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

Office of Prevention, Pesticides
and
Toxic Substances

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

July 17, 2002

TXR#: 0050894

MEMORANDUM

SUBJECT: Toxicology Chapter for **CHLORSULFURON**

PC Code: 118601
DP Barcode: D280761
Submission: S579862

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Action Requested:

The toxicology chapter for chlorsulfuron is attached.

CHLORSULFURON

PC Code: 118601

Toxicology Disciplinary Chapter for the Registration Eligibility Decision (RED) Document

Date completed: July 17, 2002

Health Effects Division
Office of Pesticide Programs
U.S. Environmental Protection Agency
Arlington, VA 22202

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1.0 HAZARD CHARACTERIZATION

The toxicity database for chlorsulfuron is adequate for the selection of endpoints for use in risk assessment. The Health Effects Division [HED] Hazard Identification Assessment Review Committee [HIARC] evaluated all the available studies in the database and established an acute and a chronic reference dose [RfD], as well as doses and endpoints for incidental oral exposure, residential, and short-term, intermediate-term, and long-term dermal and inhalation exposure scenarios. The HIARC also evaluated available studies to determine if there is a special sensitivity for infants and children.

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. Neurotoxicity was not observed in any 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.

Reproductive toxicity was observed in the rat, as evidenced by a slight decrease in maternal fertility in the F3 generation/both litters. No parental or offspring toxicity was observed. Although this study conformed to the old guideline requirements, it is unacceptable under the current guideline requirements in light of the fact that most of the parameters used for assessing susceptibility are not provided in the available study.

The data provided no indication of increased susceptibility [qualitative and quantitative] following *in utero* exposure to chlorsulfuron in either the rat or rabbit developmental toxicity study. Susceptibility cannot be assessed in the 3-generation reproduction study in rats. The HED HIARC determined that a 2-generation reproduction study is required for chlorsulfuron.

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

There was no evidence of carcinogenicity in rats or mice following oral exposure to chlorsulfuron. Although the available mutagenicity data are considered unacceptable, based mainly on the lack of adequate data presentation, they indicate that there is no concern for mutagenicity.

With oral dosing in rats, chlorsulfuron is rapidly absorbed, metabolized, and eliminated. 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) 21-day repeated dose dermal toxicity study; (3) subchronic inhalation study in the rat; (4) adequate mutagenicity studies [available studies can be upgraded]; (5) primary eye and dermal irritation studies; (6) dermal sensitization study.

2.0 REQUIREMENTS

(updated December 14, 2001)

The requirements (CFR 158.135) for Food/Feed Use for chlorsulfuron are in Table 1. Use of the new guideline numbers does not imply that the new (1998) guideline protocols were used.

Table 1.

Test	Technical	
	Required	Satisfied
870.1100 Acute Oral Toxicity	yes	yes
870.1200 Acute Dermal Toxicity	yes	yes
870.1300 Acute Inhalation Toxicity	yes	yes
870.2400 Primary Eye Irritation	yes	no
870.2500 Primary Dermal Irritation	yes	no
870.2600 Dermal Sensitization	yes	no
870.3100 Oral Subchronic (rodent)	yes	yes♪
870.3150 Oral Subchronic (nonrodent)	yes	yes
870.3200 21-Day Dermal	yes	no
870.3250 90-Day Dermal	no	no
870.3465 90-Day Inhalation	yes	no
870.3700a Developmental Toxicity (rodent)	yes	yes
870.3700b Developmental Toxicity (nonrodent)	yes	yes
870.3800 Reproduction	yes	no
870.4100a Chronic Toxicity (rodent)	yes	yes
870.4100b Chronic Toxicity (nonrodent)	yes	yes
870.4200a Carcinogenicity (rat)	yes	yes
870.4200b Carcinogenicity (mouse)	yes	yes
870.4300 Chronic Toxicity/Carcinogenicity (rodent)	yes	yes
870.5100 Mutagenicity—Gene Mutation - bacterial	yes	no
870.5300 Mutagenicity—Gene Mutation - mammalian	yes	no
870.5xxx Mutagenicity—Structural Chromosomal Aberrations	yes	yes
870.5xxx Mutagenicity—Other Genotoxic Effects	yes	no
870.6100a Acute Delayed Neurotoxicity (hen)	no	-
870.6100b 90-Day Neurotoxicity (hen)	no	-
870.6200a Acute Neurotoxicity Screening Battery (rat)	no	-
870.6200b 90 Day Neurotoxicity Screening Battery (rat)	no	-
870.6300 Develop. Neurotoxicity (rat)	no	-
870.7485 General Metabolism	yes	yes
870.7600 Dermal Penetration	no	-
Special Studies for Ocular Effects	no	-
Acute Oral (rat)	no	-
Subchronic Oral (rat)	no	-
Six-month Oral (dog)	no	-

♪ chronic toxicity study is available and satisfies this requirement

3.0 DATA GAP(S)

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; (6) mutagenicity data; (7) primary eye and dermal irritation studies; (8) dermal sensitization study.

4.0 HAZARD ASSESSMENT

4.1 Acute Toxicity

Adequacy of data base for acute toxicity: The database for acute toxicity is considered incomplete. There are no acceptable data with which to assess the skin and eye irritant potential of chlorsulfuron or its skin sensitizer potential. No additional studies are required at this time. The acute toxicity data indicate that chlorsulfuron is not acutely toxic *via* the oral [Toxicity Category IV], dermal [Toxicity Category III], and inhalation [Toxicity Category IV] routes of exposure.

The acute toxicity data on chlorsulfuron are summarized below in Table 2.

Table 2. Acute Toxicity Data on CHLORSULFURON

Guideline No.	Study Type	MRID #(S)	Results	Toxicity Category
870.1100	acute oral - rat	00031406	rat LD_{50} = **5.5** g/kg ♂ rat LD_{50} = **6.3** g/kg ♀	IV
870.1200	acute dermal - rat	00083956	rabbit LD_{50} = **3400** mg/kg	III
870.1300	acute inhalation - rat	00086825	rat LC_{50} = **5.9** mg/L	IV
870.2400	primary eye irritation -	00031414 ♪	not an eye irritant	IV
870.2500	primary skin irritation -	00031414 ♪	no adequate study	-
870.2600	dermal sensitization	00031414 ♪	no adequate study	-

♪ classified unacceptable/nonguideline

4.2 Subchronic Toxicity

Adequacy of data base for subchronic toxicity: The database for subchronic toxicity is considered incomplete. The 21-day repeated dose dermal toxicity study and the subchronic inhalation study are datagaps for chlorsulfuron. **The subchronic oral database does not identify any particular target organ.** The only treatment-related effect observed in the dog following oral exposure for 6 months was decreased body-weight gain in females, which was associated with a lower food intake. No effects were observed in the male dogs. In the rat, no effects were observed at the highest dose tested [161.1 mg/kg/day], which is well below the limit dose [1000 mg/kg/day]. In the subchronic mouse study, adverse effects [increased incidence of retinal dysplasia and adrenal capsular cell proliferation] were observed only at a dose level that exceeds the limit dose [2130

mg/kg/day]. Although there is no acceptable oral subchronic toxicity study in the rat and mouse, a chronic oral toxicity study is available in both species, and a separate subchronic oral toxicity study is not required for either species.

870.3100 Subchronic Oral Toxicity - Rat

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 00031418) chlorsulfuron technical (≈ 95% a.i., Lot # not provided) was administered to 10 **rats**/sex/dose [strain unspecified] at dietary concentrations of 0, 100, 500, and 2500 ppm (equivalent to 0, 6.5, 33.7, and 161.1 mg/kg/day in males; and 0, 8.1, 40.4, and 216.6 mg/kg/day in females) for 98 days.

No consistent compound related effects on mortality rates, food consumption, food efficiency, clinical chemistry, hematology, gross pathology, or histopathology parameters were noted. While absolute body weights were not affected by treatment with the test article, body weight gains were sporadically decreased during the study period. In males, body weight gain was decreased at the 100 and 500 ppm dose levels (↓35% and 40%, respectively) but not at the 2500 ppm dose level. Females exhibited reduced body weight gains on days 53-63 at the 500 and 2500 ppm dose levels (↓440% and 241%, respectively) as well as a dose-related decrease on days 84-91 (↓33% at the high dose). Also evident, were sporadic though substantial decreases in food efficiency for males on days 56-63 (↓552% and 262% at the 500 and 2500 ppm doses, respectively) and days 77-84 (↓3% and 66% at the 2500 and 100 ppm dose levels, respectively **[no dose response is apparent]**). Female food efficiency in test groups was comparable to the control group. Given that the body weight gain and food efficiency decreases seen during this study show no dose response and are sporadic (overall body weight gain and food efficiency are comparable throughout the dose groups), their relation to compound administration is equivocal.

Under the conditions of this study, the NOAEL is established at 2500 ppm (161.1 mg/kg/day). An LOAEL could not be determined.

This 90-day oral toxicity study in the rat is **unacceptable/guideline. It does not satisfy** the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in rats. This study **may not be upgraded** since no adverse effects were elicited at the highest dose tested (HDT), which is well below the limit dose (1000 mg/kg/day) for this study and numerous deficiencies were identified.

870.3100 Subchronic Oral Toxicity - Mouse

EXECUTIVE SUMMARY: In a 90-day oral toxicity study (MRID 00031421) chlorsulfuron technical (100% a.i., Lot # 7805-15B) was administered to 10 ChR-CD®-1 **mice**/sex/dose at dietary concentrations of 0, 500, 2500, 5000, and 7500 ppm (equivalent to 0, 150, 783, 1557, and 2130 mg/kg/day in males; and 0, 220, 1214, 2134, 3176 mg/kg/day in females) for 91 days.

No consistent compound related effects on mortality rates, food consumption, food efficiency, hematology, or gross pathology parameters were noted. While absolute body weights were not affected by treatment with the test article, body weight gains were sporadically decreased during the study period. In males, body weight gain was sporadically decreased at the 7500 ppm dose level on days 1-7, 16-21, and 70-78 (↓33%, 54%, and 150%, respectively). Similarly, at the high dose, females exhibited reduced body weight gains on days 0-7, 7-16, 28-35 (↓67%, 46%, and 57%, respectively). The decreases in body weight gain showed no dose-response relationship for either sex except on days 1-7 for females (↓40%, 60%, and 67% at the low-, mid-, and high-dose, respectively). Also evident at the high-dose, were sporadic though substantial decreases in food efficiency for

males on days 1-7(↓32%), and days 16-21 (↓47%). Female food efficiency at the high dose was decreased compared to the control group on days 1-7, 7-16, and 28-35 (↓61%, 40%, and 53%, respectively). Given that the body weight gain and food efficiency decreases seen during this study show no dose response and are sporadic (overall body weight gain and food efficiency are comparable throughout the dose groups), their relation to compound administration is equivocal.

Males exhibited statistically significant ($p < 0.05$) and dose-related decreases in absolute and relative liver weights at doses ≥ 2500 ppm (11-17% and 6-11%, respectively). Though statistically significant, these changes are not considered toxicologically relevant since the magnitude of the change was small (i.e. within normal variability) and may reflect slight decreases (≤ 6%) in body weight.

Histopathology evaluations revealed an increase in the incidence of retinal dysplasia (3/10 vs. 0 control) in high dose males (7500 ppm). Females in the high-dose group exhibited increases in the incidence of "very mild to mild" adrenal capsular cell proliferation (7/10 vs. 1/10 control). It should be noted that tissues from animals at doses < 7500 ppm were not subjected to a histopathology examination.

Under the conditions of this study, the NOAEL is established at 5000 ppm (1557 mg/kg/day). The LOAEL is set at 7500 ppm (2130 mg/kg/day) based on increase incidence of retinal dysplasia and adrenal capsular cell proliferation.

This 90-day oral toxicity study in the mouse is **acceptable/non-guideline**, and it **does not satisfy** the guideline requirement for a 90-day oral toxicity study (OPPTS 870.3100; OECD 408) in mice due to the lack of clinical chemistry data and organ weight data.

870.3150 Subchronic Oral Toxicity - Dog

EXECUTIVE SUMMARY: In a 6-month oral toxicity study (MRID 00031420), 2-chloro-N-[(4-methoxy-4-methyl-1,3,5-triazin-2-yl)amino-carbonyl] benzenesulfonamide. (95% a.i.; Lot N.B. 7427-82) was administered to purebred Beagle dogs (4/sex/dose) in the diet at dose levels of 0, 100, 500, and 2500 ppm (achieved doses 0, 3.7, 18.5, and 82.3 mg/kg/day, respectively) .

There were no deaths, and clinical signs were comparable among the groups for both sexes. There was no adverse effect on body weight or body-weight gain in the males, but the low-, mid-, and high-dose females all displayed a decrease in mean body weight [week 26: 91%, 93%, 87%, respectively] throughout the study, including prior to treatment [93%, 95%, and 93%, respectively], compared to the control. Body-weight gains in the female groups were decreased at the mid- [78% of control] and high- [78% of control] dose levels during the 0-13 week interval and overall [0-26 week interval] at all dose levels [84%, 84%, and 58%, respectively]. Due mainly to the fact that the standard deviations in the body-weight gain data are large, the lower body-weight gains at the low- and mid-dose levels are not considered treatment-related. Food consumption was not adversely affected in the males, but the high-dose females displayed a lower food intake [on a gram/animal basis] throughout the study, although since this group weighed less, a lower food intake is consistent with this finding.

No treatment-related effects were observed in any hematological, clinical chemistry, or urinalysis parameter monitored, organ weights, or gross or microscopic pathological findings in either sex. No neoplastic tissue was observed in any of the dogs.

Based on the findings in this study on adult dogs, the NOAEL is 500 ppm [18.5 mg/kg/day], based on

decreased body weight/body-weight gain in females at 2500 ppm [82.3 mg/kg/day].

This 6-month oral toxicity study in dogs is classified **acceptable/non-guideline (OPPTS 870.3150; §82-1b). Due to the lack of an assessment of the young, growing animal**, as well as to the fact that the body weights among the groups [both sexes] at study initiation (suggesting a lack of randomization), this study cannot be classified as Guideline. It is to be noted that this study was performed prior to GLP. However, all of the required parameter assessments [except ophthalmoscopic examination] were performed, and the findings are not questioned.

870.3200 Repeated Dose Dermal – Rat

There is no subchronic dermal toxicity study in rats for chlorsulfuron.

870.3265 Subchronic Inhalation Toxicity – Rat

There is no subchronic inhalation toxicity study in rats for chlorsulfuron.

4.3 Chronic Toxicity

Adequacy of data base for chronic toxicity: The data base for chronic toxicity is considered complete. No additional studies are required at this time. Decreased body-weight gains were observed in both sexes in the dog study. The females dogs displayed decreased erythrocyte counts and hemoglobin levels throughout most of the study, but not at study termination. No target organ was identified in either the rat or mouse study. Decreased body weight was observed in the male rats at the mid- and high-dose levels, and the high-dose males displayed a decrease in food efficiency. In the mouse, decreased body weight and body-weight gains were observed at the high-dose level in both sexes throughout the study. **There was no treatment-related increase in the incidence of any tumor type in either the rat or mouse carcinogenicity study**. The dose levels were considered adequate in the rat and mouse studies, based on reductions in body-weight gain in both species, although the rats probably would have tolerated higher doses.

870.4100 Chronic Feeding – Rat

EXECUTIVE SUMMARY: In a chronic toxicity study (MRID 00086003), chlorsulfuron technical (95%) was administered to CD® rats (80/sex/dose) in the diet at dose levels of 0, 100, 500, and 2500 ppm (stardard conversion factor used: 0, 5, 25, 125 mg/kg body weight/day for 2 years. At the 1 year interim sacrifice 10 rats/sex/dose were sacrificed and subjected to a gross necropsy and histopathological evaluation.

A statistically significant decrease in body weight was reported in males at the mid- (4%-5% decrease) and high-dose levels (4%-9% decrease) at various time during the study. Body-weight gains were decreased in these groups also (5%-10% decrease). Body weights and body-weight gains were comparable among the female groups. Food consumption was comparable among the groups for both sexes, but food efficiency was decreased for the males at the high-dose level. Clinical signs, palpable tissue masses, and mortality were comparable among the groups for both sexes. No treatment-related findings were observed in the hematology and clinical chemistry parameters monitored for either sex. There were no adverse effects on organ weights in either sex. There were no treatment-related gross or histopathological abnormalities observed in either sex at any dose level, and there was no increase in the incidence of any tumor. Although the high-dose males [13/69] displayed a higher incidence of unilateral interstitial cell tumors compared to the control [2/68], this was not considered treatment-

related since a compound-induced effect would be expected to affect yje testes bilaterally. The incidence of bilateral interstitial cell tumors in male rats in the control group [7/68] was greater than the incidence at the high dose [3/69]. Additionally, the unilateral incidence was within the known spontaneous range for CD® rats, and there were no other changes [e.g., interstitial cell hyperplasia] suggestive of a compound-related tumorigenic effect in the testes.

Under the conditions of this study, the NOEL is 100 ppm (5 mg/kg/day). The LOEL is 500 ppm (25 mg/kg/day) based on decreased body weight 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 toxicity/carcinogenicity study in the rat is **acceptable/guideline,** and it satisfies the general guideline requirement for a chronic toxicity/carcinogenicity study OPPTS 870.4300); OECD 453] in rats.

870.4100b Chronic Oral Toxicity (diet) - Dog

EXECUTIVE SUMMARY:

In a chronic toxicity study (MRID 41862601) 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.

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 oral toxicity study in dogs is classified **Acceptable/Guideline**, and it **satisfies** the guideline requirement for a chronic oral toxicity study in non-rodents [OPPTS 870.4100; OECD 452; §83-1(b)]

4.4 Carcinogenicity

Adequacy of Database for Carcinogenicity: The data base for carcinogenicity is considered complete. No additional studies are required at this time. There is no evidence of carcinogenicity in rats or mice following oral exposure to chlorsulfuron at dose levels considered adequate for the assessment of carcinogenic potential.

870.4200a Carcinogenicity Study - rat

See above under Chronic Toxicity.

870.4200b Carcinogenicity (feeding) - Mouse

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 classified **Acceptable/Guideline**, and it **satisfies** the guideline requirement for a carcinogenicity study [OPPTS 870.4200; OECD 451] in mice.

4.5 Developmental Toxicity

Adequacy of data base for Developmental Toxicity: The data base for developmental toxicity is considered complete. **In the rat, developmental toxicity was observed at the highest dose tested, 1500 mg/kg/day, based on decreased fetal body weight. Maternal toxicity was observed as an increased incidence of clinical signs [vaginal discharge with associated alopecia]. In the rabbit, maternal toxicity was observed as decreased**

body-weight gain. Developmental toxicity was indicated by decreased fetal body weight. Mortality was observed in both species at their respective high-dose levels, which were at or above the limit dose, and treatment-related abortions were observed in the rabbit study at the highest dose level also.

870.3700a Prenatal Developmental Toxicity Study - Rat

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 developmental toxicity study is classified **Acceptable/Guideline,** and it **satisfies** requirements for a developmental toxicity study in rats (OPPTS 870.3700; OECD 414).

870.3700b Prenatal Developmental Toxicity Study - Rabbit

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 misshapened 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 [≈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.

4.6 Reproductive Toxicity

Adequacy of data base for Reproductive Toxicity: The database for reproductive toxicity is considered incomplete. The available 3-generation reproductive toxicity study is classified Unacceptable, and it is considered a datagap. **Reproductive toxicity was observed in the F3 generation/both litters, as evidenced by decreased female fertility. Offspring toxicity was not observed.**

870.3800 Two-Generation Reproduction Study - Rat

EXECUTIVE SUMMARY: In a three-generation reproduction study (MRID 00086003), chlorsulfuron technical (95% a.i.) was administered to CD® in the diet at dose levels of 0, 100, 500, and 2500 ppm (standard conversion factor used: 0, 5, 25, and 125 mg/kg/day). Two litters were produced per generation.

No compound-related signs of parental toxicity were noted at any dose level. The only effect reported was slightly decreased fertility indices at the high-dose level compared to the control. The mean number of pups/litter, gestation lactation, and viability indices, litter survival, mean weanling body weights and body-weight gains, diet consumption and food efficiency were not adversely affected in any generation. There were no treatment- or dose-related clinical observations, and weanling organ weights were comparable among the groups. No gross or histopathological abnormalities were observed in the F3b weanlings.

The reproductive NOEL is 100 ppm (5 mg/kg/day), and the reproductive LOEL is 500 ppm (25 mg/kg/day), based on decreased female fertility.

This study is **unacceptable/non-guideline**, and it 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) no assessment of estrous cyclicity, sperm parameters, 2) no assessment of male reproductive performance, 3) parental animals not subjected to gross pathology or histopathology examinations, 4) no assessment of developmental landmarks, and 5) pup histopathology evaluations conducted only for the F3B generation. Although this reproduction study on chlorsulfuron conformed to the old guideline requirements, it is unacceptable under the current guideline requirement in light of the fact that most of the parameters used for FQPA assessment are not provided in the available study.

4.7 Neurotoxicity

Adequacy of data base for Neurotoxicity: No neurotoxicity studies [acute or subchronic] are available on chlorsulfuron. There is no evidence of neurotoxicity in any study on chlorsulfuron.

870.6100 Delayed Neurotoxicity Study - Hen

This is not a data requirement for chlorsulfuron.

870.6200 Acute Neurotoxicity Screening Battery

There is no acute neurotoxicity study available on chlorsulfuron. The HIARC concluded that an acute neurotoxicity study is not required for chlorsulfuron.

870.6200 Subchronic Neurotoxicity Screening Battery

There is no subchronic neurotoxicity study available on chlorsulfuron. The HIARC concluded that a subchronic neurotoxicity study is not required for chlorsulfuron.

870.6300 Developmental Neurotoxicity Study

There is no developmental neurotoxicity study [DNT] on chlorsulfuron. The HIARC concluded that a developmental neurotoxicity study is not required for chlorsulfuron.

4.8 Mutagenicity

Adequacy of data base for Mutagenicity: The data base for mutagenicity is considered incomplete based on pre-1991 and post-1991 mutagenicity guidelines. The studies available were completed over 20 years ago, before the current requirements for data presentation were established. The available studies may be upgraded to acceptable if the missing data are provided. **In the available studies, chlorsulfuron was negative for mutagenicity in a bacterial gene mutation [Ames] assay, negative in the mammalian cell [HGPRT] gene mutation assay, negative in the CHO chromosomal aberrations assay, negative in the dominant lethal assay, and negative in the unscheduled DNA synthesis [UDS] in rat hepatocytes assay. Overall, the data suggest that there is no concern for mutagenicity.**

Gene Mutation

Guideline 870.5100. Ames, reverse mutation; MRID 00031425 classification: **Unacceptable**	6-30 µg/plate w/ w/out S9 in *S. Typhimurium* strains TA1535, TA1537, TA1538, TA98, TA100. **No evidence of induced mutant colonies over background.** Can be upgraded.

Guideline 870.5300. Mammalian cells in culture - gene mutation [HGPRT]; MRID 00083943 classification: **Unacceptable**	0.028-2.8 mM, w/ and w/out S9 mix. No cytotoxicity at solubility limit w/ and w/out S9. **No evidence of induced mutant colonies over background.** Can be upgraded.

Cytogenetics

Guideline 870.5385. *in vitro* cytogenetics assay; chromosome aberration [CHO-WBI cells]; MRID 00088755 classification: **Acceptable**	16.7-5000 µg/mL [8.5-10 hours w/out S9; 2 hours w/ S9]. Marked cytotoxicity at 5000 µg/mL. **No evidence of chromosomal aberrations.**

Guideline 870.5450. dominant lethal assay; MRID 00083944 classification: **Unacceptable**	100, 500, 5000 ppm in diet of male CD® Sprague-Dawley rats for 10 weeks. **No difference between control and treated rats in any reported parameter.** Purity of test material not provided. No justification for dose levels. No concurrent or positive control data.

Other Genotoxicity

Guideline 870.5450. Unscheduled DNA synthesis primary rat hepatocyte assay; MRID 00090008; classification: **Unacceptable**	initial 0.0002-2.0 mg/mL, confirmatory 0.0004-4.0 mg/mL; adult male F344 primary rat hepatocytes [18 hours]; at ≥0.4 mg/mL too cytotoxic to evaluate **No evidence that unscheduled DNA synthesis, as determined by radioactive tracer procedures [nuclear silver grain counts] was induced.** . Purity of test material and # of cells scored for UDS not provided. Can be upgraded with this information.

4.9 Metabolism

Adequacy of data base for metabolism: The database for metabolism is considered to be complete. Chlorsulfuron is rapidly absorbed, metabolized, and eliminated following oral exposure [single low, single high, and repeated low dosing regimens] to rats. There were no remarkable sex-, dose-, or treatment-related differences in the absorption, distribution, and excretion of chlorsulfuron in rats. The major routes of elimination are the urine [58%-72%] and feces [20%-35%]. Small amounts [0.1%-0.2% of administered dose] were found in the tissues 3 days after dosing. The highest concentrations were in the liver and whole blood in both sexes. A major and a minor metabolic pathway were identified.

870.7485 Metabolism - Rat

EXECUTIVE SUMMARY: In a rat metabolism study (MRID 42540701), groups of Crl: CD/BR rats (5/sex) were dosed (by gavage) with ^{14}C-chlorsulfuron (labeled in the pyridine group; >97% radiochemical purity) at a single oral dose (25 or 250 mg/kg), or 14-day repeated oral doses of chlorsulfuron at 25 mg/kg followed by a single oral dose of ^{14}C-chlorsulfuron at 25 mg/kg or a single oral dose (250 mg/kg) with ^{14}C-chlorsulfuron (labeled in the pyrimidine group; >97% radiochemical purity). Chlorsulfuron was rapidly absorbed, metabolized, and excreted in rats for all dosing regimens. There were no remarkable sex-, dose- or treatment-regiment-related differences in the absorption, distribution, and excretion of chlorsulfuron in rats.

Total recovery of radioactivity ranged between 93% and 96% of the dose for all tested groups within 3 days after dosing. The major routes of elimination of radioactivity was via the urine (58-72% of the dose) and feces (20-35%). Negligible amounts (<0.08%) of radioactivity were found in the expired air as carbon dioxide.

In general, small amounts of radioactivity were found in the tissues (0.1-0.2% of the dose) 3 days after dosing. ^{14}C-concentration in all tissues was less than 1.5 ppm after single oral dose at 250 mg/kg and less than 0.15 and 0.21 ppm after a single and multiple oral doses at 25 mg/kg, respectively. Tissue ^{14}C-concentration were highest in the liver and whole blood in both sexes in all tested groups.

The results of high performance liquid chromatography (HPLC) analysis of 72-hour urinary and fecal samples following oral doses of ^{14}C-chlorsulfuron showed that most (86-90%) of the dose in the urinary and fecal samples were identified. There were no qualitative or quantitative differences in the metabolite profiles for dose level and sex of rats after oral administration of ^{14}C-chlorsulfuron.

Analysis of the urinary samples found unchanged parent compound (chlorsulfuron; 42-55% of the dose), Metabolite P5 (desmethyl IN-70942; 3-8%), IN-70941 (4-6%), and IN-E9260 {[3-(ethylsulphonyl)-2-pyridinesulphonamide]; 7-10%}. Analysis of the fecal samples showed unchanged parent compound (chlorsulfuron; 5-16%), Metabolite P4 (OH-desmethyl IN-70942; 6-9%), Metabolite P5 (0.4-1.6%), and IN-E9260 (5-7%). The identities of the metabolites were confirmed by mass spectrometry.

The major metabolic pathway was believed to be consisted of the contraction of the sulfonylurea linkage followed by oxidation and hydroxylation to form IN-70941, IN 70942, Metabolite P5 (desmethyl IN-70942), and Metabolite P4 (OH-desmethyl IN-70942). The minor metabolic pathway involves the cleave of the sulfonylurea linkage to form Metabolite IN-E9260.

This study is classified as **Acceptable/Guideline**, and it satisfies the guideline requirement for a metabolism study (OPPTS 870.7485, OECD 417) in rats.

5.0 TOXICITY ENDPOINT SELECTION

5.1 See Section 8.2 for Endpoint Selection Table

5.2 Dermal Absorption

870.7600 Dermal Absorption - Rat

Adequacy of the dermal absorption data: There is no dermal absorption study available for chlorsulfuron.

Dermal Absorption Factor: 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.

5.3 Classification of Carcinogenic Potential

5.3.1 The data available for chlorsulfuron provide no evidence of a carcinogenic effect.

5.3.2 Classification of Carcinogenic Potential

The carcinogenic potential of chlorsulfuron was classified as no evidence of carcinogenicity, according to EPA Guidelines for Carcinogen Risk Assessment [CFR September 24, 1986]. The HED RfD Peer Review Committee concluded that there was no evidence of carcinogenicity in rats or mice [TXR # 004995, dated 3/12/86].

5.3.3 Quantification of Carcinogenic Potential

Not applicable.

6.0 FQPA CONSIDERATIONS

6.1 Special Sensitivity to Infants and Children

The data provided no indication of increased susceptibility [qualitative and quantitative] following *in utero* exposure to chlorsulfuron in either the rat or rabbit developmental toxicity study. Susceptibility cannot be assessed in the 3-generation reproduction study in rats due to numerous deficiencies. In the regulatory-quality prenatal developmental toxicity studies in rats and rabbits, effects in the offspring were observed only at or above treatment levels that resulted in evidence of parental toxicity.

6.2 Recommendation for a Developmental Neurotoxicity Study

The HIARC Committee concluded that a developmental neurotoxicity study [DNT] in rats is not required [HIARC Report TXR No.].

7.0 REFERENCES in MRID order

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00031414 Brittelli, M.R. (1976) Eye Irritation Test in Rabbits: Report No. 744-76. (Unpublished study received Jun 16, 1980 under 352- EX-105; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:099460-I)

00031417 Goodman, N.C. (1976) Primary Skin Irritation and Sensitization Tests on Guinea Pigs: Report No. 794-76. (Unpublished study received Jun 16, 1980 under 352-EX-105; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:099460-L)

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00031425 Russell, J.F., Jr. (1977) Mutagenic Activity of Benzenesulfonamide, 2-Chloro-N-ó(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl|-in the Salmonella/Microsome Assay: Report No. 121-77. (Unpublished study received Jun 16, 1980 under 352-EX-105; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:099461-F)

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No. 415-79. (Unpublished study received Sep 1, 1981 under 352-EX-109; submitted by E.I. du Pont de Nemours & Co., Wilmington, Del.; CDL:245879-I)

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8.0 APPENDICES

Tables for Use in Risk Assessment

8.1 Toxicity Profile Summary Tables

8.1.1 Acute Toxicity Table - See Section 4.1

8.1.2 Subchronic, Chronic, and Other Toxicity Tables

Toxicity Profile

Subchronic Toxicity of Chlorsulfuron		
Guideline	Study Type/MRID/doses	Results
870.3100 [§82-1 (a)]	Subchronic **oral** - Rats (90 days) 100, 500, 2500 ppm [males 6.5, 33.7, 161.1/females 8.1, 40.4, 216.6 mg/kg/day] MRID: 00031418 [1980] Classification: Unacceptable/Guideline, it does not satisfy guideline.	**Chlorsulfuron (≈95% a.i.)** NOAEL: 161.1 mg/kg/day [2500 ppm; HDT]. No effects were observed. Dosing inadequate; well below the limit dose
870.3150 [§82-1 (b)]	Subchronic **oral** - Dogs (6 months) 100, 500, 2500 ppm [3.7, 18.5, 82.3 mg/kg/day] MRID: 00031420 [1980] Classification: Acceptable/non-guideline	**Chlorsulfuron (95% a.i.)** NOAEL: 18.5 mg/kg/day, based on decreased body weight/body-weight gain at the LOAEL of 82.3 mg/kg/day.
870.3100 [§82-1 (a)]	Subchronic **oral** - Mice (90 days) 500, 2500, 5000, 7500 ppm [males 150, 783, 1557, 2130/females 220, 1214, 2134, 3176 mg/kg/day] MRID: 00031421 [1980] Classification: Unacceptable/Guideline, it does not satisfy guideline.	**Chlorsulfuron (100% a.i.)** NOAEL: 1557 mg/kg/day, based on an increased incidence of retinal dysplasia and adrenal capsular cell proliferation at the LOAEL of 2130 mg/kg/day.

LOAEL = Lowest Observable Adverse Effect Level; NOAEL = No Observable Adverse Effect Level

Chronic Toxicity/Carcinogenicity of Chlorsulfuron		
Guideline	Study Type/MRID/doses	Results
870.4100 [§83-1b]	Chronic feeding study in beagle dogs 100, 2000, and 7500 ppm [males 3.5, 65.6, and 215/females 3.5, 60.6, and 254.5 mg/kg/day for 52 weeks] MRID 41862601 [1991] Classification: Acceptable/Guideline	**chlorsulfuron (97.5% a.i.)** NOAEL: 60.6 mg/kg/day LOAEL: 215 mg/kg/day, based on decreased body-weight gain, erythrocyte counts, and hemoglobin levels
870.4200 [§83-2]	Carcinogenicity study -CD-1 mice [0, 100, 500, 5000 ppm [0, 15, 108, 750 mg/kg/day] for 104 weeks MRID 00090030 [1981] Classification: Acceptable/Guideline	**chlorsulfuron (95% and 91.9%)** NOAEL = 500 ppm [108 mg/kg/day] LOAEL: 5000 [750 mg/kg/day], based on decreased body weight and body-weight gain. There was no treatment-related increase in tumor incidence in either sex.
870.4300 [§83-5]	Chronic feeding/carcinogenicity study CD® rats [0, 100, 500, and 2500 ppm (0, 5, 25, and 125 mg/kg/day] for 2 years. MRID 00086003 [1981] Classification: Acceptable/non-guideline	**chlorsulfuron (>95% a.i.)** NOAEL: 50 ppm [5 mg/kg/day] LOAEL: 500 ppm [25 mg/kg/day], based on decreased body weight in males There was no treatment-related increase in tumor incidence in either sex.

Developmental Toxicity of Chlorsulfuron		
Guideline	Study Type/MRID/doses	Results
870.3700 [§83-3a]	Developmental Toxicity - Crl:CD®(SD)BR rats [0, 55, 165, 500, and 1500 mg/kg/day] MRID 41976406 [1991] Classification: Acceptable/Guideline	**chlorsulfuron (98.22% a.i.)** Maternal NOAEL: 165 mg/kg/day Maternal LOAEL: 500 mg/kg/day, based on clinical signs [vaginal discharge with associated alopecia. At HDT, there were two deaths [GD 12 and 18], and additional clinical signs [swollen limbs and faces]. Developmental NOAEL: 500 mg/kg/day Developmental LOAEL: 1500 mg/kg/day, based on decreased fetal body weight.
870.3700 [§83-3b]	Developmental Study - Hra:(NZW)SPF Rabbits [0,25, 75, 200, 400 mg/kg/day (original study); 400 and 1000 mg/kg/day (supplemental study)] MRID 41983101 [1991] Classification: Acceptable/Guideline	**chlorsulfuron (98.2% a.i.)** Maternal NOAEL: 75 mg/kg/day Maternal LOAEL: 200 mg/kg/day, based on decreased body-weight gain. At HDT, there were 8/20 deaths and 6 abortions. Developmental NOAEL: 200 mg/kg/day Developmental LOAEL: 400 mg/kg/day, based on a slight increase in visceral malformations and decreased fetal body weight.

Reproductive Toxicity of Chlorsulfuron		
Guideline	Study Type/MRID/doses	Results
870.3800 [§83-4]	3-Generation Reproduction Toxicity in CD® Rats 0, 100, 500, 2500 ppm [0, 5, 25, 125 mg/kg/day] MRID 00086003 [1981] Classification: Unacceptable/non-guideline	**chlorsulfuron (95%-95.9% a.i.)** Parental NOAEL: 2500 ppm [125 mg/kg/day] Parental LOAEL: >2500 ppm [125 mg/kg/day], no effects observed. Reproductive NOAEL: 100 ppm [5 mg/kg/day] Reproductive LOAEL: 500 ppm [25 mg/kg/day], based on decreased female fertility. Offspring NOAEL: no effects observed Offspring LOAEL:

Neurotoxicity of Chlorsulfuron		
Guideline	Study Type/MRID/doses	Results
870.6200 [§81-8]	**acute neurotoxicity study is not required**	
870.6200 [§82-7]	**subchronic neurotoxicity study is not required**	
870.6300 [§83-6]	**developmentalneurotoxicity study is not required**	

Metabolism Studies on Chlorsulfuron		
Guideline	Study Type/MRID/doses	Results
870.7485 [§85-1]	Metabolism MRID 42540701 [1989] Classification: Acceptable/guideline	Chlorsulfuron is rapidly absorbed, metabolized, and eliminated following oral exposure [single low, single high, and repeated low dosing regimens] to rats. There were no remarkable sex-, dose-, or treatment-related differences in the absorption, distribution, and excretion of chlorsulfuron in rats. The major routes of elimination are the urine [58%-72%] and feces [20%-35%]. Small amounts [0.1%-0.2% of administered dose] were found in the tissues 3 days after dosing. The highest concentrations were in the liver and whole blood in both sexes. A major and a minor metabolic pathway were identified.

8.2 Summary of Toxicological Dose and Endpoints for Chlorsulfuron

Exposure Scenario	Dose (mg/kg/day) UF /MOE	Hazard Based Special FQPA Safety Factor	Endpoint for Risk Assessment
Dietary Risk Assessments			
Acute Dietary females 13-50 years of age	**no appropriate endpoint/dose identified**		
Acute Dietary general population including infants and children	**no appropriate endpoint/dose identified**		
Chronic Dietary all populations	NOAEL= **5 mg/kg/day** UF = **[300]** **Chronic RfD** = **0.02** mg/kg/day	1X	**rat chronic toxicity/carcinogenicity** LOAEL = **25 mg/kg/day** based on **decreased body weight 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		**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= 5 mg/kg/day		**rat chronic toxicity/carcinogenicity** LOAEL = **25** 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		**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		**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= 5 mg/kg/day		**rat chronic toxicity/carcinogenicity** LOAEL = **25** 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, and should include the database uncertainty factor of 3X for lack of an adequate 2-generation reproduction study.