

CALIFORNIA DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA
Chlorsulfuron

Chemical Code # 2143, SB # 950-156, Tolerance # 405

July 15, 1987

Revised 03/07/88, 04/25/89, 7/16/91, 9/20/91, 3/28/12, 4/16/12

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect.
Chronic toxicity, dog:	No data gap, possible adverse effect.
Oncogenicity, rat:	No data gap, no adverse effect.
Oncogenicity, mouse:	No data gap, no adverse effect.
Reproduction, rat:	No data gap, no adverse effect.
Teratology, rat:	No data gap, no adverse effect.
Teratology, rabbit:	No data gap, no adverse effect.
Gene mutation:	No data gap, no adverse effect.
Chromosome:	No data gap, no adverse effect.
DNA damage:	No data gap, no adverse effect.
Neurotoxicity:	No study required at this time.

Toxicology one-liners are attached.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

File name: T120328

Revised by Stanton Morris, 04/25/89. Revised by Thomas Kellner, 07/16/91 and 09/20/91. Revised by H. Green, 3/28/12 and 04/16/12.

All records through 248852 were examined.

These pages contain summaries only. Each individual worksheet may contain additional effects.

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

COMBINED, RAT

405-001, 007, 011, 016-020, 0102, 0103 030986 (previously 993132), 035696 (previously 993132, 031015, 037958-037964, 243726, 243738; "Long-Term Feeding Study with 2-Chloro-N-[(4-Methoxy-6-Methyl-1,3,5-Triazin-2-yl)Aminocarbonyl] Benzenesulfonamide (INW-4189) in Rats", (Du Pont Haskell Laboratory, Newark, DE, 10/8/81; (Supplement 2 was conducted by D.A. Banas, Experimental Pathology Laboratories, Inc., Sterling, VA., 8/20/2008)). Chlorsulfuron (92% to 95% purity) at 0, 100, 500, or 2500 ppm (nominal not measured) in diet to 80 rats/sex/group in a combined study (reproduction in addition to chronic toxicity and oncogenicity). NOEL = 100 ppm (bodyweight). No adverse effects. Complete, acceptable. Originally reviewed as chronic toxicity, Remsen (Gee) 1/31/86; reclassified as combined (see rebuttal in vol. 405-029), Davis 7/9/87; additional data (Supplement 1, record 243738) were submitted in regard to the incidence of interstitial tumors in the testes of the male rats as a possible adverse effect; although the unilateral incidence of interstitial tumors in the testes of the 2500 ppm males was statistically significant, when the bilateral incidence of these tumors was included in the evaluation, this significance was no longer apparent. The historical control range for the incidence of unilateral interstitial tumors cited in the original report was 5% to 15%, while the incidence reported in Supplement 1 was 18.8% (13/69); although this incidence was slightly outside the historical control range, the lack of a dose-related effect at the other treatment levels dictates against concluding that the incidence of interstitial tumors is a treatment-related effect; **no adverse effect indicated. (Moore, 3/8/12). Supplement 2 (record 243726) was submitted as an adverse effects disclosure for interstitial cell tumors of the testes. It is a peer review of microscopic pathology of the testes conducted on the testes slides from the original study using current diagnostic criteria. The incidences of unilateral and bilateral interstitial cell tumors, interstitial cell hyperplasia, and degeneration/atrophy of the seminiferous tubules were determined. The tumor incidence data provided from this evaluation was generally similar to the original evaluation. The incidence of unilateral interstitial cell tumor of the testes was 2/70 (2.9%), 5/69 (7.2%), 3/67 (4.5%), and 13/69 (18.8%) in the original evaluation, and 1/66 (1.5%), 4/68 (5.9%), 4/66 (6.0%), and 12/69 (17.4%) (statistically significant) in this peer review at 0, 100, 500, and 2500 ppm, respectively (bilateral and total interstitial cell tumor incidence was not significantly increased at any dose level). While the 17.4% incidence in this peer review remained slightly above the historical control incidence range for unilateral interstitial cell tumor of the testes (5% to 15%) noted in the original report, the lack of a dose response and absence of significant bilateral involvement, render the results inconclusive. A possible adverse effect is not indicated. (Green and Leung, 3/15/12).

405-004; 028452: This document contains statements about pathology findings in doc. # 405-001, rec. # 030986. No data were presented. No worksheet was done. Morris, 04/25/89

405-004; 028453: This document contains a summary of the study in doc. # 405-001, rec. # 030986. No data were presented. No worksheet was done. Morris, 04/25/89

405-002; 030970: This document is an index that includes the study in doc. # 405-001, rec. # 030986. No data were presented. No worksheet was done. Morris, 04/25/89

CHRONIC TOXICITY, RAT

See Combined study above.

CHRONIC TOXICITY, DOG

405-027, 037811 (With rebuttals dated 11/26/86 in 405-029, 051257, and 11/17/87, no numbers): "Six-month Feeding Study in Dogs with 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl]-benzenesulfonamide (INW-4189);" Haskell Laboratory, 2/29/80; chlorsulfuron, 95% pure, at 2500, 500, 100, or 0 ppm in the feed to 4 beagles/sex/level for 6 months; NO ADVERSE EFFECT, no MTD, NOEL>2500 ppm. Unacceptable in prior reviews (Gee, 5/8/85 and Davis, 6/26/87) - no MTD, ophthalmoscopic exams, or 1 year duration; not upgraded by rebuttal (11/17/87), still UNACCEPTABLE and not upgradeable for subchronic or chronic requirement - no MTD, target organ toxicity, or ophthalmoscopic exams. Martz, 1/12/88.
EPA 1-liner: Core Minimum, 1/30/89.

**** 405-055 92713** Atkinson, J. "A Chronic (1 Year) Oral Toxicity Study in the Dog with DPX-W4189 (Chlorsulfuron) Via the Diet" (Bio/dynamics, Inc., Du Pont Report no. HLO 163-91, 4/4/91). Chlorsulfuron, DPX-W4189-165, lot 12-51, Drum 14, Batch 12-51-88, purity 97.5%, at nominal concentrations of 0 (control), 100, 2000 and 7500 ppm in the feed was administered to 5 beagle dogs/sex/dietary level for one year. Significant decreases in high-dose female erythrocyte count, hemoglobin and hematocrit levels were seen at 3, 6 and 9 months. Abnormal erythrocyte morphology including nucleated erythrocytes, anisocytosis, poikilocytosis and target cells were seen in males and females at 7500 ppm at 3 months. **Possible adverse effect:** Anemia and lower body weight gain in females, NOEL = 2000 ppm (60.6 mg/kg/day in females, 65.6 mg/kg/day in males). **Acceptable.** (Kellner and Gee, 7/12/91).

ONCOGENICITY, RAT

See combined study, above.

ONCOGENICITY, MOUSE

**007, 011, 021-026; 031013 (previously 993134), 001764, 037965-037971, 037993 "Long-term Feeding Study with INW-4189 in Mice" (Haskell Laboratory Report No. 836-81, 12/22/81). Chlorsulfuron (95 and 91.9% purity) at 0, 100, 500, or 5000 ppm in feed to 80 mice/sex/group for 2 years; No adverse effect. Chronic toxicity (body weight) NOEL = 500 ppm. Complete, acceptable. Rensen (Gee) 1/31/86.

405-001; 030983 (formerly 993134): This document contains an interim one-year report of the study in doc. # 405-011, rec. # 001764. No data were presented. No worksheet was done. Morris, 04/25/89

405-002; 030969: This document is an index that includes the study in doc. # 405-001, rec. # 030983. No data were presented. No worksheet was done. Morris, 04/25/89

REPRODUCTION, RAT

**001, 007, 011, 016-020; 030981 (previously 993137), 035695 (previously 993132), 031014 (previously 001765), 041776, 037959-037964 "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, 10/8/81). Chlorsulfuron (92-95% purity) at 0, 100, 500, or 2500 ppm (nominal not measured) in diet to 20 rats/sex/group in a 3 generation study (subpart of combined study). No adverse effects. Complete, acceptable. Rensen (Gee) 1/31/86.

405-002; 030968: This document is an index that includes the study in doc. # 405-001, rec. # 030981. No data were presented. No worksheet was done. Morris, 04/25/89

**405-0105 248852, "Chlorsulfuron (DPX-W4189) Technical: Multigeneration Reproduction Study in Rats", (E. Mylchreest, E. I. du Pont de Nemours & Co., Haskell Laboratory for Health and Environmental Sciences, Laboratory Project ID: DuPont-13475, 9 February 2005). Thirty F0 and F1 CrI:CD® (SD)IGS BR rats per sex per group received chlorsulfuron (DPX-W4189) technical (97.6%) in the diet at 0 (untreated diet), 100, 500, 2500 and 7500 ppm through 2 generations with 1 litter per generation. Group mean Chlorsulfuron (DPX-W4189) technical intake ranges were 6.01 (F0) to 9.11 (F1) mg/kg/day for males and 6.53 to 12.62 (F0) mg/kg/day and 7.15 to 11.23 (F1) mg/kg/day for females at 100 ppm; 30.1 (F0) to 45.9 (F1) mg/kg/day for males and 32.6 to 61.2 (F0) mg/kg/day and 35.5 to 62.9 (F1) for females at 500 ppm; 151 (F0) to 226 (F1) mg/kg/day for males and 165 to 328 (F0) mg/kg/day and 180 to 312 (F1) mg/kg/day for females at 2500 ppm; and 456 (F0) to 701 (F1) mg/kg/day for males and 498 to 1040 (F0) mg/kg/day to 556 to 972 (F1) mg/kg/day for females at 7500 ppm, respectively. At 7500 ppm, significant reductions in group mean bodyweight (days 14 through 105 for F0 males; days 35 through 105 for F1 males; and pre-mating days 21 through 70 for F1 females) and bodyweight gain (days 0 to 70 and 0 to 105 for F0 males; days 0 to 70, 70 to 105, and 0 to 105 for F1 males; and pre-mating days 0 to 70 for F1 females) were noted for F0 and F1 parents vs controls. At 7500 ppm, significant increases were noted for group mean relative kidney weights (F0 males and females and F1 males), testes weights (F0 and F1 males), epididymides weight (F0 males), and right cauda epididymis weight (F0 males) vs controls. No treatment-related effects were noted for F0 and F1 clinical signs, food consumption, mortality, sperm parameters, estrous cycle parameters, mating, fertility, gestation length, number of implantation sites, necropsy results, and histology; or for F1a and F2a pup clinical signs, pup survival, pup weights, pup developmental landmarks, pup organ weights, or gross pathology. Parental NOEL = 2500 ppm (151 to 226 mg/kg/day for males during pre-mating and 165 to 261 mg/kg/day females during pre-mating and/or gestation) based on bodyweight and bodyweight gain. Reproductive NOEL = 7500 ppm (456 to 701 mg/kg/day for males during pre-mating and 498 to 810 mg/kg/day for females during pre-mating and/or gestation). Pup NOEL = 7500 ppm (no effect at highest dose level). No adverse reproductive effect. Acceptable. (Green and Leung, 4/3/12).

TERATOLOGY, RAT

405-001, 030982 (previously 993135); "Teratological study of 2-Chloro-N-[(4-Methoxy-6-Methyl-1,3,5-Triazin-2-yl) Aminocarbonyl] Benzenesulfonamide (INW-4189) in Rats" (Haskell Laboratory Report No. 583-78, 10/11/78). Chlorsulfuron (97.2% purity) at 0, 100, 500, and 2500 ppm in feed to 25, 26, 25, and 21 pregnant rats respectively on days 6-15; Maternal toxicity (body weight gain, food consumption) NOEL = 500 ppm; No developmental toxicity; No adverse effect, incomplete, unacceptable - no justification of dose. 030982 and 037818 are full reports, 051393 is supplementary data. Remsen (Gee) 1/30/86, Davis 7/13/87, Morris 5/25/89.

EPA 1-liner: Downgraded to supplementary (1/30/89), since EPA review states there was no maternal toxicity at 2500 ppm and the test material was not administered by gavage.

405-027; 037818: This document contains an exact duplicate of doc. # 405-001, rec. # 030982 and a statement of purity of the test material.

405-031; 051393: This document contains supplemental information on diet analysis, individual litter data, individual pup data, and statistical analysis of feed consumption and maternal body weights.

405-036; 064861: This document contains a more legible copy of the individual litter data previously presented in doc. # 405-031, rec. # 051393.

405-002; 030967: This document is an index that includes the study in doc. # 405-001, rec. # 030982. No data were presented. No worksheet was done. Morris, 04/25/89

** 053 096366, "Teratogenicity Study of DPX-W4189-165 (Chlorsulfuron) in Rats", (Louis Alvarez, E.I. du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE, Report # 734-90, 2/27/91). Chlorsulfuron, DPX-W4189-165, lot 12-51, batch 12-51-88, 98.2% purity, was administered by gavage to 25 inseminated female CrI:CD*BR rats per group on

gestation days 7 through 16 at 0 (0.5% methyl cellulose (w/v) in distilled water), 55, 165, 500 and 1500 mg/kg/day. Increased incidence of vaginal discharge at 500 and 1500 mg/kg/day during gestation days 7 through 16. Reduced maternal body weights and food consumption at 1500 mg/kg/day. Decreased fetal body weights at 1500 mg/kg/day. **No adverse effect indicated.** Maternal NOEL = 165 mg/kg/day (increased vaginal discharge during treatment at 500 and 1500 mg/kg/day; reduced body weights and food consumption at 1500 mg/kg/day). Developmental NOEL = 500 mg/kg/day (reduced fetal body weights at 1500 mg/kg/day). **Acceptable.** (H. Green, 3/25/91 and Gee, 7/12/91)

TERATOLOGY, RABBIT

405-027; 037817; "Teratology Study in Rabbits" (Hazleton Labs, Project No. 201-536, 7/17/80). Chlorsulfuron (94.0% purity) at 0, 10, 25, and 75 mg/kg/day by gavage to 13, 14, 17, and 16 pregnant does respectively on days 6-19; Maternal toxicity (body weight gain) NOEL = 25 mg/kg/day; Developmental toxicity (increased resorption and decreased viability) = 25 mg/kg/day; No adverse effect, incomplete, unacceptable-incomplete examination of fetuses for visceral and skeletal defects, missing individual data, missing dosing suspension analyses, no justification for revised data page, no justification of dose. Remsen (Gee) & Parker 1/31/86, Davis 7/13/87, Morris 4/25/89.
EPA 1-liner: Core Minimum, 1/30/89.

405-007; 031020 (previously 993136): This document contains only the Summary section of doc. # 405-027, rec. # 037817.

405-031; 051391: This document contains the registrants comments about CDFA's review of original study and statistical analysis of maternal body weights.

405-031; 051392: This document contains an exact duplicate of doc. # 405-027, rec. # 037817.

** 405-057 098147 Alvarez, L. "Teratogenicity Study of DPX-W4189-165 (Chlorsulfuron) in Rabbits" Du Pont, Haskell Laboratory for Toxicology and Industrial Medicine, no. HLR 306-90, 8/12/91. Chlorsulfuron, lot 12-51, drum 14, batch 12-51-88, 98.2% purity was administered by gavage to 20 inseminated New Zealand White rabbits per group on gestation days 7 through 19 at 0 (0.5% (w/v) aqueous methyl cellulose), 25, 75, 200 and 400 mg/kg/day in the original study and 0, 400 and 1000 mg/kg/day in the supplemental study. Maternal mortality, reduced body weight gain and increased clinical signs were seen at 1000 mg/kg; Maternal NOEL = 400 mg/kg/day. Reduced fetal weights at 400 mg/kg (both studies) indicted a developmental NOEL = 200 mg/kg/day. Fetal malformations (doubled aorta, ventricular septal defect and absent gallbladder) were seen at low frequency at 400 mg/kg in the original study but not at 1000 mg/kg in the supplemental study. Minor fetal skeletal defects (hemivertebra malformations) at 400 mg/kg and decreased sternbra ossification at 1000 mg/kg were also noted. No adverse teratogenic effects. Acceptable. (Kellner and Gee, 9/6/91.)

GENE MUTATION

**027 037812 "Mutagenicity Evaluation in Salmonella typhimurium" (Haskell Laboratory Report No. 459-82, 7/28/82). Bacterial strains TA98, TA100, TA1535, TA1537 treated for 48 hours with chlorsulfuron at 0, 0.001, 0.005, 0.01, 0.05, 0.1 or 0.5 ug/plate \pm activation; duplicate plates; two trials. No adverse effect, complete, acceptable. Remsen (Gee) 1/30/86.

001 030988 (previously 993139) "Mutagenic Activity of Benzenesulfonamide, 2-Chloro-N-[(4-Methoxy-6-Methyl-1,3,5-Triazin-2-yl) Aminocarbonyl]- in the Salmonella/Microsome Assay" (Haskell Laboratory Report No. 121-77, 3/4/77). Bacterial strains TA98, TA100, TA1535, TA1537, TA1538 treated for 48 hours with chlorsulfuron at 0, 6, 12, 18, 24, or 30 ug/plate \pm activation; duplicate plates. Insufficient information to assess mutagenicity. Incomplete, unacceptable-no individual plate data, no evidence of cytotoxicity, no confirmatory repeat assay, no GLP. Remsen (Gee) 5/8/85.

405-027; 037813: This document contains an exact duplicate of doc. # 405-001, rec. # 030988.

007 031021 (previously 993141) "Chinese Hamster Ovary Cell Assay for Mutagenicity" (Haskell Laboratory Report No. 475-80, 10/7/80). CHO cells exposed to chlorsulfuron (95% purity) at 0, 0.028, 0.28, 1.68, 2.24, or 2.80 mM final concentration in duplicate with a repeat trial; measured mutations at the HGPRT locus. Insufficient information to assess mutagenicity. Complete, unacceptable-lacks justification of acetone solvent which limited the dose levels tested. Remsen (Gee) 5/9/85.

405-027; 037814: This document contains an exact duplicate of doc. # 405-007, rec. # 031021.

CHROMOSOME

007 031022 (previously 993138) "Dominant Lethal Evaluation in Rats" (Hazleton Laboratories, Project No. 201-539, 9/23/80). Chlorsulfuron (no purity given) fed to 10 male rats/group at 0, 100, 500, or 5000 ppm for 10 weeks; mated for 2 weeks with two groups of 2 females/male; Possible adverse effect-decreased fetal viability and increased incidence of resorptions in second mating. NOEL = 500 ppm. Incomplete, unacceptable-too few females, no positive control, no justification of treatment protocol. Remsen (Gee) 5/9/85.

405-027; 037815: This document contains an exact duplicate of doc. # 405-007, rec. # 031022.

**007 031023 (previously 993140) "Mutagenicity Evaluation of 12,700 in an In vitro Cytogenetic Assay Measuring Chromosome Aberration Frequencies in Chinese Hamster Ovary (CHO) Cells" (Litton Bionetics Project No. 20990, 4/81). CHO cells exposed to chlorsulfuron at 0, 16.7, 50.0, 167.0, 500.0, 1670, and 5000 ug/ml for 2 hours with activation or 8.5-10 hours without activation. No adverse effect, complete, acceptable. Remsen (Gee) 5/8/85.

405-027; 037816: This document contains an exact duplicate of doc. # 405-007, rec. # 031023.

Summary: The possible adverse effects seen in the dominant lethal study (doc. # 405-007, rec. # 031022) were not seen in the first mating and were only marginally significant the second mating. These effects were seen at doses that produced toxicity in the males (10% decrease in body weight gain). The protocol used in this study was not a standard dominant lethal test. It might be characterized as male-only-exposure, one generation, two litter reproductive toxicity protocol. No adverse effects were seen in an acceptable reproductive toxicity test (doc. # 405-001, rec. # 030981). For these reasons the possible adverse effects seen in the dominant lethal test were not considered to be significant.

DNA DAMAGE

029 051258 "The Hepatocyte Primary Culture/DNA Repair Assay on Compound 12700 using Rat Hepatocytes in Culture" (Naylor Dana Institute, 11/15/81) Technical chlorsulfuron was administered to primary rat hepatocyte cultures at 0, 0.0002, 0.002, 0.02, 0.2, and 2.0 mg/ml. The 2.0 (test I), 0.4 and 4.0 (test II) mg/ml levels were not scored because of cytotoxicity. No adverse effect was indicated because both tests were negative for unscheduled DNA synthesis, though the scoring method was designed to favor negative results. The study was unacceptable because control net grain counts were too high and not all the primary data was presented. Davis, 7/8/87; Morris, 4/25/89.

EPA 1-liner: Acceptable (1/30/89).

** 054 092330, "Assessment of IN W4189-165 in the In Vitro Unscheduled DNA Synthesis Assay in Primary Rat Hepatocytes", (Daniel R. Vincent, E.I. Du Pont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE., Report # HLR 573-90, 12/10/90). Chlorsulfuron, DPX-W4189-165, lot 12-51, batch 12-51-88, 98.2%, purity was tested in the unscheduled DNA synthesis (UDS) assay using male rat primary hepatocytes in two trials with 2 two-culture slides per concentration (a total of 4 cultures per concentration) at 0 (DMSO), 0.5, 5.0, 10.0, 50.0, 100.0, 500.0, 1000.0, and 3750.0 ug/ml. Scored 25 cells per culture. **No evidence of unscheduled DNA synthesis. Acceptable.** (H. Green, 3/19/91, and Gee, 7/11/91).

NEUROTOXICITY

Not required at this time.