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DYNAMAC No. 208-B  
February 5, 1987

DATA EVALUATION RECORD

TRIFLURALIN

Chronic Toxicity/Oncogenicity Feeding Study in Rats

APPROVED BY:

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Date: \_\_\_\_\_

*2-5-87*

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DATA EVALUATION REPORT

TOX. CHEM. NO.:  
MRID NO.:

STUDY TYPE: Chronic toxicity/oncogenicity feeding study in rats.

ACCESSION NUMBER: 262521-262526.

TEST MATERIAL: Trifluralin;  $\alpha,\alpha,\alpha$ -trifluoro-2,6-dinitro-N,N-dipropyl-p-toluidine.

SYNONYMS: Digermin, Ipersan, Treflan, Triflurex.

STUDY NUMBER(S): 680 (Chronic A32718, oncogenicity A32719).

SPONSOR: Hoechst Aktiengesellschaft, Frankfurt, Federal Republic of Germany.

TESTING FACILITY: Pharma Forschung Toxikologie, Hoechst Aktiengesellschaft, Frankfurt, Federal Republic of Germany.

TITLE OF REPORT: Trifluralin (code: Hoe 38474 OH AT208) Chronic Feeding Study (24 months) in Rats and Trifluralin (Code: Hoe 38474 OH AT208) Carcinogenicity Study in Rats (28-Month Feeding Study).

AUTHOR(S): Donaubauer, Schutz, Leist, and Kramer.

REPORT ISSUED: March 26, 1985, and April 2, 1985.

## CONCLUSIONS:

When 200, 800, or 3200 ppm trifluralin was fed to Wistar rats for 24 months in a chronic toxicity study, there were no overt signs of toxicity or dose-related effects on mortality, clinical biochemistry, or histopathology. Body weight gain and food consumption were decreased throughout the study in males and females receiving 3200 ppm. Body weights were also decreased at study termination in males receiving 800 ppm. There were significant ( $p < 0.05$ ) decreases in red cell parameters in high-dose males and females. There were also nonsignificant decreases in liver and thyroid weights in males and females receiving 3200 ppm, although there were no histologic findings that correlated with the organ weight changes.

In an oncogenicity study conducted simultaneously, 200, 800, and 3200 ppm trifluralin were not oncogenic when fed to male and female Wistar rats for 28 months. Tumor incidence was found to be age, sex, or strain related and was not due to compound treatment. Body weight gain and food consumption were decreased throughout the study in males and females receiving 3200 ppm. Body weights were decreased in the 800 ppm female group during the last 6 months of the study, and in males of this group at study termination. As in the chronic study, there were nonsignificant increases in liver and thyroid weights in males and females receiving 3200 ppm. Based on the body weight changes, the LOEL is 800 ppm and the NOEL is 200 ppm. *ONCOGENIC NOEL = 3200ppm (ADT)*

Classification: Core Guideline.

## A. MATERIALS:

1. Test Compound: Trifluralin, technical, Code: Hoe 38474 OH AT208, from December 1982, Code: Hoe 38474 OH AT210; description: orange powder from batch No. 10653 OP.112/80; purity: >99 percent.
2. Test Animals: Species: rat; strain: Wistar, Hoe: Wiskf (SPF71); age: 4 weeks; mean weights: males--123-130 g and females--117-119 g; source: Hoechst breeding colony.

## B. STUDY DESIGN:

1. Animal Assignment: After 7 days of acclimation, the animals were weighed and assigned to the following groups with a computerized randomization procedure:

### CHRONIC TOXICITY STUDY

| Test Group   | Dose in diet (ppm) | Main study (24 months) |         | Residue Examination (6,12,18, & 24 months) |         | BSP/PSP Function Tests (25 months) |         |
|--------------|--------------------|------------------------|---------|--|---------|------------------------------------|---------|
|              |                    | Males                  | Females | Males                                      | Females | Males                              | Females |
| 1 Control    | 0                  | 20                     | 20      | 10   | 10      | 6                                  | 6       |
| 2 Low (LDT)  | 200                | 20                     | 20      | 10   | 10      | 6                                  | 6       |
| 3 Mid (MDT)  | 800                | 20                     | 20      | 10   | 10      | 6                                  | 6       |
| 4 High (HDT) | 3200               | 20                     | 20      | 10   | 10      | 6                                  | 6       |

### ONCOGENICITY STUDY

| Test Group    | Dose in diet (ppm) | Main Study (28 months) |         |
|---------------|--------------------|------------------------|---------|
|               |                    | Males                  | Females |
| 1. Cont.      | 0                  | 60                     | 60      |
| 2. Low (LDT)  | 200                | 60                     | 60      |
| 3. Mid (MDT)  | 800                | 60                     | 60      |
| 4. High (HDT) | 3200               | 60                     | 60      |

**Dose Selection:** The dose levels selected for this study were based on a 3-month subchronic toxicity study in rats; as a result of these studies, 3200 ppm was expected to cause intoxication and impairment of body weight gains. Two hundred and 800 ppm were selected based on user exposure concentrations and residue limits in food.

2. **Diet Preparation:** One-kilogram premixes were prepared at 21-day intervals and stored at < 6°C. Diets were prepared weekly. Food and water were available to the animals ad libitum. Samples of treated food were analyzed for concentration and homogeneity at weekly intervals; stability of test compound in diet was analyzed at monthly intervals.

**Results:** The premixes and diets were found to be homogeneous and ≥ 90 percent stable over 21 days of storage. Recovery values of the diets were within acceptable limits, e.g., 93-108 percent of the calculated values.

3. Animals received food (Altromin 1321) and water ad libitum except during scheduled urine collection periods.
4. Statistics: The following procedures were utilized in analyzing the numerical data for the chronic toxicity and oncogenicity studies. Body weights, clinical chemistry, and appropriate hematologic data were analyzed by the tests of Dunnett, Sidak, Nemenyi/Dunnett, and Nemenyi/Sidak for the chronic toxicity study; body weights were analyzed by these procedures for the oncogenicity study. Organ weights were analyzed by the tests of Sidak and Nemenyi/Sidak for both studies. Water consumption during the chronic toxicity study was analyzed by the procedure of Shapiro and Wilk. Mortality patterns for both studies were tested with the Kaplan-Meier and log-rank procedures. All methods were tested at the  $p=0.05$  level of significance. Data on the numbers of animals with tumors were analyzed by the IARC time-to-tumor method, including the tests for homogeneity, positive trend, nonlinearity, and pairwise comparison. Descriptive statistics (mean, standard deviation) were calculated for food consumption.
5. A quality assurance statement was signed and dated March 26, 1985, and April 2, 1985.

C. METHODS AND RESULTS:

1. Observations: Animals were inspected twice daily for signs of toxicity and mortality. The animals were examined once a month for neurological disturbances, opacity of the eyes, impairment of dental growth, and changes in the oral mucosa. All rats were individually examined twice monthly (from 6 to 24 months) for palpable masses.

Results: It was reported that there were no overt signs of toxicity. Palpation of the skin revealed a number of pathological findings in animals of all treatment groups; however, these pathological findings were reported to be unrelated to dosing. Individual observation data or summarized palpable mass observations were not reported.

- a. Chronic Toxicity Study - Survival was similar for all groups of males. Mortality was slightly but nonsignificantly increased in females receiving 3200 ppm relative to controls and slightly increased in females relative to males at 78 and 104 weeks. Mortality was also found earlier in the study in females receiving 3200 ppm (56 weeks) or 800 ppm (66 weeks). The first death in males was at week 78. Representative mortality and survival data are presented in Table 1.

TABLE 1. Representative Results of Mortality and Percent Survival of Rats Fed Trifluralin for 24 Months - Chronic Toxicity Study

| Dose Group<br>(ppm) | Mortality (Percent Survival) <sup>a</sup> at<br>Week |        |        |       |
|---------------------|--|--------|--------|-------|
|                     | 26   | 52     | 78     | 104   |
| MALES               |  |        |        |       |
| 0                   | 0(100)   | 0(100) | 0(100) | 1(95) |
| 200                 | 0(100)   | 0(100) | 0(100) | 3(85) |
| 800                 | 0(100)   | 0(100) | 1(95)  | 2(90) |
| 3200                | 0(100)   | 0(100) | 0(100) | 3(85) |
| FEMALES             |  |        |        |       |
| 0                   | 0(100)   | 0(100) | 1(95)  | 3(85) |
| 200                 | 0(100)   | 0(100) | 2(90)  | 5(75) |
| 800                 | 0(100)   | 0(100) | 1(95)  | 4(80) |
| 3200                | 0(100)   | 0(100) | 3(85)  | 6(70) |

<sup>a</sup>Based on 20 rats/group.

- b. Oncogenicity Study - Mortality was slightly, but nonsignificantly, increased in males receiving 800 or 3200 ppm relative to controls at 104 and 121 weeks; however, mortality was decreased in females receiving 3200 ppm relative to controls. At 104 and 121 weeks, mortality was slightly increased among males receiving 3200 ppm relative to females in the same dose group. Representative mortality and survival data are presented in Table 2.

Mortality during the chronic and oncogenicity studies was considered unrelated to dosing.

TABLE 2. Representative Results of Mortality and Percent Survival of Rats Fed Trifluralin for 28 Months - Oncogenicity Study

| Dose Group<br>(ppm) | Mortality (Percent Survival) <sup>a</sup> at |        |        |       |        |        |
|---------------------|--|--------|--------|-------|--------|--------|
|                     | 13   | 26     | 52     | 78    | 104    | 121    |
| MALES               |  |        |        |       |        |        |
| 0                   | 0(100)                                       | 0(100) | 0(100) | 1(98) | 4(93)  | 19(68) |
| 200                 | 0(100)                                       | 0(100) | 1(98)  | 2(97) | 8(87)  | 18(70) |
| 800                 | 0(100)                                       | 0(100) | 1(98)  | 4(93) | 11(82) | 22(63) |
| 3200                | 0(100)                                       | 0(100) | 1(98)  | 4(93) | 14(77) | 26(57) |
| FEMALES             |  |        |        |       |        |        |
| 0                   | 0(100)                                       | 0(100) | 1(98)  | 2(97) | 14(77) | 26(57) |
| 200                 | 0(100)                                       | 1(98)  | 2(97)  | 5(92) | 14(77) | 23(62) |
| 800                 | 0(100)                                       | 0(100) | 0(100) | 1(98) | 11(82) | 25(58) |
| 3200                | 0(100)                                       | 0(100) | 1(98)  | 1(98) | 10(83) | 20(67) |

<sup>a</sup>Based on 60 rats/group.



2. Body Weight: Rats were weighed weekly.

Results:

- a. Chronic Study - There were no effects of dosing on mean body weights at 200 ppm, whereas mean body weights of males and females receiving 800 ppm tended to be slightly lower than controls. There was no significant change among females in this dose group; males only differed significantly ( $p < 0.05$ ) at week 104. Mean body weights of males and females receiving 3200 ppm were decreased relative to controls throughout the study. Mean body weights of males receiving 3200 ppm were significantly ( $p < 0.05$ ) decreased at week 61 and from week 61 to study termination (Table 3). Mean body weights of females receiving 3200 ppm were significantly ( $p < 0.05$ ) decreased from week 26 to study termination (Table 3).
- b. Oncogenicity Study - There were no effects of dosing on mean body weights of low- or mid-dose males and low-dose females with the exception of a slight reduction in the body weight of mid-dose males at the end of the second year of the study [significantly ( $p < 0.05$ ) decreased at week 121]. Mean body weights of females receiving 800 ppm were slightly decreased from controls beginning at week 39; the decreases were significant ( $p < 0.05$ ) from weeks 73 to 112. Mean body weights of males and females receiving 3200 ppm were significantly ( $p < 0.05$ ) decreased throughout the study. Table 4 presents mean body weight data at selected intervals.

3. Food Consumption, Water Consumption, and Compound Intake: Food consumption was determined weekly at the time of body weight determinations. Food consumption and body weight were used to adjust the concentration of the test compound in the diet to maintain the targeted dosage level on a mg/kg/day basis.

Results:

- a. Chronic Study - The absolute food consumption of females receiving 3200 ppm was found to be decreased relative to controls throughout the study. The relative food consumption was found to be slightly increased in males and females receiving 3200 ppm, whereas the body weights were decreased in these groups (Table 5). Food efficiency was not calculated.

TABLE 3. Representative Results of Mean Body Weights ( $\pm$  SD) of Trifluralin for 24 Months - Chronic Study

| Dose Group (ppm) | Mean Body Weights (g $\pm$ SD) <sup>a</sup> at Week |              |               |               |               |               |           |
|------------------|---|--------------|---------------|---------------|---------------|---------------|-----------|
|                  | 0   | 13           | 26            | 52            | 65            | 78            | 104       |
| MALES            |   |              |               |               |               |               |           |
| 0                | 125 $\pm$ 8   | 410 $\pm$ 32 | 453 $\pm$ 37  | 508 $\pm$ 41  | 531 $\pm$ 44  | 535 $\pm$ 47  | 544 $\pm$ |
| 200              | 124 $\pm$ 9   | 416 $\pm$ 37 | 464 $\pm$ 44  | 515 $\pm$ 58  | 544 $\pm$ 59  | 548 $\pm$ 64  | 554 $\pm$ |
| 800              | 120 $\pm$ 12  | 406 $\pm$ 41 | 449 $\pm$ 48  | 492 $\pm$ 55  | 511 $\pm$ 57  | 511 $\pm$ 60  | 493 $\pm$ |
| 3200             | 121 $\pm$ 10  | 388 $\pm$ 41 | 439 $\pm$ 47  | 478 $\pm$ 47  | 487 $\pm$ 49* | 481 $\pm$ 47* | 449 $\pm$ |
| FEMALES          |   |              |               |               |               |               |           |
| 0                | 119 $\pm$ 7   | 233 $\pm$ 20 | 250 $\pm$ 22  | 291 $\pm$ 32  | 313 $\pm$ 43  | 330 $\pm$ 40  | 353 $\pm$ |
| 200              | 114 $\pm$ 8   | 240 $\pm$ 26 | 258 $\pm$ 31  | 299 $\pm$ 35  | 320 $\pm$ 41  | 333 $\pm$ 57  | 351 $\pm$ |
| 800              | 118 $\pm$ 6   | 228 $\pm$ 20 | 247 $\pm$ 21  | 280 $\pm$ 30  | 297 $\pm$ 41  | 314 $\pm$ 32  | 323 $\pm$ |
| 3200             | 117 $\pm$ 5   | 219 $\pm$ 11 | 234 $\pm$ 13* | 253 $\pm$ 19* | 257 $\pm$ 23* | 264 $\pm$ 18* | 262 $\pm$ |

<sup>a</sup>Based on 20 rats/group.

\*Significantly different from control value (p < 0.05).

TABLE 4. Representative Results of Mean Body Weights ( $\pm$  SD) of Rats Fed Trifluralin for 28 Months - Oncogenicity Study

| Dose Group<br>(ppm) | Mean Body Weights (g $\pm$ SD) <sup>a</sup> at week |               |               |               |               |               |               |                           |
|---------------------|---|---------------|---------------|---------------|---------------|---------------|---------------|---------------------------|
|                     | 0   | 13            | 26            | 52            | 65            | 78            | 104           | 121                       |
| MALES               |   |               |               |               |               |               |               |                           |
| 0                   | 131 $\pm$ 9   | 414 $\pm$ 35  | 466 $\pm$ 44  | 504 $\pm$ 53  | 528 $\pm$ 55  | 539 $\pm$ 59  | 530 $\pm$ 63  | 499 $\pm$ 62              |
| 200                 | 128 $\pm$ 8   | 412 $\pm$ 30  | 467 $\pm$ 35  | 510 $\pm$ 59  | 528 $\pm$ 42  | 540 $\pm$ 44  | 537 $\pm$ 49  | 496 $\pm$ 71              |
| 800                 | 130 $\pm$ 9   | 410 $\pm$ 35  | 465 $\pm$ 41  | 508 $\pm$ 49  | 523 $\pm$ 54  | 534 $\pm$ 56  | 519 $\pm$ 53  | 451 $\pm$ 58 <sup>b</sup> |
| 3200                | 130 $\pm$ 8   | 389 $\pm$ 37* | 440 $\pm$ 41* | 483 $\pm$ 45* | 495 $\pm$ 47* | 496 $\pm$ 53* | 449 $\pm$ 42* | 408 $\pm$ 20 <sup>b</sup> |
| FEMALES             |   |               |               |               |               |               |               |                           |
| 0                   | 121 $\pm$ 8   | 229 $\pm$ 18  | 251 $\pm$ 22  | 288 $\pm$ 29  | 309 $\pm$ 35  | 328 $\pm$ 38  | 347 $\pm$ 42  | 323 $\pm$ 59              |
| 200                 | 120 $\pm$ 6   | 228 $\pm$ 15  | 250 $\pm$ 18  | 287 $\pm$ 30  | 303 $\pm$ 35  | 320 $\pm$ 38  | 334 $\pm$ 44  | 321 $\pm$ 52              |
| 800                 | 118 $\pm$ 7   | 231 $\pm$ 16  | 251 $\pm$ 18  | 280 $\pm$ 28  | 295 $\pm$ 35  | 310 $\pm$ 39* | 314 $\pm$ 48* | 300 $\pm$ 45              |
| 3200                | 118 $\pm$ 7   | 215 $\pm$ 19* | 230 $\pm$ 23* | 248 $\pm$ 23* | 255 $\pm$ 24* | 259 $\pm$ 26* | 252 $\pm$ 30* | 258 $\pm$ 28*             |

<sup>a</sup>Based on 60 rats/group.

\*Significantly different from control value (p < 0.05).

TABLE 5. Mean Food and Compound Consumption for Rats<sup>a</sup> Fed Trifluralin for 24 Months - Chronic Study

| Dose Group<br>(ppm) | <u>Mean Food Consumption</u> |                                  | <u>Mean Compound Consumption</u><br>(mg/kg/day) |
|---------------------|------------------------------|----------------------------------|---|
|                     | <u>Absolute</u><br>(g/day)   | <u>Relative</u><br>(g/100 g/day) |   |
| MALES               |                              |                                  |   |
| 0                   | 24.2                         | 5.25                             | --  |
| 200                 | 24.5                         | 5.20                             | 10.39   |
| 800                 | 23.6                         | 5.26                             | 42.11   |
| 3200                | 23.1                         | 5.37                             | 171.77  |
| FEMALES             |                              |                                  |   |
| 0                   | 18.4                         | 6.62                             | --  |
| 200                 | 18.6                         | 6.63                             | 13.26   |
| 800                 | 17.7                         | 6.59                             | 52.73   |
| 3200                | 16.4                         | 6.77                             | 216.79  |

<sup>a</sup>Based on 20 rats/group.

- b. Oncogenicity Study - The absolute food consumption of males and females receiving 3200 ppm was found to be decreased relative to the controls, whereas the relative food consumption of these animals was found to be slightly increased. The increase in relative food consumption was associated with the decrease in body weights found in these groups (Table 6). Mean compound intake was higher in females at all dose levels in the chronic toxicity and oncogenicity studies (Tables 6). Food efficiency was not calculated.

TABLE 6. Mean Food and Compound Consumption for Rats<sup>a</sup> Fed Trifluralin for 28 Months - Oncogenicity Study

| Dose Group<br>(ppm) | <u>Mean Food Consumption</u> |                                  | <u>Mean Compound Consumpti</u><br>(mg/kg/day) |
|---------------------|------------------------------|----------------------------------|---|
|                     | <u>Absolute</u><br>(g/day)   | <u>Relative</u><br>(g/100 g/day) |   |
| MALES               |                              |                                  |   |
| 0                   | 24.1                         | 5.17                             | --  |
| 200                 | 23.6                         | 5.01                             | 10.03   |
| 800                 | 23.3                         | 5.04                             | 40.33   |
| 3200                | 22.8                         | 5.29                             | 169.17  |
| FEMALES             |                              |                                  |   |
| 0                   | 18.5                         | 6.56                             | --  |
| 200                 | 18.2                         | 6.55                             | 13.11   |
| 800                 | 17.8                         | 6.58                             | 52.61   |
| 3200                | 16.3                         | 6.83                             | 218.72  |

<sup>a</sup>Based on 60 rats/group.

Water consumption was recorded over a 16-hour period for 10 animals/sex/group at 6, 12, and 24 months of the chronic toxicity study. The absolute water consumption varied sporadically; there were no definite indications of a dose-related effect. The relative water consumption, however, was significantly ( $p < 0.05$ ) increased in males receiving 3200 ppm at 6 and 24 months and females receiving the same dose at 12 months; these increases in water consumption were associated with the reductions in body weight found in these groups (Table 7).

TABLE 7. Relative Water Consumption for Rats Fed Trifluralin for 24 Months - Chronic Study

| Dose Group<br>(ppm) | Mean Water Consumption (g $\pm$ SD) <sup>a</sup> at Month |                 |                 |
|---------------------|---|-----------------|-----------------|
|                     | 6   | 12              | 24              |
| MALES               |   |                 |                 |
| 0                   | 28.3 $\pm$ 2.8  | 26.0 $\pm$ 8.5  | 21.3 $\pm$ 3.3  |
| 200                 | 26.9 $\pm$ 4.9  | 22.2 $\pm$ 4.7  | 25.1 $\pm$ 8.8  |
| 800                 | 25.4 $\pm$ 5.3  | 23.3 $\pm$ 7.4  | 20.1 $\pm$ 6.8  |
| 3200                | 32.7 $\pm$ 5.9*   | 30.7 $\pm$ 6.9  | 26.1 $\pm$ 6.2* |
| FEMALES             |   |                 |                 |
| 0                   | 26.2 $\pm$ 3.7  | 23.5 $\pm$ 8.6  | 23.5 $\pm$ 8.8  |
| 200                 | 29.2 $\pm$ 5.0  | 30.3 $\pm$ 7.4  | 27.0 $\pm$ 7.6  |
| 800                 | 25.4 $\pm$ 4.2  | 26.3 $\pm$ 3.8  | 27.9 $\pm$ 7.5  |
| 3200                | 27.0 $\pm$ 5.1  | 29.7 $\pm$ 4.3* | 23.3 $\pm$ 9.9  |

<sup>a</sup>Based on 10 rats/group.

\*Significantly different from control value ( $p \leq 0.05$ )

4. Ophthalmological examinations, consisting of examination of the opacity of the refracting media of the eyes, were performed once per month on all animals. There were no changes reported.

5. Blood was collected by orbital sinus puncture before treatment and at 26, 52, and 78 weeks for hematologic and clinical analysis from 10 animals/sex/dose of the chronic toxicity study and from 10 animals/sex/dose of this study at 104 weeks.

The CHECKED (X) parameters were examined:

a. Hematology

|                            |   |
|----------------------------|---|
| X Hematocrit (HCT)†        | Total plasma protein (TP)                   |
| X Hemoglobin (HGB)†        | X Leukocyte differential count              |
| X Leukocyte count (WBC)†   | X Mean corpuscular HGB (MCH)                |
| X Erythrocyte count (RBC)† | X Mean corpuscular HGB concentration (MCHC) |
| X Platelet count†          | X Mean corpuscular volume (MCV)             |
|                            | X Reticulocytes                             |
|                            | X Heinz bodies                              |
|                            | X Coagulation time                          |
|                            | X Howell-Jolly bodies                       |

Methemoglobin was determined before treatment and at 6, 12, and 18 months for 10 males and 10 females receiving 3200 ppm and at 24 months for all high-dose survivors of the chronic study. Methemoglobin was not determined for control animals.

Results: The mean erythrocyte counts (RBC) for high-dose males and females were significantly ( $p < 0.05$ ) decreased at 26, 52, and 78 weeks (Tables 8A and 8B). Mean hemoglobin (HGB) and hematocrit (HCT) concentrations were similarly decreased at 26, 52, 78, and 104 weeks. HGB and HCT were found to be significantly ( $p < 0.05$ ) reduced in high-dose females at 52, 78, and 104 weeks. HGB was found to be significantly ( $p < 0.05$ ) reduced in high-dose males at 26 and 104 weeks but not at 52 or 78 weeks; HCT was significantly ( $p < 0.05$ ) reduced in this group at 78 and 104 weeks but not at 26 or 52 weeks (Tables 8A and 8B). There was a corresponding increase in reticulocytes at all examination intervals, and was significant ( $p < 0.05$ ) in females receiving 3200 ppm at 52 and 78 weeks. No Heinz bodies or Howell-Jolly bodies were found in erythrocytes and methemoglobin formation was detected. Significant differences occurred sporadically among leukocyte, coagulation time, and platelet parameters; these values were considered random and not of toxicologic significance.

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†Recommended by Subdivision F.

TABLE 8A. Representative Mean Hematology Data for Male Rats Fed Trifluralin for 24 Months - Chronic Study

| Mean Hematology Value ( $\pm$ SD) <sup>a</sup> at |                     |               |                  |                        |
|---|---------------------|---------------|------------------|------------------------|
| Dose Group (ppm)                                  | Pretest             |               |                  |                        |
|   | RBC ( $10^{12}/L$ ) | HGB (g/L)     | HCT (unity)      | Reticulo-cytes (unity) |
| 0   | 5.82 $\pm$ 0.46     | 122 $\pm$ 6   | 0.35 $\pm$ 0.02  | 0.017 $\pm$ 0.005      |
| 200   | 6.11 $\pm$ 0.44     | 127 $\pm$ 10  | 0.35 $\pm$ 0.03  | 0.018 $\pm$ 0.006      |
| 800   | 5.99 $\pm$ 0.46     | 126 $\pm$ 9   | 0.35 $\pm$ 0.03  | 0.019 $\pm$ 0.013      |
| 3200  | 5.77 $\pm$ 0.45     | 123 $\pm$ 9   | 0.34 $\pm$ 0.03  | 0.021 $\pm$ 0.008      |
| -----   |                     |               |                  |                        |
| Dose Group (ppm)                                  | 26 Weeks            |               |                  |                        |
|   | RBC ( $10^{12}/L$ ) | HGB (g/L)     | HCT (unity)      | Reticulo-cytes (unity) |
| 0   | 8.57 $\pm$ 0.31     | 160 $\pm$ 6   | 0.44 $\pm$ 0.02  | 0.012 $\pm$ 0.004      |
| 200   | 8.59 $\pm$ 0.36     | 159 $\pm$ 8   | 0.44 $\pm$ 0.03  | 0.013 $\pm$ 0.008      |
| 800   | 8.19 $\pm$ 0.36*    | 153 $\pm$ 6   | 0.42 $\pm$ 0.03  | 0.014 $\pm$ 0.006      |
| 3200  | 7.96 $\pm$ 0.32*    | 150 $\pm$ 8*  | 0.41 $\pm$ 0.03  | 0.018 $\pm$ 0.006      |
| -----   |                     |               |                  |                        |
| Dose Group (ppm)                                  | 52 Weeks            |               |                  |                        |
|   | RBC ( $10^{12}/L$ ) | HGB (g/L)     | HCT (unity)      | Reticulo-cytes (unity) |
| 0   | 8.87 $\pm$ 0.34     | 169 $\pm$ 8   | 0.47 $\pm$ 0.02  | 0.022 $\pm$ 0.007      |
| 200   | 8.85 $\pm$ 0.32     | 171 $\pm$ 7   | 0.47 $\pm$ 0.03  | 0.022 $\pm$ 0.007      |
| 800   | 8.60 $\pm$ 0.32     | 164 $\pm$ 7   | 0.45 $\pm$ 0.03  | 0.025 $\pm$ 0.007      |
| 3200  | 8.32 $\pm$ 0.43*    | 162 $\pm$ 8   | 0.44 $\pm$ 0.03  | 0.026 $\pm$ 0.010      |
| -----   |                     |               |                  |                        |
| Dose Group (ppm)                                  | 78 Weeks            |               |                  |                        |
|   | RBC ( $10^{12}/L$ ) | HGB (g/L)     | HCT (unity)      | Reticulo-cytes (unity) |
| 0   | 8.62 $\pm$ 0.36     | 166 $\pm$ 8   | 0.45 $\pm$ 0.02  | 0.030 $\pm$ 0.010      |
| 200   | 8.60 $\pm$ 0.43     | 166 $\pm$ 9   | 0.46 $\pm$ 0.03  | 0.028 $\pm$ 0.010      |
| 800   | 8.36 $\pm$ 0.30     | 164 $\pm$ 7   | 0.44 $\pm$ 0.03  | 0.023 $\pm$ 0.008      |
| 3200  | 7.74 $\pm$ 1.09*    | 153 $\pm$ 21  | 0.41 $\pm$ 0.07* | 0.033 $\pm$ 0.012      |
| -----   |                     |               |                  |                        |
| Dose Group (ppm)                                  | 104 Weeks           |               |                  |                        |
|   | RBC ( $10^{12}/L$ ) | HGB (g/L)     | HCT (unity)      | Reticulo-cytes (unity) |
| 0   | 7.95 $\pm$ 0.41     | 155 $\pm$ 7   | 0.43 $\pm$ 0.02  | 0.039 $\pm$ 0.012      |
| 200   | 7.67 $\pm$ 0.89     | 151 $\pm$ 15  | 0.41 $\pm$ 0.05  | 0.043 $\pm$ 0.027      |
| 800   | 8.03 $\pm$ 0.43     | 156 $\pm$ 9   | 0.44 $\pm$ 0.03  | 0.039 $\pm$ 0.009      |
| 3200  | 7.59 $\pm$ 0.92     | 145 $\pm$ 11* | 0.39 $\pm$ 0.06* | 0.039 $\pm$ 0.013      |

<sup>a</sup>Based on 10 rats/group except the terminal blood analysis in which 20 rats/group were examined.

\*Significantly different from control value (p < 0.05).

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TABLE 88. Representative Mean Hematology Data for Female Rats Fed Trifluralin for 24 Months - Chronic Study

| Mean Hematology Value ( $\pm$ SD) <sup>a</sup> at |                     |               |                  |                        |
|---|---------------------|---------------|------------------|------------------------|
| Dose Group (ppm)                                  | Pretest             |               |                  |                        |
|   | RBC ( $10^{12}$ /L) | HGB (g/L)     | HCT (unity)      | Reticulo-cytes (unity) |
| 0   | 6.17 $\pm$ 0.39     | 126 $\pm$ 4   | 0.36 $\pm$ 0.02  | 0.039 $\pm$ 0.011      |
| 200   | 5.95 $\pm$ 0.34     | 124 $\pm$ 6   | 0.35 $\pm$ 0.02  | 0.027 $\pm$ 0.009      |
| 800   | 6.12 $\pm$ 0.39     | 127 $\pm$ 4   | 0.36 $\pm$ 0.02  | 0.033 $\pm$ 0.007      |
| 3200  | 6.35 $\pm$ 0.35     | 134 $\pm$ 8*  | 0.37 $\pm$ 0.02  | 0.035 $\pm$ 0.013      |
| -----   |                     |               |                  |                        |
| Dose Group (ppm)                                  | 26 Weeks            |               |                  |                        |
|   | RBC ( $10^{12}$ /L) | HGB (g/L)     | HCT (unity)      | Reticulo-cytes (unity) |
| 0   | 7.87 $\pm$ 0.51     | 151 $\pm$ 9   | 0.43 $\pm$ 0.02  | 0.014 $\pm$ 0.007      |
| 200   | 7.64 $\pm$ 0.20     | 148 $\pm$ 4   | 0.42 $\pm$ 0.01  | 0.020 $\pm$ 0.007      |
| 800   | 7.69 $\pm$ 0.39     | 149 $\pm$ 6   | 0.42 $\pm$ 0.02  | 0.021 $\pm$ 0.006      |
| 3200  | 7.26 $\pm$ 0.33*    | 143 $\pm$ 7   | 0.41 $\pm$ 0.02  | 0.021 $\pm$ 0.006      |
| -----   |                     |               |                  |                        |
| Dose Group (ppm)                                  | 52 Weeks            |               |                  |                        |
|   | RBC ( $10^{12}$ /L) | HGB (g/L)     | HCT (unity)      | Reticulo-cytes (unity) |
| 0   | 7.95 $\pm$ 0.50     | 160 $\pm$ 6   | 0.45 $\pm$ 0.03  | 0.017 $\pm$ 0.007      |
| 200   | 7.53 $\pm$ 0.54     | 157 $\pm$ 5   | 0.43 $\pm$ 0.03  | 0.027 $\pm$ 0.008      |
| 800   | 7.89 $\pm$ 0.35     | 159 $\pm$ 3   | 0.45 $\pm$ 0.01  | 0.024 $\pm$ 0.009      |
| 3200  | 6.68 $\pm$ 1.51*    | 140 $\pm$ 24* | 0.39 $\pm$ 0.07* | 0.064 $\pm$ 0.107*     |
| -----   |                     |               |                  |                        |
| Dose Group (ppm)                                  | 78 Weeks            |               |                  |                        |
|   | RBC ( $10^{12}$ /L) | HGB (g/L)     | HCT (unity)      | Reticulo-cytes (unity) |
| 0   | 7.87 $\pm$ 0.63     | 158 $\pm$ 10  | 0.45 $\pm$ 0.02  | 0.027 $\pm$ 0.010      |
| 200   | 7.53 $\pm$ 0.30     | 155 $\pm$ 5   | 0.44 $\pm$ 0.01  | 0.029 $\pm$ 0.008      |
| 800   | 7.76 $\pm$ 0.44     | 158 $\pm$ 8   | 0.44 $\pm$ 0.02  | 0.032 $\pm$ 0.007      |
| 3200  | 7.09 $\pm$ 0.58*    | 145 $\pm$ 10* | 0.41 $\pm$ 0.03* | 0.041 $\pm$ 0.010      |
| -----   |                     |               |                  |                        |
| Dose Group (ppm)                                  | 104 Weeks           |               |                  |                        |
|   | RBC ( $10^{12}$ /L) | HGB (g/L)     | HCT (unity)      | Reticulo-cytes (unity) |
| 0   | 7.19 $\pm$ 0.59     | 148 $\pm$ 10  | 0.42 $\pm$ 0.03  | 0.032 $\pm$ 0.016      |
| 200   | 6.80 $\pm$ 0.53     | 139 $\pm$ 8   | 0.39 $\pm$ 0.02  | 0.037 $\pm$ 0.016      |
| 800   | 7.25 $\pm$ 0.45     | 144 $\pm$ 7   | 0.41 $\pm$ 0.03  | 0.032 $\pm$ 0.015      |
| 3200  | 6.76 $\pm$ 0.50     | 134 $\pm$ 7*  | 0.39 $\pm$ 0.02* | 0.040 $\pm$ 0.019      |

<sup>a</sup>Based on 10 rats/group except the terminal blood analysis in which 20 rats/group were examined.

\*Significantly different from control value (p < 0.05).

## b. Clinical Chemistry

| <u>Electrolytes</u> |  | <u>Other</u> |  |
|---------------------|--|--------------|--|
| X                   | Calcium <sup>†</sup>                                       |              | Albumin <sup>†</sup>                   |
| X                   | Chloride <sup>†</sup>                                      | X            | Blood creatinine <sup>†</sup>          |
|                     | Magnesium <sup>†</sup>                                     | X            | Blood urea nitrogen <sup>†</sup> (BUN) |
| X                   | Phosphorus <sup>†</sup>                                    | X            | Cholesterol <sup>†</sup>               |
| X                   | Potassium <sup>†</sup>                                     |              | Globulins                              |
| X                   | Sodium <sup>†</sup>  | X            | Glucose <sup>†</sup>                   |
| <u>Enzymes</u>      |  | X            | Total bilirubin <sup>†</sup>           |
| X                   | Alkaline phosphatase (ALP)                                 | X            | Direct bilirubin                       |
|                     | Cholinesterase   | X            | Total protein <sup>†</sup>             |
|                     | Creatinine phosphokinase <sup>†</sup>                      |              | Protein quotient (A/G ratio)           |
| X                   | Lactic acid dehydrogenase                                  |              | Triglycerides                          |
| X                   | Serum alanine aminotransferase (also SGPT) <sup>†</sup>    | X            | Uric acid                              |
| X                   | Serum aspartate amino-transferase (also SGOT) <sup>†</sup> | X            | Electrophoresis                        |

Bromosulfophthalein (BSP) and phenosulfonphthalein (PSP) were determined on satellite groups of six rats/sex/dose dosed 25 months. These determinations were made at 6, 12, 18, 24 months.

Results: The authors stated that there were no changes of toxicologic importance in the biochemical data. There were no significant changes in the levels for 23 parameters in males and 19 parameters in females when compared to controls; however, these were sporadic changes and were within the range of age-strain-matched historical laboratory controls. The hepatic (BSP) and renal (PSP) function tests were similar in control and dosed groups. Histological examination of the liver and kidneys correlated with these results.

6. Urinalyses: Urine was collected from fasted animals of the chronic study at the same intervals as blood. The CHECKED parameters were examined.

|   |                                     |   |                        |
|---|-------------------------------------|---|------------------------|
| X | Appearance <sup>†</sup>             | X | Glucose <sup>†</sup>   |
|   | Volume <sup>†</sup>                 | X | Ketones <sup>†</sup>   |
| X | Specific gravity <sup>†</sup>       | X | Bilirubin <sup>†</sup> |
| X | pH                                  | X | Blood <sup>†</sup>     |
| X | Sediment (microscopic) <sup>†</sup> |   | Nitrate                |
| X | Protein <sup>†</sup>                | X | Urobilinogen           |
| X | Color                               | X | Ascorbic acid**        |

<sup>†</sup>Recommended by Subdivision F.

\*\* Ascorbic acid was determined in controls and animals receiving 3200 ppm at 52, 78, and 105 weeks and in animals receiving 200 ppm at 78 and 105 weeks.

Results: The urine of dosed animals showed a dark yellow yellowish-orange discoloration which was dependent on the concentration of dose. This was reported to be attributable to excretion of trifluralin or its metabolites. Ascorbic acid was detected in the urine of males and females fed 3200 ppm.

7. Sacrifice and Pathology: All animals that died and that were sacrificed on schedule were subject to gross pathologic examination and the CHECKED (X) tissues were collected for histological examination. The (XX) organs were also weighed.

| <u>Digestive system</u> | <u>Cardiovasc./Hemat.</u> | <u>Neurologic</u>            |
|-------------------------|---------------------------|------------------------------|
| X Nasal septum          | X Aorta†                  | XX Brain†                    |
| X Tongue                | XX Heart†                 | Peripheral nerve             |
| X Salivary gland†       | XX Bone marrow†           | X (sciatic nerve)†           |
| X Esophagus†            | X Spinal marrow†          | Spinal cord (3 levels)       |
| X Stomach†              | X Lymph nodes†            | XX Pituitary†                |
| X Duodenum†             | XX Spleen†                | X Eyes (optic nerve)†        |
| X Jejunum†              | XX Thymus†                | <u>Glandular</u>             |
| X Ileum†                | <u>Urogenital</u>         | XX Adrenals†                 |
| X Cecum†                | XX Kidneys†               | Lacrimal gland               |
| X Colon†                | X Urinary bladder†        | X Mammary gland†             |
| X Rectum†               | XX Testes†                | Parathyroids†                |
| XX Liver†               | X Epididymides            | XX Thyroids†                 |
| Gall bladder†           | XX Prostate               | <u>Other</u>                 |
| X Pancreas†             | X Seminal vesicle         | X Bone (sternum)†            |
| <u>Respiratory</u>      | XX Ovaries                | X Skeletal muscle†           |
| X Trachea†              | X Uterus                  | X Skin                       |
| XX Lung†                |                           | X All gross lesions & masses |

The aorta was not collected for histological examination during the oncogenicity study; all other organs collected and weighed were similar for both studies.

### Results:

#### a. Organ Weights:

1. Chronic Toxicity Study - The absolute mean liver and thyroid weights were found to be slightly increased in males and females receiving 3200 ppm; these increases were reported to be compound related (Table 9). These increases were not statistically significant ( $p < 0.05$ ) when compared to control values. Absolute mean prostate weight in males fed 3200 ppm and absolute heart weight in females fed 800 or 3200 ppm were found to be significantly ( $p < 0.05$ ) decreased; relative prostate weight was not significantly decreased.

†Recommended by Subdivision F.

TABLE 9. Selected Mean Organ Weights ( $\pm$ SD) and Organ-To-Body Weight Ratios of Rats Fed Trifluralin for 24 Months - Chronic Study

| Dose Level (ppm) | Organ Weight (g)                         |                              |                             |                             | Organ/Body Weight (%)       |                               |                             |                            |
|------------------|--|------------------------------|-----------------------------|-----------------------------|-----------------------------|-------------------------------|-----------------------------|----------------------------|
|                  | Liver                                    | Thyroid                      | Heart                       | Prostate                    | Liver                       | Thyroid                       | Heart                       | Prost                      |
| <u>MALES</u>     |  |                              |                             |                             |                             |                               |                             |                            |
| 0                | 16.73<br>$\pm$ 2.20<br>(23) <sup>a</sup> | 0.026<br>$\pm$ 0.006<br>(22) | 1.63<br>$\pm$ 0.18<br>(23)  | 0.81<br>$\pm$ 0.22<br>(23)  | 3.18<br>$\pm$ 0.31<br>(23)  | 0.005<br>$\pm$ 0.001<br>(22)  | 0.31<br>$\pm$ 0.04<br>(23)  | 0.15<br>$\pm$ 0.03<br>(23) |
| 200              | 17.52<br>$\pm$ 2.19<br>(21)              | 0.029<br>$\pm$ 0.006<br>(20) | 1.67<br>$\pm$ 0.16<br>(21)  | 0.96<br>$\pm$ 0.28<br>(21)  | 3.22<br>$\pm$ 0.32<br>(21)  | 0.005<br>$\pm$ 0.001<br>(20)  | 0.31<br>$\pm$ 0.03<br>(21)  | 0.18<br>$\pm$ 0.04<br>(21) |
| 800              | 16.18<br>$\pm$ 2.24<br>(24)              | 0.030<br>$\pm$ 0.006<br>(24) | 1.55<br>$\pm$ 0.15<br>(24)  | 0.71<br>$\pm$ 0.22<br>(24)  | 3.29<br>$\pm$ 0.28<br>(24)  | 0.006*<br>$\pm$ 0.001<br>(24) | 0.32<br>$\pm$ 0.04<br>(24)  | 0.14<br>$\pm$ 0.04<br>(24) |
| 3200             | 17.07<br>$\pm$ 2.87<br>(23)              | 0.030<br>$\pm$ 0.006<br>(23) | 1.51<br>$\pm$ 0.17<br>(23)  | 0.65*<br>$\pm$ 0.15<br>(23) | 3.90*<br>$\pm$ 0.56<br>(23) | 0.007*<br>$\pm$ 0.001<br>(23) | 0.35*<br>$\pm$ 0.30<br>(23) | 0.15<br>$\pm$ 0.03<br>(23) |
| <u>FEMALES</u>   |  |                              |                             |                             |                             |                               |                             |                            |
| 0                | 10.85<br>$\pm$ 2.35<br>(21)              | 0.024<br>$\pm$ 0.005<br>(20) | 1.25<br>$\pm$ 0.21<br>(21)  |                             | 3.19<br>$\pm$ 0.41<br>(21)  | 0.007<br>$\pm$ 0.001<br>(20)  | 0.38<br>$\pm$ 0.09<br>(21)  |                            |
| 200              | 10.94<br>$\pm$ 1.70<br>(20)              | 0.023<br>$\pm$ 0.005<br>(18) | 1.16<br>$\pm$ 0.13<br>(20)  |                             | 3.24<br>$\pm$ 0.31<br>(20)  | 0.007<br>$\pm$ 0.001<br>(18)  | 0.35<br>$\pm$ 0.04<br>(20)  |                            |
| 800              | 11.31<br>$\pm$ 1.25<br>(21)              | 0.024<br>$\pm$ 0.005<br>(21) | 1.14*<br>$\pm$ 0.11<br>(21) |                             | 3.47<br>$\pm$ 0.37<br>(21)  | 0.008<br>$\pm$ 0.002<br>(21)  | 0.35<br>$\pm$ 0.05<br>(21)  |                            |
| 3200             | 11.25<br>$\pm$ 1.27<br>(19)              | 0.024<br>$\pm$ 0.006<br>(18) | 1.07<br>$\pm$ 0.09*<br>(19) |                             | 4.33*<br>$\pm$ 0.47<br>(19) | 0.009*<br>$\pm$ 0.002<br>(18) | 0.41*<br>$\pm$ 0.04<br>(19) |                            |

<sup>a</sup> The numbers in parentheses are the numbers of animals/sex/group; this included a satellite group of 6 animals/sex/group tested for BSP/PSP function analyses.

\* Significantly different from control value ( $p < 0.05$ ).

Organ-to-body weight ratios of the heart, lungs, liver, kidneys, spleen, testes, ovaries, adrenals, brain, and thyroid were found to be significantly ( $p < 0.05$ ) increased in high-dose males and females; however, these values are considered to be a reflection of the decreased body weights of these animals and are therefore not considered to be compound related.

2. Oncogenicity Study - The absolute mean liver and thyroid weights of males receiving 800 and 3200 ppm were found to be slightly increased relative to controls (Table 10). These increases were reported to be compound related; however, the values did not differ significantly ( $p < 0.05$ ) when compared to controls and there were no histological changes to correlate with these increased weights. The absolute mean lung weight of females fed 3200 ppm was found to be slightly increased while the absolute kidney weight of this same group was found to be slightly decreased.

Organ-to-body weight ratios of the heart, lungs, liver, kidneys, spleen, adrenals, thyroid, and brain of males fed 800 or 3200 ppm were found to be significantly ( $p < 0.05$ ) increased relative to controls, whereas the liver of females fed 800 ppm and the heart, lungs, liver, spleen, ovaries, thyroid, and brain of females fed 3200 ppm were found to be significantly ( $p < 0.05$ ) increased. As in the chronic toxicity study, these increased values are considered to be a reflection of the decreased body weights of these animals and are therefore not considered to be compound related.

A slight dose-related decrease in absolute and relative prostate weights in males was found with a significant ( $p < 0.05$ ) decrease reported in the relative weights of high-dose males. However, this was reported to be unrelated to dosing since the absolute values were within the normal range of historical controls and histological examination revealed no change in the prostates of these animals.

A significant ( $p < 0.05$ ) dose-related decrease in the absolute and relative pituitary weights was found in females fed 200, 800, or 3200 ppm; only the relative pituitary weights of females fed 3200 ppm were reported to be significantly ( $p < 0.05$ ) decreased by the study authors. This decreased trend was the result of a marked increase in the absolute pituitary weights of female rats; the increase was most pronounced in control animals. This was reported to be the result of a random increase in the incidence of pathological pituitary changes in female controls. Histological examination indicated more than a 50 percent incidence of combined adenomas (30/60) and carcinomas (2/60) in female

TABLE 10. Selected Mean Organ Weights ( $\pm$ SD) and Organ-to-Body Weight Ratios of Rats Fed Trifluralin for 28 Months - Oncogenicity Study

| Dose Level (ppm) | Organ Weight (g)                         |                              |                                | Organ/Body Weight (%)       |                               |   |
|------------------|--|------------------------------|--------------------------------|-----------------------------|-------------------------------|---|
|                  | Liver                                    | Thyroid                      | Pituitary                      | Liver                       | Thyroid                       | Pituitary                                   |
| MALES            |  |                              |                                |                             |                               |   |
| 0                | 15.65<br>$\pm 2.47$<br>(41) <sup>a</sup> | 0.027<br>$\pm 0.009$<br>(40) | 0.015<br>$\pm 0.009$<br>(41)   | 3.22<br>$\pm 0.44$<br>(41)  | 0.006<br>$\pm 0.002$<br>(40)  | 0.003<br>$\pm 0.002$<br>(41)                |
| 200              | 15.67<br>$\pm 2.02$<br>(42)              | 0.030<br>$\pm 0.009$<br>(40) | 0.016<br>$\pm 0.013$<br>(42)   | 3.22<br>$\pm 0.43$<br>(42)  | 0.006<br>$\pm 0.002$<br>(40)  | 0.003<br>$\pm 0.003$<br>(42)                |
| 800              | 16.15<br>$\pm 3.34$<br>(38)              | 0.031<br>$\pm 0.007$<br>(33) | 0.024<br>$\pm 0.034$<br>(38)   | 3.64*<br>$\pm 0.64$<br>(38) | 0.007*<br>$\pm 0.002$<br>(33) | 0.006<br>$\pm 0.010$<br>(38)                |
| 3200             | 17.52<br>$\pm 5.85$<br>(34)              | 0.030<br>$\pm 0.007$<br>(33) | 0.014<br>$\pm 0.005$<br>(34)   | 4.28*<br>$\pm 1.40$<br>(34) | 0.007*<br>$\pm 0.002$<br>(33) | 0.003<br>$\pm 0.001$<br>(34)                |
| FEMALES          |  |                              |                                |                             |                               |   |
| 0                | 10.66<br>$\pm 1.75$<br>(34)              | 0.022<br>$\pm 0.005$<br>(31) | 0.096<br>$\pm 0.11$<br>(34)    | 3.39<br>$\pm 0.40$<br>(34)  | 0.007<br>$\pm 0.002$<br>(31)  | 0.038<br>$\pm 0.054$<br>(34)                |
| 200              | 11.58<br>$\pm 2.69$<br>(37)              | 0.023<br>$\pm 0.006$<br>(37) | 0.058**<br>$\pm 0.08$<br>(37)  | 3.59<br>$\pm 0.51$<br>(37)  | 0.007<br>$\pm 0.002$<br>(37)  | 0.021** <sup>t</sup><br>$\pm 0.034$<br>(37) |
| 800              | 10.95<br>$\pm 1.76$<br>(35)              | 0.023<br>$\pm 0.005$<br>(34) | 0.036**<br>$\pm 0.056$<br>(35) | 3.72*<br>$\pm 0.50$<br>(35) | 0.008<br>$\pm 0.002$<br>(34)  | 0.013** <sup>t</sup><br>$\pm 0.024$<br>(35) |
| 3200             | 10.80<br>$\pm 1.51$<br>(40)              | 0.025<br>$\pm 0.006$<br>(37) | 0.025**<br>$\pm 0.043$<br>(40) | 4.24*<br>$\pm 0.46$<br>(40) | 0.010*<br>$\pm 0.002$<br>(37) | 0.010<br>$\pm 0.018$ **<br>(40)             |

<sup>a</sup> Numbers in parentheses are the numbers of animals/sex/group.

<sup>b</sup> Not reported as significant by authors using the method of Nemenyi/Sida

\* Significantly different from control value ( $p < 0.05$ ).

\*\* Significantly different from control value ( $p < 0.01$ ) as calculated by reviewers using ANOVA followed by Duncans' test for multiple comparison

controls, a 48 percent incidence at 200 ppm (28/60 adenomas and 1/60 carcinomas), a 37 percent incidence at 800 ppm (20/60 adenomas) and a 17 percent incidence at 3200 ppm (10/60 adenomas). Hyperplasia of the pituitary was also found in all treatment groups. The decreased trend in pituitary weight is therefore not considered to be compound related. Absolute and relative pituitary weights in males were consistent between dose levels with the exception of the 800-ppm dosed group, which was found to be slightly increased relative to controls. Histological examination indicated hyperplasia (11/60) and an 11% incidence of adenomas (7/60) in this group. There were no corresponding effects on pituitary weights or histologic changes in the chronic study. The increased incidence of adenomas and carcinomas of the thyroid found in females was not considered to be of biological importance due to the age of the animals.

b. Gross Pathology: Males and females fed 800 and 3200 ppm trifluralin during the chronic toxicity and oncogenicity studies were reported to have yellow discoloration of the fatty tissue, especially prominent in the abdominal region. This was considered to be a result of compound residues. Other findings occurred randomly and were not considered to be compound related.

c. Microscopic Pathology:

1. Nonneoplastic:

a. Chronic Toxicity Study - There were no compound-related histopathological findings. The discolored fatty tissue was considered to be a histologically undetectable deposition of trifluralin. Table 11 summarizes histologic findings; the type and frequency of these findings were reported to be common for the age, strain, and sex of the animal. Alveolar histiocytosis of the lung was increased in high-dose males and females relative to controls; this was reported due to chance variability and of no toxicologic importance. Many males and females (all groups) had chronic progressive glomerulonephropathy. In most cases, the incidence of the histologic change was markedly increased among the controls, e.g., pituitary adenomas in female rats.

b. Oncogenicity Study - There were no compound-related histopathological findings. Table 12 summarizes nonneoplastic findings; these were considered to be incidental age-related changes and were not related to dosing. Many of the findings were similar to those identified in the chronic toxicity study. Pneumonitis of the lung was increased in high-dose

TABLE 11. Selected Histologic Findings of Rats Fed Trifluralin for 24 Months - Chronic Study<sup>a</sup>

| Organ/Finding                         | Dose Level (ppm) |     |     |      |         |     |     |      |
|---------------------------------------|------------------|-----|-----|------|---------|-----|-----|------|
|                                       | Males            |     |     |      | Females |     |     |      |
|                                       | 0                | 200 | 800 | 3200 | 0       | 200 | 800 | 3200 |
| Number of tissues examined            | 26 <sup>b</sup>  | 26  | 26  | 26   | 26      | 26  | 26  | 26   |
| <u>Lung</u>                           |                  |     |     |      |         |     |     |      |
| Histiocytosis                         | 2                | 8   | 1   | 7    | 6       | 3   | 3   | 14   |
| <u>Kidney</u>                         |                  |     |     |      |         |     |     |      |
| Pelvic distention                     | 2                | 2   | 4   | 3    | 1       | 5   | 5   | 4    |
| Urinary gravel                        | 3                | 4   | 2   | 6    | 5       | 8   | 9   | 5    |
| Chronic glomerulo-nephropathy         | 8                | 11  | 12  | 10   | 3       | 2   | 3   | 5    |
| Tubular dilatation with hyaline cysts | 10               | 10  | 6   | 4    | 4       | 0   | 2   | 1    |
| <u>Liver</u>                          |                  |     |     |      |         |     |     |      |
| Bile duct proliferation               | 14               | 15  | 15  | 1    | 6       | 2   | 7   | 6    |
| Cholangiofibrosis                     | 14               | 12  | 5   | 4    | 2       | 5   | 8   | 3    |
| Biliary cysts                         | 5                | 0   | 0   | 1    | 0       | 2   | 3   | 5    |
| <u>Pancreas</u>                       |                  |     |     |      |         |     |     |      |
| Focal atrophy                         | 3                | 6   | 2   | 1    | 5       | 3   | 2   | 3    |
| <u>Stomach</u>                        |                  |     |     |      |         |     |     |      |
| Cystic dilatation of fundus glands    | 13               | 7   | 10  | 3    | 14      | 10  | 11  | 11   |
| <u>Thyroid</u>                        |                  |     |     |      |         |     |     |      |
| Colloid cyst                          | 2                | 1   | 6   | 3    | 0       | 2   | 0   | 4    |
| Papillary adenoma                     | 0                | 0   | 0   | 1    | 0       | 0   | 0   | 0    |
| Follicular adenoma                    | 0                | 1   | 0   | 0    | 0       | 0   | 1   | 1    |

(Continued)



TABLE 11. Selected Histologic Findings of Rats Fed Trifluralin for 24 Months - Chronic Study<sup>a</sup> (Continued)

| Organ/Finding                      | Dose Level (ppm) |     |     |      |         |     |     |
|------------------------------------|------------------|-----|-----|------|---------|-----|-----|
|                                    | Males            |     |     |      | Females |     |     |
|                                    | 0                | 200 | 800 | 3200 | 0       | 200 | 800 |
| <u>Pituitary</u>                   |                  |     |     |      |         |     |     |
| Adenoma of anterior lobe           | 2                | 5   | 2   | 1    | 12      | 14  | 9   |
| Focal hyperplasia of anterior lobe | 0                | 0   | 2   | 1    | 0       | 0   | 3   |
| <u>Brain</u>                       |                  |     |     |      |         |     |     |
| Granular cell tumor                | 0                | 1   | 0   | 0    | 0       | 0   | 0   |
| <u>Mammary gland</u>               |                  |     |     |      |         |     |     |
| Adenocarcinoma                     |                  |     |     |      | 2       | 6   | 1   |
| <u>Testes</u>                      |                  |     |     |      |         |     |     |
| Leydig cell tumor                  | 1                | 2   | 6   | 3    |         |     |     |
| Hyperplasia of Leydig cells        | 3                | 2   | 3   | 2    |         |     |     |
| <u>Ovary</u>                       |                  |     |     |      |         |     |     |
| Cyst                               |                  |     |     |      | 5       | 5   | 4   |
| <u>Uterus</u>                      |                  |     |     |      |         |     |     |
| Endometrial cysts                  |                  |     |     |      | 4       | 4   | 1   |
| <u>Eye</u>                         |                  |     |     |      |         |     |     |
| Retinal atrophy                    | 2                | 4   | 3   | 9    | 8       | 5   | 8   |
| Bulbar trauma                      | 1                | 4   | 4   | 5    | 0       | 2   | 2   |
| <u>Sciatic Nerve</u>               |                  |     |     |      |         |     |     |
| Degeneration of nerve fibers       | 9                | 15  | 17  | 10   | 10      | 11  | 15  |
| <u>Skeletal Muscle</u>             |                  |     |     |      |         |     |     |
| Atrophy                            | 4                | 7   | 7   | 10   | 1       | 2   | 7   |

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<sup>a</sup> Pathology conducted at Hoechst Aktiengesellschaft.

<sup>b</sup> Includes animals from the 24-month chronic study, satellite groups of a tested for BSP/PSP function analyses, animals that were sacrificed at te tion and animals that were sacrificed moribund or died.

TABLE 12. Selected Nonneoplastic Histologic Findings of Rats Fed Trifluralin for 28 Months - Oncogenicity Study<sup>a</sup>

| Organ/Finding              | Dose Level (ppm) |     |     |      |         |     |     |      |
|----------------------------|------------------|-----|-----|------|---------|-----|-----|------|
|                            | Males            |     |     |      | Females |     |     |      |
|                            | 0                | 200 | 800 | 3200 | 0       | 200 | 800 | 3200 |
| Number of tissues examined | 60 <sup>b</sup>  | 60  | 60  | 60   | 60      | 60  | 60  | 60   |
| <u>Lung</u>                |                  |     |     |      |         |     |     |      |
| Pneumonitis                | 2                | 5   | 5   | 5    | 4       | 2   | 2   | 13   |
| <u>Kidneys</u>             |                  |     |     |      |         |     |     |      |
| Glomerulonephrosis         | 24               | 19  | 23  | 27   | 8       | 8   | 3   | 10   |
| Basophilic/dilated tubules | 10               | 13  | 12  | 4    | 0       | 3   | 0   | 0    |
| Pelvic dilatation          | 3                | 6   | 12  | 17   | 14      | 17  | 19  | 13   |
| Urothelial hyperplasia     | 2                | 4   | 3   | 7    | 13      | 1   | 8   | 21   |
| Pelvic calculi             | 3                | 6   | 10  | 9    | 19      | 22  | 26  | 24   |
| <u>Spleen</u>              |                  |     |     |      |         |     |     |      |
| Hemosiderosis              | 7                | 10  | 14  | 11   | 24      | 28  | 18  | 26   |
| <u>Liver</u>               |                  |     |     |      |         |     |     |      |
| Vacuolated hepatocytes     | 10               | 16  | 16  | 9    | 4       | 3   | 11  | 2    |
| Eosinophilic hepatocytes   | 2                | 2   | 9   | 5    | 2       | 6   | 5   | 8    |
| Bile duct hyperplasia      | 21               | 15  | 21  | 4    | 12      | 13  | 19  | 11   |
| <u>Lymph nodes</u>         |                  |     |     |      |         |     |     |      |
| Dilated sinuses            | 13               | 16  | 21  | 16   | 12      | 15  | 9   | 9    |
| Histiocytosis              | 13               | 20  | 28  | 18   | 15      | 17  | 16  | 19   |
| <u>Adrenals</u>            |                  |     |     |      |         |     |     |      |
| Cortical vacuolation       | 31               | 16  | 20  | 23   | 1       | 3   | 7   | 1    |
| Congested                  | 0                | 2   | 3   | 5    | 18      | 19  | 16  | 11   |
| Cystic degeneration        | 0                | 0   | 0   | 1    | 7       | 9   | 10  | 5    |
| <u>Pituitary</u>           |                  |     |     |      |         |     |     |      |
| Hyperplasia                | 7                | 11  | 11  | 10   | 6       | 7   | 10  | 11   |
| <u>Mammary gland</u>       |                  |     |     |      |         |     |     |      |
| Hyperplasia                | 1                | 1   | 0   | 2    | 10      | 7   | 7   | 6    |
| <u>Testes</u>              |                  |     |     |      |         |     |     |      |
| Atrophy                    | 8                | 10  | 10  | 20   |         |     |     |      |
| <u>Uterus</u>              |                  |     |     |      |         |     |     |      |
| Dilated gland              |                  |     |     |      | 11      | 5   | 4   | 20   |
| <u>Sciatic nerve</u>       |                  |     |     |      |         |     |     |      |
| Nerve fiber degeneration   | 42               | 38  | 45  | 40   | 26      | 35  | 26  | 28   |
| <u>Skeletal muscle</u>     |                  |     |     |      |         |     |     |      |
| Atrophy                    | 24               | 30  | 34  | 40   | 19      | 11  | 17  | 21   |

<sup>a</sup> Pathology conducted at Huntingdon Research Center, Huntingdon, England.

<sup>b</sup> Includes animals sacrificed at termination and those that were sacrificed

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females relative to controls; this was reported due to chance variability and of no toxicologic importance. Many males and females (all groups) had dilated sinuses and histiocytosis of the lymph nodes, bile duct hyperplasia, hemosiderosis of the spleen, hyperplasia of the pituitary, and chronic glomerulonephropathy. Renal pelvic dilatation and urothelial hyperplasia found in males and females were reported to be associated with renal calculi, which were prevalent in all animals. These findings were reported to be common for the age, strain, and sex of the animals. As in the chronic study, the incidence of the finding was at least as prevalent among the controls as the dosed animals.

2. Neoplastic - Oncogenicity Study: Table 13 summarizes neoplastic histopathologic findings in rats dosed with trifluralin during the oncogenicity study. There were no compound-related increases in tumors at any site. The only statistically identified alteration in tumor incidence was reported to be an increase in granular cell meningiomas of the brain in males fed 3200 ppm trifluralin. This was significantly different from control incidence ( $p < 0.05$ ) in high-dose males and there was a significant linear trend ( $p < 0.001$ ). However, granular cell meningiomas are benign neoplasms found to occur spontaneously in older rats of various strains.<sup>1</sup> Since the Hoe WISKf(SPF71) Wistar rat strain was not referenced, the study laboratory compiled data regarding the incidence of granular cell tumors in past studies of 25-30 months (CBI pages 1111-1116). The results were found to be comparable to the referenced data. The incidence of granular cell tumors in the Hoe WISKf(SPF71) Wistar rat strain was found to be variable, ranging from 0-12 percent in collectives of 50-60 control animals of comparable ages; male rats displayed a higher incidence relative to females. In the trifluralin oncogenicity study, the granular cell tumors were found principally in high-dose males and were reported to be small in size; the incidence did not show any apparent dose relationship (0/60 in control males, 1/60 in 200-ppm males, 0/60 in 800-ppm males, and 7/60 in 3200-ppm males). In addition, the incidence of this tumor type was only minimal in females and animals of the chronic study fed trifluralin for 24 months (Table 11). Therefore, this finding was considered random and was not considered to be compound related.

A significant ( $p < 0.05$ ) linear trend was found in the incidence of benign liver cell tumors in males receiving

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<sup>1</sup>Burek, J.D. 1978. Pathology of Aging Rats. CRC Press, p. 145.

TABLE 13. Incidence of Neoplastic Lesions in Rats Fed Trifluralin for 28 Months<sup>a</sup>

| Organ/Finding                 | Dose Level (ppm)  |      |      |                 |         |      |      |                |
|-------------------------------|-------------------|------|------|-----------------|---------|------|------|----------------|
|                               | Males             |      |      |                 | Females |      |      |                |
|                               | 0                 | 200  | 800  | 3200            | 0       | 200  | 800  | 3200           |
| <u>Liver</u>                  | (60) <sup>b</sup> | (60) | (60) | (60)            | (60)    | (59) | (60) | (59)           |
| Malignant liver cell tumor    | 1                 | 2    | 1    | 1               | 0       | 0    | 1    | 0              |
| Benign liver cell tumor       | 0                 | 0    | 0    | 3 <sup>T</sup>  | 0       | 0    | 1    | 1              |
| <u>Thyroid</u>                | (60)              | (58) | (60) | (60)            | (59)    | (58) | (60) | (59)           |
| Parafollicular cell carcinoma | 3                 | 4    | 3    | 0               | 1       | 0    | 1    | 0              |
| Follicular adenoma            | 4                 | 3    | 3    | 6               | 4       | 1    | 3    | 6 <sup>T</sup> |
| Follicular adenocarcinoma     | 0                 | 0    | 2    | 0               | 0       | 1    | 0    | 2 <sup>T</sup> |
| <u>Pituitary</u>              | (53)              | (52) | (59) | (56)            | (54)    | (59) | (60) | (58)           |
| Adenoma                       | 9                 | 9    | 7    | 4               | 30      | 28   | 20   | 10             |
| Carcinoma                     | -                 | -    | -    | -               | 2       | 1    | 2    | 0              |
| <u>Brain</u>                  | (60)              | (59) | (60) | (59)            | (60)    | (60) | (60) | (59)           |
| Granular cell meningioma      | 0                 | 1    | 0    | 7 <sup>*T</sup> | 2       | 0    | 0    | 1              |
| <u>Testes</u>                 | (60)              | (60) | (60) | (60)            |         |      |      |                |
| Interstitial cell tumor       | 9                 | 8    | 7    | 4               |         |      |      |                |
| <u>Mammary gland</u>          |                   |      |      |                 | (17)    | (19) | (17) | (15)           |
| Fibroadenoma                  |                   |      |      |                 | 9       | 8    | 6    | 6              |
| Adenocarcinoma                |                   |      |      |                 | 8       | 8    | 8    | 6              |
| <u>Uterus</u>                 |                   |      |      |                 | (60)    | (59) | (60) | (59)           |
| Adenocarcinoma                |                   |      |      |                 | 2       | 0    | 3    | 5 <sup>c</sup> |

<sup>a</sup> Includes animals sacrificed at study termination and those that died or were sacrificed moribund in the course of the study. If a neoplasm occurred with an incidence of only 1/60 or if a higher incidence was found only in control animals, it was not tabulated.

<sup>b</sup> The numbers in parentheses are the numbers of tissues examined histologically.

<sup>c</sup> Reported to be a significant trend by the study authors; when recalculated by our reviewers using the Cochran-Armitage test, this trend was not found to be significant.

\*Significantly different from control value ( $p \leq 0.05$ ).

<sup>T</sup>Significant trend ( $p \leq 0.05$ ).

3200 ppm and in the incidence of follicular adenoma and adenocarcinoma of the thyroid of females receiving 3200 ppm. However, the incidence of these tumors was not found to be statistically significant ( $p \leq 0.05$ ) on pairwise comparison. Since the total incidence was low, these variations were considered to be of no toxicologic significance. Pituitary adenomas and carcinomas found in the males and females (total tumor incidence in males was 13% and in females, 40%) were principally found in controls and low-dose animals. Mammary tumors in females were also more prevalent in controls and females receiving 200 or 800 ppm. These variations were considered to be age, sex, and strain related, and of no toxicologic significance.

3. Residue Analysis - Chronic Toxicity Study - Table 14 summarizes the trifluralin residues found in organs and tissues of rats tested at 6, 12, 18, and 24 months. The residues were found to be dose related in organs and tissues and were not found to be accumulative over 24 months, with the exception of the carcass residue, where a time-related increase was reported. Females showed higher residue levels in all tissues examined relative to males.

D. STUDY AUTHORS' CONCLUSIONS:

The authors concluded that the NOEL for the studies was 800 ppm for male and female rats, which corresponded to a compound intake of 42.1 mg/kg/day in males and 52.7 mg/kg/day in females of the chronic toxicity study and 40 mg/kg/day in males and 53 mg/kg/day in females of the oncogenicity study. The occurrence of granular cell meningiomas in male rats of the oncogenicity study was reported to be age related and random. Trifluralin was reported to have no carcinogenic effect in rats.

E. REVIEWERS' DISCUSSION AND INTERPRETATION OF RESULTS:

The study design was adequate and complete and the conduct of the study and reporting of data were acceptable. However, a histopathology incidence table indicating grade of neoplasia or severity of finding as well as the results of the statistical calculation of absolute organ weights for females of the oncogenicity study were not provided. The histopathology for the chronic toxicity and oncogenicity studies was conducted in two separate pathology laboratories; this may have caused a problem if discrepancies had been found in the results of the two studies. There was some discrepancy between the study authors and the reviewers in determining the statistical significance of relative pituitary weights and establishing a positive trend in the incidence of adenocarcinomas of the uterus in females of the oncogenicity study. These differences are noted in Tables 10 and 13.

TABLE 14. Representative Results of Residue (mg/kg) Found in Organs and Tissues of Rats Fed Trifluralin for 24 Months - Chronic Study<sup>a</sup>

| Organ or Tissue                  | Months | Dose Level (mg/kg) |      |      |      |         |      |      |      |
|----------------------------------|--------|--------------------|------|------|------|---------|------|------|------|
|                                  |        | Males              |      |      |      | Females |      |      |      |
|                                  |        | 0                  | 200  | 800  | 3200 | 0       | 200  | 800  | 3200 |
| <u>Liver</u> <sup>b</sup>        | 6      | <0.01              | ND   | ND   | 0.05 | <0.01   | ND   | 0.04 | 0.8  |
|                                  | 12     | <0.01              | 0.04 | ND   | 0.07 | <0.03   | ND   | 0.04 | 1.6  |
|                                  | 18     | <0.02              | ND   | ND   | ND   | <0.01   | ND   | 0.04 | 0.3  |
|                                  | 24     | —                  | —    | —    | 0.1  | —       | —    | —    | 0.5  |
| <u>Kidney</u> <sup>c</sup>       | 6      | <0.01              | ND   | 0.1  | 7.5  | <0.03   | 0.07 | 0.3  | 5.5  |
|                                  | 12     | <0.02              | ND   | 0.7  | 3.4  | <0.04   | ND   | 0.2  | 8.4  |
|                                  | 18     | <0.03              | ND   | 0.2  | 0.6  | <0.04   | 0.06 | 0.08 | 2.5  |
|                                  | 24     | <0.01              | ND   | 0.06 | 0.4  | <0.01   | ND   | 0.3  | 1.7  |
| <u>Heart</u> <sup>c</sup>        | 6      | <0.02              | ND   | ND   | 0.9  | <0.03   | ND   | ND   | 2.9  |
|                                  | 12     | <0.02              | ND   | ND   | 0.7  | <0.02   | ND   | 0.2  | 3.3  |
|                                  | 18     | <0.03              | ND   | ND   | 1.6  | <0.02   | ND   | 0.2  | 0.7  |
|                                  | 24     | <0.01              | ND   | 0.4  | 0.9  | <0.01   | ND   | 0.2  | 1.6  |
| <u>Spleen</u> <sup>d</sup>       | 6      | <0.04              | ND   | ND   | 0.4  | <0.05   | ND   | 0.8  | ND   |
|                                  | 12     | <0.03              | ND   | ND   | 0.2  | <0.06   | ND   | 0.2  | 0.7  |
|                                  | 18     | <0.05              | ND   | ND   | 0.3  | <0.04   | ND   | ND   | 1.5  |
|                                  | 24     | <0.01              | ND   | ND   | 0.3  | <0.01   | ND   | 0.1  | 1.4  |
| <u>Brain</u> <sup>e</sup>        | 6      | <0.01              | ND   | ND   | 0.1  | <0.01   | ND   | 0.02 | 1.0  |
|                                  | 12     | <0.01              | ND   | 0.02 | 0.2  | <0.01   | ND   | 0.02 | 1.0  |
|                                  | 18     | <0.01              | ND   | 0.02 | 0.05 | <0.01   | ND   | 0.02 | 0.06 |
|                                  | 24     | <0.01              | ND   | 0.01 | 0.08 | <0.01   | 0.01 | 0.06 | 0.3  |
| <u>Intestine</u> <sup>f</sup>    | 6      | <0.02              | 0.04 | 0.9  | 11   | <0.01   | 0.04 | 2.8  | 18   |
|                                  | 12     | <0.01              | 0.03 | 1.8  | 8.2  | <0.01   | 0.03 | 2.3  | 14   |
|                                  | 18     | <0.02              | ND   | 0.9  | 19   | <0.01   | ND   | 2.6  | 32   |
|                                  | 24     | <0.01              | 0.08 | 2.2  | 9.1  | <0.01   | 0.3  | 3.3  | 27   |
| <u>Fatty Tissue</u> <sup>b</sup> | 6      | <0.02              | 0.1  | 1.7  | 43   | <0.03   | 0.1  | 16   | 190  |
|                                  | 12     | <0.01              | ND   | 2.2  | 23   | <0.01   | 0.07 | 6.9  | 100  |
|                                  | 18     | <0.01              | 0.1  | 3.4  | 10   | <0.02   | 0.2  | 4.1  | 140  |
|                                  | 24     | <0.02              | ND   | 1.9  | 51   | <0.01   | 0.1  | 20   | 190  |

(Continued)

TABLE 14. Representative Results of Residue (mg/kg) Found in Organs and Tissues of Rats Fed Trifluralin for 24 Months - Chronic Study (Continued)<sup>a</sup>

| Organ or Tissue             | Months | Dose Level (mg/kg) |      |      |      |         |      |      |      |
|-----------------------------|--------|--------------------|------|------|------|---------|------|------|------|
|                             |        | Males              |      |      |      | Females |      |      |      |
|                             |        | 0                  | 200  | 800  | 3200 | 0       | 200  | 800  | 3200 |
| <u>Muscle</u> <sup>c</sup>  | 6      | <0.04              | ND   | 0.2  | 0.9  | <0.03   | ND   | 0.3  | 8.6  |
|                             | 12     | <0.02              | ND   | ND   | 0.1  | <0.03   | ND   | 0.1  | 0.5  |
|                             | 18     | <0.03              | ND   | ND   | 0.1  | <0.02   | ND   | ND   | 7.8  |
|                             | 24     | <0.01              | ND   | 0.1  | 0.4  | <0.01   | 0.08 | 0.6  | 1.4  |
| <u>Blood</u> <sup>e</sup>   | 6      | <0.01              | ND   | —    | 0.01 | <0.01   | ND   | ND   | 0.04 |
|                             | 12     | —                  | ND   | ND   | 0.02 | <0.01   | ND   | ND   | 0.07 |
|                             | 18     | <0.01              | ND   | ND   | ND   | <0.01   | ND   | —    | 0.06 |
|                             | 24     | <0.01              | ND   | 0.01 | 0.09 | <0.01   | ND   | 0.03 | 0.2  |
| <u>Carcass</u> <sup>e</sup> | 6      | <0.01              | 0.01 | ND   | 0.4  | <0.01   | ND   | 0.2  | 3.0  |
|                             | 12     | <0.01              | 0.01 | 0.2  | 0.5  | <0.01   | ND   | 0.3  | 0.6  |
|                             | 18     | <0.01              | ND   | 0.3  | 1.4  | <0.01   | 0.05 | 0.3  | 9.3  |
|                             | 24     | <0.01              | 0.02 | 0.3  | 6.3  | <0.01   | ND   | 1.5  | 22   |

(Concluded)

<sup>a</sup>Based on two rats/group.

<sup>b</sup>Based on a detection limit of 0.04 mg/kg.

<sup>c</sup>Based on a detection limit of 0.06 mg/kg.

<sup>d</sup>Based on a detection limit of 0.09 mg/kg.

<sup>e</sup>Based on a detection limit of 0.01 mg/kg.

<sup>f</sup>Based on a detection limit of 0.03 mg/kg.

ND = Not detectable; <detection limit.

— = Samples destroyed during analysis.

We agree with the authors' assessment that there was no oncogenic response. The control incidence of tumors at specific sites was at least as large as the tumor incidence of dosed animals; these findings were generally in accord to that found for the age and sex of similar strains of rats in other laboratories. The incidence of pituitary adenomas in control and low-dose females (50 and 48 percent, respectively) was high, but was not unusual considering the age of the animals. These data were compared to an average of several NTP bioassays conducted for 24 months with Fischer 344 rats.<sup>2</sup>

Absolute liver and thyroid weights were found to be slightly but non-significantly increased in males and females of the chronic toxicity and oncogenicity studies. However, there were no histologic changes in either study that correlated with these increased weights. These changes are therefore not considered to be of biological significance. There were no other absolute organ weights which consistently showed a compound-related change in the two studies.

Based on the body weight changes at 800 ppm, we assess that the chronic toxicity LOEL for the study is 800 ppm and the NOEL is 200 ppm trifluralin. The study authors set the NOEL at 800 ppm.

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<sup>2</sup> Haseman, J. K., Huff, J. and G.A. Boorman. 1984. Use of historical control data in carcinogenicity studies in rodents. Toxicol. Pathol. 12:126-135.