate, Epithelium – Hyperplasia** in the 2500 and 5000ppm male groups, and a lower incidence of **Prostate – Inflammation, Chronic** in the 5000ppm male group as compared with the control and other treated male groups. These findings were confirmed by the QAP/PWG review. The PWG examined a typical example of hyperplasia and confirmed the diagnosis.

Microscopically, hyperplasia was observed in the ventral prostate and consisted of focal proliferation of the glandular epithelium which partially or totally filled the glandular lumen. Chronic inflammation consisted of varying amounts of neutrophilic infiltrate within glandular lumens, often accompanied by varying amounts of lymphocytic infiltrate within the glandular interstitium.

Bone

The SP had diagnosed lower incidences and severities of **Cranium – Osteopetrosis** and **Femur – Osteopetrosis** in the 2500 and 5000ppm female groups as compared with the control and 1250ppm female groups. Microscopically, osteopetrosis in the cranium consisted thickening of the bone and of filling of marrow spaces by dense bone. Osteopetrosis in the femur

consisted of thickening of the cortex, and thickening of trabeculae within the marrow spaces with consequent filling of marrow spaces with dense bone.

Cases of osteopetrosis of the cranium diagnosed by the SP had generally been observed grossly. However, the QAP noted thickening of the bone in sections of nose in several animals in each of the female groups and diagnosed these as additional cases of osteopetrosis of the cranium. The PWG Chair agreed with the QAP in most cases. The incidences of osteopetrosis of the cranium as diagnosed by the QAP were similar across groups. The QAP also diagnosed additional cases of osteopetrosis in the femur; however, in many cases the PWG Chair did not agree with the QAP. While it appears there was a treatment effect on the occurrence of osteopetrosis, at least in the femur, final determination of this must await preparation of final pathology tables and statistical analysis.

Mammary Gland

The SP had diagnosed lower incidences of Mammary Gland – Hyperplasia in treated groups of males as compared with control males, and in the 5000ppm female group as compared with the control and other treated female groups. The findings of a lower incidence in the 5000ppm female group was confirmed by the QA/PWG review, but the lower incidences in the treated male groups were not confirmed. The QAP diagnosed numerous additional cases of hyperplasia in each of the male groups, including controls, such that the QAP's incidences were similar across groups, although there appeared to be a marginal increase in severity in the control male group as compared with the other male groups. In contrast, in females there was good agreement between the SP and QAP. The PWG Chair confirmed the QAP's findings.

The PWG reviewed typical examples of the change diagnosed as mammary gland hyperplasia by the SP as well as some examples of the cases added by the QAP and confirmed that the change was present in all of the examples. The PWG noted that the change diagnosed as hyperplasia by the SP generally consisting of variably dilated glands and ducts, sometimes filled with fluid, and appeared to be the result of normal physiologic hormonal stimulation. Thus, the change appeared to be physiologic rather than pathologic. The PWG Chair noted that the SP considered mammary glands to be normal when the glands were totally atrophic, and under no apparent hormonal stimulation.

Thyroid Gland

The SP had diagnosed lower incidences of Thyroid Gland, C-Cell – Hyperplasia in the treated groups of females as compared with female controls. This was confirmed by the QA/PWG review. The QAP added a few diagnoses in each of the groups and the PWG Chair agreed with many, but not all, of the QAP's diagnoses. Microscopically, C-cell hyperplasias consisted of focal aggregates of normal-appearing C-cells that were five follicular diameters or less in diameter. Since there had been good agreement among the SP, QAP, and

PWG Chair concerning the decreased incidences of C-cell hyperplasia in treated females, the PWG opted not to review any examples.

Clitoral Gland

The SP had diagnosed a greater combined incidence of **Clitoral Gland – Adenoma and Clitoral Gland – Carcinoma** in the 2500ppm female group as compared with the control females and other treated female groups. The QAP had reviewed all diagnosed clitoral gland neoplasms and had confirmed the SP's findings. Since the clitoral gland had not been selected for complete QA review, the PWG Chair was directed to review all clitoral glands for the presence of proliferative lesions (hyperplasia, adenoma, and carcinoma). The PWG Chair noted that a number of the proliferative lesions diagnosed as adenomas were rather small and was of the opinion that they represented hyperplasias rather than adenomas. All of these lesions, several of which were from the 2500ppm female group, were shown to the PWG, which considered most of the lesions to represent hyperplasias. Thus, the PWG findings led to a reduction of the number of clitoral gland neoplasms and an increase in the number of clitoral gland hyperplasias in the 2500ppm female group. Determination of the significance of these findings must await preparation of final pathology tables and statistical analysis.

Microscopically, the proliferative clitoral gland lesions appeared typical of those seen in F344 rats. The PWG Chair noted that the SP appeared to have based the diagnosis of adenoma versus carcinoma primarily on the size of the neoplasm, with small lesions being called adenomas, and medium size to large lesions being called carcinomas.

Mandibular Lymph Node

The SP had diagnosed somewhat greater incidences of **Lymph Node, Mandibular – Pigmentation** in the 2500 and 5000ppm male groups as compared with the control and the 1250ppm male groups. This was not confirmed by the QA/PWG review. The QAP diagnosed pigmentation in numerous additional animals in each of the male groups such that the incidences as diagnosed by the QAP were similar across male groups. The PWG Chair confirmed the QAP's findings. The PWG reviewed an example of pigmentation diagnosed by the SP and one diagnosed by the QAP and agreed that the same change was present in both. Microscopically, pigmentation was a very slight change consisting generally of one to three macrophages containing dark brown intracytoplasmic material.

Preputial Gland

The SP had diagnosed higher incidences of **Preputial Gland- Inflammation, Chronic** in the 2500 and 5000ppm male groups as compared with the control and 1250ppm males. This was not confirmed by the QA/PWG review. The QAP

B 07

added a number of additional diagnoses of chronic inflammation to each of the male groups, but primarily in the control and 1250ppm dose groups, such that the QAP's incidences were similar across dose groups. The PWG Chair confirmed the QAP's findings. Microscopically, chronic inflammation consisted of varying degrees of mononuclear cell infiltrate, primarily lymphocytes or macrophages, with atrophy of the adjacent glandular parenchyma. Chronic inflammation is a common spontaneous change in the preputial gland of male F344 rats, and the microscopic appearance of the chronic inflammation in this study was typical of that seen with this spontaneous change in F344 rats. Since there had been good agreement between the QAP and PWG concerning these lesions, the PWG opted not to review any examples.

Lungs

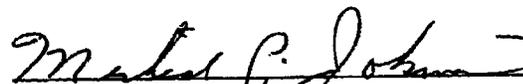
The SP had diagnosed higher incidences of Lung – Infiltration Cellular, Histiocyte and lower incidences of Lung, Alveolar Epithelium – Hyperplasia in treated groups of males as compared with control males. These findings were not confirmed by the QA/PWG review. The QAP added diagnoses of histiocyte infiltrate in each of the male groups, but primarily in controls, such that the incidences were similar in the control and treated male groups. In addition, the QAP disagreed with some of the SP's diagnoses of alveolar epithelial hyperplasia, and diagnosed a few additional hyperplasias that had not been diagnosed by the SP. The PWG Chair concurred with the QAP's findings concerning both the histiocytic infiltrate and alveolar epithelial hyperplasia. The PWG Chair noted that the diagnoses of hyperplasia with which the QAP disagreed occurred in lungs with severe mononuclear cell leukemia infiltrate, and the changes diagnosed by the SP as hyperplasia were considered to be secondary to the leukemia. As there had been good agreement between the QAP and PWG Chair regarding the lesions, the PWG opted not to review any examples.

Miscellaneous

Lymphoma, Malignant, generally an uncommon finding in F344 rats, was diagnosed by the SP in a few animals in this study. The QAP and PWG Chair concurred with the SP's diagnoses. Two examples were shown to the PWG which also concurred with the SP's diagnoses of malignant lymphoma.

POST-PWG ACTION ITEMS

It was recommended that special stains be performed to characterize the hyaline droplets and pigment in the kidneys.


Micheal P. Jokinen, DVM
Diplomate, ACVP
PWG Chairperson

12/27/99
Date

NTP Experiment-Test: 05205-08
Study Type: CHRONIC
Route: D05HD FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
P-NITROTOLUENE

Report: PEIRPT03
Date: 11/08/00
Time: 10:44:41

Facility: Southern Research Institute

Chemical CAS #: 99-99-0

Lock Date: 08/24/98

Cage Range: All

Reasons For Removal: All

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: 05205-08
 Study Type: CHRONIC
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 P-NITROPHENOL

Report: PEIRPP03
 Date: 11/08/00
 Time: 10:44:41

B6C3F1 MICE FEMALE
 0 PPM 1250 PPM 2500 PPM 5000 PPM

DISPOSITION SUMMARY

Disposition	0 PPM	1250 PPM	2500 PPM	5000 PPM
Animals Initially In Study	50	50	50	50
Early Deaths				
Morbund Sacrifice	2	1	5	1
Natural Death	2	2	2	
Survivors	46	47	41	49
Terminal Sacrifice			2	
Natural Death				
Animals Examined Microscopically	50	50	50	50

ALIMENTARY SYSTEM

Gallbladder				
Inflammation, Chronic	(49)	(48)	(48)	(49)
Intestine Small, Duodenum	(49)	(49)	(49)	(50)
Inflammation, Chronic, Focal				1 (2%)
Epithelium, Cyst		1 (2%)		
Intestine Small, Jejunum	(49)	(48)	(48)	(50)
Inflammation, Focal				
Peyer's Patch, Hyperplasia, Lymphoid	1 (2%)	1 (2%)	1 (2%)	
Serosa, Cyst				
Intestine Small, Ileum	(49)	(48)	(48)	(50)
Peyer's Patch, Hyperplasia, Lymphoid	(49)	(48)	(48)	(50)
Liver				
Angiectasis	(49)	(48)	(48)	(50)
Atrophy, Focal	(49)	(48)	(48)	(50)
Basophilic Focus	2 (4%)	(50)	(50)	
Congestion, Focal	2 (4%)	3 (6%)		1 (2%)
Eosinophilic Focus				
Hemorrhage, Focal		3 (6%)		1 (2%)
Hyperplasia, Focal, Lymphoid	1 (2%)	1 (2%)	1 (2%)	1 (2%)
Infarct	40 (82%)	41 (82%)	39 (78%)	39 (78%)
Infiltration Cellular, Mixed Cell	1 (2%)	1 (2%)		1 (2%)
Inflammation, Chronic				
Mixed Cell Focus				
Retention Lipidosis		1 (2%)		
Artery, Inflammation, Chronic		1 (2%)		
Bile Duct, Cyst		1 (2%)		
Centrilobular, Necrosis		1 (2%)		
Hepatocyte, Fatty Change, Diffuse		1 (2%)		
Hepatocyte, Necrosis, Focal		2 (4%)		1 (2%)

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

B 09

NTP Experiment-Test: 05205-08
 Study Type: CHRONIC
 Route: DOSED FEED

INCIDENCE RATES OF NEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 P-NITROPHENOL

Report: PEIRPP03
 Date: 11/08/00
 Time: 10:44:41

MPD Experiment - Test: 05205-08
 Study Type: CHRONIC
 Route: DOSED FEED

INCIDENCE RATES OF NEOPLASTIC LESIONS BY ANATOMIC SITE (A)
 P-NITROBENZENE

Report: PEIRPT03
 Date: 11/08/00
 Time: 10:44:41

B6C3F1 MICE FEMALE	0 PPM	1250 PPM	2500 PPM	5000 PPM
--------------------	-------	----------	----------	----------

ADHESIVE SYSTEM - CONT	0 PPM	1250 PPM	2500 PPM	5000 PPM
Hepatocyte, Vacuolization		1 (2%)		
Hepatocyte, Periportal, Vacuolization				3 (6%)
Cytoplasmic				1 (2%)
Portal, Inflammation, Chronic				1 (2%)
Neutrophil	(3)	(3)	(4)	(7)
Inflammation, Chronic		2 (67%)	1 (25%)	1 (14%)
Artery, Inflammation, Chronic	1 (33%)	1 (33%)	1 (25%)	1 (14%)
Fat, Necrosis	(49) (33%)	(50)	(49)	1 (14%)
Pancreas				(50)
Acinus, Atrophy, Diffuse	2 (4%)			1 (2%)
Acinus, Atrophy, Focal	1 (2%)			
Duct, Cyst	3 (6%)			
Stomach, Fore stomach	(49)	(50)		(50)
Duodenum		5 (10%)		
Stomach, Fore stomach		2 (4%)		
Esophagus, Hyperplasia	(49)	(50)	(49)	(50)
Stomach, glandular		1 (2%)		
Erosion	(3)	(6)	(7)	(6)
Malformation				
Peritoneal Tissue, Inflammation, Chronic	3 (100%)	6 (100%)	1 (14%)	6 (100%)

CARDIOVASCULAR SYSTEM	0 PPM	1250 PPM	2500 PPM	5000 PPM
Blood Vessel	(1)			
Inflammation, Chronic	1 (100%)	(50)	(50)	(50)
Heart	(50)	2 (4%)		
Infiltration Cellular, Mixed Cell	4 (8%)			6 (12%)
Inflammation, Chronic, Focal	1 (2%)			
Artery, Inflammation, Chronic	1 (2%)		1 (2%)	
Epicardium, Infiltration Cellular, Mixed Cell	2 (4%)			1 (2%)

ENDOCRINE SYSTEM	0 PPM	1250 PPM	2500 PPM	5000 PPM
Adrenal Cortex	(50)	(50)	(50)	(50)
Accessory Adrenal Cortical Nodule		1 (2%)		
Cyst	1 (2%)			
Cytoplasmic Alteration, Focal		1 (2%)		1 (2%)
Hemorrhage	(50)	(50)	(50)	(50)
Adrenal Medulla				
Hyperplasia	1 (2%)			

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

NTP Experiment-Test: 05205-08
 Study Type: CHRONIC
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (B)
 P-NITROFOLIOLENE

Report: PEIRP03
 Date: 11/08/00
 Time: 10:44:41

ENDOCRINE SYSTEM - CONT	B6C3F1 MICE FEMALE			
	0 PPM	1250 PPM	2500 PPM	5000 PPM
Parathyroid Gland	(49)	(48)	(44)	(48)
Cyst	(45)	(49)	1 (2%)	(45)
Pituitary Gland			(49)	
Angiectasis		1 (2%)		
Pars Distalis, Angiectasis		1 (2%)		
Pars Distalis, Cyst		2 (4%)	1 (2%)	
Pars Distalis, Cytoplasmic Alteration, Focal	4 (9%)	2 (4%)	3 (6%)	
Pars Distalis, Hyperplasia, Focal		2 (4%)		
Thyroid Gland	(50)	(50)	(49)	(50)
Degeneration, Cystic, Focal	18 (36%)	27 (54%)	29 (59%)	22 (44%)
Follicle, Cyst	1 (2%)	1 (2%)	1 (2%)	
Follicular Cell, Hyperplasia	1 (2%)	3 (6%)	1 (2%)	

GENERAL BODY SYSTEM
 Tissue NOS
 Abdominal, Inflammation, Chronic (2)
 1 (50%)

GENITAL SYSTEM	0 PPM	1250 PPM	2500 PPM	5000 PPM
Clitoral Gland	(50)	(45)	(49)	(48)
Degeneration, Cystic	1 (2%)	1 (2%)	2 (4%)	
Inflammation, Chronic		4 (9%)	3 (6%)	2 (4%)
Pigmentation	(48)	(50)	(50)	(49)
Ovary		2 (4%)		
Angiectasis	11 (23%)	13 (26%)	13 (26%)	13 (27%)
Cyst, Multiple	1 (2%)	1 (2%)	5 (10%)	
Hemorrhage	1 (2%)	2 (4%)		
Mineralization	1 (2%)	1 (2%)		
Bilateral, Cyst	1 (2%)			
Periovarian Tissue, Cyst	(50)	(50)	(50)	(50)
Uterus		1 (2%)	4 (8%)	3 (6%)
Angiectasis	1 (2%)			
Cyst	2 (4%)			
Hemorrhage	19 (38%)	21 (42%)	23 (46%)	25 (50%)
Hydrometra	1 (2%)			
Inflammation, Suppurative		1 (2%)		
Thrombosis				
Endometrium, Hyperplasia, Cystic	47 (94%)	45 (90%)	44 (88%)	49 (98%)

a Number of animals examined microscopically at site and number of animals with lesion
 Page 4

NTP Experiment-Test: 05205-08
 INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (B)

NTP Experiment Test: 05105-08
 Study Type: CHRONIC
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 P-NITROBOLUENE

Report: PEIRPT03
 Date: 11/08/00
 Time: 10:46:41

HEMATOPOIETIC SYSTEM	B6C3F1 NICE FEMALE				
	0 PPM	1250 PPM	2500 PPM	5000 PPM	
Bone Marrow					
Hyperplasia	(50)	(50)	(50)	(50)	
Hyperplasia, Focal, Histiocytic	1 (2%)	1 (2%)		1 (2%)	
Lymph Node					
Bronchial, Hyperplasia	(2)	(5)	(13)	(4)	
Bronchial, Hyperplasia, Lymphoid		1 (20%)	3 (23%)	1 (25%)	
Iliac, Hyperplasia, Lymphoid					
Inguinal, Hyperplasia, Histiocytic	1 (50%)		1 (8%)		
Inguinal, Hyperplasia, Lymphoid					
Mediastinal, Pylometastion					
Mediastinal, Hyperplasia, Lymphoid					
Pancreatic, Hyperplasia, Lymphoid					
Renal, Hyperplasia, Lymphoid					
Lymph Node, Mandibular	1 (50%)	1 (20%)	(48)	(47)	
Hyperplasia	(50)	(48)	(48)	(47)	
Hyperplasia, Lymphoid	1 (2%)	1 (2%)	2 (4%)		
Lymph Node, Mesenteric	(48)	(49)	(49)	(50)	
Hyperplasia					
Hyperplasia, Histiocytic		1 (2%)	1 (2%)	2 (4%)	
Hyperplasia, Lymphoid		5 (10%)	1 (2%)	2 (4%)	
Spleen					
Congestion	2 (4%)	1 (2%)	(49)	(50)	
Hematopoietic Cell Proliferation	2 (4%)	7 (14%)	11 (22%)	4 (8%)	
Hyperplasia, Lymphoid	5 (10%)	9 (18%)	4 (8%)	2 (4%)	
Thymus	(48)	(49)	(47)	(46)	
Angiectasis	1 (2%)	2 (4%)			
Cyst	1 (2%)	1 (2%)	2 (4%)		
Hyperplasia, Lymphoid			2 (4%)		

INTEGRUMENTARY SYSTEM	B6C3F1 NICE FEMALE				
	0 PPM	1250 PPM	2500 PPM	5000 PPM	
Mammary Gland					
Ectasia	(50)	(50)	(50)	(50)	
Hyperplasia					
Skin					
Subcutaneous Tissue, Angiectasis, Focal	(50)	(50)	(50)	(50)	
Subcutaneous Tissue, Cyst Epithelial					
Inclusion	1 (2%)	1 (2%)			
Subcutaneous Tissue, Degeneration, Mucoid	1 (2%)	1 (2%)			
Subcutaneous Tissue, Edema					

a Number of animals examined microscopically at site and number of animals with lesion
 Page 5

NTP Experiment-Test: 05205-06
 Study Type: CHRONIC
 Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 P-NITROTOLUENE

Report: PRT03
 Date: 11/08/09
 Time: 10:44:41

B6C3F1 MICE FEMALE
 0 PPM 1250 PPM 2500 PPM 5000 PPM

IMMUNOGENIC SYSTEM - CONT
 Subcutaneous Tissue, Inflammation, Chronic,
 Focal 2 (4%)

MUSCULOSKELETAL SYSTEM
 Bone (50)
 Callus 1 (2%) (50)
 Skeletal Muscle (1) (50)
 Artery, Inflammation, Chronic 1 (100%) (3)

NERVOUS SYSTEM

Brain (50)
 Atrophy, Focal (50)
 Meninges, Hyperplasia, Lymphoid 1 (2%) (50)
 1 (2%) (50)

RESPIRATORY SYSTEM

Lung (50)
 Congestion (50)
 Hemorrhage 1 (2%) 5 (10%) (50)
 Hyperplasia, histiocytic 2 (4%) 2 (4%) (50)
 Hyperplasia, Lymphoid 2 (4%) 1 (2%) (50)
 Infiltration Cellular, Mixed Cell 1 (2%)
 Thrombosis, Chronic 1 (2%)
 Alveolar Epithelium, Bronchiolization 33 (66%)
 Alveolar Epithelium, Hyperplasia 1 (2%) 1 (2%) (50)
 Hemorrhage 2 (4%) 1 (2%) 41 (82%)
 Inflammation, Suppurative 1 (2%) 2 (4%) (50)
 Nasolacrimal Duct, Inflammation (50)
 Squamous Epithelium, Nasolacrimal Duct, 1 (2%)
 Hyperplasia, Focal 1 (2%)

SPECIAL SENSES SYSTEM

NONE

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

NTP Experiment-Test: 05205-08
 Study Type: CHRONIC
 Route: DOSED FEED
 INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
 P-NITROFOLUENE
 Report: P21PP03
 Date: 11/08/00
 Time: 10:44:41

PRIMARY SYSTEM	B6C3F1 MICE FEMALE				
	0 PPM	1250 PPM	2500 PPM	5000 PPM	
Kidney	(49)	(50)	(50)	(50)	(50)
Congestion			1 (2%)		
Hypertlasia, Lymphoid	1 (2%)		2 (4%)		
Infiltration Cellular, Mixed Cell	1 (2%)				
Metaplasia, Focel, Ossseous	1 (2%)				
Nephropathy	11 (22%)	1 (2%)	1 (2%)	3 (6%)	
Renal Tubule, Accumulation, Hyaline Droplet		7 (14%)	9 (18%)		
Renal Tubule, Casts Protein		1 (2%)	4 (8%)		
Renal Tubule, Pigmentation			1 (2%)		
Urinary Bladder	1 (2%)	(50)	(50)	(50)	(50)
Hypertlasia, Lymphoid	(49)		1 (2%)		

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