

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
EPA SERIES 361

CHLORSULFURON HIARC MEETING

Thursday, July 11, 2000

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John Liccione
Jess Rowland
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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OPP OFFICIAL RECORD
HEALTH EFFECTS DIVISION
SCIENTIFIC DATA REVIEWS
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OFFICE OF PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

MEMORANDUM

Date: July 10, 2002

SUBJECT: **Chlorsulfuron:** Re-evaluation of the Chronic RfD and Chronic Dermal and Inhalation Endpoints for Chlorsulfuron

FROM: Linda L. Taylor, Ph.D. 
Reregistration Branch I
Health Effects Division (7509C)

THROUGH: Elizabeth Mendez, Ph.D. 
Reregistration Branch I
Health Effects Division (7509C)

TO: Health Effects Division's Hazard Identification Review Committee

The purpose of this meeting is to re-evaluate the chronic RfD and chronic dermal and inhalation endpoints for chlorsulfuron. This is necessitated by the fact that the study selected previously [MRID 40089316; a chronic toxicity/carcinogenicity study in rats] was performed on the chemical **bensulfuron methyl**; not on chlorsulfuron. The bensulfuron study also included a 2-generation reproduction study/phase.

A 2-year rat chronic toxicity study on **chlorsulfuron** was identified subsequently [MRID 00086003], as was a 3-generation reproduction study on chlorsulfuron [see DER dated 10-13-82].

The RfD for chlorsulfuron [0.05 mg/kg/day] was established by the RfD Committee in 1986 [TXR # 004995; dated 3/12/86] based on this rat chronic toxicity study [endpoint: decreased body weight; systemic **NOEL** was 100 ppm (5 mg/kg/day)/ systemic LEL 500 ppm (25 mg/kg/day)].

Although this study provides the lowest **NOEL** [100 ppm; 5 mg/kg/day], the magnitude of the effect [decreased body weight] at the LEL is minimal [4%-5%] and even at the next higher dose level [2500 ppm; 125 mg/kg/day], the magnitude is only 4%-9%. It appears that the rats would have tolerated higher dose levels. NOTE: Back in 1986, NOELs were identified but not necessarily NOAELs. NOTE: The standard conversion factor of 0.05 was used to convert ppm to mg/kg/day

In the 3-generation reproduction study on chlorsulfuron, the **NOEL** [500 ppm; 25 mg/kg/day] is based on decreased fertility in the third generation [79% vs 95%] at the LEL of 125 mg/kg/day. NOTE: The standard conversion factor of 0.05 was used to convert ppm to mg/kg/day. NOTE: In a limited review of this study,

several deficiencies were identified [male reproductive performance not evaluated; parental animals not subjected to gross pathology or histopathology examinations; only F3b generation was examined; developmental landmarks not evaluated; estrous cyclicity, sperm parameters no evaluated], and there was no indication of parental toxicity at any dose level. The study is considered Unacceptable.

3. Chronic Reference Dose (cRfD)

Proposed Study for Chronic RfD: chronic toxicity study - dog

OPPTS 870.4100; §83-1 (b)

MRID No.: 41862601

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID 41862602.) Chlorsulfuron technical (97.5% a.i.; Lot # 12-51) was administered to Beagle dogs (5/sex/dose) in the diet at concentrations of 0, 100, 2000, or 7500 ppm (equivalent to Males:0, 3.5, 65.6, 215 mg/kg bw/day; females: 0, 3.4, 60.6, 254.5) for 52 weeks.

No compound-related increases in the mortality rate, incidence of clinical signs, food consumption, ophthalmoscopic, clinical chemistry, organ weights, gross pathology, and histopathology parameters were reported. Body weights were unaffected by treatment with the test article. Females in the high-dose group, however, exhibited 30-89% decreases in body weight gain at different intervals during the study. Although they are not statistically significant, these decreases in body weight gain are considered toxicologically relevant and compound-related since they occurred in the absence of decreases in food consumption.

In males, evaluation of hematology parameters did not reveal any compound-related effects at any dose level. In contrast, females in the high-dose group exhibited statistically significant decreases in some hematology parameters. At the 3-month evaluation, statistically significant decreases in hemoglobin (24%, $p < 0.01$), hematocrit (21%, $p < 0.01$), erythrocytes (21%, $p < 0.05$), and leukocytes (48%, $p < 0.01$). Leukocytes and hematocrit parameters were comparable to control throughout the remainder of the study period. Reduced hemoglobin levels, however, were still observed at the 6-month (18%, $p < 0.05$) and 9-month (17%, $p < 0.05$) evaluations but not at the end of the study period. Also observed during the 6- and 9-month evaluations was a reduced erythrocyte count (16% [not statistically significant] and 17% [$p < 0.05$], respectively). Again, this effect was not reported at the end of the study period.

Under the conditions of this study, the NOAEL is established at 2000 ppm (60.6 mg/kg/day). The LOAEL is set at 7500 ppm (215 mg/kg/day) based on decreases in body weight gain, erythrocyte counts, and hemoglobin.

This chronic study in dogs is **acceptable/guideline** and **satisfies** the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452]

Proposed Dose and Endpoint for Establishing cRfD: **NOAEL = 60.6 mg/kg/day**, based on decreases in body-weight gain, erythrocyte counts, and hemoglobin.

Proposed Uncertainty Factor(s): 300X [10X interspecies; 10X intraspecies; 10X database uncertainty factor]

Comments about Study/Endpoint/Uncertainty Factor: The route and duration of exposure are appropriate for selection of the chronic dietary endpoint. An additional 3X database uncertainty factor may be required for the

incomplete database [pending HIARC's assessment of the adequacy of the reproduction study and the rat chronic toxicity study]. The magnitude of the body-weight gain deficit was 30%-89% at different intervals during the study. Although statistical significance was not attained, the decreases are considered toxicologically relevant and treatment-related since they occurred in the absence of decreases in food consumption. Although the existing reproduction study does not satisfy the guideline requirement [NOEL of 25 mg/kg/day; LOEL of 125 mg/kg/day] suggest that the repeated 2-generation reproduction study is unlikely to result in evidence of toxicity more than 3-fold lower than the existing endpoints.

6. Dermal Absorption

Dermal Absorption Factor: 100% (default value), based on the lack of a dermal absorption study.

9. Dermal Exposure Long-Term (> 6 Months)

Proposed Study: chronic toxicity study - dog

OPPTS 870.4100/§83-1 (b)

MRID No.: 41862601

Executive Summary: See under Chronic RfD

Proposed Dose and Endpoint for Establishing cRfD: **NOAEL = 60.6 mg/kg/day**, based on decreases in body-weight gain, erythrocyte counts, and hemoglobin.

Proposed Uncertainty Factor(s): 300X [10X interspecies; 10X intraspecies; 10X database uncertainty factor]

Comments about Study/Endpoint/Uncertainty Factor: see under Chronic RfD. The proposed study is an oral study. Since no dermal absorption data are available, toxicity by the dermal route should be considered equivalent to toxicity by the oral route of exposure.

12. Inhalation Exposure: Long-Term (> 6 Months)

Proposed Study: chronic toxicity study - dog

OPPTS 870.4100/§83-1 (b)

MRID No.: 41862601

Executive Summary: See under Chronic RfD

Proposed Dose and Endpoint for Establishing cRfD: **NOAEL = 60.6 mg/kg/day**, based on decreases in body-weight gain, erythrocyte counts, and hemoglobin.

Proposed Uncertainty Factor(s): 300X [10X interspecies; 10X intraspecies; 10X database uncertainty factor]

Comments about Study/Endpoint/Uncertainty Factor: see under Chronic RfD. The proposed study is an oral study. Since no inhalation absorption data are available, toxicity by the inhalation route should be considered equivalent to toxicity by the oral route of exposure.

ATTACHMENTS

TXR # 0050783 - HIARC report dated June 5, 2002

TXR # 004995 - RfD report dated March 14, 1986

DATA EVALUATION RECORD for chronic rat and 3-generation reproduction studies dated 10-13-82

DATA EVALUATION RECORD for chronic dog study dated 3-13-02

TOXICOLOGY PROFILE



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

OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

TXR NO. 0050783

DATE: June 5, 2002

MEMORANDUM

SUBJECT: CHLORSULFURON - Report of the Hazard Identification Assessment Review Committee.

FROM: Linda L. Taylor, Ph.D. *Linda L. Taylor*
Health Effects Division (7509C)

THROUGH: Elizabeth Doyle, Co-Chair *E. A. Doyle*
Hazard Identification Assessment Review Committee
Health Effects Division (7509C)

TO: Felicia Fort, Risk Assessor
Health Effects Division (7509C)

PC Code: 118601

On May 29, 2002 the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for chlorsulfuron with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to chlorsulfuron was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996. The conclusions drawn at this meeting are presented in this report.

Committee Members in Attendance

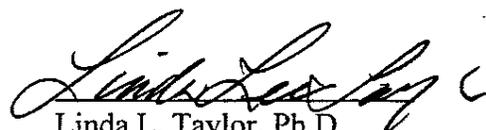
Members present were: Elizabeth Doyle (Co-Chair), William Burnam, Elizabeth Mendez, David Nixon, Jonathan Chen, John Liccione, Ayaad Assaad, Virginia Fornillo, Paula Deschamp

Member(s) in absentia: Jess Rowland (Co-Chair), Pamela Hurley, Brenda Tarplee

Data evaluation prepared by: Linda Taylor

Also in attendance were: Susan Makris, Christina Swartz, Felicia Fort, Whang, Phang, Sue Hanley, Virginia Dobozy

Data Evaluation / Report Presentation


Linda L. Taylor, Ph.D.
Toxicologist

INTRODUCTION

On May 29, 2002, the Health Effects Division (HED) Hazard Identification Assessment Review Committee (HIARC) reviewed the recommendations of the toxicology reviewer for Chlorsulfuron with regard to the acute and chronic Reference Doses (RfDs) and the toxicological endpoint selection for use as appropriate in occupational/residential exposure risk assessments. The potential for increased susceptibility of infants and children from exposure to chlorsulfuron was also evaluated as required by the Food Quality Protection Act (FQPA) of 1996.

I. FOPA HAZARD CONSIDERATIONS

1. Adequacy of the Toxicity Data Base

The HIARC concluded that the toxicology database for chlorsulfuron is not complete. There is a datagap for the 2-generation reproduction study in rats. The studies available for FQPA considerations are:

- rat developmental toxicity study (acceptable)
- rabbit developmental toxicity study (acceptable)
- two-generation reproduction study in rats (**unacceptable**)

2. Evidence of Neurotoxicity

The HIARC concluded that there is a concern for neurotoxicity resulting from exposure to chlorsulfuron, based on the hyperreactivity observed in male rats in the chronic toxicity/carcinogenicity study on chlorsulfuron. The acute neurotoxicity study and the subchronic neurotoxicity study are required for chlorsulfuron.

3. Developmental Toxicity Study Conclusions

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 41983101), chlorsulfuron (98.2% a.i.; Lot# 12-51, Drum 14/Batch # 12-51-88) was administered to 20 artificially-inseminated female Hra: (NZW)SPF rabbits/dose once daily *via* gavage at dose levels of 0, 25, 75, 200, and 400 mg/kg/day [original study] and at 400 and 1000 mg/kg/day [supplemental study] from day 7 to 19 of gestation.

Maternal toxicity was evident at the 1000 mg/kg/day dose level, as evidenced by the death of 8 of the 20 does and 6 abortions. One doe in the 200 mg/kg/day dose group and one doe in one of the 400 mg/kg/day groups also aborted. Additionally, there was a negative body-weight gain during the initial 3 days of dosing at 200 mg/kg/day and 400 mg/kg/day in the original study and a substantial decrease in body-weight gain in the supplemental study at 400 and 1000 mg/kg/day. Adjusted maternal body-weight gain was substantially lower than control at the 200 [original study], 400 [original and supplemental studies], and 1000 mg/kg/day [supplemental study] dose levels [days 0-29: 78%, 54%, 43%, and 43% of control, respectively; days 7-29: 24% of control, -24 grams, -25

grams, -67 grams, respectively].

There were no treatment-related effects on pregnancy rate, numbers of corpora lutea/doe, implantations/doe, live fetuses/doe, resorptions/doe, or the sex ratio. In the supplementary study, there was an apparent treatment-related increase in the incidence of enlarged gallbladders [0, 2, 4 at 0, 400, and 1000 mg/kg/day, respectively] and mishappened gallbladders [0, 0, 2 at 0, 400, and 1000 mg/kg/day, respectively].

The maternal toxicity LOAEL is 200 mg/kg/day, based on decreased body-weight gain. The maternal toxicity NOAEL is 75 mg/kg/day.

Developmental toxicity was observed at the 400 mg/kg/day dose level, as evidenced by the slight increase in the incidence of visceral malformations [absent gallbladder, doubled aorta, ventricular septal defect] compared to the control. Additionally, the female fetuses at the 400 mg/kg/day dose level displayed a slightly lower body weight [90% of control] compared to the control, and the mean litter weight at this dose level was slightly decreased [\approx 90% of control]. The 1000 mg/kg/day dose level resulted in severe maternal toxicity and therefore, the developmental findings at this dose level [lack of effect] are not considered reliable.

The developmental toxicity LOAEL is 400 mg/kg/day, based on a slight increase in visceral malformations and decreased fetal body weight. The developmental toxicity NOAEL is 200 mg/kg/day.

The developmental toxicity study in the rabbit is classified Acceptable/Guideline, and it satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3(b)) in rabbits.

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 41976406), chlorsulfuron (98.2%, Lot 12-51, drum 14; batch 12-51-88) was administered by gavage to Crl:CD@Br rats from gestation days 7-16. Dose groups were 0, 55, 165, 500, or 1500 mg/kg/day and there were 25 presumed pregnant rats per group.

Dams in the 500 mg/kg/day group had clinical signs (vaginal discharge with associated alopecia). There were two treatment-related maternal deaths in the 1500 mg/kg/day group. Dams in the 1500 mg/kg/day group had more clinical signs (swollen limbs and faces), and decreased corrected body weight gain which was accompanied by decreased food consumption. **The maternal NOAEL is 165 mg/kg/day based upon clinical signs (vaginal discharge with associated alopecia) at the maternal LOAEL of 500 mg/kg/day.**

Fetal toxicity was limited to decreased fetal weight in the 1500 mg/kg/day group. There were no teratogenic effects. **The developmental NOAEL is 500 mg/kg/day based upon decreased fetal weight at the developmental LOAEL of 1500 mg/kg/day.**

This study is classified **acceptable/guideline** and **satisfies** requirements for a developmental toxicity study in rats (OPPTS 870.3700; OECD 414).

4. Reproductive Toxicity Study Conclusions

EXECUTIVE SUMMARY: In a two-generation reproduction study (MRID 40089316), conducted in conjunction with a 24-month chronic/carcinogenicity study, chlorsulfuron technical ($\geq 95\%$ a.i., Batch # INF-5384-38 and INF-5384-52) was administered to CrI:CD®(SD)BR rats in the diet at dose levels of 0, 50, 750, 7500 ppm (equivalent to 0, 2.3/3.2, 35/48, 356/480 mg/kg bw/day in F₀ males/females and 0, 3.7/4.5, 55/66, 541/656 mg/kg/day in F_{1B} males/females). On day 97 of the chronic/carcinogenicity study, 20 rats/sex/dose were assigned to the reproduction component of the study (F₀ generation). Two litters were produced per generation. After the second litter (F_{1B}) was weaned, the F₀ animals were returned to the 24-month chronic/carcinogenicity portion of the study.

The only parental parameters evaluated during the reproduction phase of the study were body weight, body weight gain, food consumption, food efficiency, and compound intake during the first pre-mating period for the F_{1B} animals. No compound-related signs of toxicity were noted at any dose level. **The parental systemic NOAEL is 7500 ppm (356 mg/kg bw/day in males, 480 mg/kg bw/day in females), the highest dose tested. The parental systemic LOAEL > 7500 ppm.**

In the F_{1A} generation, a slight dose-related decrease in pup weight (↓7 and 5% in males and females at the high-dose, respectively) was noted on post-natal day (PND) 21. A concomitant 6% decrease in maternal body weight was seen at this dose level. Given the minimal magnitude of the effect (≤ 3.6 g), this decrease was not considered toxicologically relevant. Decreases in the mean litter size, number of pups born alive, as well as pups alive 24 hours after birth, and on PND 4 (pre-cull) were reported at the 7500 ppm dose level (↓5, 11, 15, and 16%, respectively) when compared to concurrent control. Similar effects were noted at the high-dose in the F_{1B} generation where pup viability at various time points decreased by approximately 9-11%. None of these effects were noted in any litter of the F₂ generation. Organ weights, gross pathology and histopathology evaluations of F_{2B} weanlings did not reveal any compound-related effects.

The offspring LOAEL is 7500 ppm (356 mg/kg bw/day in males, 480 mg/kg/day in females), based on increased number of still births and pup death during early lactation (PND 0-4)¹. The offspring NOAEL is 750 ppm (35 mg/kg bw/day).

At the 7500 ppm dose level, a 10-15% decrease in fertility index was noted in the F_{1B} generation. **The reproductive LOAEL is 7500 ppm (356 mg/kg bw/day in males, 480 mg/kg bw/day in females) based on decreased fertility. The NOAEL is established at 750 ppm (35 mg/kg/day).**

This study is **unacceptable/non-guideline** and does not satisfy the guideline requirement for a two-generation reproductive study (OPPTS 870.3800; OECD 416) in rats. This study had numerous deficiencies including but not limited to: 1) parental animals not weighed weekly as specified in guideline, 2) estrous cyclicity, sperm parameters not evaluated, 3) male reproductive performance

not evaluated, 4) parental animals not subjected to gross pathology or histopathology examinations, 5) developmental landmarks not evaluated, and 6) pup histopathology evaluations conducted only for the F_{2B} generation. The lack of an assessment of several parameters that are part of the new OPPTS 870.3800 guidelines does not disqualify this study.

5. Additional Information from Literature Sources

No other information was located in the literature for chlorsulfuron.

6. Pre-and/or Postnatal Toxicity

The HIARC concluded that there is not a concern for pre- and/or postnatal toxicity resulting from exposure to chlorsulfuron.

A. Determination of Susceptibility: There is no evidence of increased susceptibility [qualitative and quantitative] following *in utero* exposure to chlorsulfuron in either the rat or rabbit developmental toxicity study. The HIARC concluded that susceptibility cannot be assessed in the 2-generation reproduction study in rats.

B. Degree of Concern Analysis and Residual Uncertainties: There is a low degree of concern for the effects observed [fetal/pup death] in the **unacceptable** 2-generation reproduction study at a dose level that had no apparent adverse effect on the parental animals. Since parental body weight and food consumption were not monitored adequately, and there was no microscopic examination of the parental animals, among other deficiencies, a lack of effect on the parental animals cannot be substantiated. Additionally, although there was an increase in the number of still births (14) at the high-dose level compared to the control (3) and other dose groups (2 each), 13 of the 14 still births were from one litter; therefore, only two high-dose litters were affected, compared to a comparable number of affected litters in the control and other dose groups. With regard to the PND 0-4 deaths, there was no real dose-response in that the incidence was 1 in the control, 7 in the low-dose, 1 in the mid-dose, and 10 in the high-dose groups. Although the reproduction study is unacceptable, a NOAEL [35 mg/kg/day] was determined for the effect of concern [still births], and the LOAEL is at a high dose level [356 mg/kg/day]. The fetal effects observed in the developmental toxicity studies [decreased fetal body weight] occurred at dose levels that are greater than the dose levels producing maternal toxicity [decreased body-weight gain and clinical signs]. The incidence of visceral malformations in the rabbit study was slight and not of concern. There are no residual concerns.

C. Proposed Hazard-based Special FQPA Safety Factor(s): The HIARC concluded that the hazard-based special FQPA safety factor [10X] could be removed [1X].

7. Recommendation for a Developmental Neurotoxicity Study

The HIARC concluded that there is not sufficient information available to determine whether there is a concern for developmental neurotoxicity resulting from exposure to chlorsulfuron due to the lack

of the acute and subchronic neurotoxicity studies. Based on the finding of hyperreactivity in the chronic oral toxicity study in male rats, the recommendation for a developmental neurotoxicity study [DNT] in rats is RESERVED, pending the completion of the neurotoxicity battery [acute and subchronic neurotoxicity studies] on chlorsulfuron.

A. Evidence that suggest requiring a Developmental Neurotoxicity study:

The only evidence of neurotoxicity was found in the chronic toxicity study in rats where males displayed an increased incidence of hyperreactivity compared to the control males following oral exposure to chlorsulfuron [first observation on day 152 (high dose) and day 282 (control)]. There are no neurotoxicity studies [acute and subchronic] available for chlorsulfuron.

B. Evidence that do not support a need for a Developmental Neurotoxicity study:

With the exception of the hyperreactivity noted above, there is a lack of evidence of neurotoxicity in the available database on chlorsulfuron.

Based on the weight of evidence presented, the HIARC concluded that a developmental neurotoxicity study is RESERVED for chlorsulfuron.

II. HAZARD IDENTIFICATION

1. Acute Reference Dose (aRfD) - General Population

An appropriate end point to quantify a single-dose exposure was not available in the database.

2. Acute Reference Dose (aRfD) - Females 13-50

An appropriate end point to quantify a single-dose exposure was not available in the database. The decrease in fetal body weight [10%] in the rabbit study is not attributable to a single dose.

3. Chronic Reference Dose (cRfD)

Study Selected: chronic toxicity/carcinogenicity study - rat

OPPTS 870.4300; §83-5

MRID No.: 40089316

Executive Summary: In a combined chronic/carcinogenicity study (MRID 40089316), chlorsulfuron technical (>95% a.i., Batch # INF-5384-38 and INF-5384-52 was administered to CrI:CD@ (SD)BR rats (80/sex/dose) in the diet at dose levels of 0, 50, 750, 7500 ppm (equivalent to 0, 2, 30, 309 mg/kg body weight/day in males and 0, 2.7, 40, and 405 mg/kg bw/day in females) for 24 months. At the 1 year interim sacrifice 10 rats/sex/dose were sacrificed and subjected to a gross necropsy and histopathological evaluation.

A statistically significant ($p < 0.05$) decrease in body weight (8-17% decrease) was reported in males at the low- and high-dose levels during the last 6 weeks of the study. At the end of the study period, a statistically significant decrease in mean body weight - ranging from 11-16% - was seen at all dose levels. In contrast, females exhibited an 8-13% statistically significant ($p < 0.05$) decrease in body weight occurring between weeks 60-84 only. At the end of the study period, however, the body weight of females in the control and treated groups were comparable. Though marginal, these changes in body weight at the high-dose level are considered toxicologically relevant since they occurred in the absence of decreases in food consumption and were consistent with the concomitant decreases in food efficiency (14-1500% and 17-188% decreases in males and females, respectively) at the 7500 ppm dose level.

The only clinical sign of toxicity noted during the study period was an increase in the incidence of hyperreactivity in males at the 750 and 7500 ppm dose levels (15/80 and 14/80, respectively vs. 5/80 in the control group). Mortality rates, clinical chemistry, and hematology parameters were unaffected by treatment with the test article.

At the interim sacrifice (1 year), the absolute liver weights of males at the 50 and 750 ppm dose levels were decreased ($p < 0.05$) by $\approx 14\%$. Nonetheless, this change in organ weight is not considered toxicologically relevant as it was not dose-dependent and was not reflected in the relative liver/body weight ratio. It is, therefore, presumed that these changes reflect the concomitant decrease in body weight. Though not statistically significant, females exhibited a 12-15% increase at all dose levels. This increase, however, was not observed at the terminal sacrifice (2 years). Consequently, the toxicological relevance of this finding is unclear.

No toxicologically relevant compound-related effects on organ weights was reported at the end of the study period (2 years). A minimal ($\approx 3\%$) but statistically significant decrease in absolute brain weight was noted in males at the 50 and 7500 ppm dose levels only. These changes are not considered biologically relevant since the magnitude of the effect was slight.

Gross pathology examination did not reveal any compound-related effects. Histopathology evaluation revealed an increase in the incidence of centrilobular hypertrophy and cytoplasmic fatty changes in males and females treated at the 7500 ppm dose. These findings are considered to be an adaptive response to the presence of a xenobiotic agent and consequently not toxicologically significant. Finally, no increase in the incidence of masses was noted at any dose level when compared to the concurrent control.

Under the conditions of this study, the NOAEL is established at 50 ppm (2 mg/kg/day). The LOAEL is set at 750 ppm (30 mg/kg/day) based on increased incidence of hyperreactivity in males.

At the doses tested, there was not a treatment related increase in tumor incidence when compared to controls. Dosing was considered adequate based on decreases in body weight and food efficiency at the highest dose tested.

This chronic/carcinogenicity study in the rat is **acceptable/non-guideline**, and **satisfies** the general guideline requirement for a chronic toxicity/carcinogenicity study (OPPTS 870.4300); OECD 453] in rats. The study is non-guideline due to several deficiencies, but there is sufficient information for the evaluation of the potential carcinogenic and chronic toxic effects of this chemical in rats.

Dose and Endpoint for Establishing cRfD: **NOAEL = 2 mg/kg/day**, based on increased incidence of hyperreactivity in males at the LOAEL of 30 mg/kg/day.

Uncertainty Factor(s): 300X [10 interspecies; 10X intraspecies; 3X database uncertainty factor]

Comments about Study/Endpoint/Uncertainty Factor: The route and duration of exposure are appropriate for selection of the chronic dietary endpoint. An additional 3X database uncertainty factor is required for the incomplete database [lack of a 2-generation reproduction study, an acute neurotoxicity study, and a subchronic neurotoxicity study]. There is a lack of adequate assessment of potential reproductive effects following exposure to chlorsulfuron, and based on signs of hyperreactivity in adult animals, there is a need for acute and subchronic neurotoxicity studies. Although the existing 2-generation reproduction study does not satisfy the guideline requirement, the results of that study [NOAEL for fetal effects = 35 mg/kg/day; LOAEL = 356 mg/kg/day] suggest that the repeated 2-generation reproduction study is unlikely to result in evidence of toxicity more than 3-fold lower than the existing endpoints. Therefore, a 3X database uncertainty factor is protective.

$$\text{Chronic RfD} = \frac{2 \text{ mg/kg/day}}{300} = 0.007 \text{ mg/kg/day}$$

4. Incidental Oral Exposure: Short-Term (1-30 days)

Study Selected: developmental toxicity - rabbit

OPPTS 870.3700; §83-3 (b)

MRID No.: 41983101

EXECUTIVE SUMMARY: In a developmental toxicity study (MRID 41983101), chlorsulfuron (98.2% a.i.; Lot# 12-51, Drum 14/Batch # 12-51-88) was administered to 20 artificially-inseminated female Hra: (NZW)SPF rabbits/dose once daily *via* gavage at dose levels of 0, 25, 75, 200, and 400 mg/kg/day [original study] and at 400 and 1000 mg/kg/day [supplemental study] from day 7 to 19 of gestation.

Maternal toxicity was evident at the 1000 mg/kg/day dose level, as evidenced by the death of 8 of the 20 does and 6 abortions. One doe in the 200 mg/kg/day dose group and one doe in one of the 400 mg/kg/day groups also aborted. Additionally, there was a negative body-weight gain during the initial 3 days of dosing at 200 mg/kg/day and 400 mg/kg/day in the original study and a substantial decrease in body-weight gain in the supplemental study at 400 and 1000 mg/kg/day. Adjusted maternal body-weight gain was substantially lower than control at the 200 [original study], 400 [original and supplemental studies], and 1000 mg/kg/day [supplemental study] dose levels [days 0-

29: 78%, 54%, 43%, and 43% of control, respectively; days 7-29: 24% of control, -24 grams, -25 grams, -67 grams, respectively].

There were no treatment-related effects on pregnancy rate, numbers of corpora lutea/doe, implantations/doe, live fetuses/doe, resorptions/doe, or the sex ratio. In the supplementary study, there was an apparent treatment-related increase in the incidence of enlarged gallbladders [0, 2, 4 at 0, 400, and 1000 mg/kg/day, respectively] and mishappened gallbladders [0, 0, 2 at 0, 400, and 1000 mg/kg/day, respectively].

The maternal toxicity LOAEL is 200 mg/kg/day, based on decreased body-weight gain. The maternal toxicity NOAEL is 75 mg/kg/day.

There was a slight increase in the incidence of visceral malformations [absent gallbladder, doubled aorta, ventricular septal defect; one fetus/malformation; 3 litters] compared to the control at the 400 mg/kg/day dose level, but this was not considered an effect of treatment. Developmental toxicity was observed at the 400 mg/kg/day dose level, as evidenced by the slightly lower fetal body weight [90% of control] in the females compared to the control females, and the slightly decreased [~90% of control] mean litter weight. The 1000 mg/kg/day dose level resulted in severe maternal toxicity and therefore, the developmental findings at this dose level [lack of effect] are not considered reliable.

The developmental toxicity LOAEL is 400 mg/kg/day, based on decreased fetal body weight. The developmental toxicity NOAEL is 200 mg/kg/day.

The developmental toxicity study in the rabbit is classified Acceptable/Guideline, and it satisfies the guideline requirement for a developmental toxicity study (OPPTS 870.3700; §83-3(b)) in rabbits.

Dose and Endpoint for Risk Assessment: **Maternal toxicity NOAEL = 75 mg/kg/day**, based on decreased body weight/body-weight gain in females at 200 mg/kg/day.

Comments about Study/Endpoint: Although the dog 6-month study provides a lower NOAEL [18.5 mg/kg/day], due to the fact that the dogs at study initiation were between 9 and 11 months old, an assessment of the young, growing, animal was not performed. Also, body weights in older [not growing] dogs are variable, and there is little confidence in the effect level. Additionally, in the chronic dog study in which the dogs were 6.5 months old at study initiation, decreased body-weight gain [91% of control] for the 0-13 week interval was observed in females at 215 mg/kg/day [NOAEL of 60.6 mg/kg/day]. An additional 3X database uncertainty factor is required [see Comments under Chronic RfD (females 13-50)] for the incomplete database [2-generation reproduction study, acute and subchronic neurotoxicity studies] with respect to this subpopulation. The required study may provide a lower dose/endpoint for risk assessment purposes.

5. Incidental Oral Exposure: Intermediate-Term (1 - 6 Months)

Study Selected: developmental toxicity study - rabbit

OPPTS 870.3700/§83-3 (b)

MRID No.: 41983101

EXECUTIVE SUMMARY: See under Short-Term Incidental Oral Exposure.

Dose and Endpoint for Risk Assessment: **Maternal toxicity NOAEL = 75 mg/kg/day**, based on decreased body weight/body-weight gain in females at 200 mg/kg/day

Comments about Study/Endpoint: See under Short-Term Incidental Oral Exposure.

6. Dermal Absorption

Dermal Absorption Factor: 100% (default value), based on the lack of a dermal absorption study.

7. Dermal Exposure: Short-Term (1- 30 days) Exposure

Study Selected: developmental toxicity study - rabbit OPPTS 870.3700/§83-3 (b)

MRID No.: 41983101

EXECUTIVE SUMMARY: See under Short-Term Incidental Oral Exposure.

Dose and Endpoint for Risk Assessment: **Maternal toxicity NOAEL = 75 mg/kg/day**, based on decreased body weight/body-weight gain in females at 200 mg/kg/day

Comments about Study/Endpoint: See under Short-Term Incidental Oral Exposure. Since no dermal absorption data are available, toxicity by the dermal route will be considered to be equivalent to toxicity by the oral route of exposure.

8. Dermal Exposure: Intermediate-Term (1 - 6 Months)

Study Selected: developmental toxicity study - rabbit OPPTS 870.3700/§83-3 (b)

MRID No.: 41983101

EXECUTIVE SUMMARY: See under Short-Term Incidental Oral Exposure.

Dose and Endpoint for Risk Assessment: **Maternal toxicity NOAEL = 75 mg/kg/day**, based on decreased body weight/body-weight gain in females at 200 mg/kg/day

Comments about Study/Endpoint: See under Short-Term Incidental Oral Exposure. Since no dermal absorption data are available, toxicity by the dermal route will be considered to be equivalent to toxicity by the oral route of exposure.

9. Dermal Exposure Long-Term (> 6 Months)

Study Selected: chronic toxicity/carcinogenicity study - rat

OPPTS 870.4300/§83-5

MRID No.: 40089316

EXECUTIVE SUMMARY: See under Chronic RfD.

Dose and Endpoint for Risk Assessment: **NOAEL = 2 mg/kg/day**, based on increased incidence of hyperactivity in males at the LOAEL of 30 mg/kg/day.

Comments about Study/Endpoint: See under Chronic RfD. Since the selected study is an oral study. Since no dermal absorption data are available, toxicity by the dermal route will be considered to be equivalent to toxicity by the oral route of exposure.

10. Inhalation Exposure: Short-Term (1- 30 days)

Study Selected: developmental toxicity study - rabbit

OPPTS 870.3700/§83-3 (b)

MRID No.: 41983101

EXECUTIVE SUMMARY: See under Short-Term Incidental Oral Exposure.

Dose/Endpoint for Risk Assessment: **Maternal toxicity NOAEL = 75 mg/kg/day**, based on decreased body weight/body-weight gain in females at 200 mg/kg/day

Comments about Study/Endpoint: See under Short-Term Incidental Oral Exposure. Since no inhalation absorption data are available, toxicity by the inhalation route will be considered to be equivalent to toxicity by the oral route of exposure.

11. Inhalation Exposure: Intermediate-Term (1- 6Months)

Study Selected: developmental toxicity study - rabbit

OPPTS 870.3700/§83-3 (b)

MRID No.: 41983101

EXECUTIVE SUMMARY: See under Short-Term Incidental Oral Exposure.

Dose/Endpoint for Risk Assessment: **Maternal toxicity NOAEL = 75 mg/kg/day**, based on decreased body weight/body-weight gain in females at 200 mg/kg/day

Comments about Study/Endpoint: See under Short-Term Incidental Oral Exposure. Since no inhalation absorption data are available, toxicity by the inhalation route will be considered to be equivalent to toxicity by the oral route of exposure.

12. Inhalation Exposure: Long-Term (> 6 Months)

Study Selected: chronic toxicity/carcinogenicity study - rat

OPPTS 870.4300/§83-5

MRID No.: 40089316

EXECUTIVE SUMMARY: See under Chronic RfD.

Dose/Endpoint for Risk Assessment: **NOAEL = 2 mg/kg/day**, based on increased incidence of hyperactivity in males at the LOAEL of 30 mg/kg/day.

Comments about Study/Endpoint: See under Chronic RfD. Since no inhalation absorption data are available, toxicity by the inhalation route will be considered to be equivalent to toxicity by the oral route of exposure.

13. Margins of Exposure

The target Margins of Exposure (MOEs) for **occupational** exposure risk assessments are as follows:

Route Duration	Short-Term (1-30 Days)	Intermediate-Term (1 - 6 Months)	Long-Term (> 6 Months)
Dermal	100	100	100
Inhalation	100	100	100

The MOEs for dermal and inhalation exposures may be combined for occupational exposure risk assessment because the toxicity endpoints for these routes of exposure are the same.

The target MOEs for **residential** exposure risk assessments will be determined by the FQPA Safety Factor Committee. At present, there are no residential uses.

14. Recommendation for Aggregate Exposure Risk Assessments

As per FQPA, 1996, when there are potential residential exposures to the pesticide, aggregate risk assessment must consider exposures from three major sources: oral, dermal and inhalation exposures. Since there are no residential uses currently, no aggregated assessment is required at this time.

III. CLASSIFICATION OF CARCINOGENIC POTENTIAL

1. Combined Chronic Toxicity/Carcinogenicity Study in Rats

MRID No. 40089316

EXECUTIVE SUMMARY: See under Chronic RfD.

Discussion of Tumor Data There was no treatment-related increase in tumor incidence in either sex.

Adequacy of the Dose Levels Tested: In the subchronic oral toxicity study in rats, the body-weight gain and food efficiency decreases observed did not display a dose response and they were sporadic; thus their relation to chlorsulfuron exposure is considered equivocal. The highest dose tested in the subchronic study [2500 ppm (males 161/females 217 mg/kg/day)] was considered the NOAEL. In the rat chronic toxicity/carcinogenicity study, the highest dose level was 7500 ppm [males 309/females 405 mg/kg/day]. The body-weight changes at the high-dose level are considered toxicologically relevant since they were consistent with the concomitant decreases in food efficiency in the absence of food consumption decrements. However, the decreased food efficiency occurred in the latter half of the study in males and sporadically in females [during week 13, then not until week 100]. Body-weight gains for both sexes were comparable among the groups for the 0-13 week interval. It appears that the rats would have tolerated a higher dose.

2. Carcinogenicity Study in Mice

MRID No. 00090030

EXECUTIVE SUMMARY: In a carcinogenicity study (MRID 00090030) INW-4189 (91.9-95% a.i., Lots INW-4189-22 and INW-4189-57) was administered to 80 CD-1 mice/sex/dose in the diet at dose levels of 0, 100, 500 or 5000 ppm (**approximately 0, 15, 108 and 750 mg/kg bw/day based on 1 ppm in food equals 0.15 mg/kg/day**) for 104 weeks.

There were no treatment-related effects on survival, clinical observations, hematology or post-mortem examinations. Food consumption measurements were complicated by spillage. Body weight was statistically significantly decreased relative to control values for the 5000 ppm males and females during most of the study. However, the effect was marginal with decreases of mostly less than 10%. Body weight gain in the 5000 ppm males was significantly decreased at many time periods during the study (decreases for weeks 0-13, 0-26, 0-52 and 0-104 were 5%, 13%, 9% and 8%, respectively). Sporadic significant decreases were also observed in the 100 and 500 ppm males. Body weight gain was significantly decreased in the 5000 ppm females at many time periods (decreases for weeks 0-26, 0-52 and 0-104 were 13%, 16% and 9%, respectively). There were also decreases in the 500 ppm females at weeks 0-26 (10%) and 0-52 (9%). For weeks 0-52, there was a significant decrease (7%) in the 100 ppm females. Only the body weight gain decreases in the 5000 ppm males and females are considered toxicologically significant as they occurred consistently throughout the study, whereas the effects in the 100 and 500 ppm groups were sporadic.

The LOAEL is 5000 ppm (750 mg/kg/day) based on decreased body weight and body weight gain. The NOAEL is 500 ppm (108 mg/kg/day).

At the doses tested, there was no treatment related increase in tumor incidence when compared to controls. The decreases in body weight and body weight gain were marginal evidence of toxicity; therefore, the dosing is considered adequate.

This carcinogenicity study is **acceptable (guideline)** and **satisfies** the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

Discussion of Tumor Data: There were no treatment-related increases in tumor incidence in either sex.

Adequacy of the Dose Levels Tested: In the subchronic mouse study, the dose levels were 500, 2500, 5000, and 7500 ppm [equivalent to 150, 783, 1557, and 2130 mg/kg/day in males; and 220, 1214, 2134, 3176 mg/kg/day in females]. Both sexes displayed sporadic decreases in body-weight gain and food efficiency during the study, which at times were substantial, but a dose response was not evident. The NOAEL was set at 5000 ppm [males 1557/females 2134 mg/kg/day], based on an increased incidence of retinal dysplasia and adrenal capsular cell proliferation. The high dose in the carcinogenicity study was 5000 ppm; however, due to the fact that the food consumption values are inflated, the calculation of the dose on a mg/kg/day basis is flawed and the standard conversion of 1 ppm = 0.15 mg/kg/day is appropriate. The dose levels are considered adequate for the assessment of carcinogenic potential, based on the marginal decreases in body weight/body-weight gain observed throughout most of the study at 5000 ppm [750 mg/kg/day].

Classification of Carcinogenic Potential: The HED RfD Peer Review Committee concluded that there was no evidence of carcinogenicity in rats or mice [TXR # 004995, dated 3/12/86].

IV. MUTAGENICITY

The HIARC concluded that there is not a concern for mutagenicity resulting from exposure to chlorsulfuron.

V. HAZARD CHARACTERIZATION

Chlorsulfuron is not acutely toxic *via* the oral and inhalation [Toxicity Category IV] routes of exposure and *via* the dermal [Toxicity Category III] route of exposure.

Adequate data are not available for an assessment of eye or skin irritation potential or for dermal sensitization potential.

A 21-day repeat dose dermal study and a subchronic inhalation study are not available on chlorsulfuron.

The chronic data provide no evidence that chlorsulfuron is particularly toxic to any organ or tissue. In the rat chronic toxicity study, the increase in the incidence of centrilobular hypertrophy and cytoplasmic fatty

changes at the high-dose level is considered an adaptive response to the presence of a xenobiotic agent and not toxicologically significant. Males at the high-dose level displayed an increase in the incidence of hyperreactivity compared to the control males. Neurotoxicity was not observed in any other study on chlorsulfuron.

Developmental toxicity was observed in both the rat and rabbit, as evidenced by decreased fetal body weights in both species. Maternal toxicity was observed as decreased body-weight gain in the rabbit and as an increased incidence of clinical signs [vaginal discharge with alopecia] in the rat.

Although unacceptable, reproductive toxicity was observed in the rat 2-generation reproduction study in both generations/both litters, as evidenced by decreased fertility of the dams. Although no parental toxicity was observed, an adequate assessment of body weight, body-weight gain, food consumption, organ weights, and histopathology was not performed, and male fertility was not assessed.

The data provided no indication of increased susceptibility of rats or rabbits to in utero exposure to chlorsulfuron. Due to multiple deficiencies, the data from the available 2-generation reproduction study on chlorsulfuron are not interpretable with respect to whether chlorsulfuron results in increased susceptibility following in utero and/or early postnatal exposure. The HED HIARC determined that a 2-generation reproduction study is required. Additionally, the HIARC determined that both an acute neurotoxicity study and a subchronic neurotoxicity study are required for chlorsulfuron, based on the finding of hyperreactivity in males in the chronic toxicity study. The requirement for a developmental neurotoxicity study was RESERVED pending the completion of these latter two neurotoxicity studies.

No effects were observed on the endocrine system in any of the available studies on chlorsulfuron.

There is no evidence of carcinogenicity in rats or mice following oral exposure to chlorsulfuron. The mutagenic data indicate that there is no concern for mutagenicity.

Chlorsulfuron is rapidly absorbed, metabolized, and excreted in rats. There are no remarkable sex-, dose- or treatment-regiment-related differences in the absorption, distribution, and excretion of chlorsulfuron in rats. The major routes of elimination are *via* the urine (58-72% of the dose) and feces (20-35%). Negligible amounts (<0.08%) of radioactivity are found in the expired air as carbon dioxide. Small amounts of radioactivity were found in the tissues 3 days after dosing, with the highest concentrations being observed in the liver and whole blood in both sexes.

There are several data gaps: (1) 2-generation reproduction study in the rat; (2) acute neurotoxicity study in the rat; (3) subchronic neurotoxicity study in the rat; (4) 21-day repeated dose dermal toxicity study; (5) subchronic inhalation study in the rat. The requirement for a developmental neurotoxicity study is RESERVED.

VI. DATA GAPS / REQUIREMENTS The following are datagaps for chlorsulfuron: acute neurotoxicity study, subchronic neurotoxicity, 2-generation reproduction study, 21-day repeat dermal toxicity study, subchronic inhalation study. The requirement for a developmental neurotoxicity study

[DNT] is RESERVED.

VII. ACUTE TOXICITY

Acute Toxicity of Chlorsulfuron

Guideline No.	Study Type	MRID #(s)	Results	Toxicity Category
81-1	Acute Oral	00031406	LD ₅₀ = 5.5/6.3 g/kg ♀	IV
81-2	Acute Dermal	00083956	LD ₅₀ = 3400 mg/kg	III
81-3	Acute Inhalation	00086825	LC ₅₀ = 5.9 m/L	IV
81-4	Primary Eye Irritation	00031414√	not an eye irritant	IV
81-5	Primary Skin Irritation	00031417√	no adequate study	-
81-6	Dermal Sensitization	00031417√	no adequate study	-

♂ males/females; √ classified unacceptable/nonguideline

VIII. SUMMARY OF TOXICOLOGY ENDPOINT SELECTION

Summary of Toxicology Endpoint Selection for Chlorsulfuron

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment
Dietary Risk Assessments			
<u>Acute Dietary females 13-50 years of age</u>	no appropriate endpoint/dose identified		
<u>Acute Dietary general population including infants and children</u>	no appropriate endpoint/dose identified		
<u>Chronic Dietary all populations</u>	NOAEL= 2 mg/kg/day UF = [300] Chronic RfD = 0.007 mg/kg/day	1X	rat chronic toxicity/carcinogenicity LOAEL = 30 mg/kg/day based on increased incidence of hyperreactivity in males
Incidental Oral Short-Term (1 - 30 Days) Residential Only	NOAEL= 75 mg/kg/day MOE= TBD	1X	rabbit developmental toxicity LOAEL = 200 mg/kg/day based on decreased body-weight gain.
Incidental Oral Intermediate-Term (1 - 6 Months) Residential Only	NOAEL= 75 mg/kg/day MOE = TBD	1X	rabbit developmental toxicity LOAEL = 200 mg/kg/day based on decreased body-weight gain.
Non-Dietary Risk Assessments			
Dermal ^a Short-Term (1 - 30 days)	Oral NOAEL= 75 mg/kg/day	1X	rabbit developmental toxicity LOAEL = 200 mg/kg/day based on decreased body-weight gain.
Residential	MOE = TBD	1X	
Occupational	MOE = 100	1X	

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment
Dermal ^a Intermediate-Term (1 - 6 Months)	Oral NOAEL= 75 mg/kg/day	1X	rabbit developmental toxicity LOAEL = 200 mg/kg/day based on decreased body-weight gain.
Residential	MOE = TBD	1X	
Occupational	MOE = 100	1X	
Dermal ^a Long-Term (> 6 Months)	Oral NOAEL= 2 mg/kg/day	1X	rat chronic toxicity/carcinogenicity LOAEL = 30 mg/kg/day based on decreased body-weight gain.
Residential	MOE = TBD	1X	
Occupational	MOE = 100	1X	
Inhalation ^b Short-Term (1 - 30 days)	Oral NOAEL= 75 mg/kg/day	1X	rabbit developmental toxicity LOAEL = 200 mg/kg/day based on decreased body-weight gain.
Residential	MOE = TBD	1X	
Occupational	MOE = 100	1X	
Inhalation ^b Intermediate-Term (1 - 6 Months)	Oral NOAEL= 75 mg/kg/day	1X	rabbit developmental toxicity LOAEL = 200 mg/kg/day based on decreased body-weight gain.
Residential	MOE = TBD	1X	
Occupational	MOE = 100	1X	
Inhalation ^b Long-Term (>6 Months)	Oral NOAEL= 2 mg/kg/day	1X	rat chronic toxicity/carcinogenicity LOAEL = 30 mg/kg/day based on decreased body-weight gain.
Residential	MOE = TBD	1X	
Occupational	MOE = 100	1X	
Cancer	Classification: no evidence of carcinogenicity		

a Since an oral NOAEL/LOAEL was selected, absorption *via* the dermal route is assumed to be equivalent to oral absorption.

b Since an oral NOAEL/LOAEL was selected, absorption *via* inhalation is assumed to be equivalent to oral absorption.

TBD = To Be Determined. Target MOEs for residential exposures will be determined by the FQPA Safety Factor Committee.

004995

3/14/86
 G. Ghali
 W. Jones
 G.W. Hauswirth
 S. Saunders
 D. Bowen
 [Signature]

REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Chlorsulfuron

CAS #: 64902-72-3

Carcinogenicity: *Add*

Caswell #: 194AA

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RFD
Haskell Labs. (1979)	100 ppm (5 mg/kg) Systemic NOEL	100	-	0.05 mg/kg/day
2-Year Feeding/ Oncogenic Rat Study	500 ppm (25 mg/kg) Systemic LEL			
decreased body weight				

Endpoint and Experimental Doses:

Haskell Laboratory (Nov. 27, 1979)
 Two Year Feeding/Oncogenic Rat Study
 Study No. 557-81

Three hundred sixty-eight male and three hundred and seventy-one female CD rats were received from Charles River Breeding Laboratories. Following a 12 day pretest, 320 rats of each sex were divided into four groups of 80 males and 80 females and housed in pairs. Groups were fed diets containing 0, 100, 500, or 2500 ppm chlorsulfuron for two years. All rats were examined at least once daily during the first 14 weeks of the study and at least twice daily after that for abnormal behavior and clinical signs of toxicity. Three, 6, 12, 18, and 24 months after initiation of the study, ten rats from each of the study groups were subjected to clinical chemistry, hematological and urine analytical examinations. The observed results included a mild to moderate reduction in mean body weights and weight gains occurred in male rats fed 2500 ppm and and 500 ppm chlorsulfuron.

Preparation Date: 3/12/86

1/2/86

004995

REFERENCE DOSES (RfDs) FOR ORAL EXPOSURE

Chemical: Chlorsulfuron

CAS #: 64902-72-3
 Caswell #: 194AA

Carcinogenicity: No evidence of carcinogenicity in two animal (rat and mice) tests.

Systemic Toxicity: See below.

Endpoint	Experimental Doses	UF	MF	RfD
Haskell Labs. (1979)	100 ppm (5 mg/kg) Systemic NOEL	100	-	0.05 mg/kg/day
2-Year Feeding/ Oncogenic Rat Study	500 ppm (25 mg/kg) Systemic LEL			
decreased body weight				

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Preparation Date: 3/12/86

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Uncertainty Factors (UFs):

A 100 fold UF has been used to compensate for the interspecies differences in extrapolating from the rat to the human.

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Modifying Factors (MFs):

None

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Additional Comments:

Data Considered for Establishing the RfD

- 1) 2-Year Feeding/Oncogenic - Rat Systemic NOEL=100 ppm (5 mg/kg), Systemic LEL=500 ppm (25 mg/kg)(decreased body weight); Oncogenic NOEL >5000 ppm 250 mg/kg)(HJT); core grade guideline
- 2) 6-Month Feeding - Dog Systemic NOEL >2500 ppm (62.5 mg/kg)(HJT); core grade minimum
- 3) 3-Generation Reproduction - Rat Reproductive NOEL=500 ppm (25 mg/kg), Reproductive LEL=2500 ppm (125 mg/kg)(decreased fertility indices); Maternal NOEL=500 ppm, Maternal LEL=2500 ppm (decreased mean body weight); core grade guideline
- 4) Teratology - Rat Teratogenic NOEL >2500 ppm (125 mg/kg)(HDT); Maternal NOEL >2500 ppm; Fetotoxic NOEL >2500 ppm; core grade minimum
- 5) Teratology - Rabbit Teratogenic NOEL >75 mg/kg; Fetotoxic NOEL=25 mg/kg, Fetotoxic LEL=75 mg/kg (increased incidence of resorption); core grade minimum

Data Gap(s)

- 1) Chronic Dog Feeding

Other Data Considered

- 1) 2-Year Feeding/Oncogenic - Mice Oncogenic NOEL >5000 ppm (750 mg/kg)(HDT); Systemic NOEL=500 ppm (75 mg/kg), Systemic LEL=5000 ppm (decreased body weight and food consumption); core grade guideline
 - 2) 90-Day Feeding - Rat Systemic NOEL=100 ppm (5 mg/kg)(LDT), Systemic LEL=5000 ppm (25 mg/kg)(slight decrease in plasma creatinine, slight increased hematocrit); core grade minimum
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Confidence in the RFD:

Study: High

Data Base: Medium

RFD: Medium

The critical study appears to be of good quality and is given a high rating. Additional studies are also of good quality, however; a chronic dog feeding study is needed and therefore, the RFD is given a medium confidence.

.....
Documentation of RFD and Review:

Agency RFD Review:

U.S. EPA Contact:

First Review:

Primary: Reto Engler FTS 557-7491

Second Review:

Verification Date:

Secondary: George Ghali FTS 557-4382

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CHEM Chlorosulfuron

004995

BRANCH TB

DISC

TOPIC 2-Year Feeding - Rat,
3-Generation Reproduction - Ra

FORMULATION Technical

FICHE/MASTER ID

CONTENT CAT

Long-Term Feeding Study With 2-Chloro-N-[(4-Methoxy-6-Methyl-1,3,5-Triazin-2-Yl)Aminocarbonyl.]Benzenesulfonamide (INW-4189) In Rats, Haskell Laboratory Report No. 557-81, Wood, C. K.

SUBST. CLASS *

OTHER SUBJECT DESCRIPTORS

DIRECT RVW TIME * 10 hours

START-DATE

END DATE

REVIEWED BY: J. C. Summers

TITLE: Research Associate

ORG: E. I. du Pont de Nemours & Co., Inc., Biochemicals Dept.

LOC/TEL: Wilmington, Delaware / (302) 772-2367

SIGNATURE: *J. C. Summers*

DATE: November 10, 1961

APPROVED BY:

TITLE:

ORG:

LOC/TEL:

SIGNATURE:

DATE:

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Conclusion:2-Year Feeding - Rat

- A. Core Guideline
- B. A NOEL of 100 ppm was established based on body weight loss when technical chlorsulfuron was fed to rats for 2 years at dietary levels of 0, 100, 500, or 2500 ppm. No gross or histopathological abnormalities that could be attributed to chlorsulfuron were observed at any test level.
- C. This study conforms to EPA Proposed Guidelines in Section 163.83-1 Chronic Feeding Study (43 Federal Register 37375, 8/27/78).

Methods:2-Year Feeding - Rat

Three hundred sixty-eight male and three hundred and seventy-one female CD⁰ rats were received from Charles River Breeding Laboratories, Wilmington, Massachusetts. Following a twelve day pretest, 320 rats of each sex, selected on the basis of weight gain and freedom from signs of disease or injury, were divided by randomization into four groups of 80 males and 80 females and housed in pairs. Groups were fed ground Purina[®] Laboratory Chow diets containing 0, 100, 500, or 2500 ppm chlorsulfuron for two years. Diets were prepared fresh weekly and stored under refrigeration until used. Rats received test diet and water ad libitum.

All rats were examined at least once daily during the first 14 weeks of the study and at least twice daily after that for abnormal behavior and clinical signs of toxicity. Rats were weighed once a week during the first six months, once every two weeks during the next six months, and once every four weeks during the last 12 months. Diet consumed by rats was determined on a group basis at each weighing interval, and food efficiency and daily intake were calculated. Mortality was recorded.

Three, six, twelve, eighteen, and twenty-four months after initiation of the study, ten rats from each of the study groups were subjected to clinical chemistry, hematological and urine analytical examinations. Tail blood was evaluated for alkaline phosphatase, SGOT, SGPT activities, BUN, creatinine, and total plasma protein. Urine, from the same animals was collected in the same time intervals and examined for volume, pH, sugar, protein, bilirubin, urobilinogen, occult blood, color, appearance, and sediments. The blood from this same group of animals was examined for the following parameters: erythrocyte, leukocyte, and differential leukocyte counts, hematocrits, and hemoglobin concentrations. Reticulocyte counts were performed at the 18- and 24-month examination periods. Mean corpuscular hemoglobin, mean corpuscular volume, and mean corpuscular hemoglobin concentrations were calculated.

After fifty-two weeks, ten rats not subjected to the clinical tests were selected from each test group, sacrificed, and necropsied. Rats found dead or sacrificed in extremis during the study were sacrificed and necropsied. The brain, heart, spleen, thymus, stomach, pituitary, adrenals, lungs, liver, kidneys, and testes were weighed and mean final body weights, organ weights, and organ to body weight ratios were calculated. The tissues noted

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above and the following tissues were examined microscopically for all rats at all feeding levels for histopathologic changes: spinal cord, sciatic nerve, aorta, mesenteric vessels, sternbrae, and humora; bone marrow, sternbrae, lymph nodes, eye, skin with underlying mammary tissue, skeletal muscle, salivary and exorbital lacrimal glands, esophagus, duodenum, jejunum, ileum, cecum, colon, pancreas, thyroid and parathyroid glands, trachea, urinary bladder, prostate, epididymides, testes, mammary glands, ovaries, uterine horns, vagina and all masses.

Results:

2-Year Feeding - Rat

A mild to moderate reduction in mean body weights and weight gains occurred in male rats fed 2500 ppm and 500 ppm chlorsulfuron. The male rats at 100 ppm and the female rats at all dose levels were comparable to their respective control groups throughout the study. Diet consumption was comparable between control and test groups, but food efficiency was decreased in the 2500 ppm male group. Clinical signs, incidence of palpable tissue masses and mortality were comparable in test and control groups.

MALE BODY WEIGHTS

<u>Time (Weeks)</u>	<u>0</u>	<u>100</u>	<u>500</u>	<u>2500</u>
0	119.5	119.5	119.4	119.4
6	361.9	362.3	349.1*	344.1*
13	491.3	493.0	481.8	471.8*
26	580.3	578.9	572.7	554.2*
52	695.2	677.1	669.2*	637.8*
76	768.9	748.8	730.5*	702.9*
104	751.1	754.9	710.5	721.2

* Different from control at $P \leq .05$ level of significance

INCIDENCE AND MEDIAN TIME TO ONSET OF PALPABLE TISSUE MASSES

<u>Treatment Group</u>	<u># Masses</u>	<u># Animals Affected</u>	<u>Median Time to Onset (wks); Range</u>
<u>Male</u>			
Control	15	14	72; 42-100
100 ppm	12	11	72; 42-104
500 ppm	5	5	100; 88-100
2,500 ppm	16	14	88; 60-104
<u>Female</u>			
Control	35	29	84; 52-100
100 ppm	39	33	76; 44-100
500 ppm	36	28	88; 11-104
2,500 ppm	31	26	76; 42-104

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SURVIVAL

<u>Treatment Group</u>		<u>#Rats Alive at Study End (Week 104)</u>
<u>Male</u>	<u>Median Survival Time (wks)</u>	
Control	101.0	46
100 ppm	104.5	44
500 ppm	101.5	41
2500 ppm	105.0	47
<u>Female</u>		
Control	102.0	44
100 ppm	102.5	44
500 ppm	101.5	42
2500 ppm	107.0	46

During the first year of the study, male rats fed 500 and 2500 ppm of test compound exhibited dose-dependent decreased erythrocyte counts, increased hematocrits, mean corpuscular volumes and corpuscular hemoglobins, and slightly decreased mean corpuscular hemoglobin concentrations. This was suggestive of reticulocytosis. However, during the second year of the study, these abnormalities were not observed. In addition, no meaningful differences in reticulocyte counts were observed between control and test groups at 18- or 24-month examinations.

No gross or histopathological abnormalities were considered compound-related. (The pathologist concluded that the test material was not observed to be carcinogenic under conditions of the study.) A summary of incidence of microscopic observations is attached at the end of this evaluation.

In the absence of dose relatedness in the absolute and relative kidney weights of the male test groups, slight decreases observed were not considered to be compound-related. Male rats in the 2500 ppm group exhibited a higher incidence (13/69) of unilateral interstitial cell tumors than was observed in control group males (2/68). However, this was not considered compound-related since a compound-induced effect would be expected to affect the testes bilaterally. The incidence of bilateral interstitial cell tumors in male rats from the control group (7/68) was greater in male rats from the 2500 ppm group (3/69). Also the unilateral incidence was within the known spontaneous range for CD¹ rats and there were no other changes such as interstitial cell hyperplasia suggestive of a compound-related tumorigenic effect in the testes. A NOEL of 100 ppm was established based on body weight loss.

Discussion:2-Year Feeding - Rat

The methods and materials, scientific principles, validity of conclusions, and adequacy of data for conclusions were adequate for the

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004995

study. The reviewer agrees with the conclusions of the study. HLR 283-80 is a one-year interim report issued on the two-year rat study, but it was not reviewed since it was superceded by two-year report 557-81. The study was run under Medical Research Project No. 3067.

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Tox Chem No. 194-AAFile Last Updated 9/28/84

Study/Lab/Study #/Date	Material	EPA Accession No.	Results:		TOX Catego
			LD50, LC50, PIS, NOEL, LEL		
Teratology - rat; Haskell Lab; #583-78; 10/11/78	Tech DPX-4189	099460	Teratogenic NOEL > 2500ppm (highest level tested) maternal NOEL > 2500ppm Fetotoxic NOEL > 2500ppm Dose levels = 0, 100, 500, 2500 ppm		
Teratology - rabbit; Haskell Lab; #12700; 7/17/80	Tech DPX-4189	099460	Teratogenic NOEL > 75 mg/kg Fetotoxic NOEL = 25 mg/kg Fetotoxic LEL = 75 mg/kg (Increased incidence of resorption) (Doses: 0, 10, 25, 75 mg/kg)		
3-Generation reproduc- tion - rat; (combined with 2 year oncogenic study); Haskell Labs	Technical	099460	Reproductive NOEL = 500 ppm Reproductive LEL = 2500 ppm (decreased fertility indices) Maternal NOEL = 500 ppm Maternal LEL = 2500 ppm (decreased mean body weight) Animals on test diet for 103 days before start of reproduction study. Levels tested = 0, 100, 500, 2500 ppm		
14 Day oral - rat; Haskell Lab.; #97-77; 2/12/77	Tech DPX-4189	099460	2,200mg/kg/10 doses/2 weeks produce 20% mortality only (only dose tested)		
90 Day feeding - rat; Haskell Lab.; #80-80	Tech DPX-4189	099460	Sys NOEL=100ppm (LDT) Sys LEL=500ppm (slight decrease in plasma creatinine, slight increased hematocrit) Doses: 0, 100, 500, 2500 ppm		

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Tox Chem No. 194AA

Study/Lab/Study #/Date	Material	EPA Accession No.	Results:		TOX Categor
			LD50, LC50, PIS, NOEL, LEL		
90 Day feeding - mice; Haskell Lab; #69-80; 7/19/78	Tech DPX-4189	099460	Range Finding Study SYS NOEL=2,500ppm SYS LEL=5,000ppm (decreased erythro- cyte count, increased corpuscular volume, increased mean corpuscular hemoglobin and decreased relative liver weight in females Doses: 0, 500, 2500, 5000, 7500 ppm		
6 Month feeding - dog; Haskell Lab; #108-80; 7/24/79	Tech DPX-4189	099460	SYS NOEL > 2,500ppm (HDT) Doses = 0, 100, 500, 2500 ppm		
10 Day feeding - rat; Haskell; #97-77	Technical		Sys. NOEL > 2,200mg/kg (single dose tested)		
2 year feeding/oncogenic - mice; Haskell Lab.; #836-81; 2/3/81	Tech DPX-4189	099460	Oncogenic NOEL > 5000 ppm (HDT) Sys NOEL = 500 ppm Sys LEL = 5000 ppm (decreased BW and food consumption) Doses: 0, 100, 500, 5000 ppm		
2-Year feeding/oncogenic - rat; Haskell Lab.; #557-81; 11/27/79	Technical	099460	Oncogenic NOEL > 2500 ppm (HDT) Sys NOEL = 100 ppm Sys LEL = 500 ppm (decreased BW) Dose levels: 0, 100, 500, 2500 ppm		
Metabolism -rat; Haskell Lab; AMR-08-80	Tech DPX-4189	099460	95% of 14C-dose was eliminated in urine and 4% in feces; 1% was retained in tissues. Major components in urine were intact DPX-4189 (86%), 2-chlorobenzene- sulfonamide (5%) and minor metabolites (4%). Biological half- like is less than six hours.		

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REFERENCE DOSES (RFDs) FOR ORAL EXPOSURE

Chemical: Chlorsulfuron

CAS #: 64902-72-3

Caswell #: 194AA

Carcinogenicity: No evidence of carcinogenicity in two animal (rat and mice) tests.

Systemic Toxicity: See below.

Preparation Date: 3/12/86

Endpoint	Experimental Doses	UF	MF	RFD
Haskell Labs. (1979)	100 ppm (5 mg/kg/day) Systemic NOEL	100	-	0.05 mg/kg/day
2-Year Feeding/ Oncogenic Rat Study	500 ppm (25 mg/kg/day) Systemic LEL			

decreased body weight

Conversion factor (rat): 1 ppm = 0.05 mg/kg/day

Endpoint and Experimental Doses:

Haskell Laboratory (Nov. 27, 1979)
Two Year Feeding/Oncogenic Rat Study
Study No. 557-81

Three hundred sixty-eight male and three hundred and seventy-one female CD rats were received from Charles River Breeding Laboratories. Following a 12 day pretest, 320 rats of each sex were divided into four groups of 80 males and 80 females and housed in pairs. Groups were fed diets containing 0, 100, 500, or 2500 ppm chlorsulfuron for two years. All rats were examined at least once daily during the first 14 weeks of the study and at least twice daily after that for abnormal behavior and clinical signs of toxicity. Three, 6, 12, 18, and 24 months after initiation of the study, ten rats from each of the study groups were subjected to clinical chemistry, hematological and urine analytical examinations. The observed results included a mild to moderate reduction in mean body weights and weight gains occurred in male rats fed 2500 ppm and 500 ppm chlorsulfuron.

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 Uncertainty Factors (UFs):

A composite 100 fold UF has been used to compensate for both the interspecies differences in extrapolating from the human, and the expected intra-human variability to the toxicity of this chemical in lieu of specific data.

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 Modifying Factors (MFs):

None

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 Additional Comments:

Data Considered for Establishing the RfD

- 1) 2-Year Feeding/Oncogenic - Rat Systemic NOEL=100 ppm (5 mg/kg/day), Systemic LEL 500 ppm (25 mg/kg/day)(decreased body weight); Oncogenic NOEL >5000 ppm 250 mg/kg/day)(HDT); core grade guideline
- 2) 6-Month Feeding - Dog Systemic NOEL >2500 ppm (62.5 mg/kg/day)(HDT); core grade minimum
- 3) 3-Generation Reproduction - Rat Reproductive NOEL=500 ppm (25 mg/kg/day), Reproductive LEL=2500 ppm (125 mg/kg/day)(decreased fertility indices); Maternal NOEL=500 ppm, Maternal LEL=2500 ppm (decreased mean body weight); core grade guideline
- 4) Teratology - Rat Teratogenic NOEL >2500 ppm (125 mg/kg/day)(HDT); Maternal NOEL >2500 ppm; Fetotoxic NOEL >2500 ppm; core grade minimum
- 5) Teratology - Rabbit Teratogenic NOEL >75 mg/kg; Fetotoxic NOEL=25 mg/kg, Fetotoxic LEL=75 mg/kg (increased incidence of resorption); core grade minimum

Data Gap(s)

None

Other Data Considered

- 1) 2-Year Feeding/Oncogenic - Mice Oncogenic NOEL >5000 ppm (750 mg/kg)(HDT); Systemic NOEL=500 ppm (75 mg/kg), Systemic LEL=5000 ppm (decreased body weight and food consumption); core grade guideline
- 2) 90-Day Feeding - Rat Systemic NOEL=100 ppm (5 mg/kg)(LDT), Systemic LEL=5000 ppm (25 mg/kg)(slight decrease in plasma creatinine, slight increased hematocrit); core grade minimum

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Confidence in the RfD:

Study: High

Data Base: High

RfD: High

The critical study appears to be of good quality and is given a high rating. Additional studies are also of good quality, and therefore the RfD is given a high confidence rating.

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Documentation of RfD and Review:

Registration files

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Agency RfD Review:

U.S. EPA Contact:

First Review:

Primary: Reto Engler FTS 557-7491

Second Review:

Verification Date:

Secondary: George Ghali FTS 557-4382

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TDMS 10-13-82

DATA EVALUATION RECORD

Coswell 194 AA PAGE. OF
 CASWELL
 PM

CASE

CHEM Chlorsulfuron

BRANCH TB DISC TOPIC 2-Year Feeding - Rat,
 3-Generation Reproduction - Ra

FORMULATION Technical

FICHE/MASTER ID CONTENT CAT

Long-Term Feeding Study With 2-Chloro-N-[[4-Methoxy-6-Methyl-1,3,5-Triazin-2-Yl)Aminocarbonyl]Benzenesulfonamide (INW-4189) In Rats, Haskell Laboratory Report No. 557-81, Wood, C. K.

SUBST. CLASS =

OTHER SUBJECT DESCRIPTORS

DIRECT RVW TIME = 10 hours START-DATE END DATE

REVIEWED BY: J. C. Summers
 TITLE: Research Associate
 ORG: E. I. du Pont de Nemours & Co., Inc., Biochemicals Dept.
 LOC/TEL: Wilmington, Delaware / (302) 772-2367

SIGNATURE: *J. C. Summers* DATE: November 10

APPROVED BY: *e. Frick*

TITLE:

ORG:

LOC/TEL:

SIGNATURE:

DATE: 10/13/82

CONCLUSION:

- A. Core Guideline
- B. A NOEL of 100 ppm was established based on [redacted] when technical chlorsulfuron was fed to rats for [redacted] at dietary levels of 0, 100, 500 or 2500 ppm. [redacted] or histopathologic abnormalities that could be attributed to chlorsulfuron were observed at any test level.
- C. This study conforms to EPA proposed guidelines in section 163.83-1 Chronic Feeding Study (43 Federal Register 37375, 8/22/78).

Methods:2-Year Feeding - Rat

Three hundred sixty-eight male and 371 female CD® rats were received from Charles River Breeding Laboratories, Wilmington, Massachusetts. Following a 12 day pretest, 320 rats of each sex, selected on the basis of weight gain and freedom from signs of disease or injury, were divided by randomization into four groups of 80 males and 80 females and housed in pairs. Groups were fed ground Purina® Laboratory Chow diets containing 0, 100, 500 or 2500 ppm chlorsulfuron for 2 years. Diets were prepared fresh weekly and stored under refrigeration until used. Rats received test diet and water ad libitum.

All rats were examined at least once daily during the first 14 weeks of the study and at least twice daily after that for abnormal behavior and clinical signs of toxicity. Rats were weighed once a week during the first six months, once every two weeks during the next six months, and once every four weeks during the last 12 months. Diet consumed by rats was determined on a group basis at each weighing interval, and food efficiency and daily intake were calculated. Mortality was recorded.

Three, six, twelve, eighteen and twenty-four months after initiation of the study, 10 rats from each of the study groups were subjected to clinical chemistry, hematological and urine analytical examinations. Tail blood was evaluated for alkaline phosphatase, SGOT, SGPT activities, BUN, creatinine and total plasma protein. Urine, from the same animals was collected in the same time intervals and examined for volume, pH, sugar, protein, bilirubin, urobilinogen, occult blood, color, appearance, and sediments. The blood from this same group of animals was examined for the following parameters: erythrocyte, leukocyte and differential leukocyte counts, hematocrits and hemoglobin concentrations. Reticulocyte counts were performed at the 18 and 24-month examination periods. Mean corpuscular hemoglobin, mean corpuscular volume and mean corpuscular hemoglobin concentrations were calculated.

After fifty-two weeks, 10 rats not subjected to the clinical tests were selected from each test group, sacrificed and necropsied. Rats found dead or sacrificed in extremis during the study were also necropsied. At the end of 2 years, all surviving rats were sacrificed and necropsied. The brain, heart, spleen, thymus, stomach, pituitary, adrenals, lungs, liver, kidneys, and testes were weighed and mean final body weights, organ weights, and organ to body weight ratios were calculated. The tissues noted above and the following tissues were examined microscopically for all rats at all feeding levels for histopathologic changes: spinal cord, sciatic nerve, aorta, mesenteric vessels, sternbrae and humoral bone marrow, sternbrae, lymph nodes, eye, skin and with underlying mammary tissue, skeletal muscle, salivary and exorbital lacrimal glands, esophagus, duodenum, jejunum, ileum, cecum, colon, pancreas, thyroid and parathyroid glands, trachea, urinary bladder, prostate, epididymides, testes, mammary glands, ovaries, uterine horns, vagina and all masses.

Results:

2-Year Feeding - Rat

A mild to moderate reduction in mean body weights and weight gains occurred in male rats fed 2500 ppm and 500 ppm chlorsulfuron. The male rats at 100 ppm and the female rats at all dose levels were comparable to their respective control groups throughout the study. Diet consumption was comparable between control and test groups, but food efficiency was decreased in the 2500 ppm male group. Clinical signs, incidence of palpable tissue masses and mortality were comparable in test and control groups.

Male Body Weights

<u>Time, Weeks</u>	<u>0</u>	<u>100</u>	<u>500</u>	<u>2500 (ppm)</u>
0	119.5	119.5	119.4	119.4
6	361.9	362.3	349.1*	344.1*
13	491.3	493.0	481.8	471.8*
26	580.3	578.9	572.7	554.2*
52	695.2	677.1	669.2*	637.8*
76	768.9	748.8	730.5*	702.9*
104	751.1	754.9	710.5	721.2

* Different from control at $P \leq .05$ level of significance

Incidence and Median Time to
Onset of Palpable Tissue Masses

Treatment Group

<u>Male</u>	<u>#Masses</u>	<u>#Animals Affected</u>	<u>Median Time to Onset (wks); Range</u>
Control	15	14	72; 42-100
100 ppm	12	11	72; 42-104
500 ppm	5	5	100; 88-100
2,500 ppm	16	14	88; 60-104
<u>Female</u>			
Control	35	29	84; 52-100
100 ppm	39	33	76; 44-100
500 ppm	36	28	88; 11-104
2,500 ppm	31	26	76; 42-104

Survival

Treatment Group

<u>Male</u>	<u>Median Survival Time (wks)</u>	<u>#Rats Alive at Study End (Week 104)</u>
Control	101.0	46
100 ppm	104.5	44
500 ppm	101.5	41
2,500 ppm	105.0	47
<u>Female</u>		
Control	102.0	44
100 ppm	102.5	44
500 ppm	101.5	42
2,500 ppm	107.0	46

During the first year of the study male rats fed 500 and 2500 ppm of test compound exhibited dose-dependent decreased erythrocyte counts, increased hematocrits, mean corpuscular volumes and corpuscular hemoglobins, and slightly decreased mean corpuscular hemoglobin concentrations. This was suggestive of reticulocytosis. However, during the second year of the study these abnormalities were not observed. In addition, no meaningful differences in reticulocyte counts were observed between control and test groups at 18- or 24-month examinations.

No gross of histopathological abnormalities were considered compound-related. The pathologist concluded that the test material was not observed to be carcinogenic under conditions of the study. A summary incidence of microscopic observations is attached at the end of this evaluation.

In the absence of dose relatedness in the absolute and relative kidney weights of the male test groups, slight decreases observed were not considered to be compound-related. Male rats in the 2500 ppm group exhibited a higher incidence (13/69) of unilateral interstitial cell tumors than was observed in control group males (2/68). However, this was not considered compound-related since a compound-induced effect would be expected to affect the testes bilaterally. The incidence of bilateral interstitial cell tumors in male rats from the control group (7/68) was greater than in male rats from the 2500 ppm group (3/69). Also the unilateral incidence was within the known spontaneous range for CD® rats and there were no other changes such as interstitial cell hyperplasia suggestive of a compound-related tumorigenic effect in the testes. A NOEL of 100 ppm was established based on body weight loss.

Discussion:

2-Year Feeding - Rat

The methods and material, scientific principles, validity of conclusions, and adequacy of data for conclusions were adequate for the study. The reviewer agrees with the conclusions of this study. HLR-283-80 is a 1-year interim report issued on the 2-year rat study, but it was not reviewed since it was superceded by 2-year report 557-81. This study was run under Medical Research Project No. 3067.

6-1-68

NUMBER EVALUATED	68	68	68	68	65	65	67	65
UNREMARKABLE HISTOLOGICALLY MALIGNANT LYMPHOMA, METASTATIC fibrosis	0	0	3	0	1	0	1	0
lymphoid cell infiltrate, focal	0	0	0	0	1	0	1	0
lymphoid cell infiltrate	0	0	0	0	2	0	0	0
adenitis, chronic	2	0	7	0	5	0	0	0
ADRENAL GLAND							4	
NUMBER EVALUATED	63	61	63	60	56	59	62	61
UNREMARKABLE HISTOLOGICALLY ADENOCARCINOMA, NOS	62	60	61	59	51	56	62	58
MALIGNANT LYMPHOMA, METASTATIC fibrosis	0	0	0	0	1	0	0	0
fibrosis, interstitial	0	1	0	0	1	0	0	0
lymphoid cell infiltrate	0	0	0	0	0	1	0	2
adenitis	0	0	1	0	2	0	0	0
adenitis, chronic	1	0	0	1	0	2	0	0
IR								1

NUMBER EVALUATED	63	63	64	63	63	64	64	59
FIBROMA	0	0	0	0	0	0	1	0
FIBROSARCOMA	0	0	0	0	0	0	1	0
chondroplasia	1	1	1	2	3	2	0	2
ulcer, acute	0	0	0	0	0	0	1	0
ossification of cartilage	1	0	1	0	0	1	2	1
chronic cellulitis	0	0	0	1	0	0	0	0
dermatitis, chronic	0	0	0	1	0	0	0	0
DUDE EAR/ZYMBAL'S GLAND								
NUMBER EVALUATED	63	63	64	63	57	63	64	59
UNREMARKABLE HISTOLOGICALLY SQUAMOUS CELL CARCINOMA	60	58	61	63	54	60	64	58
MALIGNANT LYMPHOMA, METASTATIC	0	1	0	0	0	0	0	0
SQUAMOUS CELL CARCINOMA, INVASIVE abscess, acute	0	0	2	0	1	0	0	0
cystic ducts	0	1	1	0	0	0	0	0
otitis media	2	0	0	0	1	0	0	0
keratin cyst	0	1	0	0	0	1	0	0
ductular dilatation	0	0	0	0	1	0	0	0
ductular dilatation	0	2	0	0	0	3	0	0
ductular dilatation	1	0	0	0	0	0	0	1

	70	68	67	68	66	65	68	67	66
UNREMARKABLE HISTOLOGICALLY									
FIBROMA	1	0	4	0	3	2	0	0	0
LIPOMA	0	0	1	1	0	0	0	0	0
TRICHO-EPITHELIOMA	0	0	1	0	0	0	0	0	0
KERATO-ACANTHOMA	0	0	0	0	1	0	0	0	0
SQUAMOUS CELL CARCINOMA	0	0	0	0	1	0	0	0	0
RETICULUM CELL SARCOMA	0	0	0	0	1	0	0	0	0
MALIGNANT LYMPHOMA, METASTATIC	1	0	2	0	0	0	0	0	0
abscess, chronic	0	0	1	0	0	0	0	1	0
cyst(s), epidermal inclusion (keratin)	0	0	0	0	1	0	0	0	0
dermatitis, ulcerative, chronic	0	0	1	0	0	0	0	0	0
edema, nos	0	0	0	0	0	0	0	0	1
fibrosis	0	0	1	0	0	1	0	0	0
fibrosis, subepidermal	0	0	0	2	0	0	0	0	0
reticulocytosis	0	0	1	0	0	0	0	0	0
keratin cyst	0	0	0	0	2	0	0	0	0

	6	3	1	0	0	1	6	4
IN/SUBCUTANEOUS								
FIBROMA	4	3	0	0	0	0	2	3
LIPOMA	0	0	1	0	0	1	2	0
CARCINOSARCOMA	0	0	0	0	0	0	1	0
FIBROSARCOMA	0	0	0	0	0	0	0	1
LYMPHANGIOSARCOMA	1	0	0	0	0	0	0	0
abscess, chronic	1	0	0	0	0	0	0	0
keratin cyst	0	0	0	0	0	0	1	0

	0	1	0	0	0	0	0	0
IN/FOOT PAD, NOS								
FIBROMA	0	1	0	0	0	0	0	0
LIPOMA	0	1	0	0	0	0	0	0

	69	62	62	60	55	62	63	61
CHRONIC CELLULITIS								
SAL & VENTRAL TURBINATES								
CHRONIC CELLULITIS	0	1	0	0	0	0	0	0
SAL & VENTRAL TURBINATES	0	1	0	0	0	0	0	0

	69	62	57	43	52	48	62	60
UNREMARKABLE HISTOLOGICALLY								
MALIGNANT LYMPHOMA, METASTATIC	0	0	1	0	1	0	0	0
ADENOCARCINOMA, NOS, INVASIVE	0	0	0	0	1	0	0	0
abscess, acute	0	0	0	1	0	0	0	0
congestion	0	0	1	13	0	4	0	0
fibrosis	0	0	0	0	0	0	1	0
hemorrhage	0	0	0	2	0	10	0	0

BER EVALUATED
 dermatitis, ulcerative, chronic
 atretic hair follicles
 GS W/MAINSTEM BRONCHI

BER EVALUATED

UNREMARKABLE HISTOLOGICALLY
 ADENOCARCINOMA, METASTATIC
 CARCINOMA, NOS, METASTATIC
 CARCINOSARCOMA, METASTATIC
 LIPOSARCOMA, METASTATIC
 PAPILLARY CYSTADENOCARCINOMA, METASTATIC
 SQUAMOUS CELL CARCINOMA, METASTATIC
 RETICULUM CELL SARCOMA, METASTATIC
 MALIGNANT LYMPHOMA, METASTATIC
 RHABDOMYOSARCOMA, INVASIVE
 bronchopneumonia, acute
 calcification, dystrophic
 collapse, alveolar
 congestion
 congestion, localized
 edema, alveolar
 fibrosis
 fibrosis, interstitial
 hemorrhage, focal
 hemorrhage, localized
 metaplasia, osseous, minute focus
 microgranulomatous foci
 pigmentation, hemosiderin

IS W/MAINSTEM BRONCHI

BER EVALUATED
 pneumonitis, focal
 pleuritis, acute
 pleuritis, chronic
 hyperplasia, bronchio-alveolar
 leucocytosis
 chronic arteritis
 CHEA

BER EVALUATED

0	2	0	0	0	0	0	0	0	1
0	1	0	0	0	0	0	0	0	0
0	1	0	0	0	0	0	0	0	1
70	47	34	33	33	33	40	32	67	67
30	0	0	1	0	0	40	0	38	38
0	1	0	0	0	0	0	0	0	0
0	0	0	0	0	0	1	2	0	0
0	0	0	1	0	0	0	0	0	0
0	1	0	0	0	0	0	0	0	0
0	0	1	0	0	0	0	0	0	0
0	0	2	1	0	0	0	2	0	0
1	0	4	0	2	1	1	2	0	0
0	1	0	0	0	0	0	0	0	0
0	0	0	0	1	0	0	0	0	0
0	0	2	0	0	1	0	2	0	0
0	0	0	1	1	0	0	0	0	0
26	13	16	22	24	12	12	12	11	11
1	0	1	0	0	0	0	0	0	0
6	4	5	5	4	9	9	5	3	3
0	0	1	0	0	0	0	1	0	0
0	0	0	0	0	0	0	1	0	0
3	2	3	7	1	9	9	5	9	9
0	1	3	0	0	1	1	0	0	0
3	0	1	1	0	1	1	1	0	0
0	1	0	0	0	0	0	0	0	0
0	0	0	0	0	0	1	0	0	0
70	47	34	33	33	33	40	32	67	67
12	7	9	7	7	7	5	18	10	10
1	0	0	0	0	0	0	0	0	0
0	0	0	0	0	0	0	1	0	0
0	0	0	0	0	0	0	1	0	0
1	0	0	0	0	0	0	0	0	0
0	0	1	0	0	0	0	0	0	0
70	47	34	33	33	33	40	32	67	67
70	69	69	67	66	66	68	69	66	66

LIVER

hyperplasia, bile duct, focal	32	23	25	20	21	26	26	20
hyperplasia, bile duct, localized	2	3	3	1	1	1	0	3
hyperplasia, hepatic cell, focal	4	1	6	4	0	0	3	2
hyperplasia, hepatic cell, localized	7	3	3	8	7	16	5	4
hyperplasia, lymphoid cell	1	2	0	1	0	1	1	3
hypertrophy, hepatic cell, focal	2	0	15	0	1	0	3	1
hypertrophy, hepatic cell, localized	20	13	5	2	4	7	9	7
lipidosis, hepatic cell, focal	2	7	0	0	0	0	0	0

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lipidosis, hepatic cell, diffuse	69	70	69	68	67	68	69	67
lipidosis, hepatic cell, localized	8	5	10	23	8	23	12	11
lymphoid cell infiltrate, focal	4	5	5	2	9	1	3	0
necrosis, hepatic cell, focal	0	0	1	0	0	1	0	1
necrosis, hepatic cell, centrolobular	3	8	2	2	3	4	3	5
pericholangiolitis, chronic	0	0	0	0	0	1	0	1
pigmentation, hemosiderin	26	14	38	22	25	10	22	14
reticulocytosis	0	0	0	0	0	1	0	0
leucocytic infiltrate	0	0	0	0	0	0	0	1
extra-medullary hemopoiesis	0	1	0	0	0	0	0	1
angiectasis, localized	0	0	0	0	0	1	1	0
angiectasis, localized	10	3	12	0	8	0	5	2

PANCREAS

NUMBER EVALUATED	70	68	67	65	63	62	68	65
UNREMARKABLE HISTOLOGICALLY	42	54	49	54	52	55	51	55
ACINAR CELL ADENOMA	0	0	0	0	2	0	1	0
ISLET CELL ADENOMA	12	1	6	2	1	1	5	3
RETICULUM CELL SARCOMA, METASTATIC	2	0	1	0	0	0	0	0
MALIGNANT LYMPHOMA, METASTATIC	1	0	3	0	1	0	0	0
atrophy, acinar, focal	7	7	0	0	0	2	7	2
cytoplasmic vacuolation, nos	2	0	0	0	0	0	0	0
fibrosis, interstitial	0	1	0	0	0	0	0	0
hemorrhage	1	0	0	0	0	0	0	0
hyperplasia, acinar, localized	0	0	0	1	0	0	0	0
hyperplasia, islet cell	0	0	0	1	0	1	0	0
lipidosis, nos	0	0	1	0	0	0	0	0
pancreatitis, chronic	0	0	6	2	3	0	3	0
peri-arteritis, chronic	0	0	4	3	0	0	0	0
chronic arteritis	7	5	1	1	4	4	4	5
acinar vacuolation	1	1	0	1	0	0	0	0

NUMBER EVALUATED	70	69	68	68	66	65	68	65
UNREMARKABLE HISTOLOGICALLY UNDIFFERENTIATED CARCINOMA	0	0	1	0	0	0	0	0
LIPOSARCOMA, METASTATIC	0	0	0	0	1	0	0	0
MALIGNANT LYMPHOMA, METASTATIC	0	0	2	0	1	0	0	0
abscess, acute	1	0	0	0	0	0	0	0
congestion	0	0	0	0	1	0	0	0
lymphoid cell infiltrate	0	0	0	0	0	0	0	1

NUMBER EVALUATED	70	69	68	68	66	65	68	65
UNREMARKABLE HISTOLOGICALLY	1	1	0	0	0	0	1	1

NUMBER EVALUATED	70	69	68	68	66	65	68	65
UNREMARKABLE HISTOLOGICALLY	1	1	0	0	0	0	1	1

NUMBER EVALUATED	70	69	68	68	66	65	68	65
abscess, chronic	0	0	0	0	0	0	0	1
dermatitis, ulcerative, chronic	0	0	0	0	0	0	0	1

NUMBER EVALUATED	70	69	68	68	66	65	68	65
ESOPHAGUS	0	0	0	0	0	0	0	0

NUMBER EVALUATED	70	69	68	68	66	65	68	65
UNREMARKABLE HISTOLOGICALLY	69	68	69	68	66	67	69	66
esophagitis	0	0	0	0	0	0	1	0

NUMBER EVALUATED	70	69	68	68	66	65	68	65
STOMACH	68	70	68	68	66	68	69	67

NUMBER EVALUATED	70	69	68	68	66	65	68	65
UNREMARKABLE HISTOLOGICALLY	63	69	64	64	61	63	68	63
SQUAMOUS CELL CARCINOMA	0	0	0	0	0	0	0	1
RETICULUM CELL CARCINOMA, METASTATIC	1	0	0	0	0	0	0	0
MALIGNANT LYMPHOMA, METASTATIC	0	0	1	0	0	0	0	0
congestion	0	0	0	0	1	0	0	0
edema, nos	0	0	0	1	1	1	0	0
edema, inflammatory	0	0	0	0	0	2	0	0
erosion, mucosal	0	0	0	0	1	0	1	0
fibrosis	0	0	0	1	0	0	0	0
gastritis, ulcerative, chronic	1	0	0	0	1	1	0	0
hyperkeratosis (cardia)	0	0	1	2	3	0	0	1

NUMBER EVALUATED	70	69	68	68	66	65	68	65
gastritis, acute, cardia	0	1	0	0	0	1	0	1
gastritis, fundus, acute	1	0	0	0	0	0	0	0
gastritis, ulcerative, acute, cardia	1	0	0	0	0	0	0	0

601000

NUMBER EVALUATED 70 70 69 68 65 67 69 66

UNREMARKABLE HISTOLOGICALLY
RETICULUM CELL SARCOMA, METASTATIC
lipogranuloma 1 0 1 0 0 0 0 0
serositis, chronic 0 0 0 0 0 0 1 0
chronic arteritis 1 0 1 0 0 0 1 2

UNUM

NUMBER EVALUATED 70 70 68 68 66 67 69 67

UNREMARKABLE HISTOLOGICALLY
interitis 70 70 68 67 66 67 69 67
0 0 0 1 0 0 0 0

NUM

NUMBER EVALUATED 68 69 68 68 64 67 69 66

UNREMARKABLE HISTOLOGICALLY
hyperplasia, lymphoid cell 68 69 67 68 64 67 68 66
0 0 0 0 0 0 1 0
microgranulomatous foci 0 0 1 0 0 0 0 0

NUM

NUMBER EVALUATED 67 70 69 68 66 67 68 68

UNREMARKABLE HISTOLOGICALLY
LEIOMYOMA 63 68 62 66 65 66 67 64
0 1 0 0 0 0 0 0
RETICULUM CELL SARCOMA 0 1 0 0 0 0 0 0
MALIGNANT LYMPHOMA, METASTATIC 0 0 1 1 0 0 0 0
edema, nos 0 0 1 1 0 0 0 0
edema, inflammatory 0 0 1 1 0 0 0 0
fibrosis 1 0 4 1 1 0 1 3
microgranulomatous foci 4 0 0 0 0 0 0 0
perivasculitis 0 0 0 0 0 0 0 0
chronic arteritis 0 0 0 0 0 1 0 1

NUM

NUMBER EVALUATED 69 70 69 65 66 67 69 67

UNREMARKABLE HISTOLOGICALLY
RETICULUM CELL SARCOMA, METASTATIC
hyperplasia, lymphoid cell 69 71 69 65 66 66 67 65
0 0 0 0 0 0 0 1
ulcer, acute 0 0 0 0 0 0 2 0
chronic arteritis 0 0 0 0 0 0 0 1
colitis, ulcerative, acute 0 0 0 0 0 1 0 0

NUMBER EVALUATED 1 1 0 0 5 0 1 0
 UNREMARKABLE HISTOLOGICALLY 1 1 0 0 5 0 1 0

NE MARROW/STERNUM

NUMBER EVALUATED 68 70 69 68 66 67 65 65
 UNREMARKABLE HISTOLOGICALLY 0 0 0 0 0 0 1 0
 RETICULUM CELL SARCOMA, METASTATIC 0 0 1 0 0 0 0 0
 MALIGNANT LYMPHOMA, METASTATIC 1 0 3 0 1 0 2 0
 hemopoietic/cellularity unremarkable 67 69 63 68 65 67 62 65
 hemorrhage 0 1 1 0 0 0 0 0
 pigmentation, lipochrome 0 0 0 0 0 1 0 0
 fatty replacement 0 0 1 0 0 0 0 0

NE MARROW/FEMUR

NUMBER EVALUATED 63 55 63 61 56 62 62 61
 UNREMARKABLE HISTOLOGICALLY 2 0 1 0 0 1 1 0
 RETICULUM CELL SARCOMA, METASTATIC 0 0 1 0 0 0 0 0
 MALIGNANT LYMPHOMA, METASTATIC 0 0 2 0 1 0 1 0
 hemopoietic/cellularity unremarkable 60 54 57 61 55 61 60 60
 hemorrhage 0 0 1 0 0 0 0 0
 hemorrhage, localized 0 0 0 0 0 0 0 1
 hyperplasia, acinar, localized 0 1 0 0 0 0 0 0
 pigmentation, hemosiderin 1 0 0 0 0 0 0 0
 fatty replacement 0 0 1 0 0 0 0 0

PLEEN

NUMBER EVALUATED 70 69 69 68 67 67 68 67

UNREMARKABLE HISTOLOGICALLY 48 27 45 30 46 32 48 30
 FIBROMA 1 0 0 0 0 0 0 0
 HEMANGIOSARCOMA 0 0 0 0 0 0 0 1
 MALIGNANT LYMPHOMA, NOS 2 0 4 1 2 2 2 1
 RETICULUM CELL SARCOMA, METASTATIC 0 0 1 0 0 0 0 0
 atrophy, nos 0 3 0 0 0 0 0 0
 congestion 6 0 11 3 2 1 2 1
 depletion, lymphoid cell 1 0 0 0 2 0 0 0
 hemopoietic/cellularity unremarkable 0 0 0 1 0 0 0 0
 hemorrhage 0 0 0 1 0 0 0 3
 hyperplasia, lymphoid cell 3 3 1 1 2 1 1 0
 pigmentation, hemosiderin 4 29 5 24 9 22 8 20
 splenitis, acute 0 0 0 1 0 0 0 0
 extra-medullary hemopoiesis 5 13 3 11 4 10 8 14

cyst, medullary	1	0	0	1	1	1	0	0
hemopoietic/cellularity unremarkable	1	0	0	0	0	0	0	0
hemorrhage	0	0	0	0	1	0	0	0
hydronephrosis, unilateral	25	24	28	17	28	13	15	18
hydronephrosis, bilateral	10	3	5	5	5	7	14	7
hyperplasia, reticulum cell	1	0	0	0	0	0	0	0
hyperplasia, transitional cell	0	0	0	0	0	1	0	0
infarct(s)	0	1	0	0	0	0	0	0
infarct(s), healed	0	0	1	0	1	0	0	0

KIDNEY

IMBER EVALUATED	70	70	69	68	66	68	69	67
lipidosis, cortical, diffuse	0	0	0	0	0	1	0	1
mineralization/minute foci	3	46	3	47	7	36	9	36
nephritis, chronic	56	25	57	36	59	27	51	25
pericholangiolitis, chronic	1	0	0	0	0	0	0	0
pigmentation, hemosiderin	1	0	0	0	0	0	0	0
pyelonephritis, acute	1	1	2	2	1	1	4	0
pyelonephritis, suppurative	0	0	0	0	1	0	0	0
thrombus, septic	1	0	0	0	0	0	0	0
angiectasis, localized	0	0	0	0	1	0	0	1
cortical cyst(s)	6	2	6	0	4	3	5	0
pyelonephritis, subacute	0	0	0	0	0	1	0	1
chronic inflammation, capsular	0	0	0	0	0	0	0	1

URINARY BLADDER

IMBER EVALUATED	69	67	68	64	62	66	67	65
UNREMARKABLE HISTOLOGICALLY	66	65	63	60	58	64	62	62
HEMANGIOSARCOMA, METASTATIC	0	0	0	0	0	1	0	0
RETICULUM CELL SARCOMA, METASTATIC	1	0	1	0	0	0	0	0
MALIGNANT LYMPHOMA, METASTATIC	1	0	2	0	1	0	0	0
calcareous debris/intraluminal	0	0	0	1	1	0	1	0
edema, submucosal	0	0	0	0	0	0	0	1
hemorrhage	0	1	0	0	0	0	0	0
hyperplasia, transitional cell	0	0	2	0	1	0	2	0
cystitis, acute	1	0	2	1	0	0	3	1
cystitis, chronic	0	1	0	2	2	1	1	2

NUMBER EVALUATED	61	62	63	64	65	66	67	68	69	70
UNREMARKABLE HISTOLOGICALLY ADENOMA, NOS (PARS ANTERIOR)	28	12	29	6	23	11	25	22	29	44
CARCINOMA, NOS	1	3	0	0	2	0	2	0	0	0
MALIGNANT LYMPHOMA, METASTATIC	0	0	3	0	1	0	0	0	0	0
congestion	0	0	0	0	0	3	1	0	0	0
cyst, serous (pars anterior)	2	1	4	0	9	0	4	0	0	0
hemorrhage	0	0	0	0	0	0	0	0	0	1
pigmentation, hemosiderin	0	0	0	0	0	0	1	0	0	0

RENAL

NUMBER EVALUATED	67	68	69	70	66
UNREMARKABLE HISTOLOGICALLY PHEOCHROMOCYTOMA, UNILATERAL	33	9	30	8	14
PHEOCHROMOCYTOMA, BILATERAL	2	0	3	1	2
CORTICAL ADENOMA, UNILATERAL	0	0	0	0	1
CORTICAL ADENOMA, BILATERAL	3	0	1	3	1
CORTICAL ADENOMA, NOS	0	0	0	0	0
CORTICAL CELL CARCINOMA, NOS	0	1	0	0	0
CORTICAL CELL CARCINOMA, UNILATERAL	0	0	0	0	0
CORTICAL CELL CARCINOMA, UNILATERAL	0	0	0	0	0
HEMANGIOSARCOMA	1	0	0	0	0
PHEOCHROMOCYTOMA, MALIGNANT	0	0	0	0	0
CARCINOSARCOMA, METASTATIC	0	0	0	0	0
RETICULUM CELL SARCOMA, METASTATIC	0	0	0	0	0
MALIGNANT LYMPHOMA, METASTATIC	0	0	4	0	0
angiectasis	13	43	3	32	45
congestion	14	52	5	45	46
congestion, localized	0	0	1	0	0
fibrosis	0	0	1	0	0
hemorrhage	0	1	0	0	0
hyperplasia, cortical cell, localized	0	2	5	7	4
hyperplasia, medullary cell, unilateral	1	2	1	0	0
hyperplasia, medullary cell, bilateral	1	0	0	0	0
hyperplasia, medullary cell	1	0	1	1	1
hypertrophy, cortical cell, localized	0	0	0	0	0
lipidosis, cortical, focal	0	0	4	0	0
lipidosis, cortical, diffuse	16	7	11	27	7
lipidosis, cortical, localized	1	2	8	0	0
mineralization/minute foci	0	0	1	0	0
necrosis, nos	0	1	0	0	1
necrosis, cortical, focal	0	0	0	0	0
pigmentation, hemosiderin	0	1	0	0	0
pigmentation, lipochrome	0	1	0	0	0

NUMBER

NUMBER EVALUATED	65	59	59	61	51	49	65	56
UNREMARKABLE HISTOLOGICALLY	62	53	50	57	49	45	64	53
C-CELL ADENOMA, UNILATERAL	2	5	4	2	1	3	1	3
CYSTADENOMA, UNILATERAL	0	1	0	0	0	0	0	0
MALIGNANT LYMPHOMA, METASTATIC	0	0	1	0	0	0	0	0
cyst, follicular, unilateral	1	0	1	0	1	0	0	0
dilatation, acinar, unilateral	0	0	0	0	1	0	0	0
hyperplasia, microfollicular, diffuse	0	0	1	0	0	1	0	0
keratin cyst	0	0	1	2	0	0	0	0
hyperplasia, C-cell, nos	0	0	1	0	0	0	0	0

ARATHYROID

NUMBER EVALUATED	27	35	24	41	27	25	41	24
UNREMARKABLE HISTOLOGICALLY	27	35	24	40	27	24	41	20
ADENOMA	0	0	0	1	0	0	0	0
fibrosis	0	0	0	0	0	1	0	0
MMARY GLAND								

NUMBER EVALUATED

NUMBER EVALUATED	27	64	20	57	21	60	35	59
UNREMARKABLE HISTOLOGICALLY	25	20	19	16	19	21	29	15
ADENOMA	0	0	0	1	0	0	1	1
CYSTADENOMA	0	0	0	1	0	1	0	1
FIBRO-ADENOMA	0	21	0	27	1	23	2	26
FIBROCYSTADENOMA	0	12	0	0	0	6	0	12
PAPILLARY CYSTADENOMA	0	1	0	5	0	1	0	3
ADENOCARCINOMA, NOS	0	3	0	2	0	3	0	1
CARCINOSARCOMA	0	0	0	0	0	1	0	0
CYSTADENOCARCINOMA, NOS	0	0	0	1	0	0	0	0
FIBROSARCOMA	0	0	0	1	0	0	0	0
PAPILLARY ADENOCARCINOMA	0	7	0	0	0	0	0	4
PAPILLARY CYSTADENOCARCINOMA, NOS	0	3	0	5	0	6	0	1
abscess, chronic	0	0	1	0	0	0	0	0
fibrosis, interstitial	0	0	0	0	0	1	0	0
galactocoeles	3	5	1	13	1	12	1	7
mastitis, chronic	0	0	0	2	0	0	0	0
secretory (lactation)	0	0	0	0	0	0	2	1
keratin cyst	0	0	0	1	0	0	0	0

NUMBER EVALUATED 68 0 69 0 66 0 68 0

UNREMARKABLE HISTOLOGICALLY
 INTERSTITIAL CELL TUMOR, UNILATERAL 49 0 47 0 53 0 54 0
 INTERSTITIAL CELL TUMOR, BILATERAL 2 0 13 0 3 0 5 0
 MESOTHELIOMA 7 0 3 0 2 0 2 0
 atrophy, tubular, unilateral 0 0 1 0 1 0 0 0
 atrophy, tubular, bilateral 11 0 7 0 5 0 7 0
 chronic arteritis 5 0 5 0 2 0 6 0
 7 0 0 0 1 0 2 0

IDIDYMIS

NUMBER EVALUATED 68 0 69 0 66 0 68 0

UNREMARKABLE HISTOLOGICALLY
 RETICULUM CELL SARCOMA, METASTATIC 61 0 67 0 64 0 65 0
 atrophy, nos 1 0 0 0 0 0 0 0
 epididymitis, chronic 5 0 0 0 1 0 3 0
 fibrosis, interstitial 0 0 2 0 1 0 0 0
 chronic arteritis 0 0 1 0 0 0 0 0
 1 0 0 0 0 0 0 0

ROSTATE

NUMBER EVALUATED 68 0 67 0 65 0 67 0

UNREMARKABLE HISTOLOGICALLY
 ACINAR CELL ADENOMA 57 0 56 0 53 0 53 0
 RETICULUM CELL SARCOMA, METASTATIC 1 0 0 0 0 0 0 0
 MALIGNANT LYMPHOMA, METASTATIC 1 0 1 0 0 0 0 0
 abscess, chronic 1 0 1 0 1 0 1 0
 edema, nos 0 0 0 0 0 0 1 0
 fibrosis 1 0 0 0 0 0 0 0
 fibrosis, interstitial 0 0 0 0 0 0 0 0
 hemorrhage, focal 0 0 0 0 1 0 0 0
 hyperplasia, acinar, localized 1 0 0 0 2 0 1 0
 prostatitis, acute 4 0 3 0 2 0 5 0
 prostatitis, suppurative, acute 1 0 2 0 0 0 0 0
 prostatitis, chronic 2 0 4 0 6 0 4 0
 prostatitis, suppurative, chronic 0 0 0 0 1 0 0 0

MINAL VESICLE

NUMBER EVALUATED 17 0 8 0 9 0 7 0

UNREMARKABLE HISTOLOGICALLY
 MALIGNANT LYMPHOMA, METASTATIC 15 0 5 0 9 0 5 0
 atrophy, nos 0 0 2 0 0 0 0 0
 vesiculitis, acute, suppurative 1 0 1 0 0 0 0 0

NUMBER EVALUATED	66	67	68	69	70	71	72	73	74	75
UNREMARKABLE HISTOLOGICALLY	0	0	0	0	0	0	0	0	0	0
FIBROMA	0	43	0	44	0	44	0	44	0	42
GRANULOSA CELL TUMOR	0	0	0	1	0	0	0	0	0	0
GONADAL STROMAL SARCOMA	0	2	0	0	0	0	0	0	0	1
RETICULUM CELL SARCOMA, METASTATIC	0	0	0	0	0	0	0	1	0	0
cyst(s), nos	0	0	0	1	0	0	0	0	0	1
cyst, corpus luteum	0	0	0	0	0	0	0	0	0	0
cyst, follicular	0	0	0	4	0	4	0	1	0	2
cyst, follicular, unilateral	0	16	0	17	0	17	0	15	0	21
cyst, follicular, bilateral	0	3	0	0	0	0	0	2	0	0
bursal cyst	0	0	0	1	0	1	0	0	0	0
bursal cyst, unilateral	0	1	0	1	0	1	0	4	0	2
bursal cyst, bilateral	0	0	0	0	0	0	0	0	0	0
stromal hyperplasia, unilateral	0	0	0	1	0	1	0	0	0	0

TERUS WITH HORNS

NUMBER EVALUATED	67	68	69	70	71	72	73	74	75
UNREMARKABLE HISTOLOGICALLY	0	0	0	0	0	0	0	0	0
ENDOMETRIAL STROMAL POLYP	0	38	0	33	0	28	0	28	0
FIBROMA	0	3	0	5	0	7	0	7	0
LEIOMYOMA	0	0	0	1	0	0	0	0	0
PAPILLARY CYSTADENOMA	0	0	0	0	0	0	0	0	0
HEMANGIOSARCOMA	0	0	0	0	0	1	0	1	0
RETICULUM CELL SARCOMA, METASTATIC	0	0	0	0	0	0	0	0	1
cyst(s), endometrial	0	25	0	26	0	29	0	29	0
endometritis, acute	0	0	0	1	0	2	0	2	0
fibrosis	0	0	0	0	0	1	0	1	0
hydrometra	0	5	0	1	0	5	0	5	0
metaplasia, squamous	0	0	0	0	0	1	0	1	0
pigmentation, hemosiderin	0	0	0	0	0	0	0	0	1
fibroplasia	0	0	0	0	1	0	0	0	0

NUMBER EVALUATED

UNREMARKABLE HISTOLOGICALLY	62	55	63	61	55	62	60	61
TERNUM	62	55	63	61	55	62	60	61

NUMBER EVALUATED	68	70	69	68	66	48	65	65
UNREMARKABLE HISTOLOGICALLY	68	70	69	68	66	60	65	65

SCAPULAR MUSCLE/RIGHT FORELEG

MEMBER EVALUATED 0 0 1 0 0 0 0 0 0 0

RETICULUM CELL SARCOMA, METASTATIC

SCAPULAR MUSCLE/RIGHT SHOULDER 0 0 1 0 0 0 0 0 0 0

MEMBER EVALUATED

0 0 1 0 0 0 0 0 0 0

RETICULUM CELL SARCOMA

0 0 1 0 0 0 0 0 0 0

SCAPULAR MUSCLE, NOS

MEMBER EVALUATED 70 68 68 65 67 68 66

UNREMARKABLE HISTOLOGICALLY

FIBROSARCOMA 69 68 66 64 64 69 66

RETICULUM CELL SARCOMA

0 0 0 1 0 0 0

HEMANGIOSARCOMA, METASTATIC

1 0 0 0 1 0 0

MALIGNANT LYMPHOMA, METASTATIC

0 0 0 0 1 0 0

fibrosis, interstitial

0 0 1 0 0 0 0

ABDOMINAL WALL

MEMBER EVALUATED 0 0 0 0 0 0 1 0

RETICULUM CELL SARCOMA

0 0 0 0 0 0 1 0

NECK/HEAD

MEMBER EVALUATED 0 0 0 0 0 0 1 0

CARCINOSARCOMA

0 0 0 0 0 0 1 0

ulcer, chronic

0 0 0 0 0 0 1 0

SS/RIGHT SIDE

MEMBER EVALUATED 0 1 0 0 0 0 1 0

FIBROMA

0 0 0 0 0 0 1 0

SQUAMOUS CELL CARCINOMA

0 1 0 0 0 0 0 0

SENTINEL

MEMBER EVALUATED 2 0 2 0 0 0 0 0

RETICULUM CELL SARCOMA

1 0 0 0 0 0 0 0

chronic arteritis

1 0 2 0 0 0 0 0

NUMBER EVALUATED
 0 1 0 0 0 0 0 0 0 0
 LIPOMA
 0 1 0 0 0 0 0 0 0 0

NUMBER EVALUATED
 0 0 0 1 0 0 0 0 0 0
 FIBROSARCOMA
 0 0 0 1 0 0 0 0 0 0

NUMBER EVALUATED
 0 0 0 0 0 0 0 0 1 0
 abscess, chronic
 0 0 0 0 0 0 0 0 1 0
 OT, NOS

NUMBER EVALUATED
 0 0 1 0 0 0 0 0 0 1
 dermatitis, ulcerative, chronic
 0 0 1 0 0 0 0 0 0 1
 DT/LEFT HIND

NUMBER EVALUATED
 5 5 5 5 5 3 8 2 4
 dermatitis, ulcerative, chronic
 5 4 4 4 4 3 8 2 4
 dermatitis, chronic
 0 0 1 1 0 0 0 0 0
 chronic fibrosis(collagenous)
 0 1 0 0 0 0 0 0 0

NUMBER EVALUATED
 2 7 1 8 4 8 3 6
 UNREMARKABLE HISTOLOGICALLY
 dermatitis, ulcerative, chronic
 2 6 1 6 4 8 3 5
 dermatitis, chronic
 0 0 0 2 0 0 0 0
 chronic fibrosis(collagenous)
 0 1 0 0 0 0 0 0

NUMBER EVALUATED
 1 0 0 0 0 0 0 0
 OSTEOGENIC SARCOMA
 1 0 0 0 0 0 0 0
 ulcer, chronic
 1 0 0 0 0 0 0 0
 TISS/ABDOMINAL

NUMBER EVALUATED
 1 0 0 0 0 0 0 0
 OSTEOGENIC SARCOMA
 1 0 0 0 0 0 0 0
 ulcer, chronic
 1 0 0 0 0 0 0 0
 TISS/ABDOMINAL

NUMBER EVALUATED
 1 0 0 0 0 0 0 0
 OSTEOGENIC SARCOMA
 1 0 0 0 0 0 0 0
 ulcer, chronic
 1 0 0 0 0 0 0 0
 TISS/ABDOMINAL

Conclusion:3-Generation Reproduction - Rat

- A. Core guideline
- B. A NOEL of 500 ppm based on decreased fertility indices was established when technical chlorsulfuron was fed to rats in a 3-generation 6-litter reproduction study at dietary levels of 0, 100, 500 and 2500 ppm.
- C. This study generally conforms to EPA proposed guidelines in section 163.83-4 Reproduction study (43 Federal Register 37384, 8/22/78) with some modifications.

Methods:3-Generation Reproduction - Rat

Charles River CD® male and female rats were fed diets that contained 0, 100, 500 or 2500 ppm chlorsulfuron in a long term feeding study. After 103 days of feeding, 20 rats/sex/level were selected for the three-generation six-litter reproduction study and temporarily removed from the long-term study.

Male and female F₀ rats within each dietary group were mated for a 15-day period to produce F_{1a} litters. During the mating and reproduction phases, F₀ rats continued to receive their respective test group's diets. Approximately seven days after weaning the F_{1a} litters, the F₀ rats were mated a second time for a 15-day period to different rats to produce F_{1b} litters. At weaning, the F₀ rats were returned to their respective groups in the long-term feeding study. The number of pups in each F_{1b} litter was reduced to ten and twenty-one days after delivery, surviving pups in the F_{1b} litters were weighed and sexed. 20 Pups/sex/level were then representatively selected to initiate the second feeding/reproduction period to produce F_{2a} and F_{2b} litters. Similarly F_{3a} and F_{3b} litters were produced. Twenty-one days after delivery of the F_{3b} litters, 10 male and 10 female weanlings were sacrificed and subjected to gross and histopathological examinations. During the study diet consumption and body weight data were taken, and values for food efficiency and daily intake were calculated. Rats were examined at least once daily for abnormal behavior, mortalities and clinical signs of toxicity. The following tissues from the F_{3b} rats/sex/level were examined histopathologically: brain, adrenals, spinal cord (cervical, thoracic, lumbar, sacral), pancreas, lungs, trachea, thyroid and parathyroid glands, heart, skeletal muscle, sciatic nerve, spleen, thymus, liver, kidneys, testes (with epididymides), ovaries, uterus, stomach, duodenum, jejunum, ileum, colon and bone marrow.

Results:3-Generation Reproduction - Rat

Rats in the 2500 ppm group had slightly decreased fertility indices when compared to controls. Mean number of pups/litter, gestation, lactation, and viability indices, litter survival, mean weanling body weights and weight gains, diet consumption and food efficiency were not adversely influenced. Slight differences in mean weanling body weights in the 2500 ppm group were not consistently related to dietary concentrations and were not considered biologically significant. Clinical observations were not dose-related and were not considered to be compound-related. Mean organ weights and organ weight ratios of weanling rats from the test groups were comparable to those of the controls. No gross or histopathological abnormalities that could be related to dietary administration were observed in the F_{3b} weanlings. The no observable effect level was considered to be 500 ppm based on decreased fertility indices.

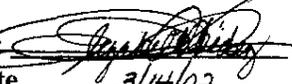
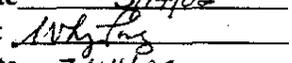
<u>Treatment Group (ppm):</u>	<u>0</u>	<u>100</u>	<u>500</u>	<u>2500</u>
<u>Litter</u>	<u>Fertility Index (%)</u>			
F _{1a}	95	90	95	95
F _{1b}	100	95	95	89
F _{2a}	95	90	85	84
F _{2b}	100	95	89	100
F _{3a}	95	100	90	79
F _{3b}	95	100	100	79

Discussion:3-Generation Reproduction - Rat

The methods and materials, scientific principles, validity of conclusions, and adequacy of data for conclusions were adequate for the study. Modifications in the guideline such as reproduction through 3 generations rather than the guideline's two, breeding twice within each generation to produce F_a and F_b litters, and doing histopathology on F_{3b} weanlings rather than on weanlings of each generation are variations which do not affect the validity of the study. This study was reviewed in connection with teratology study HLR-583-78.

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EPA Reviewer: Elizabeth Méndez, Ph.D.
 Reregistration Branch I, Health Effects Division (7509C)
 EPA Secondary Reviewer: Whang Phang, Ph.D.
 Reregistration Branch I, Health Effects Division (7509C)

Signature: 
 Date: 3/14/02
 Signature: 
 Date: 3/14/02

TXR#:0050460

DATA EVALUATION RECORD

STUDY TYPE: Chronic toxicity - dog (Dietary Administration); OPPTS 870.4100b [§83-1b]; OECD 452.

PC CODE: 118601

DP BARCODE: D280761
SUBMISSION NO.: S579862

TEST MATERIAL (PURITY): Benzenesulfonamide, 2-chloro-N-[[[(4-methoxy-6-methyl-1,3,5,-triazin-2-yl)-amino]carbonyl]-; Chlorsulfuron (97.5%)

SYNONYMS: IN W4189-165; DPX-W4189-165

CITATION: Atkinson, J.E. (1991) A Chronic (1 Year) Oral Toxicity Study in the Dog with DPX-4189 (Chlorsulfuron) via the Diet. Bio/dynamics, Inc., East Millstone, NJ. Report No. HLO 163-91, April 4, 1991. MRID 41862601. Unpublished

SPONSOR: E.I. du Pont de Nemours & Company

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID 41862602.) Chlorsulfuron technical (97.5% a.i.; Lot # 12-51) was administered to Beagle dogs (5/sex/dose) in the diet at concentrations of 0, 100, 2000, or 7500 ppm (equivalent to Males:0, 3.5, 65.6, 215 mg/kg bw/day; females: 0, 3.5, 60.6, 254.5) for 52 weeks.

No compound-related increases in the mortality rate, incidence of clinical signs, food consumption, ophthalmoscopic, clinical chemistry, organ weights, gross pathology, and histopathology parameters were reported. Body weights were unaffected by treatment with the test article. Females in the high-dose group, however, exhibited 30-89% decreases in body weight gain at different intervals during the study. Although they are not statistically significant, these decreases in body weight gain are considered toxicologically relevant and compound-related since they occurred in the absence of decreases in food consumption.

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In males, evaluation of hematology parameters did not reveal any compound-related effects at any dose level. In contrast, females in the high-dose group exhibited statistically significant decreases in some hematology parameters. At the 3-month evaluation, statistically significant decreases in hemoglobin (24%, $p < 0.01$), hematocrit (21%, $p < 0.01$), erythrocytes (21%, $p < 0.05$), and leukocytes (48%, $p < 0.01$). Leukocytes and hematocrit parameters were comparable to control throughout the remainder of the study period. Reduced hemoglobin levels, however, were still observed at the 6-month (18%, $p < 0.05$) and 9-month (17%, $p < 0.05$) evaluations but not at the end of the study period. Also observed during the 6- and 9-month evaluations was a reduced erythrocyte count (16% [not statistically significant] and 17% [$p < 0.05$], respectively). Again, this effect was not reported at the end of the study period.

Under the conditions of this study, the NOAEL is established at 2000 ppm (60.6 mg/kg/day). The LOAEL is set at 7500 ppm (215 mg/kg/day) based on decreases in body weight gain, erythrocyte counts, and hemoglobin.

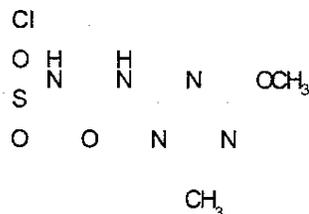
This chronic study in dogs is **acceptable/guideline** and **satisfies** the guideline requirement for a chronic oral study [OPPTS 870.4100, OECD 452]

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided.

I. MATERIALS AND METHODS

A. MATERIALS:

1. Test Material:	DPX-W4189 (Chlorsulfuron)
Description:	Technical, beige powder
Lot/Batch #:	Lot # 12-51
Purity:	97.5% a.i.
Compound Stability:	14 days at room temperature
CAS # of TGAI:	64902-72-3



2. Vehicle and/or positive control: None

3. Test animals:

Species:	Dog
Strain:	Beagle

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Age/weight at study initiation: 6½ months old. Males mean body weight: 9.8 kg
 Females mean body weight: 8.2 kg
Source: Marshall Research Animals, Inc.
Housing: Individually in elevated metal grid cages
Diet: 400 g Purina® Certified Canine Diet #5007 offered for 4.5 hours
Water: *ad libitum*
Environmental conditions: **Temperature:** 60-80°C
Humidity: 11-99%
Air changes: Not described
Photoperiod: 12 hrs dark/light
Acclimation period: 45 days

B. STUDY DESIGN:

1. **In life dates** - Start:11/10/89 End: 11/15/90

2. **Animal assignment** - Animals were randomly assigned to the test groups noted in Table 1.

TABLE 1: STUDY DESIGN

Test Group	Conc. in Diet (ppm)	Dose to animal (mg/kg/day)	Main Study # months	
			Male	Female
Control	0	0	5	5
Low (LDT)	100	3.5/3.4 (M/F)	5	5
Mid (MDT)	2000	65.6/60.6 (M/F)	5	5
High (HDT)	7500	215/254.5 (M/F)	5	5

3. **Dose selection rationale:** The dose levels were selected based on the results from a 2-week palatability study where dietary administration of up to 15000 ppm resulted in marked decreases in food consumption (↓25-54%) and reduced body weight gain (males: 67%, females: 13%).

4. **Diet preparation and analysis**

Diet was prepared weekly by mixing appropriate amounts of test substance with Purina Certified Canine Diet #5007. Homogeneity and stability were tested prior to the initiation of the study. During the study, samples of treated food were analyzed 5 times during the study period concentration.

Results - Homogeneity Analysis: 100 ppm: 88 - 98.4 ppm; 2000 ppm: 1896-1904 ppm;
7500 ppm: 7345-8175 ppm

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Stability Analysis: 84-100% stable after 14 days at room temperature.

Concentration Analysis: 77-100% of nominal concentration (the concentration of one sample taken at the initiation of the study was 77% of the nominal concentration. For the remainder of the study, sample concentrations ranged from 84-100% of the nominal concentration).

The analytical data indicated that the mixing procedure was adequate and that the variance between nominal and actual dosage to the animals was acceptable.

5. Statistics - Statistical evaluations of equality of means were performed using the one way ANOVA method, followed by a multiple comparison procedure if needed. Initially, Bartlett's test¹ was used to determine if groups had equal variance. If they did, a parametric procedure was used (one way ANOVA using the F distribution) to assess significance. If significant differences among the means were determined, the Dunnett's test was used to ascertain which means were significantly different from the control. If the variances were not equal, a non-parametric procedure for testing equality of means was used (Kruskal-Wallis test). If differences were determined, the Dunn's summed rank test was used to determine which treatments were different from the control. A statistical test for trend in the dose levels was also undertaken. In the cases of equal variance, standard regression methods with a test for trend and lack of fit was used. If variances were not equal, the Jonckheere's test for monotonic trend was performed.²

C. METHODS:

1. Observations:

Animals were inspected twice daily for signs of toxicity and mortality. A detailed physical evaluation was conducted once during the pre-test period and weekly thereafter.

2. Body weight

Animals were weighed twice before during the pre-test period, weekly during the study period, and prior to terminal sacrifice.

3. Food consumption and compound intake

Food consumption for each animal was determined and mean daily diet consumption was

¹ Conducted at the 1%, two-sided risk level.

² With the exception of Bartlett's test, all statistical tests were conducted at the 5% and 1%, two-sided risk level.

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calculated as g food/kg body weight/day. Food efficiency (body weight gain in kg/food consumption in kg per unit time X 100) and compound intake (mg/kg bw/day) values were calculated as time-weighted averages from the consumption and body weight gain data.

4. Ophthalmoscopic examination

Eyes were examined before initiation of the study and one week prior to terminal sacrifice.

5. Hematology and Clinical Chemistry: Blood was collected from the jugular vein for all animals after an overnight fast. Blood collection was performed twice before initiation of the study, and at the 3, 6, 9, 12 month of the study period.. The CHECKED (X) parameters were examined.

a. Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count*
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)*
X	Leukocyte count (WBC)*	X	Mean corpusc. HGB conc.(MCHC)*
X	Erythrocyte count (RBC)*	X	Mean corpusc. volume (MCV)*
X	Platelet count*	X	Reticulocyte count
	Blood clotting measurements*		
	(Thromboplastin time)		
	(Clotting time)		
	(Prothrombin time)		

* Recommended for chronic studies based on Guideline 870.4100.

b. Clinical Chemistry

ELECTROLYTES		OTHER	
X	Calcium*	X	Albumin*
X	Chloride*	X	Creatinine*
	Magnesium*	X	Urea nitrogen*
X	Phosphorus*	X	Total Cholesterol*
X	Potassium*		Globulins
X	Sodium*	X	Glucose*
	ENZYMES (more than 2 hepatic enzymes)*	X	Total bilirubin
X	Alkaline phosphatase (ALK)*	X	Total protein (TP)*
	Cholinesterase (ChE)		Triglycerides
X	Creatine phosphokinase		Serum protein electrophoresis
	Lactic acid dehydrogenase (LDH)		
X	Alanine aminotransferase (ALT/ SGPT)*		
X	Aspartate aminotransferase (AST/ SGOT)*		
	Gamma glutamyl transferase (GGT)*		
	Glutamate dehydrogenase		

* Recommended for chronic studies based on Guideline 870.4100.

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6. Urinalysis

Urine was collected from non-fasted animals twice during the pre-test period, at month 3, 6, 9, and 12 of the study period. The CHECKED (X) parameters were examined.

X	Appearance*	X	Glucose*
	Volume*	X	Ketones
X	Specific gravity / osmolality*	X	Bilirubin
X	pH*	X	Blood*
X	Sediment (microscopic)		Nitrate
X	Protein*	X	Urobilinogen

* Recommended for chronic studies based on Guideline 870.4100.

7. Sacrifice and Pathology

All animals that died and those sacrificed on schedule were subjected to gross pathological examination and the CHECKED (X) tissues were collected and subjected to a histological examination. The collected tissues were preserved in 10% neutral buffered formalin with the exception of the eyes, testes, and epididymides (preserved in Bouin's solution for the initial 48-72 hours). The (XX) organs, in addition, were weighed.

	DIGESTIVE SYSTEM		CARDIOVASC./HEMAT.		NEUROLOGIC
	Tongue	X	Aorta, abdominal*	XX	Brain (multiple sections)*+
X	Salivary glands*	XX	Heart*+	X	Periph.nerve*
X	Esophagus*	X	Bone marrow*	X	Spinal cord (3 levels)*
X	Stomach*	X	Lymph nodes*	X	Pituitary*
X	Duodenum*	X	Spleen**	X	Eyes (retina, optic nerve)*
X	Jejunum*	X	Thymus		GLANDULAR
X	Ileum*			X	Adrenal gland*+
X	Cecum*		UROGENITAL		Lacrimal gland
X	Colon*	XX	Kidneys*+	X	Parathyroids*
X	Rectum*	X	Urinary bladder*	XX	Thyroids*
XX	Liver*+	XX	Testes*+		OTHER
X	Gall bladder*	X	Epididymides*+	X	Bone (sternum and/or femur)
X	Pancreas*	X	Prostate*	X	Skeletal muscle
	RESPIRATORY	X	Ovaries*+	X	Skin*
X	Trachea*	X	Uterus*+	X	All gross lesions and masses*
X	Lung*++	X	Mammary gland*		
	Nose*				
	Pharynx*				
	Larynx*				

* Required for chronic studies based on Guideline 870.4100.

+Organ weight required in chronic studies.

++Organ weight required if inhalation route.

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II. RESULTS**A. OBSERVATIONS:**

1. **Clinical signs of toxicity** - No evidence of clinical signs of toxicity were noted during the study period.

2. **Mortality** - No compound-related mortalities were reported.

3. **Neurological Evaluations** - The behavior, movements, reactivity to stimuli, muscle tone, pupil size and secretions were examined as part of the physical examinations. None of these parameters were affected by treatment with the test article.

B. BODY WEIGHT AND WEIGHT GAIN:

In males, body weights were unaffected by treatment with the test article. Females in the high-dose group, however, exhibited a 30-89% decrease in body weight gain at several intervals during the study. Although these weight gain reductions are not statistically significant, they are considered toxicologically relevant and compound-related since they occurred in the absence of decreases in food consumption.

TABLE 2: Mean body weights (BW) and body weight gains (BWG)^a (kg ± SD)

Observation Period	0 ppm	100 ppm	2000 ppm	7500 ppm
MALES				
Initial BW	9.5 ± 0.8	9.8 ± 1.0	9.8 ± 0.8	9.7 ± 0.9
BW Wk 13	11.0 ± 1.2	10.7 ± 1.4	10.8 ± 1.4	10.6 ± 2.0
BW Wk 26	11.8 ± 1.5	10.8 ± 1.3	11.3 ± 1.6	12.3 ± 0.8
BW Wk 36	12.4 ± 1.9	11.2 ± 1.3	11.8 ± 1.8	13.0 ± 1.2
Final BW	12.4 ± 2.6	10.9 ± 1.4	11.7 ± 2.0	13.6 ± 1.4
BWG Wk 1-13	1.5 ± 0.7	0.9 ± 0.8	1.0 ± 0.7	0.9 ± 1.6
BWG Wk 1-26	2.2 ± 1.4	1.0 ± 0.9	1.5 ± 0.7	2.5 ± 0.3
Overall BWG Wk -1-52	2.9 ± 2.4	1.1 ± 0.8	1.9 ± 1.2	3.7 ± 1.0
FEMALES				
Initial BW	8.8 ± 0.9	8.2 ± 0.5	8.3 ± 0.7	7.9 ± 0.6
BW Wk 13	9.4 ± 1.1	9.0 ± 1.6	9.1 ± 1.4	8.6 ± 0.8
BW Wk 26	9.5 ± 0.7	9.0 ± 1.6	9.8 ± 1.5	8.7 ± 0.4
BW Wk 36	9.8 ± 0.7	9.4 ± 1.9	9.8 ± 1.9	9.3 ± 0.7
Final BW	9.6 ± 0.7	9.7 ± 2.2	10.1 ± 2.6	8.8 ± 1.0

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Observation Period	0 ppm	100 ppm	2000 ppm	7500 ppm
BWG Wk 1-13	1.1 ± 0.4	0.8 ± 1.5	0.8 ± 1.0	0.6 ± 0.4 (-46%) ^b
BWG Wk 1-26	1.1 ± 0.5	0.7 ± 1.5	1.0 ± 1.0	0.8 ± 0.3 (-27%)
Overall BWG Wk 1-52	^a 1.3 ± 0.7	1.4 ± 2.1	1.8 ± 2.2	0.9 ± 0.8

^a Data obtained from Appendices E & F in the study report.^b Numbers presented parenthetically represent percent change from control**C. FOOD CONSUMPTION AND COMPOUND INTAKE:**

- 1. Food consumption** - Food consumption was unaffected by treatment with the test article.
- 2. Compound consumption** - See Table 1
- 3. Food efficiency** - Food efficiency was extremely variable. No consistent compound-related effects on food efficiency were noted during this study.

D. OPHTHALMOSCOPIC EXAMINATION:

Ophthalmoscopic evaluations did not reveal any compound-related changes.

E. BLOOD ANALYSES:

- 1. Hematology** - In males, hematology parameters were unaffected by treatment with the test article. Females, however, exhibited statistically significant decreases in some hematology parameters at several evaluation periods.

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Table 3: Summary of Selected Mean Hematology Parameters (Females)

Observation Period (Month)	Observation	Dose (ppm)			
		0	100	2000	7500
0	RBC x 10 ⁶ /μl	6.22 ± 0.51	6.07 ± 0.20	6.37 ± 0.44	5.95 ± 0.22
	Hgb (g/dL)	16.0 ± 1.0	15.1 ± 0.5	16.2 ± 0.9	14.9 ± 0.7
	Hct (%)	47 ± 3	44 ± 1	47 ± 3	43 ± 2
	Leukocytes x 10 ³ /μl	10.3 ± 1.6	9.0 ± 1.7	10.1 ± 2.0	10.1 ± 0.9
3	RBC x 10 ⁶ /cumm	6.90 ± 0.33	7.10 ± 0.97	7.21 ± 0.55	5.42 ± 0.82* (121%)
	Hgb (g/dL)	17.4 ± 0.6	17.7 ± 2.4	18.3 ± 1.1	13.3 ± 2.0** (124%)
	Hct (%)	53 ± 1	53 ± 6	54 ± 3	42 ± 6** (21%)
	Leukocytes x 10 ³ /μl	12.2 ± 2.6	11.3 ± 1.7	11.7 ± 1.7	6.4 ± 3.3** (48%)
6	RBC x 10 ⁶ /cumm	7.52 ± 0.46	7.50 ± 1.03	7.80 ± 0.59	6.30 ± 0.83 (116%)
	Hgb (g/dL)	18.8 ± 1.0	18.1 ± 2.6	19.4 ± 1.2	15.5 ± 2.2* (118%)
	Hct (%)	54 ± 3	53 ± 8	56 ± 4	46 ± 8
	Leukocytes	10.0 ± 1.7	8.4 ± 0.7	9.3 ± 0.9	11.1 ± 4.0
9	RBC x 10 ⁶ /cumm	7.91 ± 0.41	7.66 ± 0.99	7.68 ± 0.60	6.59 ± 0.43* (117%)
	Hgb (g/dL)	19.4 ± 1.2	18.5 ± 2.2	19.1 ± 1.5	16.2 ± 1.3* (117%)
	Hct (%)	53 ± 3	50 ± 6	51 ± 5	45 ± 4
	Leukocytes	9.6 ± 2.8	9.0 ± 0.8	9.3 ± 1.1	8.7 ± (unreadable std. deviation)
12	RBC x 10 ⁶ /cumm	7.61 ± 0.35	7.11 ± 0.76	7.35 ± 0.43	7.08 ± 0.27
	Hgb (g/dL)	19.0 ± 1.3	17.5 ± 1.9	18.6 ± 0.7	17.5 ± 0.4
	Hct (%)	55 ± 3	50 ± 5	53 ± 3	52 ± 2
	Leukocytes	8.7 ± 1.0	8.8 ± 2.5	9.0 ± 1.8	10.3 ± 2.2

* p < 0.05; ** p < 0.01

Numbers presented parenthetically represent percent change from control.

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2. **Clinical Chemistry** - Clinical chemistry parameters were unaffected by treatment with the test article.

F. **URINALYSIS** - Urinalysis parameters were not affected by treatment with the test compound.

G. SACRIFICE AND PATHOLOGY:

1. **Organ weight** - Organ weights were unaffected by treatment with the test compound.

2. **Gross pathology** - No compound-related changes in gross pathology parameters were noted during the study.

3. **Microscopic pathology** - No treatment related changes in histopathology were reported.

III. DISCUSSION and CONCLUSIONS

A. INVESTIGATORS' CONCLUSIONS:

The study author established the NOEL at 2000 ppm (59.4 mg/kg/day). The LOEL was set at 7500 ppm (215 mg/kg/day) based on hematological changes and slight body weight changes in females

B. REVIEWER COMMENTS:

No compound-related effects on mortality rates, incidence of clinical signs, food consumption, ophthalmoscopic, clinical chemistry, organ weights, gross pathology, or histopathology parameters were reported. Body weights were unaffected by treatment with the test article. At the 7500 ppm dose level, however, females exhibited a 30-89% decrease in body weight gain at different intervals during the study. Although these changes are not statistically significant, they are considered toxicologically relevant and compound-related since they occurred in the absence of decreases in food consumption.

In males, hematology parameters were not affected by treatment with the test compound. However, females in the high-dose group exhibited statistically significant changes in hematology parameters at several test intervals. The most consistent changes were statistically significant decreases in RBC and hemoglobin (16-21% and 17-24% decreases, respectively) which were seen at the 3, 6, and 9 month evaluations. Also noted at the 3 month evaluation was a decrease in hematocrit (21%, $p < 0.01$) and leukocytes (48%, $p < 0.01$).

Under the conditions of this study, the NOAEL is set at 2000 ppm (60.6 mg/kg/day). The LOAEL is established at 7500 ppm (215 mg/kg/day) based on decreases in body weight gain, RBC, and hemoglobin.

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C. STUDY DEFICIENCIES: A number of deficiencies have been identified in this study and are listed below. These deficiencies, however, did not compromise the integrity of the study or the evaluation of the results.

- Lack of blood clotting, magnesium, and gamma glutamyl transferase evaluations.
- Urine volume was not measured
- Lack of organ weight data for adrenals, spleen, epididymides, ovaries and, uterus.



13544

051596

Chemical: Chlorsulfuron

PC Code: 118601

HED File Code

Memo Date: 07/11/2002

File ID: 0000000

Accession Number: 412-03-0016

HED Records Reference Center
09/27/2002