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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 ongoing studies, a copy of the Pathology Working Group (PWG) report and the Summary Pathology Tables for the chronic dosed feed study on P,P'-DICHLORODIPHENYL SULFONE (80-07-9) 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.

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William Eastin

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

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CHAIRPERSON'S REPORT
PATHOLOGY WORKING GROUP (PWG)
OF THE CHRONIC STUDY OF p,p'-DICHLORODIPHENYL SULFONE (C88120B/88120-03) ADMINISTERED BY DOSED FEED TO F344 RATS AT BATTELLE COLUMBUS LABORATORIES

Date of PWG: August 13, 1999

Site of PWG: National Toxicology Program (NTP/NIEHS)
Research Triangle Park, NC

PWG Participants:

Paul K. Hildebrandt, D.V.M., Chairperson	PATHCO
Ronald Herbert, D.V.M., Ph.D.	NIEHS
Abraham Nyska, D.V.M.	NIEHS
Gary Boorman, D.V.M., Ph.D.	NIEHS
Cynthia Shackelford, D.V.M., M.S., Ph.D.	EPL
Glen Marrs, D.V.M., M.S.	EPL
Nobuyuki Izumisawa, D.V.M., Ph.D.	Yamanouchi USA, Inc.

Study Pathologist: Dr. Allen Singer
Reviewing Pathologist: Dr. Glen Marrs

I. SUMMARY AND CONCLUSION

A. The administration of p,p'-Dichlorodiphenyl Sulfone for two years in Fischer 344 Rats did not have a carcinogenic effect on any organ/tissue.

B. Minimal, with occasional mild, degrees of centrilobular hypertrophy of hepatocytes were present in the livers of the male 100 ppm dose group and female 300 ppm dose group. A few females in the 100 ppm dose group had very minimal centrilobular hypertrophy.

C. A number of common spontaneous lesions in various organs were evaluated by the PWG. None of these were considered to be related to compound administration.

II. STUDY DESIGN

Male and female Fischer 344 rats, 50/group/sex, were administered p,p'-Dichlorodiphenyl Sulfone in the feed for up to two years at the following doses: male rats - 0 ppm (control), 100 ppm, 30 ppm and 10 ppm; female rats - 0 ppm (control), 300 ppm, 100 ppm and 30 ppm.

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III. ANIMAL DISPOSITION SUMMARY

Chronic Toxicity/Carcinogenicity Study

FEMALE RATS

	0 PPM	30 PPM	100 PPM	300 PPM
Animals Initially in Study	(50)	(50)	(50)	(50)
Early Deaths				
Natural Death	3	3	4	10
Moribund Sacrifice	11	9	12	5
Accidentally Killed				
Survivors - Terminal Sacrifice	36	38	34	35
Animals Examined Microscopically	50	50	50	50

MALE RATS

	0 PPM	30 PPM	100 PPM	300 PPM
Animals Initially in Study	(50)	(50)	(50)	(50)
Early Deaths				
Natural Death	7	4	6	7
Moribund Sacrifice	19	16	24	15
Accidentally Killed				
Survivors - Terminal Sacrifice	24	30	20	28
Animals Examined Microscopically	50	50	50	50

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IV. CONDUCT OF THE PWG

Prior to the PWG the chairperson reviewed the pathology incidence tables, the study pathologist's narrative, the report prepared by the reviewing pathologist, and microscopic slides of potential target organs and lesions with discrepancies in diagnoses between the study pathologist (SP) and reviewing pathologist (RP). Potential target organs in this study were considered to be:

Male Rats	Female Rats
Liver	Liver

Sections of the following organs/tissues from sex indicated were examined from all animals in all groups for the lesions listed.

Male Rats

Pituitary Gland - cyst
Lung - pigmentation

Female Rats

Adrenal Medulla - hyperplasia
Pituitary Gland - Pars Distalis - hyperplasia
Thyroid Gland, C-cell - hyperplasia
Mammary Gland - galactocele
Uterus - hyperplasia
Spleen - leukemia mononuclear

At the PWG the chairperson led a short discussion in the form of introductory remarks which included the following:

1. Study design

2. Survival of treated groups - Male 10 ppm and 100 ppm groups had slightly better survival than controls.

3. Body weights - Weight values for treated males were less than controls but did not exceed a 10% weight loss. In females, the 300 ppm dose group was 14.04% less than controls.

4. Food consumption in treated groups was similar to that of controls.

5. No compound related gross lesions were recorded at necropsy. There was a decrease in liver "foci" in treated females compared to controls.

6. Centrilobular hypertrophy of the liver was observed in the 90-day subchronic study in both sexes. (Males 100 ppm and above and female 300 ppm and above).

V. RESULTS

Liver

The liver was considered to be a target organ due to the higher incidence of centrilobular hypertrophy in the high dose groups of both sexes. This lesion was similar to that described in the subchronic study and was characterized by larger than normal hepatocytes in the centrilobular area. The cytoplasm of these enlarged hepatocytes was slightly smudged and not composed of the finely granular cytoplasm of normal hepatocytes. The degree of severity of this hypertrophy was mostly minimal with a few graded as mild.

There were many other diagnoses of liver changes, including basophilic focus, clear cell focus, adenomatous hyperplasia, bile duct hyperplasia, pigmentation and centrilobular degeneration. Most of these lesions are common background lesions in two-year old Fischer 344 rats. Also, rats with advanced mononuclear cell leukemia have most of these liver lesions which are generally not diagnosed; however, in this study, all the individual liver changes were individually diagnosed in addition to leukemia. This resulted in a much higher incidence of these common background lesions than is generally diagnosed.

The PWG examined a series of livers from control and high dose females and recognized that centrilobular hypertrophy was present but it was very minimal in degree of severity in most livers examined. The PWG acknowledged the incidence of centrilobular hypertrophy in the 100 ppm dose group reported by the SP and RP and accepted the incidence following the chairperson's review. Other lesions were recognized to be present in some livers, but were sporadic in occurrence and not considered to be directly related to compound administration. Centrilobular degeneration was noted to occur only in livers with advanced mononuclear cell leukemia.

Eosinophilic foci was noted to occur at a higher incidence in treated male livers than controls. The majority of lesions diagnosed as eosinophilic foci were little more than one or two hepatic lobules that had liver cords and sinusoids that were somewhat curved between the portal triad and central vein rather than the straight cords and sinusoids normally seen. The PWG chairperson was directed to examine all livers from male rats with the diagnosis of eosinophilic foci to assure that these changes were consistent with the criteria established for eosinophilic foci.

The criteria utilized by the chairperson were those of Eustis, et.al.[1] and basically consisted of foci of hepatocytes with a homogeneous eosinophilic cytoplasm. Hepatocytes in eosinophilic foci tended to be larger than the surrounding hepatocytes and occasionally caused compression of the adjacent parenchyma. The hepatic cords in eosinophilic foci merged with normal hepatic cords at a small angle.

The PWG chairperson diagnosed fewer eosinophilic foci than the SP or RP in all groups. Although a slight increase in eosinophilic foci was present in treated rats over that of controls, a statistical significance is questioned. Also, in livers with a compound effect (centrilobular hypertrophy) a slight increase in a few other non-neoplastic lesions can be expected.

There were few neoplastic liver lesions and very few discrepancies between the RP and SP regarding hepatic neoplasm. Tumor versus non-tumor hepatic lesions were evaluated by the PWG and results are presented in the pathology worksheets. The PWG agreed that no compound related neoplastic lesions were present in the liver.

Lung

A number of lungs had been diagnosed with pigment. This cytoplasmic pigment was present within the small focal clusters of histiocytes often observed in the subplural region of most rat lungs. There was some inconsistency in the diagnosis of this pulmonary pigment; however, it was the opinion of the RP and chairperson that the pigment was present in most rats of all dose groups. The PWG examined a small series of lungs and agreed that the pigment was part of the common background lesion of histiocytosis observed in most Fischer 344 rats of advanced age. It was the PWG opinion that the diagnosis of pigment in the lung should be deleted.

Mammary Gland

There were some discrepancies in the diagnosis of mammary lesions. This involved galactocele versus mammary fibroadenoma. A series of mammary glands were examined by the PWG. The PWG was of the opinion that the majority of these lesions diagnosed as galactocele were mammary fibroadenomas with a large fluid-containing space. The diagnosis of galactocele should be utilized only for lesions in which a large fluid space existed without any proliferating mammary tissue present.

There was also some discrepancy between hyperplasia of the mammary gland versus dilated ducts. The PWG was of the opinion that a number of these mammary glands had dilated ducts and acini rather than a proliferation of acinar cells or ductal epithelium. Mammary glands with hyperplasia were characterized by acini or ducts that had more cells per unit area than normal. Also, these cells were more basophilic with nuclei that were larger and darker than normal.

Mammary glands with a rather flat vesicular, non-active appearing epithelium that was lining dilated acini and ducts should be diagnosed as ductal dilatation rather than hyperplasia. The PWG was of the opinion that no compound effect was present in the mammary gland.

Uterus

There were a few discrepancies in the uterus concerning uterine hyperplasia versus cystic glandular hyperplasia and/or glandular dilatation.

It was the PWG opinion that uterine hyperplasia should be diagnosed when there was hyperplasia of the endometrial glands with an accompanying increase in stromal elements. Cystic glandular hyperplasia should be diagnosed when there is hyperplasia of mucosal glands that are considerably dilated, lined by proliferating epithelium and many contain fluid material.

Dilatation of endometrial glands consisted of greatly dilated mucosal glands with very flattened, non-proliferating epithelial cells. Often, the section of uterus had only one dilated mucosal gland. An occasional uterus was greatly distended with no or very few endometrial gland(s) dilated. In such cases the diagnosis of hydrometra was rendered. The PWG chairperson was directed to utilize the criteria discussed above for lesions in the mammary gland and uterus and to diagnose the lesions accordingly in female rats of all groups. The PWG was of the opinion that no compound effect was present in the uterus.

Pituitary Cysts

There was a suggestion that an increase in pituitary cysts was present in treated male rats over that of controls. On closer examination of pituitaries, it was determined that many pituitary glands from male controls had small pituitary cysts that had not been diagnosed. The PWG examined these control pituitary glands and verified the presence of small cysts.

The PWG agreed that some of the pituitary cysts were lined with a layer of epithelium and were by definition a true cyst. Such cysts are considered to be embryologic remnants or rests. Pituitary cysts not lined with a layer of epithelium are considered pseudocysts, the etiology of which is not known.

There were a few discrepancies between the RP and SP regarding pituitary hyperplasia versus adenoma. The PWG accepted the chairperson's diagnoses in these discrepancies and recognized that a decrease in pituitary adenomas occurred in treated rats. This is frequently observed when a reduced weight gain exists as occurred in this study.

Mesotheliomas

The PWG examined all mesothelial hyperplasias and mesotheliomas diagnosed in male rats. Several of the lesions were considered to be little more than a few hypertrophied mesothelial cells; however, others were proliferating neoplastic mesothelial cells. The PWG agreed there were more mesotheliomas in treated male rats over that of controls, but, because the incidence was so low, believed a biologic significance did not exist.

Miscellaneous Lesions

A number of interesting and unusual lesions were presented to the PWG for review and a few lesions with discrepancies in diagnosis of tumors in non-target organs were also evaluated (see PWG worksheets).

Paul K. Hildebrandt, D.V.M.
Diplomate, American College of
Veterinary Pathologists

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REFERENCE

Eustis, S.L. and Boorman, G.A., (1990). Liver. In: Pathology of the Fischer Rat. Boorman, G.A., Eustis, S.L., Elwell, M.R., Montgomery, C.A., MacKenzie, William F. (Eds.) pp. 71-94. Academic Press, Santiago, CA.

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PATHOLOGY WORKING GROUP CHAIRPERSON'S REPORT

2-Year Chronic Study of p,p'-Dichlorodiphenyl Sulfone in B6C3F1 Mice

Participants: Drs. M. Jokinen (PAI - PWG Chairperson), A. Brix (EPL- QA Pathologist), E. Gaillard, (EPL), L. Healey (CIIT-Observer), R. Herbert (NIEHS), J. Mahler (NIEHS), and D. Wolf (EPA).

Date: July 29, 1999
Site: NIEHS, Research Triangle Park, NC

The PWG was convened to evaluate selected slides from B6C3F1 mice administered p,p'-dichlorodiphenyl sulfone 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
30ppm	50	50
100ppm	50	50
300ppm	50	50

The study was conducted at Battelle Columbus. The Study Pathologist (SP) was Dr. M. Ryan and the Quality Assessment Pathologist (QAP) was Dr. A. Brix 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:

Male Mice	Female Mice
Liver	Liver
	Uterus

In addition, a number of tissues were reviewed from all males or all females for the presence of specific lesions. These were as follows:

Male Mice

Oral Mucosa – Ulcer; and Oral Mucosa, Gingival – Inflammation, Chronic
Adrenal Cortex, Subcapsular – Hyperplasia
Preputial Gland – Cyst; Inflammation, Chronic Active; and Inflammation, Suppurative
Spleen – Hematopoietic Cell Proliferation

Lung – Alveolar Epithelium – Hyperplasia, Alveolar/Bronchiolar Adenoma, and Alveolar/Bronchiolar Carcinoma

Female Mice

Pituitary Gland, Pars Distalis – Angiectasis
Spleen, Lymphoid Follicle – Hyperplasia
Kidney, Renal Tubule – Casts Protein

SUMMARY OF REVIEW FINDINGS

Minimal to moderate Liver, Centrilobular – Hypertrophy was present in all treated groups of males, and in the 100ppm and 300ppm female groups. The incidence and severity increased with increasing dose.

The combined incidences of **Liver – Eosinophilic Focus** and **Liver – Eosinophilic Focus, Multiple** were somewhat increased in all treated male groups and in the 100ppm and 300ppm female groups, as compared with controls.

The incidences of **Pituitary Gland, Pars Distalis – Adenoma** were marginally increased in 100ppm and 300ppm females as compared with controls, and the incidence of **Pituitary Gland, Pars Distalis – Hyperplasia** was increased in the 300ppm female group as compared with control females.

The combined incidences of **Lung – Alveolar/Bronchiolar Adenoma** and **Adenoma, Multiple**, and **Lung – Alveolar/Bronchiolar Carcinoma** and **Carcinoma, Multiple** were moderately decreased in the 100ppm and 300ppm male groups as compared with control and 30ppm 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

Liver

The SP had diagnosed minimal to moderate **Liver, Centrilobular – Hypertrophy** in all treated groups of males and in the 100ppm and 300ppm

groups of females. The average severity was somewhat greater in males than in females, and incidence and severity increased with increasing dose. In addition, the SP had diagnosed somewhat greater combined incidences of **Liver – Eosinophilic Focus** and **Liver – Eosinophilic Focus, Multiple** in all treated groups of males and in the 100ppm and 300ppm groups of 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.

Microscopically, the hypertrophy involved hepatocytes of all centrilobular areas in the affected livers, and was characterized by hepatocellular enlargement due to an increase in the amount of cytoplasm. The cytoplasm of the affected hepatocytes was lightly eosinophilic and finely granular, usually with fine clear vacuolation.. Hepatocyte nuclei were also enlarged in some of the more severely affected livers. The severity of the hypertrophy was graded according to the increase in the size of the affected hepatocytes with slight enlargement seen with minimal hypertrophy and pronounced enlargement seen with moderate hypertrophy. Eosinophilic foci had the typical microscopic appearance for these lesions in B6C3F1 mice, and consisted of discrete foci of somewhat enlarged hepatocytes with pink cytoplasm that were arranged in normal hepatic cords that blended with the adjacent normal parenchyma. Larger foci sometimes caused slight compression of the surrounding parenchyma.

Pituitary Gland

The SP had diagnosed a slightly higher incidence of **Pituitary Gland, Pars Distalis – Adenoma** in the high dose females, as compared with the other female groups. In addition, the SP had diagnosed higher incidences of **Pituitary Gland, Pars Distalis – Angiectasis** in the high dose group females as compared with the control females and other treated female groups. The QAP considered one of the lesions diagnosed as angiectasis to be **Hemorrhage**, another to represent no remarkable lesion, and the others to be **Pituitary Gland, Pars Distalis, – Hyperplasia, Focal**; the PWG chair agreed in each case. During review of the pituitary gland, the PWG chair noted a few cases of pars distalis hyperplasia that had not been diagnosed previously and added these diagnoses. In addition, the PWG chair noted two pituitaries in which the SP had diagnosed hyperplasia but that the PWG chair considered to be adenomas.

The PWG examined (1) two of the adenomas diagnosed by the SP each from the control and 300 ppm high dose female and agreed with the SP's diagnoses in each case, (2) all of the lesions diagnosed originally as angiectasis by the SP and agreed with the QAP's diagnoses in each case, (3) the additional hyperplasias diagnosed by the PWG chair and agreed in each case that hyperplasia was present, and (4) the two lesions diagnosed as hyperplasia by the SP that the PWG chair considered to be adenomas, and agreed with the PWG chair in each case.

The incidences of adenoma resulting from the QA/PWG review were somewhat greater in the 100ppm and 300ppm female groups as compared with the control and the 30ppm female groups. The incidences of pars distalis hyperplasia resulting from the QA/PWG review were moderately greater in the 300 ppm female group than in the other treated female groups and female controls.

Microscopically, hyperplasia and adenoma had the typical appearance for these lesions in B6C3F1 mice. There appeared to be a morphologic continuum from hyperplasia to adenoma. Both were focal lesions consisting of sheets, cords, or clusters of densely packed cells with pale staining cytoplasm that were smaller than normal, normal sized or, most commonly, somewhat larger than normal. Hyperplasias tended to blend with the surrounding parenchyma producing little or no compression. Adenomas were larger lesions with distinct borders that compressed and displaced the adjacent parenchyma.

Kidney

The SP diagnosed greater incidences of **Kidney Renal Tubule – Casts Protein** in all treated groups of females than in female controls. The severity of the casts was diagnosed by the SP as minimal in each case. The QAP agreed with the SP's diagnoses, and added several diagnoses to each of the groups so that the incidences as diagnosed by the QAP were slightly increased in the 100ppm dose group and moderately increased in the 300ppm high dose group compared with female controls. The PWG chair agreed with the QAP's added diagnoses almost without exception. However, the PWG chair also saw casts in several animals that had not been diagnosed previously. These occurred mainly in the controls, but were also seen in a few treated animals, especially in the low dose group. The incidences of casts as diagnosed by the PWG chair were similar among the control and treated groups of females.

Microscopically, casts consisted of short focal segments of renal tubules, generally located at the corticomedullary junction or, less often, in the medulla, which were normal sized or dilated up to four to five times normal diameter, and filled with homogeneous eosinophilic proteinaceous material. The PWG chair noted that the larger diameter casts occurred primarily in the treated groups. In nearly every animal with casts only one to three tubules were affected; thus, even though casts in some treated animals were larger than those in controls, the number of tubules affected was very low and similar in control and treated animals. The SP had diagnosed some of the small casts as well as the larger casts, but appeared to have diagnosed the larger casts more consistently than the smaller ones. The casts diagnosed by the QAP and the PWG chair usually were small casts.

The PWG reviewed some examples of casts, ranging in size from the smaller casts to larger ones, diagnosed by the SP in control and treated females. The

PWG confirmed the presence of the casts in each case. The PWG then reviewed examples of the small casts diagnosed by the QAP and the PWG chair in control and treated females, and confirmed the presence of casts in each case. The PWG noted that the severity of the change was very minimal in all kidneys examined. The PWG members also noted some of the casts were larger than others but that the number of casts was small and similar numbers of casts were seen in each of the kidneys examined. After the slide review was completed, the PWG chair asked the PWG to comment on whether the presence of larger casts in treated females could indicate a treatment effect. The PWG opinion was that if a treatment effect were present then larger numbers of tubules in treated females should contain casts than in controls. However, since similar low numbers of affected tubules were seen in the control and treated groups, the PWG was of the opinion that the casts represented a background change unrelated to treatment. The PWG noted that the SP had diagnosed small casts similar to those diagnosed by the QAP and PWG chair and, to maintain consistency of diagnosis, recommended all the additional diagnoses of cast made by the QAP and PWG chair be added to the pathology findings.

Lung

The SP had diagnosed lower combined incidences of **Lung – Alveolar/Bronchiolar Adenoma; Alveolar/Bronchiolar Adenoma, Multiple; Alveolar/Bronchiolar Carcinoma; and Alveolar/Bronchiolar Carcinoma, Multiple** in the 100ppm and 300ppm male groups as compared with 30ppm and control male groups. This finding was confirmed by the QA/PWG review. Also, the SP had diagnosed no alveolar/bronchiolar neoplasms in control females, a moderately high incidence in the 30ppm female group, and relatively low incidences in the 100ppm and 300ppm female groups. Since the lung had not been chosen for review in females, the PWG chair was directed to review the lungs for additional neoplasms. No additional alveolar/bronchiolar neoplasms were found in females during the PWG chair's review. The PWG reviewed all diagnosed alveolar/bronchiolar neoplasms in females and confirmed the unusual trend in these neoplasms in the females.

Adrenal Cortex

The SP had diagnosed higher incidences of **Adrenal Cortex, Subcapsular – Hyperplasia** in treated groups of males than in control males. This finding was not confirmed by the QA/PWG review. The QAP added additional diagnoses to each of the male groups, primarily in the controls, such that the incidences as diagnosed by the QAP were similar in the control and treated groups. The PWG chair found a few additional adrenal glands with subcapsular hyperplasia that had not been diagnosed previously. The PWG reviewed examples of subcapsular hyperplasia diagnosed in the control and high dose 300ppm male groups by the SP or by the QAP, and the few additional cases of subcapsular

hyperplasia diagnosed by the PWG chair. The PWG confirmed the presence of the change in each case and noted that it appeared morphologically similar in control and treated animals. Subcapsular hyperplasia is a commonly occurring spontaneous change in B6C3F1 mice, and was a focal to multifocal lesion consisting of clusters of deeply basophilic spindle shaped cells extending inward from the adrenal capsule into the underlying adrenal cortex. The findings of the QA/PWG review indicated there was no treatment effect on the incidence of subcapsular hyperplasia in the adrenal cortex of male mice.

Spleen

The SP diagnosed a somewhat higher incidence of **Spleen – Hematopoietic Cell Proliferation** in control males than in treated males, and a higher incidence of **Spleen, Lymphoid Follicle – Hyperplasia** in control females than in treated females. The QAP added a few diagnoses of hematopoietic cell proliferation, primarily in the treated groups, such that the incidences in control and treated males were similar. The QAP also added diagnoses of lymphoid follicle hyperplasia in treated groups of females such that the incidences were similar in the control and treated groups. The PWG chair confirmed the QAP's findings and added a diagnosis of hematopoietic cell proliferation in the males and a few diagnoses of lymphoid follicle hyperplasia in the females.

The PWG examined examples of hematopoietic cell proliferation diagnosed in control and 300ppm high dose males by the SP or the QAP, and the additional diagnosis made by the PWG chair and confirmed the presence of the change in each case. The PWG noted the change was the same morphologically in control and treated animals. The PWG also examined examples of lymphoid follicle hyperplasia diagnosed in control and high dose females by the SP or by the QAP and the additional diagnoses of hyperplasia made by the PWG chair, and confirmed the presence of the change in each case. The PWG noted the change was morphologically the same in control and treated females. The findings of the QA/PWG review indicated there were no treatment effects on the incidences of hematopoietic cell proliferation in males and lymphoid follicle hyperplasia in females.

Preputial Gland

The SP diagnosed a lower incidence of **Preputial Gland – Cyst** in the 300ppm high dose males than in the control and other treated male groups. This was confirmed by the QA/PWG review. The QAP added a few diagnoses of cysts and the PWG chair confirmed the QAP's findings. Microscopically, preputial gland cysts consisted of variably dilated preputial gland ducts that often contained small to moderate amounts of keratin. The SP had also diagnosed **Preputial Gland – Inflammation, Suppurative** in a few more control males than in treated males. This change consisted of small to moderate amounts of

suppurative infiltrate within preputial gland ducts and usually was seen in glands with cysts, and so appeared to be associated with the cysts. The QAP added a few diagnoses of suppurative inflammation in treated groups of males and the PWG chair confirmed the QAP's findings. Since there was good agreement among the SP, QAP, and PWG chair concerning the cysts, the PWG opted not to review any examples.

The SP had also diagnosed **Preputial Gland – Inflammation, Chronic Active** in a few animals. The QAP noted that minimal chronic active inflammation was present in the majority of animals in each of the groups and added these diagnoses. The PWG chair confirmed the QAP's findings. Microscopically, the inflammation consisted of a few scattered, focal aggregates of small to moderate numbers of mononuclear inflammatory cells, primarily lymphocytes. The incidences of chronic active inflammation diagnosed by the QAP were somewhat lower in the 100ppm and 300ppm male dose groups than in the control and 30ppm dose groups. The QAP and PWG chair noted that, like suppurative inflammation, chronic active inflammation was usually seen in preputial glands containing cysts, and appeared to be related to the presence of the cysts.

The PWG examined the slides of the chronic active inflammation diagnosed by the SP as well as examples of the diagnoses added by the QAP, and confirmed the presence of the change in each case. The PWG noted that, except in those animals in which the SP had diagnosed chronic active inflammation, the lesion was of very minimal severity in each case. The PWG was of the opinion that the cysts and inflammation represented spontaneously occurring background changes. The significance of the lower incidence of cyst in the 300ppm dose group and the lower incidences of inflammation in the 100ppm and 300ppm dose groups was uncertain, but was not considered to represent a treatment related effect. The lower incidence of chronic active inflammation in the 300ppm dose group may have been related to the lower incidence of cysts in that group.

Uterus

The SP had diagnosed higher incidences of **Uterus, Endometrium – Hyperplasia, Cystic** in the 100ppm and 300ppm dose females, as compared with control and 30ppm dose females. The QAP added hyperplasia to each of the groups, primarily in the control and low dose groups, such that the incidences were similar in the control and treated groups. With rare exception the PWG chair agreed with the QAP.

The PWG examined uteri from control and 300ppm dose group females in which the SP or the QAP had diagnosed cystic hyperplasia and confirmed the presence of the change in each case. Microscopically, cystic hyperplasia had the typical appearance of this change in B6C3F1 mice and was characterized by few to several variably dilated glands within the endometrium. In some uteri the

dilation was of sufficient magnitude to cause enlargement of the uterus. The findings of the QA/PWG review indicated there was no treatment effect on the incidence of uterine endometrial cystic hyperplasia.

Gingiva and Oral Mucosa

The SP had diagnosed a lower incidence of **Oral Mucosa – Ulcer** in the 300ppm dose group of males as compared with the control and other treated male groups. The QAP added some diagnoses of ulcer, primarily in the 300ppm males; the PWG chair confirmed the QAP's findings. The incidence of ulcer in the 300ppm male group, as diagnosed by the QAP, was still lower than that in the control males and other treated male groups, but was considered to be similar enough to that in the other groups to indicate there was no treatment effect on the incidence of oral mucosal ulcers in the 300ppm male dose group. Ulcers were small to moderate sized lesions located at the base of the molars in nose Level III. They consisted of focal areas of ulceration of the oral epithelium that generally contained small to moderate amounts of inflammatory cell infiltrate. In most cases, several hairs were embedded in the oral mucosa at the site of the ulcer and appeared to be the cause of the ulcer and the accompanying inflammation.

The SP had diagnosed similar incidences of **Oral Mucosa, Gingival – Inflammation, Chronic** in control and treated groups of males. These findings were confirmed by the QA/PWG review, with excellent agreement among the SP, QAP, and PWG chair. Chronic inflammation occurred in nose Level III and consisted of local infiltrates of small numbers of mononuclear inflammatory cells, sometimes mixed with a few neutrophils, in the connective tissue beneath the oral epithelium. Sometimes a piece of embedded hair shaft was present within the inflammatory cell infiltrate.

Both the ulcer and chronic inflammation were considered to be incidental findings. Since neither of these was considered to be related to treatment and since there had been good agreement among the SP, QAP, and PWG chair, the PWG opted not to review any examples.

POST-PWG ACTION ITEMS

There were no post-PWG action items.

Micheal P. Jokinen, DVM — 8/5/99
Date
Diplomate, ACVP
PWG Chairperson

NATIONAL TOXICOLOGY PROGRAM

TR-501 p,p'-Dichlorophenyl Sulfone

Pathology Tables - Rats

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

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

P08 - Statistical Analysis of Primary Tumors

Pathology Tables - Mice

P03 - Incidence Rates of Non-Neoplastic Lesions

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

P08 - Statistical Analysis of Primary Tumors

B 07

TP Experiment-Test: 88120-03
Study Type: CHRONIC
Route: DOSED FEED

INCIDENCE RATES OF NONNEOPLASTIC LESIONS BY ANATOMIC SITE (a)
P,P'-DICHLORODIPHENYL SULFONE

Report: PEIRPT03
Date: 10/27/99
Time: 12:45:07

FINAL #1 CORE STUDY RATS

Facility: Battelle Columbus Laboratory

Chemical CAS #: 80-07-9

Lock Date: 08/11/98

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

R 09