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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF
PREVENTION, PESTICIDES
AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Diuron Qualitative Risk Assessment Based On Wistar Rat and NMRI (SPF HAN) Mouse Dietary Studies

P.C. Code 035505

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## Background

A chronic oral toxicity and oncogenicity study with Diuron in Wistar rats was conducted by the Institute of Toxicology, Bayer AG, Germany, and the Institute of Experimental Pathology, Hanover Medical University, Germany, for Agricultural Products Department, E.I. du Pont de Nemours & Co., Inc., Newark, Delaware, and issued November 29, 1985 (Study No. Bayer AG T 8010647; MRID No. 408865-01).

The study design allocated groups of 50 rats per sex to dose levels of 0, 25, 250, or 2500 ppm of Diuron for 104 weeks. An additional 10 rats per sex per dose were designated for interim sacrifice at week 52.

A chronic oral toxicity and oncogenicity study with Diuron in NMRI (SPF HAN) mice was conducted by the Institute of Toxicology - Industrial Chemicals (in-life study) and the Institute of Toxicology - Pharmacology (clinical laboratory tests and pathology studies), Bayer AG, Germany, for Agricultural Products Department, E.I. du Pont de Nemours & Co., Inc., Newark, Delaware, and completed October 29, 1983 (Study No. Bayer AG T 4010922; MRID No. 421595-01).

The study design allocated groups of 50 mice per sex to dose levels of 0, 25, 250, or 2500 ppm of Diuron for 103 weeks. An additional 10 mice per sex per dose were designated for interim sacrifice at week 53.

Survival Analyses

The statistical evaluation of mortality indicated no significant incremental changes with increasing doses of Diuron in male or female rats or mice. See Tables 1 and 2 for rat mortality test results, and Tables 6 and 7 for mouse mortality test results.

The statistical evaluation of mortality was based upon the Thomas, Breslow and Gart computer program.

Tumor Analyses

Male rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm dose group with the controls, for urinary bladder epithelial carcinomas, and papillomas and/or carcinomas combined, all at $p < 0.01$. Male rats also had a significant increasing trend in kidney renal pelvis epithelial papillomas and/or carcinomas combined at $p < 0.05$.

Female rats had significant increasing trends, and significant differences in the pair-wise comparisons of the 2500 ppm dose group with the controls, for urinary bladder epithelial carcinomas, and papillomas and/or carcinomas combined, all at $p < 0.01$.

There were no statistically significant tumors observed in male mice.

Female mice had significant increasing trends in mammary gland adenocarcinomas and ovarian luteomas, both at $p < 0.05$. There were no significant differences in the pair-wise comparisons of the dosed groups with the controls.

The statistical analyses of the rats and mice were based upon the Exact trend test and the Fisher's Exact test for pair-wise comparisons. See Tables 3 through 5 for rat tumor analysis results, and Table 8 for mouse tumor analysis results.

Table 1. Diuron - Wistar Rat Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

| Dose (ppm) | Weeks 1-26 | 27-52 | 52[i] | 53-78 | 79-104[f] | Total |
|---|---|---|---|---|---|---|
| 0 | 1/60 | 0/59 | 10/59 | 0/49 | 1/49 | 2/50 (4) |
| 25 | 0/60 | 0/60 | 10/60 | 1/50 | 7/49 | 8/50 (16) |
| 250 | 0/60 | 0/60 | 10/60 | 1/50 | 4/49 | 5/50 (10) |
| 2500 | 1/60 | 1/59 | 10/58 | 0/48 | 5/48 | 7/50 (14) |

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 52.

[f]Final sacrifice at week 104.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 2. Diuron - Wistar Rat Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

| Dose (ppm) | Weeks 1-26 | 27-52 | 52[i] | 53-78 | 79-104[f] | Total |
|---|---|---|---|---|---|---|
| 0 | 1/60 | 1/59 | 10/58 | 2/48 | 7/46 | 11/50 (22) |
| 25 | 0/60 | 0/60 | 10/60 | 5/50 | 4/45 | 9/50 (18) |
| 250 | 0/60 | 0/60 | 10/60 | 1/50 | 2/49 | 3/50 (6) |
| 2500 | 1/60 | 1/59 | 10/58 | 0/48 | 9/48 | 11/50 (22) |

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 52.

[f]Final sacrifice at week 104.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 3. Diuron - Wistar Rat Study

Male Urinary Bladder Epithelial Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

| | Dose (ppm) | | | |
|---|---|---|---|---|
| | 0 | 25 | 250 | 2500 |
| Papillomas (%) | 0/49 (0) | 0/50 (0) | 0/49 (0) | 1[a]/48 (2) |
| p = | 0.245 | 1.000 | 1.000 | 0.495 |
| Carcinomas (%) | 1/49 (2) | 0/50 (0) | 1/49 (2) | 35[b]/48 (73) |
| p = | 0.000** | 0.495[n] | 0.753 | 0.000** |
| Combined (%) | 1/49 (2) | 0/50 (0) | 1/49 (2) | 35[c]/48 (73) |
| p = | 0.000** | 0.495[n] | 0.753 | 0.000** |

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53. Also excludes week 52 interim sacrifice animals.

[a]First papilloma observed at week 104, dose 2500 ppm.

[b]First carcinoma observed at week 81, dose 2500 ppm.

[c]One animal in the 2500 ppm dose group had both a papilloma and a carcinoma.

[n]Negative change from control.

Note: Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 4. Diuron - Wistar Rat Study

Male Kidney Renal Pelvis Epithelial Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

| | Dose (ppm) | | | |
|---|---|---|---|---|
| | 0 | 25 | 250 | 2500 |
| Papillomas (%) | 0/49 (0) | 0/50 (0) | 0/50 (0) | 1[a]/48 (2) |
| p = | 0.244 | 1.000 | 1.000 | 0.495 |
| Carcinomas (%) | 0/49 (0) | 0/50 (0) | 0/50 (0) | 2[b]/48 (4) |
| p = | 0.058 | 1.000 | 1.000 | 0.242 |
| Combined (%) | 0/49 (0) | 0/50 (0) | 0/50 (0) | 3/48 (6) |
| p = | 0.014* | 1.000 | 1.000 | 0.117 |

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 53. Also excludes week 52 interim sacrifice animals.

[a]First papilloma observed at week 104, dose 2500 ppm.

[b]First carcinoma observed at week 104, dose 2500 ppm.

Note: Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 5. Diuron - Wistar Rat Study

Female Urinary Bladder Epithelial Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

| | Dose (ppm) | | | |
|---|---|---|---|---|
| | 0 | 25 | 250 | 2500 |
| Papillomas (%) | 0/47 (0) | 0/49 (0) | 2[a]/50 (4) | 0/49 (0) |
| p = | 0.560 | 1.000 | 0.263 | 1.000 |
| Carcinomas (%) | 1/47 (2) | 0/49 (0) | 1/50 (2) | 13[b]/49 (27) |
| p = | 0.000** | 0.490[n] | 0.737 | 0.001** |
| Combined (%) | 1/47 (2) | 0/49 (0) | 3/50 (6) | 13[c]/49 (27) |
| p = | 0.000** | 0.490[n] | 0.332 | 0.001** |

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 44. Also excludes week 52 interim sacrifice animals.

[a]First papilloma observed at week 104, dose 250 ppm.

[b]First carcinoma observed at week 44, dose 2500 ppm.

[c]One animal in the 2500 ppm dose group had both a papilloma and a carcinoma.

[n]Negative change from control.

Note: Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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**Table 6.** Diuron - NMRI (SPF HAN) Mouse Study

Male Mortality Rates[+] and Cox or Generalized K/W Test Results

| Dose (ppm) | Weeks 1-26 | 27-52 | 53[i] | 53-78 | 79-104[f] | Total |
|---|---|---|---|---|---|---|
| 0 | 1/60 | 1/59 | 10/58 | 6/48 | 26/42 | 34/50 (68) |
| 25 | 0/60 | 4/60 | 10/56 | 9/46 | 15/37 | 28/50 (56) |
| 250 | 0/60 | 4/60 | 10/56 | 3/46 | 21/43 | 28/50 (56) |
| 2500 | 2/60 | 3/58 | 10/55 | 9/45 | 15/36 | 29/50 (58) |

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 103.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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Table 7. Diuron - NMRI (SPF HAN) Mouse Study

Female Mortality Rates[+] and Cox or Generalized K/W Test Results

| | Weeks | | | | | |
|---|---|---|---|---|---|---|
| Dose (ppm) | 1-26 | 27-52 | 53[i] | 53-78 | 79-104[f] | Total |
| 0 | 2/60 | 8/58 | 10/50 | 9/40 | 23/31 | 42/50 (84) |
| 25 | 1/60 | 6/59 | 10/53 | 11/43 | 22/32 | 40/50 (80) |
| 250 | 1/60 | 0/59 | 10/59 | 13/49 | 26/36 | 40/50 (80) |
| 2500 | 2/60 | 1/58 | 10/57 | 14/47 | 19/33 | 36/50 (72) |

[+]Number of animals that died during interval/Number of animals alive at the beginning of the interval.

[i]Interim sacrifice at week 53.

[f]Final sacrifice at week 104.

( )Percent.

Note: Time intervals were selected for display purposes only.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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**Table 8.** Diuron - NMRI (SPF HAN) Mouse Study

Female Mammary Gland and Ovarian Tumor Rates[+] and Exact Trend Test and Fisher's Exact Test Results (p values)

| | Dose (ppm) | | | |
|---|---|---|---|---|
| | 0 | 25 | 250 | 2500 |
| Mammary Gland Adeno-carcinomas (%) | 2/34 (6) | 1[a]/29 (3) | 1/44 (2) | 6/37 (16) |
| p = | 0.016* | 0.560 | 0.403 | 0.159 |
| Ovarian Luteomas (%) | 3/34 (9) | 1/32 (3) | 2/46 (4) | 7[b]/41 (17) |
| p = | 0.024* | 0.330[n] | 0.358[n] | 0.243 |

[+]Number of tumor bearing animals/Number of animals examined, excluding those that died before week 54. Also excludes week 53 interim sacrifice animals.

[a]First mammary gland adenocarcinoma observed at week 78, dose 25 ppm.

[b]First uterine luteoma observed at week 53, dose 0 ppm, in an interim sacrifice animal. Second uterine luteoma observed at week 72, dose 2500 ppm, in an animal that died on study.

[n]Negative change from control.

Note: One animal in the control group of the interim sacrifice group had a uterine luteoma. Interim sacrifice animals are not included in this analysis.

Significance of trend denoted at control.

Significance of pair-wise comparison with control denoted at dose level.

If *, then $p < 0.05$. If **, then $p < 0.01$.

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