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OFFICE OF
PESTICIDES AND TOXIC
SUBSTANCES

MEMORANDUM

SUBJECT: Review of Chronic/Oncogenicity Study of Diuron in the Diet Fed to Rats. Guideline 82-5

TO : Ms. Carol Peterson, PM-74
Registration Division (H7508C)

FROM: David S. Liem, Ph.D. David Liem 11/7/90
Section II, Toxicology Branch II/HED (H-7509C)

THROUGH: K. Clark Swentzel, Section Head K. Clark Swentzel 11/9/90
Section II, Toxicology Branch II/HED (H-7509C)
and
Marcia van Gemert, Branch Chief Marcia van Gemert 11/12/90
Section II, Toxicology Branch II/HED (H-7509C)

EPA RECORD No.: 268,431 IDENTIFYING No.: 0046

MRID No.: 408865-01 CASWELL No.: 410

Action Requested:

Review a Study on the Chronic/Carcinogenic Effects of Diuron Fed in the Diet of Wistar Rats submitted by E.I. Du Pont de Nemours & Co., Inc.

Conclusions:

Technical diuron administered in the diet of Wistar rats at 0, 25, 250, and 2500 ppm for 2 years produced the following effects.

From the results of the study as presented in the study report, the systematic NOEL cannot be determined. The LOEL was determined to be 25 ppm (lowest dose tested) based on increased spleen weight (including swelling and dark discoloration in the first year), increased hemosiderin deposit in the spleen, increased swelling of the liver and increased iron deposit in the liver during the first year, increased urinary bladder wall thickening in the males, and a significant increase in erythrogenic activities as indicated by an increase hematopoietic and a decrease of fat marrow surface areas of the bone marrow. Increased hematopoietic marrow and reticulocytes, and the decreased of fat marrow suggest an increase in erythrogenic activity of the bone marrow.

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Statistically significant body weight reduction was observed in the high (2500 ppm) dose group in both sexes and in the male mid (250 ppm) dose group, as compared to the control.

Increased incidences of urinary bladder wall thickening in the mid (250 ppm) and high (2500 ppm) dose, and urinary bladder and renal pelvis epithelial papillomas and carcinomas in the high (2500 ppm) dose groups were considered to be related to treatment.

The doses employed in this study were sufficient to produce a compound related effect and were also adequate to evaluate the carcinogenicity potential of the test material.

Because the systematic NOEL cannot be determined from data presented in the study report and because numerous discrepancies were noted (see study deficiencies on p. 21-22 of the attached DER), this study does not satisfy USEPA's guideline 83-5 requirements for a chronic toxicity/carcinogenicity study, and it is therefore classified as core supplementary data. Based on the results of this study, the carcinogenic potential of diuron was demonstrated at the 2500 ppm dose level (HDT).

Since a large number of discrepancies were noted in the study report, it is recommended that the testing facilities, Institute of Toxicology, Bayer AG, Wuppertal, Friedrich-Ebert-Strasse 217-333, West Germany and Institute of Experimental Pathology, Hanover Medical University, West Germany, be audited by USEPA.

CLASSIFICATION: Core-Supplementary. This study does not satisfy USEPA's guideline 83-5 requirements for a chronic toxicity/carcinogenicity study.

Primary Reviewer: David S. Liem, Ph.D. David Liem 11/7/90
Section II, Toxicology Branch II/HED
Secondary Reviewer: K. Clark Swentzel, Section Head K. Clark Swentzel 11/9/90
Section II, Toxicology Branch II/HED

DATA EVALUATION REPORT

Study Type: Oncogenicity Study Guideline 83-5

Test Animal: Wistar Rats

EPA Identification No.s: MRID (Accession) No.: 408865-01
Record No.: 268,431 Caswell No.:410
HED Project No.: 0-1839

Test Material: Diuron with a purity of 98.7%; batch No.23114080

Synonym: N'-(3.4-dichlorophenyl)-N,N-dimethyl urea

Dosages: 0, 25, 250, and 2500 ppm

Sponsor: Agricultural Products Department,
E.I. du Pont de Nemours & Co., Inc.

Study Number: Bayer AG T 8010647; Du Pont Report No. D/Tox 17

Study Period: September 1, 1981 to September 9, 1983
(In Life Study)

Testing Facilities: Institute of Toxicology, Bayer AG, Wuppertal,
Friedrich-Ebert-Strasse 217-333, West Germany
and
Institute of Experimental Pathology, Hanover
Medical University, West Germany

Title of Report: Diuron: Study for Chronic Toxicity and
Carcinogenicity with Wistar Rats (Administration
in diet for up to two years)

Author: Dr. W.M. Schmidt and Prof. Dr. U. Mohr

Report Issued: November 29, 1985

Conclusions:

Technical diuron administered in the diet of Wistar rats at 0, 25, 250, and 2500 ppm for 2 years produced the following effects.

From the results of the study as presented in the study report, the systematic NOEL cannot be determined. The LOEL was determined to be 25 ppm (lowest dose tested) based on increased spleen weight (including swelling and dark discoloration in the first year), increased hemosiderin deposit in the spleen, increased swelling of the liver, increased iron deposit in the liver during the first year, increased urinary bladder wall thickening in the males, and a significant increase in erythrogenic activities as indicated by an increase of hematopoietic and a decrease of fat marrow surface areas of the bone marrow. Increased hematopoietic marrow and reticulocytes, and decreased fat marrow suggest an increase in erythrogenic activity of the bone marrow.

Statistically significant body weight reduction was observed in the high (2500 ppm) dose group in both sexes and in the male mid (250 ppm) dose group, as compared to the control.

Increased incidences of urinary bladder wall thickening in the mid (250 ppm) and high dose (2500 ppm), and urinary bladder and renal pelvis epithelial papillomas and carcinomas in the high (2500 ppm) dose group were observed. Therefore, diuron appears to be carcinogenic in this study based on increased incidences of urinary bladder and renal pelvis epithelial papillomas and carcinomas in the high (2500 ppm) dose group.

The doses employed in this study were sufficient to produce a compound related effect and were also adequate to evaluate the carcinogenicity potential of the test material.

Because the systematic NOEL cannot be determined from data presented in the study report and because numerous discrepancies were noted (see study deficiencies on p. 21-22 of this DER), this study does not satisfy USEPA's guideline 83-5 requirements for a chronic toxicity/carcinogenicity study, and it is therefore classified as core supplementary data. Based on the results of this study, the carcinogenic potential of diuron was demonstrated at the 2500 ppm dose level (HDT).

Since a large number of discrepancies were noted in the study report, it is recommended that the testing facilities, Institute of Toxicology, Bayer AG, Wuppertal, Friedrich-Ebert-Strasse 217-333, West Germany and Institute of Experimental Pathology, Hanover Medical University, West Germany, be audited by USEPA.

CLASSIFICATION: Core-Supplementary. This study does not satisfy USEPA's guideline 83-5 requirements for a chronic toxicity/carcinogenicity study.

Study Title: Diuron: Study for Chronic Toxicity and Carcinogenicity with Wistar Rats (Administration in diet for up to two years)

Author: Dr. W.M. Schmidt and Prof. Dr. U. Mohr

Report Date: November 29, 1985

Study No.: Bayer AG T 8010647; Du Pont Report No. D/Tox 17

Testing Facility: Institute of Toxicology, Bayer AG, Wuppertal, Friedrich-Ebert-Strasse 217-333, West Germany
and
Institute of Experimental Pathology, Hanover Medical University, West Germany

Test Material: Diuron with a purity of 98.7%; batch No.23114080; N'-(3.4-dichlorophenyl)-N,N-dimethyl urea

Test Animal: Wistar Rats

1. OBJECTIVE

This study was designed to evaluate the oncogenicity potential of diuron following a lifetime dietary administration of technical diuron to Wistar rats.

2. MATERIALS AND METHODS

The in-life and necropsy phases of this study were conducted at the Institute of Toxicology, Bayer AG, Wuppertal, Friedrich-Ebert-Strasse 217-333, West Germany and the histopathologic phase was conducted at the Institute of Experimental Pathology, Hanover Medical University, West Germany.

The following account described below is a summary of the study materials and protocol:

Test Material: Physical Description: Not given; test article with a purity of 98.7%
Lot No.: 232114080 Compound ID #: Not given
Sources: Not given Storage: Not given

Test Animals: Species: SPF Rats; BPOR:WISW (SPF Cpb) Strain
Source: Winkelmann, Borchen (address not given)
Total Number: 325 males and 325 females
Age: About 6-7 weeks old at start of study
Mean Starting Weight: Males = 85 g; females = 84 g (ranges not provided)
Caging: In individual Makrolon cages with dust-free wood chips
Acclimation period: About 7 days
Feed: Altromin 1321 basal diet from Altromin GmbH, Lage & water were provided ad libitum. Feed was withheld prior to urine collection.

Environmental Parameter: Air temperature = 20°C; Relative Humidity = approximately 50%; 12 hours dark/light cycle (6:00 AM to 6:00 PM light); (temperatures and RH ranges were not provided)

Study Duration

The study was scheduled to terminate at the end of the 24 months of compound administration. Ten animals/sex from each group were necropsied after 12 months of compound administration. All surviving rats were terminated during month 24.

Group Arrangement

At the start of the study the rats were sorted into two weight groups, and randomly assigned to the study as follows:

Test Group	Dosage (ppm)	Main Males/Females	Satellite@ Males/Females
Control	0	50/50	10/10
Low Dose	25	50/50	10/10
Mid Dose	250	50/50	10/10
High Dose	2500	50/50	10/10

@ = All rats from satellite groups were sacrificed after 12 months on study

Diet Preparation

The diets containing diuron were prepared weekly. Concentration of the test material was not adjusted during the course of the study.

Diet Analyses

Prior to the study initiation, the homogeneity and stability of the compound in the diet were determined. The test material content in the diet was analyzed at the initiation of the study, and approximately every three months thereafter, throughout the study.

Clinical Observations

The rats were checked at least twice daily (once on weekends and on public holidays) for mortality, moribundity and signs of toxicity. Detailed physical examinations were conducted weekly.

Body Weights

Individual body weights were taken at the start of the study, prior to scheduled sacrifices, weekly through week 27, and every two weeks thereafter to termination.

Food Consumption

Group food consumption was recorded weekly.

Compound Intake

The test compound intakes were calculated from the food consumption values.

Clinical Pathology Evaluation

Blood samples were collected from the tail vein for glucose determination and from the orbital sinus (under anesthesia) of rats for other determinations. Bleeding was conducted at 6, 12, 18, and 24 months. It was not noted how rats were selected for these clinical pathological evaluations, and whether rats were fasted prior to blood collections.

a. Hematology

Hematology tests were conducted at 6, 12, 18, and 24 months. Parameters evaluated were hemoglobin concentration, mean cell volume (MCV), erythrocyte, leucocyte and thrombocyte counts, hematocrit: mean corpuscular hemoglobin (MCH) and mean corpuscular hemoglobin concentration (MCHC), and differential blood count from blood smears. Reticulocyte count was determined at 12 and 24 months, and the thromboplastin time was determined at 24 months.

b. Clinical Chemistry

Clinical chemistry tests were conducted at 6, 12, 18 and 24 months. At each interval, blood serum from the same rats selected for hematologic study were used. Parameters evaluated were as follows: alkaline phosphatase, blood urea nitrogen (BUN), alanine aminotransferase, aspartate aminotransferase, glucose, total protein, creatinine, bilirubin and cholesterol. The following parameters were not determined: lactic dehydrogenase, albumin, globulin, albumin/globulin (A/G) ratio, inorganic phosphate, calcium, sodium, potassium, chloride, and creatine phosphokinase.

c. Urinalysis

Urine was collected overnight from ten randomly selected rats of each sex/group at 6, 12, 18 and at termination of the study. At each interval, rats selected for hematologic and clinical chemistry evaluations were utilized for urinalysis. Parameters evaluated were occult blood, protein, bilirubin, pH, ketones, glucose, urobilinogen and microscopic examination of sediment.

The following parameters were not determined: color, volume, appearance, and specific gravity.

Ophthalmologic Examination

Rats on study were not subjected to ophthalmologic examination by a Veterinary ophthalmologist.

Gross Macroscopic Examinations

All rats which died or were sacrificed in extremis and all rats sacrificed at the scheduled necropsies were subjected to gross macroscopic examination. At twelve months, an interim necropsy of 10 animals of each sex in each group was conducted. Terminal necropsy of surviving high dose male rats was conducted at 24 months. Rats sacrificed at scheduled necropsy were anesthetized with ether, killed by exsanguination, and then necropsied. All moribund rats were also necropsied after they were killed by the same procedure described above.

Tissues harvested from all rats were fixed in 10% buffered formalin. The following tissues, all of which are required by EPA's subdivision F, guideline 83-5, were harvested:

- eyes
- brain
- pituitary gland
- thyroid/parathyroid
- salivary gland
- thymus
- cervical lymph nodes
- larynx
- trachea
- lung
- esophagus
- stomach
- duodenum
- jejunum
- ileum
- colon
- mesenteric lymph nodes
- liver
- spleen
- pancreas
- kidneys
- adrenal glands
- urinary bladder
- testes
- epididymides
- prostate gland
- seminal vesicles
- ovaries
- uterus
- vertebral column with spinal cord
- sternum
- femur with skeletal musculature and sciatic nerve
- all gross lesions

However, four other tissues (i.e. cecum, rectum, oviduct, skin and mammary gland) that are required for a chronic toxicity/carcinogenicity study were not routinely harvested and were not subjected to routine histopathological evaluations.

Organ Weights

The heart, lung, liver, spleen, kidneys, adrenals, and testes from all animals killed at the interim (12 months) and terminal necropsies were weighed. Ovaries and the brain as required for a chronic toxicity/carcinogenicity study were not weighed.

Histopathological Evaluation

The fixed tissues were trimmed, embedded in paraplast, sectioned, and stained with hematoxylin-eosin. In addition, kidney sections from interim sacrificed animals were stained with the periodic acid Schiff reaction (PAS); to reveal fat, frozen liver sections were stained with oil red O (ORO); and Prussian blue was used to demonstrate hemosiderin deposits in the lung, liver, spleen, and kidney tissues. The number of animals examined and the organs and tissues evaluated histopathologically are listed in the attached Appendix A (copied from p. 363-368 of the study report). The following tissues were not harvested and were not subjected to histopathological evaluations: cecum, rectum, skin, oviduct, and mammary glands.

In addition, Prussian blue stained tissue sections of the spleen and bone marrow (femur) were also subjected to morphometric evaluations, and automatic evaluation of the tissues using the image analysis system IBAS II (Zeis). Bones were decalcified in an ethylene diamine tetra-acetic acid solution (EDTA).

Statistical analysis

The arithmetic group means, standard deviations, upper and lower confidence limits ($P < 0.05$ and $P < 0.01$) were calculated. The combined values were tested and compared with combined control using the Mann and Whitney U test and Wilcoxon's method at $P < 0.05$ and $P < 0.01$.

Compliance Statements

- o A signed Statement of Confidentiality Claim was provided.
- o A signed Statement of compliance with EPA GLP's was provided.
- o A signed Quality Assurance Statement was provided.
- o The pathologist did not signed the pathology report.

RESULTS

a. Analyses of Test Article and Diet

Analysis of diet samples collected on the day of diet preparation indicated that the diets containing diuron for all dose levels at various intervals were prepared at or near the intended concentrations, i.e. between 92% and 107% of nominal. Based on the study report, the compound in the low (25 ppm) and high (2500 ppm) dose diet mixtures were stable for 9 days and recovery rates were between 102% to 123%. The homogeneity of test article in the diet analyzed at start of study was 85% and approximately 100% of theoreticals for the 25 ppm and 2500 ppm diets, respectively (see Appendix C).

b. Mortality

The cumulative mortality data of rats that died spontaneously or were sacrificed *in extremis* during the study and number of rats sacrificed at terminal necropsy are presented in the attached Appendix D. One control female, and one male and one female of the high dose groups died within the first four weeks of study. After week 88, mortality of the treated males was higher than the controls. Mortality among the females were comparable.

c. Clinical Signs Observations

The investigators stated that the only significant clinical sign was the reddish discolored urine observed in the high dose males after 12 months on study. The significance of this observation is unclear. The summary and individual clinical sign observation data were not presented in the study report.

d. Body weight data

The mean body weights are presented in Appendix E. As seen from this Appendix, consistent statistically significant reductions in body weights were observed in the male mid and high dose groups (starting from week 3) and in the female high dose group (starting from week 4) throughout the study as compared to the control. The calculated percent mean body weight difference between the high dose groups as compared to the controls was between -11.6% to -20.1% for the males and between -4.2% to -13.6% for the females. In the study report, the body weight data were illustrated in a graph (p. 20 of the study report), but it is not legible. Body weight reductions of the high dose group in both sexes and in the male mid dose group are judged to be related to treatment.

Body weight gains of animals were not calculated by the investigators nor were they discussed in the report. This

reviewer calculated the body weight gain group means at various intervals and these values are presented in Appendix F. As seen from this Appendix, body weight gain group mean reductions were observed primarily in the high dose groups at various intervals throughout the study. The overall body weight gain group mean values (BW at termination minus BW on week 0) for the high dose groups for both sexes were drastically reduced (18 % for the males and 23 % for the females). Since the food intake values were generally comparable among the groups throughout the study (see discussions below), they further support that the observed body weight gain reduction was related to treatment.

e. Food Consumption Data

Summary data of food intake per group and per animal/day are presented in the attached Appendix G. As seen from this Appendix, food consumption data are comparable among all dose groups. The investigators did not calculate the mean food intake efficiency (body weight gain divided by food consumed multiplied by 100) nor were they discussed in the study report.

f. Compound Intake

Summary mean food intakes and the calculated test compound intakes over the course of the study are as follows:

Food and Test Compound Intakes@

	Control (0 ppm)	Low Dose (25 ppm)	Mid Dose (250 ppm)	High Dose (2500 ppm)
Food Intake	M/F	M/F	M/F	M/F
Total Grams per Rat	11902/11362	11727/11117	11616/11055	11505/11922
Gm/Rat/Day	16/16	16/15	16/15	16/16
Test Compound Intake	M/F	M/F	M/F	M/F
Mg/Rat	0/0	293/278	2904/2764	28262/29405
Mg/Rat/Day	0/0	0.40/0.38	4.98/3.79	38.77/40.89
Mg/Kg/Day	0/0	1.02/1.69	10.46/16.88	111.17/202.22

@ = Extracted from Table 2, p. 21 of the study report

As seen from the above Table, food intake values were comparable among all dose groups. In the treated groups, the test compound intakes per day per rat were proportional to dose concentrations administered. Since food consumption values were comparable among all groups while the body weights of the high dose groups were lower as compared to the controls, test compound intake relative to body weight was proportionally higher, 20% for the males and 7% for the females.

g. Clinical Pathology

The results of hematological and clinical chemistry data at 6, 12, 18, 24 months are presented in the attached summary tables, Appendices H and I, respectively.

1. Hematology (see attached Appendix H)

The hematology measurements were conducted at 6, 12, 18, and 24 months. As seen from Appendix H, leucocyte counts were elevated in the high dose groups in both sexes and in the male mid dose group as compared to the control at 6, 12, and 24 months intervals. Most of these elevated values were slightly outside the normal ranges.

The mean erythrocyte count, hematocrit, and hemoglobin concentration in plasma (HCB) were statistically decreased in the mid and high dose groups in both sexes at most intervals tested except for erythrocyte counts and hematocrit in mid dose males at 12, 18, and 24 months, and hemoglobin concentrations in the mid dose males at 12 and 24 months. Mean corpuscular hemoglobin concentration (MCHC) was statistically decreased in the mid and high dose males and females at 6 and 18 months as compared to the controls. The mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and reticulocyte count (RETI) were elevated for the mid and high dose rats of both sexes as compared to the controls. Most of these values were outside their normal range. Evaluation of the red blood cell morphology at 6, 12, 18, and 24 month intervals showed higher incidences of abnormal erythrocyte forms in the high dose group in both sexes and to some extent in the mid dose group. Pathological forms observed included Jolly bodies, anisocytosis, polychromatosis, anulocytosis and Heinz bodies. The thrombocyte (THR) counts, thromboplastin times (TP), and differential blood counts were comparable among all groups at all intervals tested.

The elevated leucocyte counts, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and reticulocyte counts in the mid and high dose groups and the decreased erythrocyte count, hematocrit (HCT), and hemoglobin concentration in plasma (HCB) and mean corpuscular hemoglobin concentration (MCHC) as well as higher incidences of abnormal erythrocyte forms in the high dose groups as compared to the control, are considered to be related to treatment. All other scattered instances of statistically significant differences between the treated groups as compared to the control were judged to be artifactual and were not considered to be dose related.

2. Clinical Chemistry (see attached Appendix I)

Clinical chemistry parameters were conducted at 6, 12, 18 and 24 months. As seen from Appendix I, bilirubin was elevated in

the high dose groups at all intervals tested, but it was not statistically significant in the male high dose groups at 6, 12, and 18 months intervals, as compared to the control. The blood urea nitrogen was statistically elevated in the high dose group in both sexes (except female high dose group at 6 month interval), as compared to the control. Elevation of these two values is judged to be related to treatment. Other scattered instances of statistically significant differences between the treated groups as compared to the control are judged to be artifactual and are not related to treatment.

3. Urinalysis (p. 295-310)

Based on the data presented, a slight increased of occult blood in urine was noted in the high dose male at 12 and 24 month intervals and in the high dose females at 18 and 24 month intervals as compared to the control (p. 295-310 of study report). The toxicological significance of this observation is unclear. Quantitative determinations of protein (prot/u) in the urine did not reveal any treatment related effect at any interval. All other urinalysis parameters were comparable among the groups (p. 295-310 of the study report).

Gross Macroscopic Findings

All rats which died or were sacrificed in extremis or at scheduled necropsies were subjected to gross macroscopic examinations. The individual gross macroscopic data are presented in Appendix L of the study report (p. 633-1473), but the investigators failed to summarized these findings. This reviewer summarized pertinent gross macroscopic observation data from individual gross macroscopic data (p. 637-1473 of the study report) and they are presented on the next page. As seen from th t table, the following conclusions can be made:

a. 0 to 12 months

Increased incidences of spleen swelling (enlargement) and dark discoloration were observed in both sexes of the mid and high dose group as compared to the control. One incidence of spleen and liver swelling/discoloration was observed in one low dose female that was sacrificed in extremis (no. 235). Liver swelling and discoloration were observed in six high dose females. No urinary bladder wall thickening was observed in any animal in the first 12 months of the study.

b. 12 Months to Termination

Increased incidence of spleen swelling/discoloration was observed in both sexes of all treated dose groups as compared to the control (only 2 incidences in 2 female controls were noted). It is noted that this incidence increased in a dose related

fashion. As compared to the control, high incidence of urinary bladder wall thickening was observed in both sexes of the high dose group, but this observation was only observed in the males of the low and mid dose groups. Higher incidences of urinary bladder thickening were observed in the males than in the females. As compared to the control, increased incidence of liver swelling/discoloration was noted in male and female low dose, in the male mid dose, and in the female high dose groups.

Based on the data presented in the study report, increased incidences of spleen swelling/discoloration and urinary bladder wall thickening (at least in the males) are considered treatment related. This conclusion is supported by the organ weight and histopathological data (see discussions below). Based on gross macroscopic data, increased liver swelling/discoloration is judged to be equivocal. See further discussions under organ weight and histopathological evaluation below.

Pertinent Gross Macroscopic Findings@

	Control	Low Dose	Mid Dose	High Dose
Through 12 Months Interim Sacrifice	M/F	M/F	M/F	M/F
+ Total Number	10/10	10/11&	10/10	11&/11&
+ Spleen Swelling/ Discolorations	-/-	-/1^	3/4	11/11
+ Urinary Bladder Wall Thickening	-/-	-/-	-/-	-/-
+ Liver Swelling/ Discolorations	-/-	-/1^	-/-	-/6
After 12 Months Interim Sacrifice	M/F	M/F	M/F	M/F
+ Total Number	50/50$	50/49	50/50	49#/49
+ Spleen Swelling/ Discolorations	-/2	5/7	32/24	44/39
+ Urinary Bladder Wall Thickening	-/-	9/-	7/-	29/10
+ Liver Swelling/ Discolorations	12/7	28/17	30/6	9/21

@ = Extracted from Appendix L, p. 633-1473 of the study report, and the data included all found dead and moribund sacrificed rats; M/F = Males/ Females; # = one male rat autolyzed; $ = Two female rats autolyzed; ^ = Incidence observed in one female moribund sacrificed rat (no. 235); & = Including 1 moribund rat.

Organ Weights

Only the heart, lung, liver, spleen, paired kidneys, adrenal glands, and testes from all animals killed at the interim (12 months) and terminal necropsies were weighed. The brain and ovaries were not weighed. The absolute and relative organ weight data are summarized in the attached Appendix J.

a. 12 Months Interim Sacrifice (Appendix J, Table A)

The mean absolute and relative (to body weights) spleen weights in both sexes of all treated groups (except the female low dose group), as compared to the control were statistically significant. The absolute adrenal gland weights were statistically increased in the mid dose female and decreased in the high dose male groups. Other statistically significant increased mean relative organ weights observed were the heart and kidneys of the high dose males, and the lung in both sexes of the high dose groups, as compared to the controls.

b. 24 Months Terminal Sacrifice (Appendix J, Table B)

Except for the male low dose group, both the absolute and relative spleen weights in all treated groups in both sexes were statistically increased, as compared to the control. As compared to the controls, the absolute and relative liver weights were statistically increased in all treated females as well as the relative liver weights of the high dose males. Scattered statistically significant increases and/or decreases of absolute and relative organ weight values as compared to the control were observed in the following organs: heart, lung, kidneys, and testes.

Increased spleen weight in all treated groups in both sexes and increased liver weight of the female mid and high dose groups are judged to be related to treatment.

Histopathological Evaluation

Not all tissues harvested were subjected to histopathological evaluations. Some tissues of the low and mid dose groups (e.g. brain, lymph nodes, adrenal glands, thymus, skin, and some others) were not routinely subjected to histopathological evaluations at the 12 month interim sacrifice (p. 363-364). Tissues that were routinely evaluated were the lung, liver, spleen, bone marrow, kidney, renal pelvis, urinary bladder, ovaries, uterus, sternum, and femur. Cecum, rectum, skin, mammary glands, and oviduct were not routinely subjected to histopathological evaluations. Numerous entries in summary tables of the study report (p. 369-403) were left blank. In summary tables compiled by this reviewer (App. K-L), these discrepancies were noted as "ne" (=not evaluated) and "?" (status unknown).

a. Non-neoplastic Lesions

Incidences of pertinent non-neoplastic lesions are summarized in the attached Appendix K, Tables A and B. As seen from attached Appendix K, some tissues were not evaluated (indicated as "ne" or "?" on the Tables). At the 12 month interval, lung, liver, spleen and kidney tissues were stained with Prussian Blue to demonstrate the presence of iron deposit. After 12 months, except for the spleen, no other tissues were stained with Prussian blue, and no reasons were given in the study report. Thus incidences of iron deposits in the lung, liver and kidneys tissues during the second year can not be compared with the 12 month interval data.

In the first 12 months, incidences of positive iron staim in lung tissues were lower for the mid and high dose male groups as compared to the control; all other groups were comparable with the control. Second year data were not available.

Except for the male mid dose group, incidences of iron stain positive liver tissues of interim sacrificed rats were increased for all treated groups as compared to the control. Second year data were not available.

Iron stain positive kidney tissues of the 12 month interim sacrificed rats were increased in the male high (2500 ppm) dose group as compare to the control. Second year data were not available.

At 12 month interim sacrifice, spleen tissues of all rats were iron stain positive. Comparable high incidences of iron stain positive spleen tissues in all groups were also observed throughout the second year.

Increased hemosiderin storage in spleen tissues was only observed in all treated groups as compared to the control in the first 12 months of study. Based on morphometric evaluations, throughout the study, hemosiderin storage in the spleen was increased in all treated groups as compared to the control (see discussions on p 14-15 of this DER).

No spleen fibrosis was observed in any 12 month interim sacrificed rats. Fibrosis of the spleen was increased in the high dose group as compared to the control during the second year of study (see further discussions below under morphometric evaluations of the spleen).

Increased incidences of renal pelvis and urinary bladder epithelial hyperplasia were observed throughout the study in the mid (250 ppm) and the high (2500 ppm) dose groups as compared to the control.

For 12 month interim sacrificed rats, incidence of thyroid C cell hyperplasia was comparable between the high dose group (2500 ppm; and the control. Thyroid tissues of the low (25 ppm) and mid (250 ppm) dose groups were not evaluated by the investigators at the 12 month interim sacrifice. During the second year, thyroid C cell hyperplasia was increased in the mid (250 ppm) and high (2500 ppm) dose groups as compared to the control.

In the first 12 months, incidence of bone marrow activation was comparable among the groups. In the second year, increased incidence of bone marrow activation was observed in all treated groups as compared to the control (see further discussion below).

b. Morphometric Evaluations of the Spleen and Bone Marrow

In order to accurately quantify the iron-containing pigment deposits (hemosiderin) in the spleen, and hematopoietic activity of the bone marrow, morphometric evaluations were performed. The results of these evaluations are as follows:

Morphometric Evaluations of the Spleen and the Bone Marrow@

	Control (0 ppm) M/F	Low Dose (25 ppm) M/F	Mid Dose (250 ppm) M/F	High Dose (2500 ppm) M/F
Spleen[a]				
12 Months	11.66/17.79	13.16/17.94	15.14/33.14	12.97/28.92
24 Months	6.79/9.22	7.55/12.70	13.97/17.74	12.87/18.03
Bone Marrow[b] (hematopoietic)				
12 Months	38.67/45.16	41.55/43.96	45.07/58.09	ne /60.72
24 Months	56.83/50.39	57.43/51.33	60.96/71.08	81.38/81.26
Bone Marrow[c] (fat marrow)				
12 Months	33.55/29.19	31.94/29.70	22.98/11.28	ne /5.36
24 Months	ne / ne	ne / ne	ne / ne	ne / ne

@ = Extracted from Table 11 on p. 39, and Appendices K1-K3 on p.470-633; a = Percent surface area of hemosiderin; b = Percent surface area of hematopoietic (activated) bone marrow; c = Percent surface area of fat marrow; ne = not evaluated.

As seen from the Table presented on the previous page, based on morphometric evaluations, the quantity of hemosiderin deposit in the spleen was higher in the females as compared to the males at 12 and 24 months intervals. In general the quantity of hemosiderin deposits was higher in the treated groups in both sexes as compared to the control. The above data also showed a dose related trend. Based on conventional histopathological evaluation, increased hemosiderin storage in all treated groups was only observed during the first 12 months of study (see p. 14 of this DER and Appendix K, Tables A and B).

Except for the female low dose group at 12 month interval, the percent surface area of hematopoietic bone marrow was increased in all treated groups as compared to the control at both the 12 and 24 months intervals. This suggest an increased in hematopoietic activity of the bone marrow. These values increased with increasing dose.

At 12 month interval, the percent surface area of fat marrow in the mid and high dose groups of both sexes were drastically reduced as compared to the control. Reduction of fat marrow surface area was accompanied with the increase of hematopoietic bone marrow surface area. Morphometric evaluations of the fat marrow were not conducted by the registrant at 24 months interval.

Based on the above morphometric measurements, the increased hemosiderin quantity in the spleen, and the increase of hematopoietic surface areas together with the decrease fat marrow surface areas in the bone marrow, are considered to be related to treatment.

c. Neoplastic Lesions

Only one neoplastic lesion was observed in one 12 months interim sacrificed rat (ovarian granulosa cell tumor in the high dose female no. 427). Tumor incidences of all, except interim sacrificed rats, are summarized in a the attached Appendix L. As seen from this Appendix, the total number of tumor incidences (both benign and malignant) were greater in the high dose group as compared to the control. So were the total number of rats with tumors and the number of rats with malignant tumors only.

Since the Summary Tumor Incidence Table presented in Tables 13a-d (p. 44-47) and Tables 14-15 (p. 50-51) of the study report contained incomplete and/or inaccurate information (see explanations in the Study Deficiencies on p. 21-22 of this DER), this reviewer tabulated a new summary table of pertinent tumor incidences based on the individual tumor incidence table presented on p. 404-460 of the study report. Only pertinent neoplastic tumor incidences are presented in the attached Appendix M.

As seen from Appendix M, only tumor incidences in the renal pelvis (males only) and urinary bladder, and probably in the mammary gland, uterus, and the skin appear to be of toxicological importance.

Incidences of uterine adenocarcinoma in the high dose group were slightly increased (18%) as compared to the control (10%). Two incidences of endometrial sarcoma in the high dose group, and one incidence each of squamous cell carcinoma in the high and mid dose groups were observed. These incidences may be related to treatment.

Skin sarcoma was observed in two mid dose and one high dose males. Fibrosarcoma was observed in one low and in one high dose males. In addition, four incidences of mammary gland fibroadenoma and one incidence of adenocarcinoma were observed in the low dose females. Since only gross abnormal skin tissues were histopathologically evaluated, more neoplastic lesions may have been found in the treated groups if all skin tissues were routinely evaluated.

One incidence of papilloma and two incidences of carcinoma of the renal pelvis were observed in the high dose males. Since these neoplastic lesions in the renal pelvis are relatively rare and since these lesions are correlated with incidences of transitional epithelial carcinoma of the urinary bladder (see discussion below) and since a significant increased renal pelvis epithelial hyperplasia was also observed in the mid and the high dose groups (see p. 13 of this DER), incidences of papilloma and carcinomas in the renal pelvis, although low in number, are probably related to treatment.

Increased incidences of urinary bladder epithelial papilloma (6% in males and 4% in females) and carcinoma (67% in males and 22% in females) were observed in the high dose groups in both sexes as compared to the control. This increase is considered to be a dose related effect.

Historical control data for neoplastic ~~incidences~~ were not provided with the study report.

DISCUSSION

Administration of technical diuron at 25, 250, and 2500 ppm in the diet of Wistar rats for 24 months produced numerous compound related changes and they are summarized in Appendix B.

In the second year, a reddish urine color was observed in some rats of the high dose group (2500 ppm) and this was probably due to urothelial alterations of the renal pelvis and urinary bladder.

Statistically significant reduction in body weights was observed in the high dose group in both sexes as compared to the control. Body weight reduction was also noted in the mid dose groups at most intervals.

The calculated body weight gain group mean reductions were observed primarily in the high dose groups at various intervals throughout the study.

The mean individual food consumption over the entire study was comparable among all dose groups. In most cases food consumption per kg body weight was higher in the high dose (2500 ppm) group as compared to the control. Since the food intake values were generally comparable throughout the study, this further suggest that the body weight gain reduction was related to treatment.

The elevated leucocyte count, mean corpuscular volume (MCV), mean corpuscular hemoglobin (MCH), and reticulocyte count in the mid (250 ppm) and high dose (2500 ppm) groups and the decreased erythrocyte count, hematocrit (HCT), and hemoglobin concentration in plasma (HCB) and mean corpuscular hemoglobin concentration (MCHC) as well as higher incidences of abnormal erythrocyte forms in the high dose (2500 ppm) groups as compared to the control, all are considered to be related to treatment. The reduction of erythrocyte count, hematocrit (HCT), and hemoglobin concentration in plasma (HCB) and mean corpuscular hemoglobin concentration (MCHC) as well as higher incidences of abnormal erythrocyte forms suggest a condition of a non-progressive hemolytic anemia, and erythrocytes being the primary target. The elevated leucocyte count was in response to an increase hematopoiesis as well as an increase erythrocyte destructions. Elevated reticulocytes together with the increased hematopoietic marrow of the bone marrow suggest an increased erythrogenic activity.

Except for the male mid dose group, incidences of positive iron stain in the liver were higher for all treated groups as compared to the control.

Elevated blood urea nitrogen in the high dose (2500 ppm) group in both sexes is considered to be related to treatment and probably due to urothelial alteration or increased amino acid catabolism.

Macroscopically, increased spleen discoloration/swelling was observed in all treated groups as compared to the control. This observation was confirmed by the mean absolute and relative (to body weight) spleen weight data. Microscopically, increased fibrosis in the spleen observed in the male mid dose (250 ppm) group (6%), and in the male (37%) and female (34%) high dose (2500 ppm) groups was probably the result of chronic functional overburden due to erythrocyte destruction. Based on conventional

histopathological evaluations, increased hemosiderin storage in the spleen was observed in all treated groups as compared to the control during the first 12 months. Hemosiderin storage in the spleen was comparable among all groups during the second year. However, based on morphometric evaluations of the spleen, increased hemosiderin deposits were observed in all treated groups as compared to the control throughout the study. Hemosiderin and iron deposits in the spleen were observed in one high dose male at month 9 of study (June 9, 1982). Increased hematopoietic marrow surface area of the bone marrow and increased iron deposit in the liver and the kidneys as well as the spleen were probably a reflection of an increased red blood cell destruction which in turn evoked increased erythrogenic activities.

Macroscopically, urinary bladder wall thickening was observed in the males of the low (25 ppm) and mid (250 ppm) dose groups as well as in both sexes of the high (2500 ppm) dose group. Histopathologically, increased incidences of urinary bladder urothelial hyperplasia in the mid and high dose groups, and increased incidences of papillomas and carcinomas in the high dose group were noted as compared to the controls. These increased incidences are judged to be related to treatment.

In another feeding/carcinogenic study on rats conducted by Hodge (reviewed by this Agency, DER dated 2/7/89), showed slight anemia, enlarged spleens, increased erythrogenic activity in the bone marrow and abnormal pigments in the blood. The systematic NOEL was determined to be 25 ppm and the systematic LOEL was 125 ppm. There was no evidence of carcinogenicity effects up to the highest dose level tested at 2500 ppm.

CONCLUSIONS

From the results of the study as presented in the study report, the systematic NOEL cannot be determined. The LOEL was determined to be 25 ppm (lowest dose tested) based on increased spleen weight (including swelling and dark discoloration in the first year), increased hemosiderin deposit in the spleen, increased swelling of the liver, increased iron deposit in the liver during the first year, increased urinary bladder wall thickening in the males, and a significant increase in erythrogenic activities as indicated by an increase of hematopoietic and a decrease of fat marrow surface areas of the bone marrow. Increased hematopoietic marrow and reticulocytes, and decreased fat marrow suggest an increase in erythrogenic activity of the bone marrow.

Statistically significant body weight reduction was observed in the high (2500 ppm) dose group in both sexes and in the male mid (25 ppm) dose group, as compared to the control.

Increased incidences of urinary bladder wall thickening in the mid (250 ppm) and high dose (2500 ppm), and urinary bladder and renal pelvis epithelial papillomas and carcinomas in the high (2500 ppm) dose group were observed. Therefore, diuron appears to be carcinogenic based on increased incidences of urinary bladder and renal pelvis epithelial papillomas and carcinomas in the high (2500 ppm) dose group.

The doses employed in this study were sufficient to produce a compound related effect and were also adequate to evaluate the carcinogenicity potential of the test material.

Because the systematic NOEL cannot be determined from data presented in the study report and because numerous discrepancies were noted (see study deficiencies on p. 21-22 of this DER), this study does not satisfy USEPA's guideline 83-5 requirements for a chronic toxicity/carcinogenicity study, and it is therefore classified as core supplementary data. Based on the results of this study, the carcinogenic potential of diuron was demonstrated at the 2500 ppm dose level.

Since a large number of discrepancies were noted in the study report, it is recommended that the testing facilities, Institute of Toxicology, Bayer AG, Wuppertal, Friedrich-Ebert-Strasse 217-333, West Germany and Institute of Experimental Pathology, Hanover Medical University, West Germany, be audited by USEPA.

CLASSIFICATION: Core-Supplementary. This study does not satisfy USEPA's guideline 83-5 requirements for a chronic toxicity/carcinogenicity study.

STUDY DEFICIENCIES:

- The study report is an English translation of the original German language version. This study report is not well written and is difficult to read. Some technical terms used in this study report are not quite accurate or are not commonly used in a toxicological report.
- Pathology report was not signed by the pathologists.
- Physical properties, source, and storage conditions of test article were not given in the study report.
- Ranges of animal room temperatures and relative humidities readings were not provided in the study report. Data of fresh air exchanges in animals rooms was not presented
- Address of the source of test animals was not given.
- The following clinical chemistry parameters were not determined: lactic dehydrogenase, albumin, globulin, albumin/globulin (A/G) ratio, inorganic phosphate, calcium, sodium, potassium, chloride, and creatine phosphokinase.
- The following urinalysis parameters were not determined: color, volume, appearance, and specific gravity.
- No summary nor individual clinical sign observation data were presented in the study report.
- Body weight curves presented in Fig. 1, p. 20 of the study report were not legible.
- Body weight gains were not presented in the study report.
- The mean food intake efficiency data (body weight gain divided by food consumed multiplied by 100) were not calculated nor were they discussed in the report.
- Reticulocyte counts for 6 and 18 months intervals were not determined.
- Pertinent gross macroscopic observations were not tabulated in a summary table.
- The following tissues were not harvested and thus were not subjected to histopathological evaluations: cecum, rectum, skin, mammary glands, and oviduct. Brain and ovaries were not weighed.

- At 12 month interim sacrifice only the following tissues of the low and mid dose groups were subjected to histopathological evaluations: lung, liver, spleen, bone marrow, kidney, renal pelvis, urinary bladder, ovaries, uterus, sternum, and femur. Some tissues (e.g. brain, lymph nodes, adrenal gland, thymus, and other) were not subjected to histopathological evaluations for the low and mid dose groups at the 12 month interim sacrifice. It is of great concern that the thyroid gland of the low and mid dose groups were not evaluated at 12 month interval, because increased incidence of thyroid C-Cell hyperplasia occurred at 24 month interval (see Appendix K of this DER). On p. 4 of the study report the investigator noted that all organ and tissues from all animals were subjected to macroscopical and histopathological evaluations. No explanation was presented in the study report.

- Numerous entries were left blank in the non-neoplastic histopathological summary table (p. 369-376 and p. 389-403). No explanations were given.

- It was noted that kidneys of 10 rats were histopathologically evaluated for the control male group at 12 Month Interim Sacrifice (p. 364 of study report), however only 9 rat kidneys were evaluated. Histopathological evaluation of kidney tissues of one control male no. 7 (see p. 643 of study report) was not reported. No explanation was given.

- Although iron staining results for the spleen, lung, liver and kidney were presented in the individual microscopic findings tables (p. of the study report), they were not summarized in the summary table on p. of the study report. The registrant must provide this information so that comparison can be made with the result of 12 month interim sacrifice data.

- Morphometric evaluations of percent surface area fat marrow of the bone marrow were not conducted at the 24 months interval

- Discrepancies were noted in Tables 13 of the study report. In Table 13a on p. 40, it was noted that one incidence of hemangioendothelioma of the blood system (lymph node?) occurred in the female mid dose group, but none was recorded in the individual incidence table on p. 450-451 of the study report.

- It was noted in Table 13c on p. 46 of the study report that no neoplastic lesions were found in the blood forming system (lymph node?). However in the individual incidence table on p. 444-460 of the study report, two neoplastic incidences in the mesenteric lymph nodes were noted, an adenocarcinoma in the female mid dose and a carcinoma in the female low dose groups.

APPENDICES

APPENDIX A: The Number of Animals and the Number and Types of Organs that Were Subjected to Histopathclogical Evaluations (copied from p. 363-368 of the study report).

APPENDIX B: Summary of Treatment Related Observations

APPENDIX C: Summary Diet Analysis Results (derived from p. 65-66 of the study report)

APPENDIX D: Cumulative Mortality for Rats on Study (copied from p. 19 of the study report)

APPENDIX E: Summary Mean Body Weights at Selected Intervals (derived from p. 75-86 of the study report)

APPENDIX F: Calculated Body Weight Gain Group Mean Values (Derived from Summary Mean Body Weight Values on p. 75-86 of the study report)

Appendix G: Summary Food Intake per Animal/Day (derived from p. 67-74 of the study report)

APPENDIX H: Hematology Data

Table A: Summary of Pertinent Hematology Data (derived form p. 24-27 of the study report)

Table B: Reference Values of Some Hematological Parameters (copied from p. 58 of report)

APPENDIX I: Clinical Chemistry Data

Table A: Summary of Pertinent Clinical Chemistry Data (derived from p. 29-30 of the study report)

Table B: Reference Values of Some Clinical Chemistry Parameters (copied from p. 59 of report)

APPENDIX J: Summary of Absolute and Relative Organ Weights Data (copied from p. 33-34 of the study report)

APPENDIX K: Summary of Selected Histopathological Findings of Non-neoplastic Lesions.

Table A: At Twelve Month Interim Sacrifice (extracted from p. 369-376 of study report)

Table B: Terminal Sacrifice and Rats that Died Spontaneously or Sacrificed <u>in extremis</u>. (extracted from p. 389-403 of study report)

Diuron

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____ Identity of product impurities.

____ Description of the product manufacturing process.

____ Description of quality control procedures.

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APPENDIX B

SUMMARY OF TREATMENT RELATED OBSERVATIONS

Reddish urine		2500 ppm
Decreased Body Weight		2500 ppm
Hematology		
Depressed:		
Hematocrit (HCT)		250, 2500 ppm
Erythrocyte Count	25(f),	250, 2500 ppm
Hemoglobin Conc. (HCB)		250, 2500 ppm
Mean Corp. Hem. Conc. (MCHC)		250, 2500 ppm
Elevated:		
Leucocyte count (WBC)		250, 2500 ppm
Mean Corpuscular volume (MCV)		250, 2500 ppm
Mean Corpuscular Hem. (MCH)		250, 2500 ppm
Reticulocyte count (RETI)		250, 2500 ppm
Abnormal erythrocytes		250, 2500 ppm
Clinical Chemistry		
Blood urea nitrogen elevated		2500 ppm
Bilirubin elevated		2500 ppm
Spleen: Fibrosis		2500 ppm in 2nd year
Hemosiderin storage increased	25,	250, 2500 ppm
Swelling/black discolorations		250, 2500 ppm
Weight increase	25,	250, 2500 ppm in 2nd year
Bone Marrow: Activation	25,	250, 2500 ppm
Hematopoietic marrow elevated	25,	250, 2500 ppm
Fat marrow decreased	25,	250, 2500 ppm in 1st year
Liver: Swelling	25,	250(m), 2500(f) ppm
Weight increased		250(f), 2500(f) ppm
Iron positive	25,	250, 2500 ppm in 1st year
Kidney: Iron positive		2500 ppm
Thyroid C Cell Hyperplasia		250, 2500 ppm in 2nd year
Uterine Adenocarcinoma		2500 ppm
Urinary Bladder: Wall thickened	25(m),	250(m), 2500 ppm
Hyperplasia		250, 2500 ppm
Papilloma/Carcinoma		2500 ppm
Renal pelvis: Hyperplasia		250, 2500 ppm
Papilloma/carcinoma		2500 ppm

APPENDIX C

Summary Diet Analysis Results@

	Low Dose 25 ppm	Mid Dose 250 ppm	High Dose 2500 ppm
Compound Concentration (% of theoreticals)			
August 1981	95	107	89
November 1981	96	96	90
March 1982	99	100	101
June 1982	125	115	108
August 1982	108	102	95
November 1982	94	104	101
March 1983	103	100	102
May 1983	92	93	97
August 1983	96	105	102
Homogeneity (3 samples) (% of theoreticals)			
Sample 1	85	ne	100
Sample 2	86	ne	99
Sample 3	85	ne	100
Stability[a] (% of theoreticals)			
Day 0	104	ne	102
Day 1	114	ne	123
Day 7	110	ne	112
Day 9	102	ne	111

@ = Derived from p. 65-66 of the study report); a = stored at room temperature;

Diuron

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APPENDIX E

Summary Mean Body Weights (g) at Selected Intervals@

Week	Control 0 ppm M/F	Low Dose 25 ppm M/F	Mid Dose 250 ppm M/F	High Dose 2500 ppm M/F
1	114/103	115/103	112/107	104/98**
2	128/113	134*/115	133/116	124**/111
3	169/123	178*/127	149**/131	145**/124
4	202/141	202/142	160**/144*	156**/135**
5	227/143	231/143	170**/146	165**/136*
6	250/148	246/151	213**/151	198**/145*
7	264/157	268/158	238**/161	220**/154
8	272/151	279/163	253**/166	234**/156*
10	290/176	299/178	273**/173	246**/162**
12	314/182	318/185	294**/187	266**/171**
16	338/189	341/191	321**/192	292**/179**
20	350/194	353/198	329**/196	306**/178**
26	364/206	364/209	346**/208	318**/192**
31	368/210	372/215	355*/212	327**/195**
39	381/218	386/220	367*/219	336**/197**
51	397/219	396/223	381**/218	351**/196**
67	414/235	409/239	395**/237	357**/211**
73	419/240	412/245	400*/242	359**/212**
81	429/244	415/249	404**/249	360**/215**
89	420/245	415/252	403*/249	361**/216**
95	420/245	411/254	401*/252	361**/213**
103	418/247	415/260	401*/257	357**/215**

@ = Derived from p. 75-86 of the study report); * = P < 0.05;
** = P < 0.001

APPENDIX F
Calculated Body Weight Gain Group Mean Values
(Derived from Summary Mean Body Weight Values,
p. 75-86 of the study report)

Body Weight Gain Group Means in Grams (Males/Females)@

Interval (Weeks)	Dosages			
	Control M/F	Low M/F	Low-mid M/F	High Dose M/F
0-2	42/27	49/33	48/24	39/27
2-5	99/30	97/28	27/28	41/27
5-10	63/33	68/35	103/27	84/24
10-16	48/13	42/13	48/19	43/17
16-20	12/5	12/7	8/4	14/-1
20-26	14/12	11/11	17/12	12/11
26-39	17/12	18/10	16/10	18/5
39-51	16/1	10/3	14/-1	16/-1
51-67	17/16	15/16	14/19	6/15
67-81	15/9	6/10	9/12	3/4
81-95	-9/1	-8/5	-3/3	-1/-2
95-103	-2/2	5/6	0/5	-4/2
0-2	42/27	49/33	48/24	39/27
0-14	242/106	245/111	224/108	195/93
0-26	276/122	275/128	261/125	233/108
0-51	311/135	309/141	296/132	266/122
0-81	343/160	324/167	319/165	275/131
0-95	336/161	326/172	316/168	276/127
0-103	332/163	329/178	316/173	272/125

@ = Derived from Summary Mean Body Weight Values on p. 75-86 of the study report

APPENDIX G

Summary Food Intake per Animal/Day (g) at Selected Intervals@

Week	Control 0 ppm M/F	Low Dose 25 ppm M/F	Mid Dose 250 ppm M/F	High Dose 2500 ppm M/F
1	14.0/12.8	13.9/12.8	12.1/13.0	13.5/12.2
2	13.6/12.7	15.0/12.7	13.9/12.7	13.9/12.8
3	17.0/13.1	17.3/13.7	14.7/15.0	14.7/14.8
4	17.8/14.9	18.8/14.8	15.2/14.6	15.1/15.1
5	19.1/14.1	19.2/14.1	15.3/14.6	16.9/14.9
6	19.4/14.8	19.2/15.4	17.0/15.0	14.3/14.8
7	18.5/15.1	19.8/15.6	19.6/15.7	16.2/15.8
8	18.9/14.9	18.9/15.0	18.5/14.9	17.4/15.3
10	17.5/18.1	18.3/17.3	17.6/15.7	15.7/15.5
12	12.5/16.0	16.1/14.5	17.6/15.9	17.4/15.8
16	18.3/16.4	17.4/15.7	17.5/15.0	15.9/16.9
20	16.3/13.2	17.2/12.8	16.6/13.3	20.8/14.3
26	16.3/15.1	15.9/14.2	16.5/13.5	15.1/14.3
31	17.2/14.8	16.8/14.2	17.0/14.5	16.4/15.5
39	15.8/15.2	15.4/14.2	15.4/15.1	14.5/17.2
51	15.6/13.7	15.0/13.5	14.9/13.0	15.1/14.8
67	16.3/16.2	15.4/15.7	16.1/15.6	15.9/16.5
73	16.0/16.3	15.3/16.2	15.4/15.2	15.1/17.0
81	16.9/16.0	16.4/15.6	16.4/15.6	16.2/16.7
89	16.0/16.2	15.9/15.7	16.1/14.6	15.5/16.2
95	16.1/16.1	15.3/15.9	16.0/14.7	16.2/18.7
103	15.6/18.2	14.8/17.3	14.6/17.4	14.5/17.9

@ = Derived from p. 67-74 of the study report;

APPENDIX H
Table A
Summary of Pertinent Hematology Data@

	Control 0 ppm M/F	Low Dose 25 ppm M/F	Mid Dose 250 ppm M/F	High Dose 2500 ppm M/F
Leucocyte(Giga/L)				
Month 6	8.9/7.2	9.2/6.7	10.2*/11.1**	11.1**/11.1**
Month 12	8.9/7.9	8.0/9.0	8.3/7.5	11.7**/12.8**
Month 18	7.0/6.4	7.6/5.9	7.6/7.1	10.3**/14.0**
Month 24	6.7/7.3	6.1/7.3	8.6**/6.1	11.3**/13.4**
Erythrocyte(Tera/L)				
Month 6	8.3/7.8	8.3/7.4*	7.5**/6.5**	6.4**/5.9**
Month 12	8.9/7.9	8.6/6.9**	8.7/6.7**	7.1**/6.0**
Month 18	8.4/7.8	8.2/7.2*	8.0/6.6**	7.0**/6.0**
Month 24	8.2/7.7	8.1/6.9*	8.0/6.4**	6.8**/6.0**
Hemoglobin(Gram/L)				
Month 6	158/151	160/147	146**/133**	140**/131**
Month 12	163/152	164/140**	165/140**	152**/137**
Month 18	156/150	153/164	149*/139**	144**/132**
Month 24	155/155	158/144	151/141**	143*/138**
MCV (FL)				
Month 6	58/64	60*/66	61/70**	70**/75**
Month 12	57/61	59*/64*	58/67**	67**/72**
Month 18	61/60	62/64*	63/68**	70**/70**
Month 24	57/59	58/63*	59/65**	65**/67**
Reticulocyte(0/00)				
Month 6	ne/ne	ne/ne	ne/ne	ne/ne
Month 12	16/17	19/38	24*/32**	41**/66**
Month 18	ne/ne	ne/ne	ne/ne	ne/ne
Month 24	17/17	22/23	21/30**	72**/62**
Hematocrit(L/L)				
Month 6	0.49/0.50	0.50/0.49	0.45*/0.46**	0.45**/0.45**
Month 12	0.51/0.48	0.50/0.44**	0.50/0.45**	0.48**/0.43**
Month 18	0.51/0.47	0.51/0.46	0.50/0.45*	0.48*/0.41**
Month 24	0.47/0.45	0.47/0.43	0.46/0.42**	0.44/0.40**
MCH (PG/E)				
Month 6	18.9/19.2	19.2/20.0	19.6/20.6**	21.9**/22.1**
Month 12	18.4/19.1	19.0*/20.4*	18.9/21.0**	21.1**/22.9**
Month 18	18.5/19.3	18.7/20.1*	18.6/21.0**	20.7**/22.1**
Month 24	18.8/20.2	19.5/21.2*	19.1/22.1**	20.9**/23.2**
MCHC (Giga/L)				
Month 6	324/302	321/300	323*/292**	312**/293**
Month 12	322/316	326/318	326/315	317/319
Month 18	305/320	302/314*	297**/310*	297*/317
Month 24	332/344	336/336*	326/338	325/346

@ = Derived form p. 24-27 of the study report; * = $P < 0.05$; ** = $P < 0.01$; ne = not evaluated; Giga/L = 10^{9};L/L = Liter/Liter PG/E = Picogram(10^{-12} gram)/Erythrocyte; Tera/L = 10^{12}/Liter; Ft = Femtoliter(10^{-12} liter); ;; MCV = Mean Corpuscular Volume; MCH = Mean Corpuscular Hemoglobin; MCHC = Mean Corpuscular Hemoglobin Concentration.

Diuron

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____ Sales or other commercial/financial information.

____ A draft product label.

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APPENDIX I

Table A

Summary of Pertinent Clinical Chemistry Data@

	Control 0 ppm M/F	Low Dose 25 ppm M/F	Mid Dose 250 ppm M/F	High Dose 2500 ppm M/F
Alk. Phosphatase[a]				
Month 6	195/161	191/132*	173/136	178/159
Month 12	206/168	233/136**	188/151	197/160
Month 18	178/152	175/117	161/124	175/174
Month 24	187/165	170/138	154/140	188/166
Aspartate Amino.[a]				
Month 6	39.5/41.8	41.4/55.6	40.3/37.0	35.0/40.7
Month 12	43.6/64.6	46.7/55.4	39.1/83.0	39.2*/47.0
Month 18	59.0/63.1	53.2/61.7	48.9/56.9	39.7**/46.4
Month 24	36.0/75.3	37.3/49.6*	35.4/58.2	37.8/43.2**
Alanine Amino.[a]				
Month 6	48.3/48.7	49.1/49.9	44.5/45.5	42.7/46.5
Month 12	53.6/61.3	63.0/56.8	49.6/65.9	47.5/55.2
Month 18	53.7/55.9	53.6/52.3	48.9/53.2	38.7**/53.9
Month 24	46.1/61.3	45.0/48.1	41.7/48.9	39.4/52.1
Bilirubin[b]				
Month 6	3.4/2.7	3.3/2.7	3.1/2.9	3.6/4.0**
Month 12	2.5/4.3	3.0/2.8	2.9/3.5	3.1/4.1
Month 18	4.2/4.0	4.4/4.4	3.8/4.4	4.4/5.6**
Month 24	2.8/3.3	2.6/3.2	3.0/2.6*	4.2**/4.6**
Blood Urea Nitrogen[c]				
Month 6	6.2/7.4	6.8/6.7	7.0*/7.0	8.1**/7.5
Month 12	6.4/7.4	7.2/8.0	7.3*/8.3	8.2**/10.3**
Month 18	6.9/7.5	7.1/8.3	7.1/8.1	11.2**/9.5**
Month 24	5.7/6.9	5.9/7.1	6.4/7.7*	7.7**/8.5**
Creatinine[b]				
Month 6	59/57	68/49	59/70	55/55
Month 12	63/54	56/59	57/75**	58/61**
Month 18	62/58	59/62	54/71*	78/70**
Month 24	55/62	57*/62	64*/55	60/57
Glucose[c]				
Month 6	5.4/5.4	5.5/5.4	5.4/5.8*	5.4/5.5
Month 12	5.1/4.8	5.1/4.8	5.2/4.8	4.9/4.3*
Month 18	5.0/4.8	5.3/4.5	5.2/4.8	5.0/4.5
Month 24	5.6/5.2	5.7/4.8	5.6/4.7	4.8*/5.0
Protein[d]				
Month 6	64.5/60.0	67.1/62.4	64.4/60.6	63.7/56.9*
Month 12	64.7/65.4	67.0/68.7	65.1/68.3	62.7/66.8
Month 18	71.3/68.5	72.4/68.2	69.8/66.8	67.8**/65.1*
Month 24	69.0/71.1	68.9/69.7	69.3/71.7	65.0/71.0

@ = Derived from p. 29-30 of the study report; a = U/L, b = Micromole/Liter; c = Millimole/Liter; d = Gram/Liter; Alk. = Alkaline; Amino. = Aminotransferase;

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APPENDIX J

Table A

Mean Absolute and Relative Organ Weights at 12 Months@

	Control M/F	Low Dose M/F	Mid Dose M/F	High Dose M/F
Rat BW (g)	384/211	393/220	373/210	355/190**
Absolute Weight (g)				
Heart	1.06/0.71	1.14/0.74	1.08/0.69	1.04/0.66
Lung	1.30/0.94	1.36/0.93	1.32/0.95	1.39/0.95
Liver	13.37/7.56	14.12/8.65	12.98/7.70	13.40/7.97
Spleen	0.60/0.41	0.72**/0.46	0.71**/0.63**	1.33**/1.17**
Kidneys	2.22/1.53	2.41/1.53	2.21/1.56	2.30/1.43
Adrenal Glands	0.04/0.04	0.04/0.06*	0.03/0.06	0.03*/0.05
Testes	3.66/ na	3.86/na	3.75/na	3.67/na
Relative Weight to Body Weight (mg/g)				
Heart	2.74/3.35	2.92/3.37	2.88/3.29	2.94*/3.47
Lung	3.39/4.45	3.48/4.26	3.53/4.52	3.93**/5.00*
Liver	3.48/3.67	3.60/3.96	3.48/3.65	3.77/4.21**
Spleen	1.55/1.92	1.85**/2.12	1.90**/3.00**	3.75**/6.15**
Kidneys	5.77/7.26	6.14/7.54	5.93/7.45	6.46**/7.57
Adrenal Glands	0.10/0.26	0.09/0.29	0.09/0.28	0.09/0.25
Testes	9.57/na	0.99/na	1.01/na	1.03/na

@ = Extracted from Table 9 on p. 33 of the report and values were rounded off; BW = Body Weight; M/F = Males/Females; na = not applicable; * = $p < 0.05$; ** = $P < 0.01$.

APPENDIX J (continued)

Table B

Mean Absolute and Relative Organ Weights at 24 Months@

	Control M/F	Low Dose M/F	Mid Dose M/F	High Dose M/F
Rat BW (g)	421/249	418/256	401*/257	354**/220**
Absolute Weight (g)				
Heart	1.18/0.93	1.20/0.96	1.18/0.92	1.10*/0.79**
Lung	1.60/1.08	1.55/1.23**	1.44**/1.15**	1.58/1.10
Liver	15.01/8.28	14.88/9.93**	15.35/9.23**	14.51/9.85**
Spleen	0.79/0.49	0.84/0.72**	0.88**/0.80**	1.51**/1.27**
Kidneys	2.72/1.84	2.73/1.89	2.58*/1.80	2.72/1.69**
Adrenal Glands	0.05/0.06	0.04*/0.07	0.05/0.06	0.04/0.05*
Testes	3.94/ na	3.92/na	3.75/na	3.91/na
Relative Weight to Body Weight (mg/g)				
Heart	2.82/3.75	2.86/3.77	2.95**/3.59	3.13**/3.58
Lung	3.82/4.40	3.72/4.83*	3.62/4.52	4.52**/5.00*
Liver	3.58/3.35	3.60/3.90**	3.81**/3.59**	4.10**/4.49**
Spleen	1.88/2.00	2.01/2.77**	2.18**/3.11**	4.27**/5.70**
Kidneys	6.49/7.44	6.55/7.44	6.46/7.05*	7.72**/7.71
Adrenal Glands	0.12/0.26	0.10/0.26	0.12/0.25	0.12**/0.24
Testes	9.37/na	0.37/na	9.35/na	11.06**/na

@ = Extracted from Table 10 on p. 34 of the report and values were rounded off; BW = Body Weight; M/F = Males/Females; na = not applicable; * = $p < 0.05$; ** = $P < 0.01$.

APPENDIX K
Table A

Pertinent Non-neoplastic Lesions at 12 Month Interim Sacrifice@

	Control M/F	Low Dose M/F	Mid Dose M/F	High Dose M/F
# of Animals	10/10	10/10	10/10	10/10
Lung				
+ Iron Stain (+)	8/10	8/9	3/9	1/7
+ Macrophage foci/Granuloma	?/0	?/0	?/1	?/0
Liver				
+ Iron Stain (+)	5/5	8/7	0/10	10/10
+ ORO Stain (+)	10/7	10/9	10/10	10/9
+ Bile Duct Proliferation	3/ne	2/ne	0/ne	2/ne
+ Round Cell Infiltration	2/1	1/0	1/0	2/1
Spleen				
+ Iron Stain (+)	10/10	10/10	10/10	10/10
+ Hemosiderin Storage	0/3	10/10	9/10	10/10
+ Fibrosis	-/-	-/-	-/-	-/-
Kidney				
+ Iron Stain (+)	3#/5	5/9	4/6	9/6
+ PAS Stain (+)	1/0	0/3	0/0	3/0
+ Cortical Scars	?/?	?/?	?/?	?/?
+ Round Cell Infiltration	?/?	?/?	?/?	?/3
Renal Pelvis				
+ Focal Hyperplasia Epithelium 1-3	5/1	4/3	6/4	10/4
Urinary Bladder				
+ Urothelial Hyperplasia^	4/0	5/3	5/5	10/9
Thyroid				
+ C-Cell Hyperplasia	4/3	ne/ne	ne/ne	4/1
Bone Marrow Activation	0/1	0/0	0/0	1/0

@ = Extracted from p.369-376 of study report; # = one rat was not evaluated; ne = not evaluated; ? = Not indicated in Summary Incidence Table on p. 369-376 of the study report; ^ = Including Papillary urothelial hyperplasia.

APPENDIX K
Table B

Pertinent Non-neoplastic Lesions Observed in Spontaneously Dead, and Moribund and Terminal Sacrificed Animals@

	Control M/F	Low Dose M/F	Mid Dose M/F	High Dose M/F
Lung (# of Rats)	50/48	50/50	50/50	49/50
+ Iron Stain (+)	?/?	?/?	?/?	?/?
+ Macrophage foci/Granuloma	3/7	3/5	1/14	7/12
Liver (# of Rats)	50/48	50/50	50/50	50/50
+ Iron Stain (+)	?/?	?/?	?/?	?/?
+ ORO Stain (+)	?/?	?/?	?/?	?/?
+ Bile Duct Proliferation	40/16	37/10	27/15	34/25
+ Round Cell Infiltration	15/4	10/9	9/10	17/13
Spleen (# of Rats)	50/48	50/50	50/50	49/50
+ Iron Stain (+[a])	47[b]/48[b]	50/45[b]	48/49[b]	48[b]/46
+ Hemosiderin Storage[a]	49/44[b]	45/46	47/50	46[b]/47[c]
+ Fibrosis	-/-	-/-	3/-	16d/17
Kidney (# of Rats)	50/48	50/50	50/50	49/50
+ Iron Stain (+)	?/?	?/?	?/?	?/?
+ PAS Stain (+)	?/?	?/?	?/?	?/?
+ Cortical Scars	19/6	27/8	28/6	27/8
+ Round Cell Infiltration	3/1	12/3	9/2	31/7
Renal Pelvis (# of Rats)	50/48	50/50	50/50	50/47
+ Focal Hyperplasia Epithelium 1-3	37/23	37/25	45/46	43/42
Urinary Bladder + Urothelial Hyperplasia^	13/11	5/7	16/17	15/30
Thyroid (# of Rats)	50/47	48/49	50/50	49/48
+ C-Cell Hyperplasia	29/17	27/23	37/30	39/28
Bone Marrow Activation	0/5	5/12	7/22	42/42

@ = Derived from p. 389-403 and p. 635-1472 of study report; ? = Was left blank in Summary Table of study report; a = Tabulated by this reviewer from individual incidence data; b = One rat was not evaluated; c = Was 47 based on individual incidence data and not 49 as reported on p. 400 of study report; d = Was 16 based on individual incidence data and not 18 as reported on p. 392 of the study report; ^ = Including papillary urothelial hyperplasia.

APPENDIX L

Tumor Incidences Excluding Interim Sacrifice Rats@

	Control M/F	Low Dose M/F	Mid Dose M/F	High Dose M/F
Total Rats	50/48$	50/50	50/50	49&/50
Total Tumors	21/31	12/20	19/31	57/39
+ Benign	18/23	12/20	11/19	18/19
+ Malignant	3/8	4/11	8/12	39/29
# of Rats with Tumors	19/26	14/27	16/22	41/29
# of Rats With Multiple Tumors	2/4	2/4	3/7	13/9
# of Rats with + Benign Tumors Only	17/18	10/16	8/10	4/4
+ Malignant Tumors Only	2/6	2/10	6/6	25/19
# of Rats with Both Benign and Malignant Tumors	0/2	2/1	2/6	12/6

@ = Derived from Table 12 and Appendix J on p. 38 and 444-460 of the study report ; $ = Two rats autolyzed; & = One rat autolyzed

APPENDIX M

Incidences of Pertinent Tumors Excluding Interim Sacrifice Rats@

	Control M/F	Low Dose M/F	Mid Dose M/F	High Dose M/F
Total Rats	50/48$	50/50	50/50	49&/50
Pituitary				
+ Adenoma (b)	3/10	1/5	1/7	1/2
+ Carcinoma (m)	0/0	0/0	1/0	0/0
Thyroid				
+ Follicular Cell Adenoma (b)	0/1	0/1	0/2	0/1
+ Carcinoma (m)				
-Medullary Cell	1/2	1/1	1/4	1/1
-Follicular Cell	0/0	0/0	0/0	0/1
+ Lymphoma (b)	0/0	1/0	0/0	0/0
Liver				
+ Hepatocellular Adenoma (b)	0/0	1/0	0/0	0/1
+ Metastatic				
- Carcinoma (m)	0/0	0/1	0/0	0/0
- Sarcoma (m)	0/0	0/1	0/0	0/0
+ Leukemia (m)	0/0	0/0	1/0	0/0
Spleen				
+ Malignant Lymphoma (m)	0/0	1/0	0/0	1/0
+ Metastatic Carcinoma (m)	0/0	0/2	0/0	0/0
+ Fibrosarcoma (m)	0/0	0/1	0/0	0/0
+ Leukemia (m)	0/0	0/0	1/0	0/0
Mesenteric Lymph Node				
+ Adenocarcinoma (m)	0/0	0/0	0/1	0/0
+ Carcinoma (m)	0/0	0/1	0/0	0/0
+ Fibroma (m)	1/0	0/0	0/0	0/0
+ Hemangio-endothelioma (b)	2/0	0/0	0/0	0/0
+ Malignant Lymphoma (m)	0/0	0/0	1/0	1/0
+ Sarcoma (m)	0/0	0/0	1/0	0/0
Cervical Lymph Node				
+ Malignant Lymphoma (m)	0/0	1/0	0/0	1/0
+ Squamosal Carcinoma (m)	0/0	1/0	0/0	0/0

APPENDIX M (continued)

Incidences of Pertinent Tumors Excluding Interim Sacrifice Rats@

	Control M/F	Low Dose M/F	Mid Dose M/F	High Dose M/F
Total Rats	50/48$	50/50	50/50	49&/50
Kidney				
Epithelial				
+ Papilloma (b)	0/0	0/0	0/0	1/0
+ Carcinoma (m)	0/0	0/0	0/0	2/0
+ Sarcoma (m)	0/0	1/0	0/0	0/0
Renal Pelvis				
+ Papilloma (b)	0/0	0/0	0/0	1[a]/0[a]
+ Carcinoma (m)	0/0	0/0	0/0	2[a]/0[a]
Urinary Bladder				
Epithelial				
+ Papilloma (b)	0/1	0/0	0/2	3/2
+ Carcinoma (m)	1/0	0/0	1/1	33/11
Testes				
+ Leydig Cell Tumor (b)	4/na	1/na	2/na	5/na
Ovaries				
+ Adenocarcinoma (m)	na/0	na/1	na/0	na/1
Uterus				
+ Polyp (b)	na/7	na/7	na/6	na/3
+ Adenocarcinoma (m)	na/5	na/5	na/5	na/9
+ Endometrial Sarcoma (m)	na/0	na/0	na/0	na/2
+ Squamous Cell Carcinoma (m)	na/0	na/0	na/1	na/1
+ Leiomyosarcoma (m)	na/0	na/1	na/0	na/0
Mammary Gland[c]				
+ Fibroadenoma (b)	ne/ne	ne/4	ne/ne	ne/ne
+ Adenocarcinoma (m)	ne/ne	ne/1	ne/ne	ne/ne
Skin[c]				
+ Fibroadenoma (b)	ne/1	ne/ne	ne/ne	ne/ne
+ Sarcoma (m)	ne/ne	ne/ne	2/ne	1/ne
+ Fibrosarcoma (m)	ne/ne	ne/1	ne/ne	1/ne

@ = Derived from Tables 13a-d, 14, and 15 and Appendix J on p. 44-47, p. 50-51, and p. 444-460 of the study report; $ = Two rats autolyzed; & = One rat autolyzed; a = only 47 rats evaluated; (b) = benign; c = Only tissues with tumors were evaluated; (m) = malignant; na = Not applicable; ne = Not evaluated.