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Arthur L. Lawyer, Ph.D.
President

April 29, 2014

DuPont Crop Protection:
Chlorsulfuron: Proposition 65:
Submission of Proprietary References

Ms. Cynthia Oshita
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
PO Box 4010, MS-19B
1001 I Street
Sacramento, CA 95814

Dear Ms Oshita,

On behalf of DuPont Crop Protection, this is a follow up to our April 28, 2014 letter regarding chlorsulfuron, which will be considered by the DART-IC during their May 21st meeting as to whether the compound should remain listed under Proposition 65 as known to cause reproductive toxicity. The references cited in our letter are being provided in an electronic manner that, hopefully, will be convenient for referencing by DART-IC members and OEHHA staff alike. Some of the scientific studies that are referenced in our letter are proprietary and, accordingly, we are requesting special handling of these documents as detailed below.

For the convenience of the members of the DART-IC and OEHHA staff, we have enclosed two searchable CDs. The CDs contain all references in our April 28th letter. The two CDs have the following material:

- **CD-1: Public Documentation**: This includes the references that are available to the public, including documents, evaluations, and decisions produced by the US EPA and published scientific literature. For your convenience, all enclosed references can be "clicked" to within the April 28th letter's reference list to open up the citation.

- **CD-2: Proprietary Scientific Studies.** This disc includes the 5 key studies on chlorsulfuron developmental and reproductive effects, in their entirety, along with their subsequent Supplements. The public documentation included in CD1 are also enclosed

(i.e., this proprietary CD has all references cited in the April 28th letter). These references are also enclosed so the members of the DART-IC and OEHHA staff can easily "click" onto the studies and supplements in the Reference section of the letter.

These "non-published" studies are the foundation of the Authoritative Body's evaluation of developmental and reproductive effects of chlorsulfuron. These scientific studies on chlorsulfuron are proprietary because these studies were generated to satisfy the requirements for pesticide registration under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA) and California's equivalent pesticide approval program under the California Food and Agricultural Code.

As with our previous submission to OEHHA and the DART-IC with these chlorsulfuron studies, we propose that, consistent with previous OEHHA practice, that the full copies of the proprietary studies be provided to the members of the DART-IC and that the Committee members be asked to return their copies to OEHHA after the conclusion of the May 21st DART-IC meeting in which the delisting of chlorsulfuron is considered. Further, OEHHA would indicate in its public record of the proceeding that any person with an interest in these studies may review them at the DPR data library or file a request through the Public Records Act, consistent with previous OEHHA practices with proprietary studies.

NOTE: These full-length proprietary studies have been previously provided to OEHHA and members of the DART-IC, as part of our February 25, 2014 letter requesting delisting of chlorsulfuron under Proposition 65. However, the naming convention we used for the Supplemental studies to the proprietary studies was different than the naming convention that OEHHA utilized for these same supplements on March 14, 2014. So we are resubmitting the proprietary studies to OEHHA and the DART-IC members using the OEHHA naming convention, so that all of the documents being considered by the DART-IC match.

The proprietary references included in CD-2 are the following:

Alvarez, L. (1991a). Teratogenicity study of DPX-W4189-165 (Chlorsulfuron) in Rabbits. DuPont Haskell Laboratory for Toxicology and Industrial Medicine. Study ID No. HLR 306-90. August 12, 1991. DPR Doc. No. 405-57. DPR Record No. 98147.

Mylchreest, E. (2005a) Supplement 1 to Alvarez, L. (1991a). Teratogenicity Study of DPX-W4189-165 (Chlorsulfuron) in Rabbits. E. I. DuPont de Nemours and Company. Laboratory Project ID 306-90. Haskell Laboratory for Health and Environmental Sciences, Newark DE 19714. USA.

Lewis, J.M. (2008) Supplement 2 to Alvarez, L. (1991a). Teratogenicity Study of DPX-W4189-165 (Chlorsulfuron) in Rabbits. E. I. DuPont de Nemours and Company.

Laboratory Project ID 306-90. Haskell Laboratory for Health and Environmental Sciences, Newark DE 19714. USA.

Munley, S.M. (2012a) Supplement 3 to Alvarez, L. (1991a). Teratogenicity Study of DPX-W4189-165 (Chlorsulfuron) in Rabbits. E. I. DuPont de Nemours and Company. Laboratory Project ID 306-90. Haskell Laboratory for Health and Environmental Sciences, Newark DE 19714. USA.

Alvarez, L. (1991b). Teratogenicity Study of DPX-W4189 (Chlorsulfuron) in Rats. E.I. du Pont de Nemours & Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, DE, Laboratory Project ID: 734-90, February 27, 1991. Unpublished.

Hoberman AM, Wolfe GW, Durloo RS, (1980). Chlorsulfuron (DPX-W4189) Technical: Teratology Study in Rabbits. HLO-534-80. E. I. DuPont de Nemours and Company. Laboratory Project ID 201-536. Haskell Laboratory for Toxicology and Industrial Medicine, Newark DE 19714. USA.

Hoberman AM (2010). Supplement 1 to Hoberman (1980). Chlorsulfuron (DPX-W4189) Technical: Teratology Study in Rabbits. HLO-534-80. E. I. DuPont de Nemours and Company. Laboratory Project ID 201-536. Haskell Laboratory for Toxicology and Industrial Medicine, Newark DE 19714. USA.

Hoberman, A. (2011). Supplement 1, Revision 1 to Hoberman et al., (1980). Chlorsulfuron (DPX-W4189) Technical: Teratology Study in Rabbits. HLO-534-80. E. I. DuPont de Nemours and Company. Laboratory Project ID 201-536. Haskell Laboratory for Toxicology and Industrial Medicine, Newark DE 19714. USA.

Munley S.M. (2014). Supplement 1, Revision 2 to Hoberman et al., (1980). Chlorsulfuron (DPX-W4189) Technical: Teratology Study in Rabbits. HLO-534-80. E. I. DuPont de Nemours and Company. Laboratory Project ID 201-536. Haskell Laboratory for Toxicology and Industrial Medicine, Newark DE 19714. USA.

Mylchreest E, 2005b. Chlorsulfuron (DPX-W4189) Technical: Multigeneration Reproduction Study in Rats. DuPont Haskell Laboratory for Health and Environmental Sciences. Project No. DUPONT 13495, 14601, 904. DPR Doc. No. 405-105. DPR Record No. 248852.

Wood C.W., Wollenberg E.J., Turner D.T. (1981). Long-Term Feeding Study with 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl]benzenesulfonamide (INW-4189) in Rats. E. I. DuPont de Nemours and Company. Laboratory Project ID 557-81. Haskell Laboratory for Toxicology and Industrial Medicine, Newark DE 19714. USA.

Munley S.M. (2010). Supplement 3 to Wood et al. (1981). Long-Term Feeding Study with 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl]benzenesulfonamide (INW-4189) in Rats. E. I. DuPont de Nemours and Company. Laboratory Project ID 557-81. Haskell Laboratory for Toxicology and Industrial Medicine, Newark DE 19714. USA.

Munley S.M. (2011). Supplement 3, Revision 1 to Wood et al. (1981). Long-Term Feeding Study with 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl]benzenesulfonamide (INW-4189) in Rats. E. I. DuPont de Nemours and Company. Laboratory Project ID 557-81. Haskell Laboratory for Toxicology and Industrial Medicine, Newark DE 19714. USA.

Munley S.M. (2012b). Supplement 3, Revision 2 to Wood et al. (1981). Long-Term Feeding Study with 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl]benzenesulfonamide (INW-4189) in Rats. E. I. DuPont de Nemours and Company. Laboratory Project ID 557-81. Haskell Laboratory for Toxicology and Industrial Medicine, Newark DE 19714. USA.

We truly appreciate your continued activities on chlorsulfuron under California's Proposition 65. We look forward to completing this process. Please contact me if you have any questions or need further information.

Sincerely,

ALL:/DuPont Chlorsulfuron Proprietary Data Logistics – Apr 29 2014.docx

CC: C. Oshita, OEHHA
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Arthur L. Lawyer, Ph.D.
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April 28, 2014

DuPont Crop Protection:
Chlorsulfuron: Comments to DART-IC
Notice of Consideration to Delist under Prop 65

Ms. Cynthia Oshita
Office of Environmental Health Hazards Assessment
PO Box 4010, MS-19B
1001 I Street
Sacramento, CA 95812-4010

Dear Ms. Oshita,

On behalf of DuPont Crop Protection, we are providing comments on the March 14, 2014 Notice from OEHHA regarding chlorsulfuron, which will be considered by the DART-IC during their May 21st meeting as to whether the compound should remain listed under Proposition 65 as known to cause reproductive toxicity. DuPont is the sponsor of the health effects studies on chlorsulfuron. Copies of all the relevant studies have been provided to the DART-IC in advance of their May meeting. We are providing these studies again with this letter so that the naming conventions used by DuPont for referencing these studies match the conventions used by OEHHA in their communications with the Panel.

The purpose of these comments is to provide additional clarification on the scientific issues that have led to the recent conclusion by the U.S. EPA, the Authoritative Body behind the listing of chlorsulfuron under Proposition 65, that chlorsulfuron is not a developmental or reproductive toxicant. As summarized by OEHHA in the March 2014 "Reconsideration of Three Chemicals Listed under Proposition 65 as Known to Cause Reproductive Toxicity," chlorsulfuron no longer meets the criteria for inclusion on the Proposition 65 list on the basis of the Authoritative Bodies mechanism. This is because no Authoritative Body recognized under Proposition 65, or other regulatory authority for that matter, concludes that chlorsulfuron is a developmental, female reproductive, or male reproductive toxicant.

Our comments summarize the scientific rationale for why chlorsulfuron does not meet the DART-IC criteria as clearly shown to be a reproductive toxin. We are providing these comments because some of the relevant issues involve studies that were performed 35 years ago and, due to updated guidelines and/or new information, have required further clarification.

This letter consists of a brief history of chlorsulfuron under Proposition 65, an executive summary of the studies that led to the Proposition 65 action along with other, subsequent DART studies, and, finally, a more detailed assessment of these studies. As the amount of data is rather large, and the U.S. EPA-compliant studies are extensive and complex and include important "Supplements," the executive summary and details that follow are intended to assist the members of the DART-IC in their evaluations and accompany the very useful summaries that have already been provided to the Committee by OEHHA. We hope our comments to the DART-IC members are a helpful addendum to the full-length studies that have been provided to the Committee.

BRIEF HISTORY

Chlorsulfuron was listed under Proposition 65 on May 14, 1999 as a developmental and reproductive toxicant. The listing was based on the Authoritative Body mechanism, using the U.S. EPA's decision in 1994 to add chlorsulfuron to their Toxic Release Inventory (TRI) under the Emergency Planning and Community Right-to-Know Act (EPCRA) (US EPA, 1994). The TRI decision was based on single sentence summaries of two older studies on chlorsulfuron in a U.S. EPA secondary source called "Tox One Liners" (US EPA, 1993a). The two studies were a 1981 3-generation reproductive toxicity study and a 1980 developmental toxicity study in rabbits. Interestingly, the 1980 rabbit developmental toxicity study was replaced by a 1991 guideline study, but since the database that the TRI program was using was not updated, the new study was not taken into consideration at that time.

Now, both studies have been replaced by newer, more comprehensive guideline studies. Furthermore, formal supplements to the original studies have been able to clarify the relevance of the original observations in the older studies. This expanded scientific information on the developmental and reproductive effects of chlorsulfuron has recently led the U.S. EPA to conclude that chlorsulfuron is neither a developmental or reproductive toxicant under U.S. EPA's Community Right-to-Know Toxic Chemicals Release Reporting criteria (US EPA, 2013). Details of the U.S. EPA decisions on chlorsulfuron, including the Agency's summary documents were provided in our February 25, 2014 letter to OEHHA, which has been provided to the members of the DART-IC (TSG, 2014).

EXECUTIVE SUMMARY

This summary is separated into the three endpoints that will be considered by the DART-IC; developmental toxicity, female reproductive toxicity, and male reproductive toxicity.

Developmental toxicity considerations:

The developmental toxicity database for chlorsulfuron, involves studies performed in rabbits and rats. A cursory review of a 1980 rabbit study led to the developmental toxicity listing by U.S. EPA in 1994 for the TRI listing. New guideline compliant rat and rabbit studies were generated in 1991.

The original 1980 study in rabbits reported a statistically significant, but not dose-dependent increase in resorptions at 75 mg/kg/day. This finding was not repeated in the 1991 developmental toxicity study in rabbits. The original study was deficient in several ways in comparison to current guidelines, including the fact that the number of animals used per group was low. While most regulatory bodies have disregarded the 1980 rabbit study in favor of the more robust 1991 study, OEHHA's interest in this study has led to further analysis of the older study, resulting in a supplemental report. Since the number of animals per group is low in the 1980 report, the historical control data become more relevant. Thus, the chlorsulfuron resorption data have been compared to the historical control data in the supplemental report. Decisions on what animals to include or exclude in the calculations were reviewed. One key point in assessing resorption data was how to utilize rabbits with 100% resorptions and their impacts in the 1980 study compared to the 1991 study and historical control data. The 1991 study reported animals with 100% resorptions separately. It is not clear how studies included in the historical control data handled animals with 100% resorptions. It is likely that the historical data include both types of resorption data. Thus, the final revised study supplement of the 1980 rabbit study presents resorption data both with and without animals with 100% resorptions included. Based on this analysis, we interpret the increase in resorptions reported at 75 mg/kg/day in the 1980 study to be a spurious finding based on the following:

- It was not dose-dependent;
- It was either within or only slightly exceeding the historical control range; and
- The finding was not repeated in a subsequent developmental toxicity study that used a wider range of doses and a more robust number of animals.

For the 1991 guideline study in rabbits, discussions with OEHHA have led to a reanalysis of decreased fetal body weight. In the 1991 study, chlorsulfuron was tested at doses of up to 400 mg/kg/day in one trial and 1000 mg/kg/day in a second trial. There was a reported decrease in fetal body weight at 400 mg/kg/day. The decrease in fetal weight at 400 mg/kg/day was considered to be not biologically significant in the 1991 report, since it fell within the historical control range and there was no pronounced decrease at the higher dose of 1000 mg/kg/day. While the 1991 study did acknowledge that there were increased numbers of fetuses at 400 mg/kg/day, it did not examine if there was a correlation between the decreased fetal body weight and the number of fetuses in that group. Since it is known that larger litters result in the same nutritional supply being divided between more fetuses, with the possible consequence of lower fetal weights, statistical analyses were recently performed to test if there was a correlation between offspring number and offspring weight. The statistical tests demonstrated

that the decreased fetal weight correlates well with litter size and does not correlate well with dose. Thus, the reanalysis of the data in this study support the position that the lower fetal weights in this study at 400 mg/kg/day do not present evidence for developmental toxicity from chlorsulfuron.

For the 1991 guideline study in rats, the data indicate that there was a decrease in fetal body weight at the highest dose tested, 1500 mg/kg/day. In the study, maternal toxicity was evident in rats at the two highest doses, 500 and 1500 mg/kg/day. At 500 mg/kg/day, clinical signs of vaginal discharge were observed with increasing frequency over controls, and decreased food consumption and decreased weight gain of the dams were observed during some dosing intervals. At 1500 mg/kg/day, vaginal discharge was observed with increasing frequency (observed in 12/25 dams, at 27 observation times), observations of swollen leg, paw and face were noted in a few rats, as were stained and wet perineum and staining in other regions. At this high dose, adjusted final body weight was decreased by 4%, food consumption was 18 to 33% lower than controls over gestation days 7-17, weight gain decreased 50% over gestation days 7-17, and adjusted weight gain was significantly different from control values and was decreased 30% over gestation days 7-22. Finally, two treatment-related deaths occurred at this dose. Given the findings observed in dams at 1500 mg/kg/day, it is clear that maternal toxicity played a role in the decreased fetal weight.

Developmental toxicity conclusions: In view of the developmental toxicity data in rabbits and rats, it has not been clearly shown, through scientifically valid testing, according to generally accepted principles, that chlorsulfuron causes developmental toxicity. The original finding that was suggested to be an indication of developmental toxicity (increased resorptions) was not reproduced when a study using a more robust design was employed. Other potential issues have been clarified to be the result of increases in offspring numbers that were not previously taken into consideration in the case of rabbits and, in the case of rats, maternal toxicity.

<u>Reproductive toxicity considerations:</u>

In a 1981 combined chronic toxicity and reproduction study in rats that tested up to 2500 ppm chlorsulfuron in the diet, no decrease in fertility was observed in the first two generations, but a decrease in fertility to 79% of control values was reported by the author when producing both 3rd generations at the top dose (this study had two matings per generation). The U.S. EPA's cursory Tox One-Liner summary describing this decrease in fertility led to the TRI listing for reproductive effects. Due to multiple deficiencies in the 1981 study, the U.S. EPA required a new, guideline-compliant reproduction study. The study was completed in 2005. Since the trend in reproduction studies has been toward decreasing the number of generations, the new study had two generations. However, the high dose of 7500 was triple the dose in the 1981 study. No test substance-related decrease in fertility was observed in the new study. No indications of toxicity were observed in the extensive examinations of the reproductive organs or in developmental landmarks in either sex in this modern study.

In order to understand the possible reasons for the fertility rate of 79% seen in the 1981 study, and to determine whether the observation was significant, a retrospective analysis was initiated. A comparison of the old study's fertility index to that of control animals from the same era revealed that the fertility rate of 79% was well within the historical control range of the laboratory (historical control fertility index range: 60 to 100%, mean: 88%, S.D.: 11.6%). Finally, the statistical tests recommended by U.S. EPA in its draft 1993 "Standard Evaluation Procedures, Reproductive Toxicity Studies" (US EPA, 1993b), were not in use when the 1981 study was originally reported. Statistical analyses of the 3rd generation data, carried out according to U.S. EPA recommendations, show that there was no statistically significant treatment-related effect on fertility. Further examination of the two matings producing the 3rd generations demonstrated that all females were fertile in at least one of the two pairings performed in the 3rd generation. Three males were unsuccessful in mating in both F3 generations. This finding is in line with in-breeding problems that were reported to Charles River Laboratories (the main breeder of Sprague-Dawley rats), which eventually led Charles River to develop a practice of proving the fertility of males before admitting them into fertility tests. Ultimately, this problem led to the re-derivation of this rat strain. When in-breeding strategies were discontinued, litter sizes normalized.

***Female reproductive toxicity conclusions*:** In view of the reproduction studies with chlorsulfuron, including the retrospective analysis of the 3-generation study that demonstrated that the fertility index was within the historical control range, was not a statistically significant finding and there were no test substance-related changes seen in a guideline study that increased dosing 3-fold, it is clear that chlorsulfuron has not been determined, through scientifically valid testing, according to generally accepted principles, to cause female reproductive toxicity.

***Male reproductive toxicity conclusions*:** In view of the reproduction studies with chlorsulfuron, including a retrospective analysis of the 3-generation study that demonstrated that the fertility index was within the historical control range, was not a statistically significant finding and there were no test substance-related changes seen in a guideline study that increased dosing 3-fold, we can conclude that chlorsulfuron has not been determined through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity.

DETAILED ASSESSMENT OF DEVELOPMENTAL TOXICITY DATA

The developmental toxicity database for chlorsulfuron involves studies performed in rabbits and rats. A 1980 rabbit study by Hoberman et al. led to the developmental toxicity listing by U.S. EPA in 1994 for the TRI listing. Due to numerous deficiencies in the 1980 study, U.S. EPA required a new guideline-compliant rabbit study, which was performed by Alvarez (1991a). In addition, a guideline study in rats was performed by Alvarez (1991b). These studies and their supplements are discussed in this section.

1980 Developmental Toxicity Study in Rabbits (Hoberman et al., 1980) and Supplement (Munley, 2014)

This original rabbit study on chlorsulfuron, along with its associated supplements, was clearly summarized in a table by OEHHA for the DART-IC (OEHHA, 2014). We have added explanations to the table with red text below in Table 1. As indicated in the table, mistakes were made in making the study supplement. The final, corrected version of the supplement is Munley (2014), which is Supplement 1, Revision 2 to the original report by Hoberman et al. (1980).

In Hoberman et al. (1980), artificially inseminated rabbits (16-17 per dose) received gavage doses of 0, 10, 25, or 75 mg/kg bw/day chlorsulfuron in corn oil on gestation days (GD) 6-19, and were sacrificed on GD 29. There was a reduction in maternal body weight gain during dosing that was not statistically significant. Non-adjusted body weight gain at 10, 25, and 75 mg/kg/day were 48, 36, and 47% of control values, respectively. Food consumption was also lower (not statistically significant) in treated animals. Gross pathological changes were noted in 1/16, 3/16, 5/17, and 12/17 rabbits receiving the 0, 10, 25, and 75 mg/kg/day, respectively[1]. The author noted that "findings did appear to increase with treatment level." No statistically significant effects were observed in clinical signs, survival, or implantation efficiency.

In offspring, the mean incidence of resorptions per litter at 0, 10, 25, and 75 mg/kg/day was originally reported as 11.6, 23.9, 13.8, and 31.3% respectively, with the incidence at 75 mg/kg reported as statistically significant. The NOEL for developmental effects was considered by the author to be 25 mg/kg/day.

[1] see Hoberman et al., 1980, pg. 10 and Table 4

Table 1: Summary of Hoberman et al. (1980) by OEHHA, Annotated by DuPont

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/ Sex/ Age) N	Study Design	Exposure (Route/Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Parents	Offspring	
Hoberman 1980 (Haskell Laboratory)	Haskell #12,700 (an off-white powder from E.I. du Pont de Nemours & Co., Inc. (Haskell Laboratory)) (purity not specified by author but reported by CA Department of Pesticide Regulation to be 94%)	Pregnant New Zealand White Rabbits N=66 Group 1:controls, 16 rabbits Group 2: low dose, 16 rabbits Group 3: mid dose, 17 rabbits Group 4: high dose, 17 rabbits	Teratology study	Oral intubation GD 6-19 Vehicle: corn oil	0 (vehicle), 10, 25, 75 mg/kg-d	Maternal body weight change, food consumption, clinical observations, survival, gross pathology, implantation efficiency, offspring viability, and development	Reduced maternal body weight gain and food consumption in all treated groups compared to controls during GD 6-19 Gross pathological changes were noted in 1/16, 3/16, 5/17, and 12/17 does at 0, 10, 25, 75 mg/kg (see Table 4, Hoberman). Reported NOEL = 25 mg/kg-d	Increased resorptions and decreased fetal viability reported at all dose levels (Reported to be significant at 75 mg/kg-d, p value not provided). The p-value was 0.05 (see pg.8). Group mean resorptions of 11.6, 23.9, 13.8, and 31.3% per litter at 0, 10, 25, and 75 mg/kg-d, respectively.	Study not valid based on current methodological standards: incomplete examination of fetuses for visceral & skeletal defects, missing some individual data, no dose analyses, food consumption not recorded after dosing ended, low number of animals.
Hoberman 2010 (Haskell Laboratory) Supplement 1 to Hoberman, 1980	Supplemental analysis of data from Hoberman (1980), reviewing fetal resorption data. States that single conceptus litters are known to be an insufficient number of implantations to support pregnancy in New Zealand White Rabbits based on insufficient hormone production [original study data show 3 pregnancies at 25 mg/kg and 1 at 75 mg/kg with one implantation – 1 pregnancy at each dose level resulted in resorption of the conceptus, and 2 pregnancies at 25 mg/kg each produced a live fetus]. Other justifications for separating these data were: (1) fetal resorption results were not reproducible in subsequent studies at even higher doses (up to 1000 mg/kg/day); and (2) in the current and subsequent developmental toxicity studies in rabbits, there was no other evidence of corroborative developmental toxicity. Note: The Alvarez 1991a study did not include rabbits with total resorptions in its calculation of mean % resorptions per litter, hence the recalculation was a better way to compare studies. When data from totally resorbed litters were excluded (0 in the control and one each in each of the 3 dose groups) group mean resorptions were 11.6, 17.3, 9.7, and 14.8% per litter at 0, 10, 25, and 75 mg/kg-d, respectively [resorbed litter in the 10 mg/kg group had 4 implantations]. Note: Some of these numbers were found to be miscalculations. The author considered the historical control database (mean % resorptions range from 0 - 29.2%) and the author's recalculated resorption rates (excluding resorbed litters), and concluded that dosages of chlorsulfuron as high as 75 mg/kg-d when administered during the period of major organogenesis did not produce developmental toxicity (embryo/fetal toxicity or teratogenicity).								

Hoberman 2011 (Haskell Laboratory) Supplement 1, Revision 1 to Hoberman, 1980	This revision of supplement 1 was done after a calculation error was discovered after the supplement was issued. (In the original supplement, the mean percent resorptions per litter was calculated two ways, either including or excluding the litters with total resorptions in the calculations. The authors considered that the decision of whether to include or exclude totally resorbed litters in the calculations to derive group means for numbers of resorptions per litter or percent resorptions per litter is a consideration that is best made on a case-by-case basis in the context of the entire set of data from a study.) The purpose of Revision 1 of supplement 1 is to provide all data as individual animal data, to correct a calculation error, and to present group means that both include and exclude animals with total resorptions. Hoberman 2011 questioned the fetal resorption data in the Hoberman 1980 study. First, increased fetal resorptions were not seen in a subsequent study (Alvarez 1991~~ba~~) which tested doses up to 1000 mg/kg/day. Second, several of the totally resorbed litters in Hoberman 1980 were quite small and very small litters are often less likely to be sustained given the diminished production of hormones needed to sustain pregnancy. Third, in the current and subsequent developmental toxicity studies in rabbits, there was no other evidence of corroborative developmental toxicity. Therefore, the case was made that exclusion of the totally resorbed litters was warranted and the erroneous calculation yielded a mean value at 75 mg/kg/day that was much closer to that reported for the concurrent control group (i.e., 26% resorptions in the new calculation versus 31.3% in the original; note that the 26% value was revised up to 28% in Munley 2014). The resorption incidence data were similar to background levels, lacked dose dependency, and were not reproducible even at doses of up to 1000 mg/kg/day which warranted reconsideration of the findings from the 1980 study in which there was no other evidence of developmental toxicity. The author stated the weight of evidence justified a revision of the conclusion to reflect that dosages of chlorsulfuron as high as 75 mg/kg/day when administered during the period of major organogenesis did not produce any developmental toxicity (embryo/fetal toxicity or teratogenicity).
Munley 2014 (Haskell Laboratory) Supplement 1, Revision 2 to Hoberman, 1980	This second revision of supplement 1 was done to correct calculations and table entries; also, a literature reference was added to the first paragraph of the following section, "Reason for Revision 1". The corrected calculations resulted from consideration of whether data from selected females should be excluded from the calculations. In Revision 2, data from the female that was found dead on gestation day 18 have been appropriately excluded from all litter mean calculations. The second set of calculations that have been corrected pertain to data from two females in group 4 which were erroneously included previously. For the first female, it was noted at study termination that uterine scars were present which were indicative of pregnancy at some prior time. Since the timing of the prior pregnancy and the identification of any uterine contents is unknown, data from this female should be excluded from all litter mean calculations. For the second female, data from this animal that was euthanized following clinical observations suggestive of abortion recorded on gestation day 28 have been appropriately excluded. The conclusion of Supplement 1, Revision 2 was the same as that of Supplement 1, Revision 1.

*Table from OEHHA, 2014. Red text is DuPont's annotations.

In light of the fact that an increase in resorptions was not observed in the subsequent rabbit study (Alvarez, 1991a), a retrospective analysis of the 1980 resorption data was conducted in which it was compared to the historical database. A case was made that consideration of the data with the exclusion of the totally resorbed litters was warranted based on:

- The fact that the resorption data in the subsequent Alvarez (1991a) study were reported that way;
- The possibility that the historical control data contained data reported this way, or both with and without 100% resorptions included; and
- The fact that it has been reported in the literature that litters with low numbers of implantations may have low hormone production, and thus may not as efficiently support pregnancy in New Zealand White Rabbits (Feussner et al., 1992).

Some of the totally resorbed litters in the Hoberman et al. study were quite small and therefore may have been resorbed as a result of insufficient hormone levels in these animals, rather than from an effect of the test substance.

A comparison of the original resorption data to the historical control data was presented in a Supplement to Hoberman et al. (Munley, 2014). As detailed in Munley (2014), the fetal resorption data from the Hoberman et al. study were analyzed in order to determine if removal of certain data points from calculations was appropriate. One mid-dose doe that had been found dead on gestation day 18 and one high dose female that had uterine scars suggestive of a previous pregnancy were removed from the calculations. One other high dose female that had clinical signs suggestive of abortion on GD28 and had essentially not eaten during dosing was euthanized one day early. These data were not included in the original calculations (it was erroneously added back in an early revision of Supplement 1). With these considerations, the mean percent resorptions in the Hoberman et al. study, excluding litters with 100% resorptions, was reported to be 11.6, 18.0, 8.5, and 28.2% for the control, 10, 25 and 75 mg/kg/day groups, respectively. All are within the historical control range of 0% to 29.2% (Table 2). When the same calculation was made to include fully resorbed litters, the percent resorptions were 11.6, 23.9, 8.5, and 33.7%, respectively.

The mean incidence of resorptions at 75 mg/kg/day either lies within or slightly exceeds the top of the historical control values (Table 2). The increased percent resorptions at 75 mg/kg/day was statistically significant, however, it was not dose dependent, suggesting that it could have been a spurious result. This position is further supported by the fact that fetal resorption results were not reproducible in the subsequent studies at even higher doses (up to 400 and 1000 mg/kg/day in Alvarez, 1991a), and an absence of any other evidence of developmental toxicity in the current and subsequent developmental toxicity studies in rabbits.

Table 2: Mean Incidence (%) Resorptions per Litter from Hoberman et al.(1980) compared to historical control data from Munley (2014)

	Control	10 mg/kg	25 mg/kg	75 mg/kg	Notes
Hoberman et al., 1980	11.6	23.9	13.8	31.3	100% resorbed litters included in calculation; also included a doe at 75 mg/kg/day that was not pregnant but had scar sites from a previous pregnancy.
Munley, 2014 (Supplement 1, Rev. 2)	11.6	23.9	8.5	33.7	100% resorbed litters included in calculation; non-pregnant doe at 75 mg/kg/day with pregnancy scars excluded.
Munley, 2014 (Supplement 1, Rev. 2)	11.6	18.0	8.5	28.2	100% resorbed litters excluded from calculation; non-pregnant doe at 75 mg/kg with pregnancy scars excluded.
Historical Control Data from the Middle Atlantic Reproduction and Teratology Association (MARTA))					
Mean % Resorptions	8.2				
SD	6.5				
Range	0-29.2				

The Hoberman et al. (1980) data, no matter the treatment of fully resorbed litters, lack dose-dependency. The interpretation of the increase in resorptions at 75 mg/kg as spurious and generally within background levels is maintained based on the:

- Similarity of treated groups' resorption level to the historical control data,
- Lack of dose dependency,
- Lack of reproducibility at a dose level more than five to ten times higher than the dose level in question in the replacement study (Alvarez, 1991a), and
- Lack of any other corroborative evidence of developmental toxicity.

Thus, the weight of evidence justifies a revision of the original conclusion of Hoberman et al. (1980) to reflect that doses of chlorsulfuron as high as 75 mg/kg/day did not produce any developmental toxicity.

1991 Developmental Toxicity Study in Rabbits (Alvarez, 1991a) and Supplements

The 1991 developmental toxicity study in rabbits (Alvarez, 1991a) was carried out to replace the outdated, non-guideline study by Hoberman et al. (1980). In this guideline study, the resorption incidence was similar to background levels even at doses of up to 400 and 1000 mg/kg/day (doses that were more than 5- to 10-fold higher than the highest dose in the original 1980 rabbit study). Table 3 below is the clear summary that was produced by OEHHA for the DART-IC (OEHHA, 2014). We have added some comments to the table in red text to clarify several aspects of the study.

Alvarez followed U.S. EPA's guideline, used a greatly expanded dose range and filled in many endpoints that were missing or deficient from the original Hoberman et al. study, including a full examination of fetuses for visceral and skeletal defects, presentation of *all* data, analysis of actual dose, record-keeping with respect to animal food consumption, and a sufficient number of animals.

Table 3: Summary of Alvarez (1991a) by OEHHA, Annotated by DuPont

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/ Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Parents	Offspring	
Alvarez 1991a (Haskell Laboratory)	Chlorsulfuron DuPont Crop Protection 98.2% purity	Main Study Inseminated, New Zealand White Rabbits 5 - 5.5 months old N=20 per group Total N = 100	Teratogenicity study	Gavage, once a day GD 7-19 Vehicle: aqueous 0.5% methyl cellulose (w/v) solution	0 (vehicle), 25, 75, 200, 400 mg/kg-d	Body weights, clinical signs, feed consumption, incidence of pregnancy, litter and fetal parameters, and malformations	Reported that no maternal toxicity was evident No statistical differences in body weight or BW gain, but: - Signif downward trend in BW gain existed on GD7-10, GD13-16. Also: Decreased food consumption: significant trend on days 13-16 and 20-29.	Reported that no fetal toxicity was evident	No biologically meaningful fetal effects.
		Supplemental Study Inseminated, New Zealand White Rabbits 5 - 5.5 mo's old N=20 per group Total N=60	As above	As above	0 (vehicle), 400, 1000 mg/kg-d	As above	Decreased maternal body weight gain on days 7-29 at 400 mg/kg-d; also, signif. decreasing trend in BW gain during this period over dose range*; Signif decrease in adjusted bw gain at 400 and 1000 mg/kg on days 0-29 Maternal toxicity at the highest dose (significant	Reduced fetal weights at 400 mg/kg (but still within range of historical controls); not reduced at 1000 mg/kg; Fetal malformations (double aorta, ventricular septal defect and absent gallbladder) were seen at low frequency at 400 mg/kg-d (1 of each in 3/16 litters). Minor fetal skeletal defects (hemivertebra malformations) at 400 mg/kg-d (with the exception of the one doubled aorta, all findings within range of internal historical	

							incidence of mortality, reduced body weight gain and increased clinical signs at 1000 mg/kg-d)	control). None of the findings at 400 mg/kg seen when retested. Number of dams that aborted was significantly higher in the 1000 mg/kg-d group compared with controls. Decreased sternebra ossification at 1000 mg/kg-d (within range of internal historical controls).	
Mylchreest 2005a (Haskell Laboratory) Supplement 1 to Alvarez 1991a (Volume 4 of Alvarez 1991a)	This supplement to the Alvarez 1991a study report was conducted to add one row of information (percent resorptions per litter) to the reproductive outcome tables for the main study and the supplemental study. For the main study, the percent resorptions per litter were 2.5, 10.5, 8.8, 9.6, and 5.6 for the control, 25, 75, 200, and 400 mg/kg-d dose groups, respectively. For the supplemental study, the percent resorptions per litter were 9.6, 4.1, and 9.4 for the control, 400, and 1000 mg/kg-d dose groups, respectively.								
Lewis 2008 (Haskell Laboratory) Supplement 2 to Alvarez 1991a	Retabulation of data and retrospective statistical analysis of maternal and developmental findings from Alvarez (1991a). Lewis re-evaluated the findings of skeletal variation, partially ossified sternebrae from the main study [incidence reported as 13(6/16), 5(4/17), 10(7/15), 7(4/16), 13(5/16) fetuses (litters affected/total) at 0, 25, 75, 200, and 400 mg/kg/day, respectively] and the supplemental study [incidence reported as 5(1/10), 12(5/13), and 4(2/4) fetuses (litters affected/total) at 0, 400, and 1000 mg/kg/day, respectively], as reported by Alvarez 1991a. The author stated the incidences from all treated groups were low and not statistically different from the concurrent controls. In addition, Lewis reevaluated these findings of skeletal variation and other maternal and developmental findings in the context of historical control data (1983-1994) from multiple studies conducted in the same testing laboratory. Lewis did not consider these results to be test substance-related. The skeletal variations unossified sternebrae and/or partially ossified skull were observed in some treatment groups, but not the concurrent control group. Skeletal variations (unossified and partially ossified sternebrae; partially ossified skull bones) observed in treatment grps were typical of those seen in control rabbits from this lab in the timeframe of this study.								

<table>
<tr><td>Munley 2012a

(Haskell Laboratory)

Supplement 3 to Alvarez 1991a</td><td>Additional statistical analyses to support the interpretation of the fetal body weight data from the main and supplemental studies reported by Alvarez (1991a).

Pairwise analysis indicated that the only group with a mean value that was significantly different from the control group was the 75 mg/kg/day group and only for females. There was no effect on males in either study or when data from both the main and supplemental studies were combined (Alvarez, 1991a).

The original offspring data were tabulated for both males and females. The purpose of the analyses in this Supplement was to determine whether there were any treatment-related changes in male or female fetal weights. Alvarez (1991a) had classified two fetuses at 200 mg/kg/day and one fetus at 400 mg/kg-d as stunted; these animals were excluded in the fetal body weight analyses conducted by Alvarez (1991a), which was standard protocol in this lab at this time, but they were included in the Munley (2012a) fetal body weight analysis. The inclusion of the weights from these fetuses had no significant impact on either the means or the outcome of the analysis. The ANCOVA performed by Munley (2012a) did not identify any test compound-related effects on fetal weight. The ANCOVA verified that fetal body weights were highly dependent on litter size (limited nutrition shared among more offspring). Once litter size was accounted for, the effect of the test compound on fetal body weight was not significant, except in females @75 mg/kg. Because there is no dose-response relationship, this lone significant response was considered spurious.</td></tr>
<tr><td>U.S. EPA 2002a</td><td>* Adjusted maternal body-weight gain was lower than control on days 0-29 at 200 [original study], 400 [original and supplemental studies], and 1000 mg/kg/day [supplemental study] [78%, 54%, 43%, and 43% of control, respectively; also significantly lower on period of days 7-29

<table>
<tr><td></td><td colspan="2">Adjusted bw change</td></tr>
<tr><td></td><td>Days 0-29</td><td>Days 7-29</td></tr>
<tr><td>0</td><td>125</td><td>34</td></tr>
<tr><td>25</td><td>124</td><td>42</td></tr>
<tr><td>75</td><td>169</td><td>62</td></tr>
<tr><td>200</td><td>97</td><td>8</td></tr>
<tr><td>400</td><td>67</td><td>-24</td></tr>
<tr><td></td><td></td><td></td></tr>
<tr><td>0</td><td>202</td><td>90</td></tr>
<tr><td>400</td><td>86</td><td>-25</td></tr>
<tr><td>1000</td><td>86</td><td>-67</td></tr>
</table>

Values from US EPA 2002a, Tables 2a and 2b
Therefore maternal NOAEL= 75 according to US EPA (2002a).</td></tr>
</table>

*Table from OEHHA 2014. Red text is DuPont's annotations.

U.S. EPA's evaluation of the new developmental toxicity study (US EPA, 2002a) concluded that there were no effects of chlorsulfuron on incidence of resorptions, consistent with the author's conclusion. The original 1980 rabbit teratology study (Hoberman et al., 1980) was not further assessed by the U.S. EPA once the replacement study was made available.

The Alvarez (1991a) study was run in two parts, an "original study" and a "supplemental study." In both, female rabbits (20/dose) were artificially inseminated. On gestation days (GDs) 7 through 19, rabbits received 0, 25, 75, 200, or 400 mg/kg/day chlorsulfuron (original study) or 0, 400, or 1000 mg/kg/day (supplemental study) by gavage, in 0.5% methyl cellulose. Does were sacrificed on GD29. The following parameters were examined: body weight, clinical signs, feed consumption, pregnancy rate, litter and fetal parameters, and malformations.

In the original study, there was a significant downward trend in maternal body weight gain on GD 7-10 and on GD 13-16 as well as a significant downward trend in food consumption on GD 13-16 and 20-29. Over the course of the whole study (days 0-29), adjusted maternal body-weight gain in rabbits receiving doses of 200 and 400 mg/kg was noticeably lower than control rabbits. In the supplemental study (Alvarez, 1991a), high-dose animals (1000 mg/kg) displayed frank toxic effects including 35% mortality and a high incidence of clinical signs of toxicity. Additionally, these animals had significantly reduced body weight gains. The supplemental study animals receiving 400 mg/kg/day had significantly lower adjusted body weight gains on days 7-29 compared to controls. According to the U.S. EPA, the adjusted maternal body weight gain was substantially lower than control on days 0-29 at 200, 400 (both studies) and 1000 mg/kg/day. Across both studies, adjusted body weight gains over GD 0-29 were 78%, 54%, 43%, and 43% of control, for dose groups 200, 400 (original study), 400 (supplemental study), and 1000 mg/kg respectively. During GD 7-29 the adjusted body weight gain for dose groups 200, 400 (both studies), and 1000 mg/kg/day was also substantially lower than controls. Adjusted body weight gain over GD 7-29 at 200 mg/kg/day was 24% of the control and body weight change was -24 grams, -25 grams, and -67 grams in both 400 mg/kg/day groups and the high dose group, respectively (US EPA, 2002a).

Alvarez (1991a) determined that the NOAEL for maternal toxicity was 200 mg/kg/day, based on decreased body weight gain. The U.S. EPA determined that the maternal NOAEL was 75 mg/kg/day based on the same endpoint (US EPA, 2002a).

The incidence of pregnancy was higher in both treated groups of the supplemental study than in the control group. The number of pregnant does that aborted (6/17) was significantly higher in the 1000 mg/kg/day group compared with controls (0/13). The per litter mean number of implantations, live fetuses, and live male fetuses were all significantly *higher* at 400 mg/kg/day than in the control.

In the original study's 400 mg/kg/day group, when data on fetal weights were divided by sex, females were statistically lower: 90% compared to controls. In the supplemental study, reduced fetal body weights (90% compared to controls) were observed at 400mg/kg/day when

data for both sexes were pooled. Fetal weights were not reduced at 1000 mg/kg/day; however, there were only four litters at that high dose due to maternal toxicity so the data at this dose may be limited. The decreased fetal weight was reassessed in view of the fact that increased fetal numbers can influence fetal weight as shown below (see summary of Alvarez 1991a by Munley (2012a), below).

Visceral malformations (double aorta, ventricular septal defect and absent gallbladder) were seen at a low frequency at 400 mg/kg/day (3/16 litters) in the original study. This incidence was not significant, but did account for a statistically significant trend. None of these findings reoccurred in the supplementary study at the same dose or at 1000 mg/kg/day. The skeletal finding of hemivertebra seen at 400 mg/kg/day in the original study was also seen at the same frequency in the supplemental study control. Skeletal variations observed in fetuses were partially and unossified sternebrae, fused sternebrae, partially ossified vertebra centrum, bent hyoid and partially ossified skull. Only unossified sternebrae showed a slight increase compared to the concurrent control (0, 0, 1, 2, and 3 in the original study dose groups of 0, 10, 25, 75, and 400 mg/kg/day, respectively). These variations were assessed by comparison to historical control data in Lewis (2008), a supplement to Alvarez (1991a), and, as discussed below, were found to be insignificant.

Alvarez determined the developmental NOAEL to be 1000 mg/kg/day, the highest dose tested.

Supplements to Alvarez (1991a): Supplement 1 (Mylchreest, 2005a); Supplement 2 (Lewis, 2008); and Supplement 3 (Munley, 2012a)

Mylchreest (2005a), Supplement 1 to Alvarez (1991a), was produced merely to present the Alvarez data in terms of mean number of resorptions per litter.

Lewis (2008), Supplement 2 to Alvarez 1991a, re-evaluated the skeletal variation findings and compared the historical control data from the performing laboratory between 1983 and 1994. Skeletal variations of unossified sternebrae and/or partially ossified skull were observed in the treated groups, but not the concurrent control group. According to the historical control data of the laboratory, the skeletal variations noted in the controls of Alvarez (1991a) were atypical and not representative of the range of these variations typically found. Additionally, the incidence of partially ossified sternebrae in controls and treated groups was not statistically different. Lewis (2008) concluded that none of the skeletal variations observed in the Alvarez study were test substance-related. Supplement 2 maintained the developmental NOAEL of 1000 mg/kg/day, the highest dose tested in Alvarez (1991a).

Munley (2012a), Supplement 3 of Alvarez (1991a), tested the hypothesis that the decreased fetal weight observed at 400 mg/kg/day in the 1991 rabbit study may have been due to increased numbers of fetuses. Litter size is routinely used as the covariate in analyses of fetal weight data, since mean fetal weight is highly dependent on litter size. Larger litters tend to

have smaller fetuses whereas smaller litters tend to have larger fetuses. Given the variability in litter sizes in the original study, it was deemed appropriate to perform an analysis of covariance (ANCOVA). Results of the ANCOVA verified that fetal body weights were highly dependent on litter size. Once litter size was accounted for, the effect of the test compound on fetal body weight was not significant, except in females at 75 mg/kg/day, a lone significant response that is considered spurious, rather than treatment-related. The results of the ANCOVA analyses provide quantitative support for the original conclusion that there was no test substance-related effect on fetal body weight at any dose level tested and maintained the developmental NOAEL of 1000 mg/kg/day.

In summary, a developmental toxicity study in rabbits was carried out by Alvarez (1991a) to replace an outdated, less robust study by Hoberman et al. (1980). In Alvarez's guideline study, the resorption incidence was similar to background levels at all dose levels up to 400 mg/kg/d, nor was there any suggestion of increased resorptions in the presence of excessive toxicity at doses of 1000 mg/kg/day (a dose more than 10-fold higher than the highest dose in the original 1980 rabbit study). These findings warrant the reconsideration of the 1980 study, in which no other evidence of developmental toxicity was reported. The decrease in fetal weight in Alvarez (1991a) was shown to be related to the increased number of fetuses at 400 mg/kg/day.

Developmental Toxicity in Rats (Alvarez, 1991b)

Table 4 is the clear summary of the developmental toxicity study in rats completed by Alvarez (1991b) that was produced by OEHHA for the DART-IC (OEHHA, 2014). We have supplemented OEHHA's table with comments in red text.

Table 4: Summary of Alvarez (1991b) by OEHHA, Annotated by DuPont

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/ Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Parents	Offspring	
Alvarez 1991b (Haskell Laboratory)	Chlorsulfuron 98.2% purity	Crl:CD*BR rats 25 inseminated females/group	Teratogenicity study (Guideline developmental toxicity study)	Oral (gavage) GD 7-16 Vehicle 0.5% methyl cellulose (w/v) in distilled water	0, 55, 165, 500,1500 mg/kg/day	Clinical observations, body weights (maternal and fetal) and food consumption External, skeletal, visceral examination of fetuses	Increased vaginal discharge during treatment at 500 (8 dams, observed 10x) and at 1500 mg/kg/day (in 12 dams, observed 27x); reduced body weights, body weight gain, and food consumption, plus wet perineum, swollen limbs & face, adjusted final body weight ↓ 4%, food consumption ↓ (18 to 33% over GD 7-17), weight gain ↓50% over GD 7-17, adjusted weight gain significantly different from control values, ↓ 30% over GD 7-22, two treatment-related deaths at 1500 mg/kg/day (p≤0.05). 500 mg/kg: food consumption decreased significantly on days 9-11, increased on days 17-22 Reported Maternal NOEL = 165 mg/kg/day	Reduced fetal body weights at 1500 mg/kg/day (p≤0.05). No significant increase in malformations in exposed groups. Reported Developmental NOEL = 500 mg/kg/day	Although not statistically significant, less severe reductions in maternal body weight gain and fetal body weights were noted at 500 mg/kg/day Slight to significant effects in dams at 500 mg/kg correspond to these slight (n.s.) effects in fetal endpoints. No fetal effects or trends, even statistically insignificant ones, were reported at 165 mg/kg. Trends in fetal parameters were sometimes significant, but this always relied on the presence of the high dose group

*Table from OEHHA 2014. Red text is DuPont's annotations.

Mated female Crl:CD®BR rats (25 per dose) received gavage doses of chlorsulfuron in a 0.5% aqueous suspension of methyl cellulose at 0, 55, 165, 500, or 1500 mg/kg/day on gestation days (GDs) 7-16. Endpoints evaluated were clinical signs of toxicity, body weight (maternal and fetal), food consumption, and external, skeletal, and visceral examinations of fetuses.

In dams receiving the highest dose, food consumption decreased by 18 to 33% over GD 7-17, weight gain decreased by 50% over GD 7-17, adjusted weight gain was significantly different from control values and decreased by 30% over GD 7-22. Finally, there were two treatment-related deaths at the high dose, as well as observations of vaginal discharge in 12 dams (observed 27 times), stained perineum, alopecia, and swollen limbs and face. At 500 mg/kg, food consumption was statistically significantly lower on days 9-11, and there was a trend for lower food consumption over GD 7-9, 11-13 and 13-15. Less severe reductions in maternal body weight gain were noted at this dose; they were not statistically significant. Adjusted body weight change on GD 1-22 and 7-22 showed significant trends (only when considered with the high dose), and the mean changes for GD 7-22 were significantly reduced. There was an increased incidence of clinical signs during treatment compared to controls, including vaginal discharge in 8 dams (observed 10 times) and alopecia. Based on these observations, the maternal NOAEL was reported as 165 mg/kg/day.

Although a trend in the incidence of litters with malformed fetuses was seen, no significant increase in the incidence of malformations was observed. Similarly, a significant trend with dose existed for mean fetal body weights decreases (total, in males, and in females), however the statistical significance of these trends relied on the presence of the high dose group. No fetal effects or trends, even statistically insignificant ones, were reported at 165 mg/kg. The NOAEL for developmental effects in rats was reported as 500 mg/kg/day.

The author (Alvarez, 1991b) concluded that significant maternal toxicity was evident at lower doses than observations relating to developmental toxicity. The Maternal NOAEL and Developmental NOAEL for rats were 165 mg/kg/day and 500 mg/kg/day, respectively. Maternal toxicity included effects such as alopecia, vaginal discharge, and decreased body weight gain and food consumption at 500 mg/kg/day. These maternal findings were more severe at 1500 mg/kg/day and in addition included swelling of the limbs and face, nasal discharge and 2 treatment-related deaths.

Developmental Toxicity Conclusion: The collective developmental toxicity studies summarized above lead to the conclusion that chlorsulfuron has not been clearly shown through scientifically valid testing, according to generally accepted principles, to cause developmental toxicity.

DETAILED ASSESSMENT OF FEMALE REPRODUCTIVE TOXICITY DATA

The original 3-generation reproductive toxicity study on chlorsulfuron (Wood et al., 1981) was initially interpreted to show decreased fertility in the third generation only. Subsequent assessment of this study, as detailed below, demonstrate that these purported effects on fertility were not significant and fall within the historical control range (Munley, 2012b). Furthermore, an updated EPA-Guideline 2-generation reproductive toxicity study (Mylchreest, 2005b) is also available which demonstrates that chlorsulfuron has no adverse effects on reproduction, including no effect on the fertility index (US EPA, 2007). These studies are described below.

Wood et al. (1981) 3-Generation Reproductive Toxicity Study and Supplement 3 Revision 2 by Munley (2012b)

A brief summary of the 1981 study (Wood et al., 1981) is presented here and below in Table 5, along with an updated supplement to this study which compared the original data to the laboratory's historical control data (Munley 2012b[2]), as well as provided statistical analyses according the U.S. EPA's 1993 draft Standard Evaluation Procedures, Reproductive Toxicity Studies (US EPA, 1993b), which were not routinely practiced in 1981. The table is the same as provided to the DART-IC members in March (OEHHA, 2014) with annotations added by DuPont in red text.

The 3-generation reproductive toxicity study in CD rats was carried out to assess effects of dietary chlorsulfuron on reproductive toxicity (Wood et al., 1981). This study was a part of a combined chronic toxicity study in rats. In the first generation (F0), male and female rats were fed chlorsulfuron at dietary levels of 0, 100, 500, or 2500 ppm for 103 days, at which time 20/sex/dose were bred. Seven days after weaning of the F1a generation, F0 rats were bred a second time and produced the F1b generation. The F1a generation was sexed, weighed, and sacrificed while the F1b generation was sexed, weighed and bred to produce the F2a and F2b generations. In the same manner, the F2b generation was subsequently bred two times, giving rise to the F3a and F3b generations. Dosing continued via the diet throughout the study, and body weights and feed consumption were monitored.

[2] Munley (2010) was originally written as Supplement 3 to Wood (1981) to show historical control data: it was updated in 2011 to provide statistical analyses (Revision 1) and again in 2012 (Revision 2) to provide details on the statistical test and details on reproductive success

Table 5: Summary of Wood et al., 1981 as Presented by OEHHA (2014) and Annotated by DuPont

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/ Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency/ Vehicle)	Doses/ Concen-trations		Systemic Toxicity	Reproductive Toxicity	
Wood 1981	Chlorsulfuron Purity 92-95%	CD® rats, males and females Mated at 90-103 days of age 20/sex/group	3 generation reproduction study (Male and female rats from a two-year feeding study received the chemical in the diet for 103 days and then were allowed to mate for a 15 day period) 6 litters (2 litters per generation) F1a, F1 b F2a, F2b F3a, F3b F1b → F2 generation; F2b - → F3 generation	Oral (diet)	0, 100, 500, 2500 ppm	Food consumption, body weights and weight gains, organ weights and clinical measurements (erythrocyte counts and other hematological effects) from feeding study. For the Reproduction study - Clinical observations, mean number of pups/litter, gestation, lactation and viability indices, litter survival, mean weanling body weights and weight gains Histopathology of organs from 21 day old F3b animals	Decreased body weights and body weight gains in males at 2500 ppm. Short-lived dose-dependent decreases in erythrocyte counts and other hematological effects during the first year of the study observed at 500 and 2500 ppm. Reported Systemic NOEL = 100	Decrease in fertility index at 2500 ppm for F2b animals. 95% in controls vs. 79% for both F2b matings (to produce F3a and F3b groups) Fertility index still within historical control range of 60 to 100%. Reported Reproductive NOEL = 500 ppm	Subpart of combined study (Two-year feeding study and 3 generation reproduction study).

Munley 2011 Supplement 3, Revision 1 to Wood 1981	Supplemental analysis of data from Wood (1981). The following additional material and analyses were provided: 1. Relevant Historical Control Data (1974-1983) to aid in the interpretation of fertility index data from the original study. 2. Conclusions from the additional review and the results of the additional statistical analyses of fertility index data for F3a and F3b (Cochran Armitage Test). 3. Male Fertility index data showing individual matings for F2b animals to result in F3a and F3b to aid in the interpretation of the findings for the third generation. 4. Correction of minor report errors The historical control data for fertility index collected between 1974 and 1983 provided in the supplement ranged from 60-100% (mean = 87.7; SD=11.63). Only 6 of the 12 studies had a third generation and the authors compared the fertility index of the chlorsulfuron study to F1 to F3 values and concluded that all data from the current study fell well within the ranges seen in historical control groups. Results of individual mating data for each pairing of males and females provided in the supplement demonstrate that females unsuccessful in first pairing were successful in subsequent pairings. Authors stated there was no significant lack of mating success in any treatment group by step-down exact permutation Cochran-Armitage test. For males, 3 individuals out of 19 (#257753, #257755, #257757) were found to be unsuccessful in both pairings
Munley 2012b Supplement 3, Revision 2 to Wood 1981	Supplemental analysis of data from Wood (1981). Prepared to clarify information in the previous Revision 1 and to put the study in perspective in view of the more recent multigeneration reproduction study. Details to the statistical analysis section specifying the mating pairs were included in the analysis The authors reiterated the information about the historical data. In the section which provides the Cochran-Armitage trend test calculations, the values for both the asymptotic and exact tests were previously provided as the direct output from the statistical analysis software. In this review, the authors state that for the current data sets, the exact test calculations were the most appropriate given the sample sizes and accordingly, the exact test results were provided and the asymptotic values were removed. Also chi-square analysis was used to analyze fertility data. In the conclusions the authors state that the female fertility indices of all the control and treatment groups on study ranged from 79 to 100%, and were well within the historical control range of 60 to 100%. In addition, they stated that there were "problems in longevity and reproductive performance" in Sprague-Dawley rats as a result of inbreeding practices that were in place around the time of the conduct of the study. The authors concluded that no effects on fertility were evident in the subsequent multigeneration reproductive toxicity study which tested dietary concentrations of up to 7500 ppm, a dose that is three times higher than the highest dose of the 1981 study. They reported that statistical analyses of the Generation 3A and 3B litter data showed no significant treatment effect in any dose group and both the Cochran-Armitage test and a chi-square analysis showed that there were no significant decreases in mating success in any treatment group, both by trend and pair-wise assessments, respectively. The authors mention that for males, 3 individuals #257753, #257755, #257757 were found to be unsuccessful in both pairing and also state that the study was conducted prior to the male proven breeder program (in which all males destined to become breeders would undergo an initial timed mating with a known fertile female and sire a litter before being admitted into the breeding program) possibly explaining the less than optimal fertility in the rats.

*Table from OEHHA 2014. Red text is DuPont's annotations.

The body weights and body weight gain of males of the F0 generation were significantly reduced at the high dose starting before mating and lasting nearly the full span of the two-year chronic study. The body weights of the mid-dose males were also significantly reduced before and after mating. Food efficiency was decreased significantly in males receiving 2500 ppm. There was no significant systemic effect on female rats. The NOEL for systemic toxicity was 100 ppm based on body weight decreases in males. In the production of both F3 generations, the fertility index (# F3 litters delivered/# F2 females mated *100) was 79% versus 95% in controls (see Table 8). Based on the comparison of the fertility index at 2500 ppm to the controls, without the use of the statistical tools the U.S. EPA would later recommend, the author reported a reproductive toxicity NOEL of 500 ppm based on decreased fertility.

Given that there was no effect on fertility observed in the subsequent guideline reproduction study in rats described below (Mylchreest, 2005b) a review of the original 1981 reproduction study was conducted. A supplement with two subsequent revisions was written as the analysis was expanded over time after discussions with OEHHA. First, the original 1981 fertility indices were compared to the historical control data. Later, statistical tests were conducted. All of the information is included in Munley (2012b).

The relevant historical data from the time of the 1981 study, as reported in Munley (2012b), are presented in Table 6 to give perspective on the range of fertility indices seen in rats at that time. The range of control fertility indices in this time period was 60 to 100%, with a mean of 87.7 and a standard deviation of 11.63. The fertility indices of all control and treated groups in the Wood et al. study ranged from 79 to 100%, which is well within the historical control range of 60 to 100% (Munley, 2012b).

Table 6: Historical Control Data from 1974 to 1983 – Rat Fertility Index (Munley, 2012b)

Report ID	Year of In- Life Conduct	F_1A	F_1B	F_2A	F_2B	F_3A	F_3B
HL-432-85	1983	90	75	70	63.2	...	...
HL-524-84	1983	60	60	60	75	...	...
HL-281-84	1983	90	75	94.7	78.9	...	...
HL-422-85	1983	80	77.8	...	...	...	...
HL-436-84	1982	90	85	100	95	89.5	...
HL-294-90	1981	91.4	...	94.7	...	...	...
HL-367-84	1981	95	90	85	95	...	...
HL-**557-81**	**1978**	**95**	**100**	**95**	**100**	**95**	**95**
HL-25-78	1978	90	90	85	75	90	95
HL-353-77	1974	80	...	95	...	100	...
HL-24-74	1974	100	...	100	...	100	...
HL-24-74	1974	95	...	100	...	100	...
	Mean:	88.0	81.6	89.0	83.2	95.8	95.0
	S.D.:	10.13	11.51	12.56	12.61	4.60	0
	Minimum:	60	60	60	63.2	89.5	95
	Maximum:	100	100	100	100	100	95
Overall Mean:	**87.7**						
S.D.:	**11.63**						
Minimum:	**60**						
Maximum:	**100**						

In addition, Munley (2012b) performed statistical analyses of the fertility index data for the first time, as recommended in U.S. EPA's Standard Evaluation Procedure (SEP) (US EPA, 1993b), procedures that are available now but which were not available when Wood et al. was conducted in 1981. In the SEP, fertility index is listed as an endpoint for which statistical analyses are recommended. Both a chi-square test and the Cochran-Armitage Test were performed. The statistical analyses demonstrated that there was no significant lack of mating success in any treatment group ($p \geq 0.05$ for both F3 generations). It is also worth noting that the 2005 replacement study for reproductive effects in rats (Mylchreest, 2005b), which is discussed below, found no compound-related effects on fertility, in spite of a tripling of the dietary concentration over the Wood et al. study. In summary, the statistical analyses in Munley (2012b) of the data from Wood et al. (1981) support the conclusion that the NOEL for fertility effects from dietary exposure to chlorsulfuron was the highest dose tested, 2500 ppm.

2-Generation Reproductive Toxicity Study (Mylchreest, 2005b)

The original 1981 study by Wood et al. followed an old and rarely used combined chronic toxicity study protocol that incorporated a 3-generation reproductive toxicity study. In 2002, the U.S. EPA concluded that the 1981 study was an "unacceptable/non-guideline" study. That study has been replaced by a state-of-the-art 2-generation rat reproduction study (Mylchreest, 2005b).

Mylchreest (2005b) has been evaluated by the U.S. EPA and found to be acceptable (US EPA, 2007). A summary of this guideline reproductive toxicity study is presented in Table 7. This summary table is the one provided to the DART-IC by OEHHA (2014).

In the Mylchreest (2005b) study, chlorsulfuron was fed to 30 Crl:CD®(SD)IGS BR rats/sex/dose at dietary concentrations of 0, 100, 500, 2500, or 7500 ppm. Rats were fed chlorsulfuron diets during a 10-week premating period, then throughout mating, gestation and lactation. Each generation (P[3] and F1) mated and produced only one set of litters (F1 and F2, respectively).

Significant treatment-related effects were limited to decreased body weights and body weight gains, with an accompanying reduction in food efficiency in high-dose males in both the P and F1 generations. There were no effects of chlorsulfuron on survival, clinical signs, organ weights or gross microscopic findings in either generation. There were no significant effects, at any dose, on reproductive parameters, including litter size, live birth index, number born dead, viability and lactation indices, clinical observations, and sex ratio or sexual maturation in F1 pups. Similarly, organ weights were not affected in either generation. No indications of toxicity were observed in the extensive examinations of the reproductive organs or developmental landmarks of vaginal opening. The study authors and the U.S. EPA (2007) concluded that the NOAEL for systemic toxicity was 2500 ppm, based on decreased body weight, body weight gain, and food efficiency. For reproductive toxicity, the NOAEL was the highest dose tested, 7500 ppm.

Table 8 compares the results of the two reproductive toxicity studies on rats with chlorsulfuron, Wood et al. (1981) and Mylchreest (2005b). The Table summarizes the data behind the U.S. EPA's conclusions that there were no effects of chlorsulfuron on the fertility index.

[3] P is equivalent to F0 used in the study by Wood (1981)

Table 7: Summary of Mylchreest, 2005b as Presented by OEHHA (2014)

Reference	Experimental Parameters					Endpoints Assessed	Results (Effects/NOEL/LOEL)		Comments
	Chemical (Source/ Purity/ Preparation)	Animal Model (Species/ Strain/ Sex/ Age) N	Study Design	Exposure (Route/ Period/ Frequency/ Vehicle)	Doses/ Concentrations		Systemic Toxicity	Reproductive Toxicity	
Mylchreest 2005b	Chlorsulfuron (DPX-W4189) technical Purity 97.6%	Crl:CD® (SD)IGS BR rats 30/sex/group for P1 and F1	Guideline two-generation reproduction study 1 litter per generation	Oral (diet) Premating – about 70 days, during mating, gestation and through the study for the two generations	0, 100, 500, 2500, 7500 ppm 100 ppm: M: 6.01 (P1); 9.11 (F1) mg/kg/day F: 6.53 to 12.62 (P1) mg/kg/day; 7.15 to 11.23 (F1) mg/kg/day 500 ppm M:30.1 (P1); 45.9 (F1) mg/kg/day F:32.6 to 61.2 (P1) mg/kg/day; 35.5 to 62.9 (F1) mg/kg/day 2500 ppm M: 151 (P1); 226 (F1) mg/kg/day F:165 to 328 (F0) mg/kg/day;180 to 312 (F1) mg/kg/day 7500 ppm M: 456 (P1); 701 (F1) mg/kg/day F: 498 to 1040 (P1) mg/kg/day; 556 to 972 (F1) mg/kg/day	Parents: clinical signs, food consumption, mortality, sperm parameters, estrous cycle parameters, mating, fertility, gestation length, number of implantation sites, necropsy results, and histology. Pups: clinical signs, survival, weights, developmental landmarks, organ weights, and gross pathology.	Reduction in bodyweight and bodyweight gain at 7500 ppm. Reported Parental NOEL = 2500 ppm (151 to 226 mg/kg/day for males during premating and 165 to 261 mg/kg/day for females during premating and/or gestation)	No adverse effects reported even at highest dose level. Reported Reproductive NOEL = 7500 ppm (456 to 701 mg/kg/day for males during premating and 498 to 810 mg/kg/day for females during premating and/or gestation).	Dose levels estimated by authors for premating, gestation and lactation periods. The test substance-related effects on body weights and body weight gains were noted at ≥500 ppm; however, only effects observed in P1 males at 7500 ppm were statistically significant and considered adverse by authors where overall mean body weight gain (test days 0-105) at 7500 ppm was 11% lower than the control.
							Parents	Offspring	
							As above	No adverse effects reported even at highest dose level. Pup NOEL = 7500 ppm	

*Table by OEHHA (2014).

Table 8. Comparison of Fertility Index Results Obtained From 1981 and 2005 Reproductive Toxicity Studies on Rats with Chlorsulfuron

Dose (ppm)	**0**	**100**	**500**	**2500**	**7500**
Wood et al., 1981: 3-Generation Study CD® Rats					
F1a	95	90	95	95	
F1b	100	95	95	89	
F2a	95	90	85	84	
F2b	100	95	89	100	
F3a	95	100	90	79	
F3b	95	100	100	79	
Mylchreest, 2005b: 2-Generation Study Crl:CD®(SD)IGS BR Rats					
P1	88.5	89.3	93.3	96.7	93.3
F1	81.5	88.5	92.6	96.6	78.6

*Fertility Index = (# litters delivered/# copulated) x 100. Mating Index = (# copulated/# cohabited) x 100. None of the values are statistically significant compared to the control. Please refer to text.

***Female Reproductive Toxicity Conclusion*:** The data generated on the female reproductive effects of chlorsulfuron, as summarized above, lead to the conclusion that chlorsulfuron has not been clearly shown through scientifically valid testing, according to generally accepted principles, to cause female reproductive toxicity.

DETAILED ASSESSMENT OF MALE REPRODUCTIVE TOXICITY DATA

Chlorsulfuron is not identified as a male reproductive toxicant under Proposition 65. There are no data that would support including chlorsulfuron on the Proposition 65 list for this endpoint.

Wood et al. (1981) did not identify any male reproductive effects by chlorsulfuron. The study is summarized above in Table 5. The supplement to Wood et al. (1981), Munley (2012b), analyzed the male fertility data of Wood et al. (1981). A summary of this analysis is presented in Table 9 below. Table 9 represents the male fertility outcomes for the F3A and F3B generations at 2500 ppm. The male and female F2 breeders that produced the generation F3a and also produced the F3b generation. However, it should be noted that each female mated in the first pairing was subsequently paired with a different male for the second pairing. The table shows that each female at 2500 ppm had successfully produced a viable litter after at least one of the 2 pairings. The data also show that for 3 of the 5 females that had *not* successfully produced a viable litter in both pairings, the unsuccessful mating was associated with the use of one of three males (IDs 257753, 257755, and 257757) that were unsuccessful in both attempted

matings, regardless of the female utilized. While it is interesting that three of nineteen males (15.8%) mated in the F2b generation did not produce a litter, this finding is in line with in-breeding problems that were being reported to Charles River Laboratories (the main breeder of Sprague-Dawley rats), that eventually led Charles River to develop a practice of proving the fertility of males before admitting them into fertility tests (Charles River Laboratories, 1999). Ultimately, this problem led to the re-derivation of this rat strain. When in-breeding strategies were discontinued, litter sizes normalized.

Table 9: Male Fertility Analysis of Wood et al. (1981), presented in Munley (2012b)

Male Fertility Analysis for F3A and F3B Litter outcomes - 2500 ppm				
	1st Mating		2nd Mating	
Male ID	Female ID	F3A Outcome	Female ID	F3B Outcome
257752	257832	+	257851	+
257753	257833	-	257832	-
257754	257834	+	257833	+
257755	257835	-	257834	-
257756	257836	+	257835	+
257757	257837	-	257836	-
257758	257838	+	257837	+
257759 S.E.	257839	N.M.	257838	N.M
257760	257840	+	257839	+
257761	257841	+	257840	+
257762	257842	+	257841	+
257763	257843	+	257842	+
257764	257844	+	257843	+
257765	257845	+	257844	+
257766	257846	+	257845	+
257767	257847	+	257846	+
257768	257848	+	257847	-
257769	257849	-	257848	+
257770	257850	+	257849	+
257771	257851	+	257850	+

+ delivered a litter
- not pregnant
N.M. male died prior to cohabitation
S.E. sacrificed *in extremis*

The 2005 guideline 2-generation reproductive toxicity study by Mylchreest (2005b), summarized above in Table 7, with expanded examination of male reproductive organs, sperm parameters and delays in preputial separation found no evidence of male reproductive toxicity, including at doses higher than the highest doses tested in Wood et al. (1981). The U.S. EPA

evaluation of the study supported the conclusion that chlorsulfuron does not have an adverse effect on male reproduction (US EPA, 2007). The study author and the U.S. EPA (2007) concluded that the NOAELs for systemic toxicity and (male) reproductive toxicity were 2500 ppm and 7500, the highest dose tested.

Male Reproductive Toxicity Conclusion. The data generated on the male reproductive effects of chlorsulfuron, as summarized above, lead to the conclusion that chlorsulfuron has not been clearly shown through scientifically valid testing, according to generally accepted principles to cause male reproductive toxicity.

CONCLUSIONS

We appreciate the opportunity to provide comments to the DART-IC on chlorsulfuron. The regulatory studies on chlorsulfuron are complex and detailed, as are their supplements, so we hope this summary has been a helpful addendum to the members of the Committee in advance of the May 21st meeting.

Sincerely,

Enclosures
ALL:/DuPont Chlorsulfuron Comments to Mar 14 DART-IC Notice – April 28 2014 FINAL

cc: Dr. Michael Battalora, DuPont Crop Protection
DART-IC members
Dr. Gary Patterson, California Department of Pesticide Regulation
Files

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