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**DuPont Crop Protection:
Chlorsulfuron: Proposition 65:
Request to Delist**

Dr. Joan Denton, Director
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency
1001 I Street
Sacramento, CA 95814

Dear Dr. Denton,

On behalf of DuPont Crop Protection, we are requesting that chlorsulfuron be removed from the list of chemicals established under the Safe Drinking Water and Toxic Enforcement Act of 1986 (Proposition 65). Chlorsulfuron was added to the list on May 14, 1999 as a developmental, male reproductive, and female reproductive toxicant via the "Authoritative Bodies" listing mechanism.

The "authoritative body" cited by the Office of Environmental Health Hazard Assessment (OEHHA) to support listing chlorsulfuron was the United States Environmental Protection Agency (USEPA) and the "decision process" cited was the 1994 addition of chlorsulfuron to the USEPA's Toxic Release Inventory (TRI). Subsequent to this 1994 action by the USEPA, new developmental and reproductive toxicity studies with chlorsulfuron have been conducted. The USEPA has determined that these new studies replace and supersede the previous studies that had been the sole basis of the 1994 TRI decision by the USEPA. Subsequent to their 1994 TRI decision on chlorsulfuron, the USEPA, in a comprehensive process that resulted in the USEPA's 2005 Reregistration Eligibility Decision (RED) on chlorsulfuron, has thoroughly evaluated the scientific data on the developmental and reproductive effects of chlorsulfuron, including both of the original studies that were the basis of the 1994 TRI decision along with several new USEPA-Guideline studies on chlorsulfuron that had been developed subsequent to the TRI decision. The USEPA, in their 2005 RED, no longer uses or even mentions the studies used in their 1994 TRI process and does not conclude that chlorsulfuron is either a developmental or reproductive toxin. The Agency's decisions are based on the unambiguous results of the new scientific data on chlorsulfuron.

Request. For these reasons, we are requesting that OEHHA remove chlorsulfuron from the Proposition 65 list for all three developmental and reproductive toxicity (DART) endpoints using the processes established under California Code of Regulations (CCR) Title 27, Subsections 25306(j) and 25306(h) since, respectively, “the chemical is no longer identified as causing -- reproductive toxicity by the authoritative body” and “scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria” for listing under Proposition 65 .

BACKGROUND AND HISTORY OF CHLORSULFURON UNDER PROP 65

To assist OEHHA staff in assessing our request to delist chlorsulfuron under Proposition 65, this section provides a background on the process to date.

Listing of Chlorsulfuron. Chlorsulfuron was listed under Proposition 65 on May 14, 1999. The general listing was as a “reproductive toxin” (OEHHA 1999c). The subcategories listed for chlorsulfuron were:

1. Developmental toxicant
2. Female reproductive toxicant
3. Male reproductive toxicant

“Authoritative Bodies” Process Used. The listing was processed by OEHHA under the “Authoritative Bodies” provisions of Proposition 65, citing the USEPA as the “authoritative body”. The USEPA is one of five “Authoritative Bodies” recognized under Proposition 65 for reproductive toxicity (27 CCR 25306(l)). For chlorsulfuron, the process included the initial Request for Information, dated October 30, 1998 (OEHHA 1998a), which included OEHHA’s summary of the relevant studies and the rationale for listing chlorsulfuron (OEHHA 1998b), and the February 26, 1999 Notice of Intent to List (OEHHA 1999a) which included a revised summary of chlorsulfuron (OEHHA 1999b).

USEPA’s TRI Process Cited. The USEPA process cited by OEHHA for Proposition 65 was the USEPA’s 1994 Toxic Release Inventory (TRI) program. In 1994, the TRI list was expanded to include new chemical compounds (USEPA 1994a, 1994b). This expansion included chlorsulfuron. The USEPA final rule published in the Federal Register 59(8):1788 *et seq.* (USEPA 1994b) made the following statement regarding chlorsulfuron (the entire text regarding chlorsulfuron is provided here):

“52. Chlorsulfuron (*2-chloro-N-[[4-methoxy-6-methyl-1,3,5-triazin-2-yl]amino]benzenesulfonamide*) (CAS No. 064902-72-3) (FIFRA AI) (Ref. 3). In

a rabbit developmental study, an increased incidence of fetal resorptions was observed at the LOEL of 75 mg/kg/day. The NOEL was 25 mg/kg/day.”

“In a 3-generation rat reproduction study, a decrease in fertility index was observed at 125 mg/kg/day (LOEL). The NOEL was 25 mg/kg/day. EPA believes that there is sufficient evidence for listing chlorsulfuron on EPCRA section 313 pursuant to EPCRA section 313(d)(2)(B) based on the available developmental and reproductive toxicity data for this chemical.” (USEPA 1994b)

USEPA’s TRI Conclusions Based on cursory Compilation Process. The exclusive basis for the TRI program’s conclusion on chlorsulfuron was a minimal review. The document used by TRI staff to make their Proposed Rule (USEPA 1994a) was the “Support Document for the Addition of Chemicals from Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Active Ingredients to EPCRA Section 313.” (USEPA 1993) This document was prepared for the USEPA under a contract. The brief summary presented in this support document for chlorsulfuron was used as the text for the USEPA’s Proposed Rule. The *entire* summary in that document for chlorsulfuron was the following:

“Chemical Name: Chlorsulfuron
[2-chloro-N-[[[4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]benzenesulfonamide]

CAS No.: 064902-72-3

Key Effects: Developmental, reproductive

Developmental: In a rabbit developmental study, an increased incidence of fetal resorptions was observed at the LOEL of 75 mg/kg/day. The NOEL was 25 mg/kg/day (route and duration not reported) (24)

Reproductive: In a 3-generation rat reproduction study, a decrease in fertility index was observed at 125 mg/kg/day (LOEL). The NOEL was 25 mg/kg/day. (24)”

A copy of the relevant pages from this Support Document is enclosed (USEPA 1993).

TRI Support Document’s Evaluation was Limited to a Secondary Source Summary: USEPA’s “Tox Oneliners”. The “Support Document” (USEPA 1993) was prepared for the USEPA Office of Prevention, Pesticides, and Toxic Substances by an outside contractor, ICF, Inc. and Clement International Corporation under USEPA contract 68-D2-0064. Only a single

reference was used by the contractor to come to these conclusions regarding chlorsulfuron. The single reference was an outline computer printout, secondary source document, the USEPA's "Office of Pesticides/HED/SACB "Tox Oneliners" database (sanitized version)" (USEPA 1990).

Two Old (and Ultimately Unacceptable/Non-Guideline) Studies Cited in "Tox Oneliners".

We have enclosed a copy of the USEPA's "Tox Oneliners" (USEPA 1990) that was the sole source document used to prepare the Support Document for the 1994 TRI process (USEPA 1993). Only two studies were cited in this brief summary document, the 1980 rabbit developmental toxicity study and the 1981 3-generation reproductive toxicity study on rats. As discussed below, both of these studies have been subsequently rejected by the USEPA as being incomplete and non-Guideline, and are no longer used by the USEPA for assessing chlorsulfuron. The studies have been replaced with new, Guideline studies. Neither of the new studies has replicated the "results" that were identified in the old "Tox Oneliners" document. Note that these "results" were the *only* "results" used by the USEPA in their 1994 TRI decision.

- *Rabbit Developmental Toxicity Study.* (Hoberman et al. 1980) The "Tox Oneliners" document outlined this 1980 rabbit developmental toxicity study. The Tox Oneliners summary simply lists the study, the doses used, the NOEL, the LOEL, and the developmental effect (increased resorptions). The Tox Oneliners summary does not mention a maternal NOEL or any conclusions that would be included in a typical USEPA Data Evaluation Report (DER) relative to possible developmental fetotoxicity in a study and are required under the regulations for "Authoritative Bodies" listing under Proposition 65 (27 CCR 25306(g)). The Tox Oneliners states that the USEPA Core-Grade for this study is "Minimum", the lowest classification for a study to be considered by the USEPA.
- *3-Generation Reproductive Toxicity Study.* (Wood et al. 1981) The "Tox Oneliners" document (USEPA 1990) outlined this 3-generation reproductive toxicity study. The Tox Oneliners outline for the rat three-generation reproduction toxicity portion of this unusual combined study describes a maternal NOEL at the same dose as the "decreased fertility index" NOEL. Presumably, the decreased fertility index NOEL was used by OEHHA as the bases for listing chlorsulfuron as both a female and male reproductive toxicant under Proposition 65. The Tox Oneliners lacks any information on paternal toxicity and other conclusions that would be included in a complete DER to enable the proper evaluation of potential female and/or male reproductive toxicity such as decreased fertility index. As discussed below, the USEPA has subsequently concluded that this study (Wood et al. 1981) is unacceptable, ceased using the results of this early study due to its numerous study inadequacies, and required a new reproductive toxicity study to be conducted. The new reproductive toxicity study (Mylchreest 2005), as discussed below, clearly illustrates that the fertility index is not impacted by chlorsulfuron.

Proposition 65 Decision by OEHHA was Debated by DuPont. The process that resulted in the listing of chlorsulfuron under Proposition 65 took 8 months to complete from the initial OEHHA Notice on October 30, 1998 that chlorsulfuron was under consideration for listing under Proposition 65 to the final listing on May 14, 1999. During this period, DuPont interacted several times with OEHHA attempting to reverse the proposed listing of chlorsulfuron due to concerns that the TRI “decision” was made using inappropriate studies and an inadequate evaluation process. Though these arguments were not successful at the time, many of the same arguments can now be supported by the existence of the new, superseding studies and documentation of numerous formal decisions by the USEPA subsequent to their 1994 TRI process where the Agency’s decisions on developmental and reproductive effects of chlorsulfuron have been clarified, as detailed below.

CRITERIA FOR DELISTING UNDER PROPOSITION 65.

For compounds such as chlorsulfuron that have been listed under Proposition 65 via the “Authoritative Bodies” mechanism, the regulations establish a process for delisting these compounds. The criteria and process for delisting under Section 27 CCR 25306(j) is:

“(j) Subsequent to the addition of a chemical determined to have been formally identified by an authoritative body as causing cancer or reproductive toxicity to the list of chemicals known to the state to cause cancer or reproductive toxicity, the lead agency shall reconsider its determination that the chemical has been formally identified as causing cancer or reproductive toxicity if the lead agency finds:

- (1) There is no substantial evidence that the criteria identified in subsection (e) or subsection (g) have been satisfied, or
- (2) The chemical is no longer identified as causing cancer or reproductive toxicity by the authoritative body.

Reconsideration may be initiated by the lead agency on its own motion, or on a request from an interested party, including any member of the appropriate Committee. The lead agency shall refer chemicals under reconsideration pursuant to this subsection to the appropriate Committee for a recommendation concerning whether the chemical should continue to be included on the list of chemicals known to the state to cause cancer or reproductive toxicity. Pending such reconsideration, the chemical shall remain on the list.”

For reproductive toxins, the relevant criteria of subsection (g) referred to above is the following (27 CCR 25306(g)(2)):

“(2) Studies in experimental animals indicate that there are sufficient data, taking into account the adequacy of the experimental design and other parameters such as, but not limited to, route of administration, frequency and duration of exposure, numbers of test animals, choice of species, choice of dosage levels, and consideration of maternal toxicity, indicating that an association between adverse reproductive effects in humans and the toxic agent in question is biologically plausible.”

Finally, the regulations under Proposition 65 further clarify the impact of new studies on the “authoritative body” listing mechanism. Subsection 27 CCR 25306(h) states:

“(h) The lead agency shall find that a chemical does not satisfy the definition of "as causing reproductive toxicity" if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria of subsection (g), paragraph (1) or subsection (g), paragraph (2).”

RATIONALE FOR PROPOSING DELISTING OF CHLORSULFURON

We believe that chlorsulfuron satisfies these criteria for delisting an “authoritative body” compound under Proposition 65. The original evaluation by the USEPA in 1994 did not satisfy the criteria established for Authoritative Bodies listing, the USEPA has subsequently evaluated chlorsulfuron and concluded that the compound is neither a developmental nor a reproductive toxicant, and new scientific data are available that were not considered by the USEPA in 1994 that clearly establish that chlorsulfuron does not meet the criteria for listing under Proposition 65. These criteria for delisting can now be documented. The following paragraphs summarize the primary arguments that support our contention that the criteria for delisting have been satisfied.

Delisting Criteria 1: No Substantial Evidence that Scientific Criteria are Satisfied. (27 CCR 25306(j)(1)) Additions to the scientific database on chlorsulfuron, and new, more thorough evaluations of these data by the USEPA compared to the cursory evaluations performed under the USEPA’s TRI process in 1994, illustrate that there is no substantial evidence that the scientific criteria have been satisfied. These supporting factors include:

1. **1980 Rabbit Developmental Toxicity Study No Longer Used.** The 1980 Rabbit developmental toxicity study (Hoberman et al. 1980), cited by the USEPA in their 1990 Tox OneLiners that, in turn, was used by consultants to the USEPA as the source for summarizing chlorsulfuron for the 1994 TRI process, is no longer used for hazard characterization by the USEPA. The study was replaced by a new developmental toxicity study on rabbits in 1991 (Alvarez 1991). Though the new, 1991 study had been submitted to the USEPA prior to the USEPA's TRI process in 1994, it had not been added to the USEPA's Tox Oneliners database that was used in the cursory review leading to the 1994 TRI summary on chlorsulfuron (and, apparently, the USEPA's Tox Oneliners database on chlorsulfuron has not been updated since January 1, 1990, the Tox Oneliners version that was used for the cursory review in 1993. See USEPA 2009). The new 1991 developmental toxicity study on rabbits (Alvarez 1991a) is now the only rabbit developmental toxicity study used by the USEPA for assessing the potential health hazards of chlorsulfuron. As detailed later in this letter, the new study has been evaluated by the USEPA (USEPA 2002a and 2002e). The new study did not find increased resorptions as the Hoberman et al. (1980) study had. The 1980 rabbit study (Hoberman et al. 1980) is no longer even mentioned or noted in the USEPA documents produced over the last 15 years.
2. **1981 Rat 3-Generation Reproductive Toxicity Study No Longer Used.** The 3-generation rat reproductive toxicity study that was cited by the USEPA in their 1994 TRI process (Wood et al. 1981) is not being used for hazard characterization by the USEPA. The Toxicity Chapter for Chlorsulfuron (USEPA 2002e at pg 14) concluded that the original reproductive toxicity study was an "unacceptable/non-guideline" study, and was considered at "datagap" by the Agency, that detailed several reasons for their conclusion and required that a new reproductive toxicity study be generated (USEPA 2002e at pg 6). A NOEL (but not a NOAEL) of 100 ppm was established for the old study by the USEPA based on decreased female fertility (USEPA 2002e at pg 14, USEPA 1981a). The study has been replaced by a state-of-the-art 2005 2-generation rat reproduction study (Mylchreest 2005), as required by the USEPA. As detailed later in this letter, the new reproductive toxicity study clearly illustrates that chlorsulfuron does not have an effect on the fertility index, the effect that was observed in the old study (Wood et al. 1981). Furthermore, the new study does not have any other significant effect on reproductive parameters: the offspring and reproductive NOAELs were both set by the USEPA at the highest dose tested, 7500 ppm (USEPA 2007 at pgs 2 and 18).
3. **Both Adverse Effects Identified by the USEPA in 1994 TRI Process Have Been Rebuked by New Experimentation.** The 1994 TRI process by the USEPA identified two adverse effects for chlorsulfuron from the Tox Oneliners database;

- a. Increased resorptions in rabbits from the 1980 developmental toxicity study (Hoberman et al. 1980), and
- b. Decreased fertility index in rats from the 1981 3-generation reproductive toxicity study (Wood et al. 1981).

Two new studies were required by the USEPA to replace these older studies after the USEPA ultimately determined these old studies were unacceptable and not upgradeable. These new replacement studies have been conducted (Alvarez 1991a and Mylchreest 2005). Neither of these new, USEPA-Guideline studies reproduced the original “adverse effects” summarized in the USEPA’s 1990 Tox Oneliners database. Neither of these new studies was considered by the USEPA in their 1994 TRI process. Also, neither of the old studies used by the USEPA in their 1994 TRI process have been used or cited by the USEPA subsequent to the TRI process, since neither of the old studies is considered sufficiently reliable by the authoritative body. Both new studies establish that the USEPA’s TRI decision no longer satisfies the criteria for listing under Proposition 65, since neither study reproduced the “adverse effects” noted in the earlier studies. Again, the regulations under Proposition 65 (Section 27 CCR 25306(h)) state:

“(h) The lead agency shall find that a chemical does not satisfy the definition of "as causing reproductive toxicity" if scientifically valid data which were not considered by the authoritative body clearly establish that the chemical does not satisfy the criteria of subsection (g), paragraph (1) or subsection (g), paragraph (2).”

4. **Subsequent Thorough Evaluations of Chlorsulfuron by the USEPA Do Not Conclude that Compound is a Developmental or Reproductive Toxin.** The USEPA has recently completed a thorough evaluation of chlorsulfuron, including an extensive hazard characterization, culminating in the 2005 Reregistration Eligibility Decision (RED) (USEPA 2002a, 2002b, 2002c, 2002d, 2002e, 2002f, and 2005). These numerous documents on chlorsulfuron produced by the USEPA support the conclusion that the Agency does not consider chlorsulfuron to be either a developmental or reproductive toxin. For example, the USEPA Second Report of the Hazard Identification Assessment Review Committee (HIARC) “concluded that there is not a concern for pre-and/or postnatal toxicity resulting from exposure to chlorsulfuron.” (USEPA 2002c at pg 5) The detailed conclusions of the HIARC are provided below. The USEPA FQPA Safety Factor Committee (USEPA 2002d) established the hazard-based uncertainty factor at 1X, and the database uncertainty factor at 3X (based on the inadequacy of the old 1981 reproductive toxicity study) in the absence of a replacement reproductive toxicity study at that time. The FQPA Safety Factor Committee concluded (USEPA 2002d at pg 2) that:

“The toxicology database for Chlorsulfuron is not complete. There is a datagap for the 2-generation reproduction study in rats. On July 11, 2002, the HIARC concluded that a developmental neurotoxicity study is not required. HIARC further concluded that an additional 3X database uncertainty factor is needed for the lack of an acceptable 2-generation reproduction study conducted with Chlorsulfuron. Although the existing 3-generation reproduction study [Wood et al 1981] does not satisfy the guideline requirement, the results of that study suggest that the repeated 2-generation reproduction study is unlikely to result in evidence of toxicity more than 3-fold lower than the existing endpoints. Therefore, a 3X database uncertainty factor is protective (HED No. 118601).”

“The HIARC concluded that there is no indication of increased susceptibility (quantitative or qualitative) of rats or rabbits following *in utero* exposure to Chlorsulfuron. The HIARC could not assess susceptibility in the 2-generation reproduction study in rats.”

“The HIARC concluded that there are no residual uncertainties for prenatal toxicity in the acceptable guideline developmental studies with Chlorsulfuron. Although susceptibility could not be assessed in the unacceptable reproduction study, this uncertainty has been accounted for by the application of a database uncertainty factor. Therefore, the hazard-based special FQPA safety factor can be removed (1X) when assessing dietary and nondietary residential exposure resulting from the uses of Chlorsulfuron.” [USEPA 2002d emphasis added.]

Delisting Criteria 2: USEPA No Longer Identifies Chlorsulfuron as a Developmental or Reproductive Toxin. Subsequent to the cursory review of chlorsulfuron under the 1994 TRI process (USEPA 1994a, 1994b), the USEPA has thoroughly evaluated chlorsulfuron (USEPA 2002a, 2002b, 2002c, 2002d, 2002e, 2002f, 2005, 2007). These evaluations do not identify chlorsulfuron as a developmental or reproductive toxin.

1. **USEPA Evaluations in 2002 Indicate that Chlorsulfuron is Not a Developmental or Reproductive Toxin.** Several documents were released in 2002 by the USEPA as part of their thorough “reevaluation” of chlorsulfuron. These documents conclude “that there is no concern for pre- and post-natal toxicity resulting from exposure to chlorsulfuron” (Fed. Reg. 67:52870 (USEPA 2002f), emphasis added) and that “there is no evidence of increased susceptibility [qualitative and quantitative] following *in utero* exposure to chlorsulfuron in either the rat or rabbit developmental toxicity study.” (USEPA 2002c, emphasis added) For the original 3-generation reproductive

toxicity study, the agency concludes that “it was determined that there is low level of concern and no residual uncertainties for the effects (decreased fertility in F3 generation) seen because there was no decrease in fertility in either the F1 or F2 generations, and **the decrease in fertility seen in the F3 generation was minimal and of questionable toxicological significance at the highest dose tested (125 mg/kg/day).**” (USEPA 2002c, emphasis added) These conclusions were drawn by the USEPA’s primary authority on pesticide active ingredients, the Office of Pesticide Programs (in contrast to the TRI process, which was coordinated by a group within the USEPA that has no specific expertise in pesticides nor internal procedures that are designed to thoroughly evaluate the available scientific data). The key documents produced in 2002 by the USEPA as a lead up to the production of the ultimate decision document on chlorsulfuron, the 2005 RED, are:

- a. **Evaluation of New Developmental Toxicity Study in Rabbits.** The USEPA’s Data Evaluation Record (DER) for the 1991 developmental toxicity study in rabbits (Alvarez 1991a) was completed on May 2, 2002 (USEPA 2002a). The USEPA concluded that the maternal toxicity NOAEL was 75 mg/kg/day, based on substantially decreased body weight gain and that the developmental toxicity NOAEL was 200 mg/kg/day, “based on a slight increase in visceral malformations and decreased fetal body weight” described further in the DER as a slight decrease (90% of control). The study was determined to be an acceptable (Guideline) study.

Table 1 compares the results from the two rabbit developmental toxicity studies on chlorsulfuron. The Table illustrates the data behind the USEPA’s conclusion that chlorsulfuron does not increase fetal resorptions (including early and/or late resorptions, either total or per dam resorptions, or the number of litters with resorptions). Increased resorptions was the finding from the original, non-guideline developmental toxicity study on rabbits (Hoberman et al. 1980) that the Tox Onliners (USEPA 1990) cited and was subsequently used as the basis of the developmental effects statement in the 1994 TRI process (USEPA 1994a, 1994b), but that has not been used or cited by the USEPA since that time. It is also worth noting that Fetal Viability, which was decreased at the highest dose (75 mg/kg/day) in Hoberman et al. (1980) was not affected in the new Guideline study, Alvarez (1991a), up until the high dose of 1000 mg/kg/day, where a slight decrease was noted. Also, in Hoberman et al. (1980) the resorption rates (which are highest in the low and high doses) appear to correlate to decreases in body weight gain from days 0 to 29, whereas in Alvarez (1991a), the resorption rates are not impacted by equal decreases in body weight gain during the same period. Finally, note that

the USEPA concludes that, for 1000 mg/kg/day, “the developmental findings at this dose level [lack of effect] are not considered reliable” due to the severe maternal toxicity at this dose level (USEPA 2002a).

Table 1: Comparison of Results Obtained From 1980 and 1991 Developmental Toxicity Studies on Rabbits with Chlorsulfuron

Dose (mg/kg/day)	0		10	25	75	200	400		1000
1980 Study	0		10	25	75				
Resorptions^a									
Number per Dam	0,7		1.4	0.7	1.9				
Mean Incidence (%)	11.6		23.9	13.8	31.3				
Fetal Viability^a (%)	88.5		76.3	79.2	59.8				
Maternal Wt. to Control:									
Maternal body wt. (%) ^b	-		91	92	93				
Maternal body wt. gain (%) ^c	-		48	86	47				
1991 Study (2 Part Study: Original and Supplemental)	0 Orig.	0 Supp.		25 Orig.	75 Orig.	200 Orig.	400 Orig.	400 Supp.	1000 Supp.
Resorptions – Total¹									
Total	3	4		8	5	8	4	4	2
Early	3	3		7	5	7	3	3	0
Late	0	1		1	0	1	1	1	2
Mean Incidence (%)	3.4	9.6		10.5	8.8	9.6	5.6	4.1	9.4
Resorptions per Dam¹									
Total	0.2	0.4		0.5	0.3	0.5	0.3	0.3	0.5
Early	0.2	0.3		0.4	0.3	0.4	0.2	0.2	0
Late	0	0.1		0.1	0	0.1	0.1	0.1	0.5
Litters w Resorptions¹	2	2		1	2	0	1	1	1
Fetal Viability (%)²	95.5	77.2		90.5	94.1	92.8	96.2	95.9	89.5
Maternal Deaths	1	0		0	1	0	0	0	8
Maternal Wt. to Control:									
Maternal body wt. (%) ³	-	-		101	102	99	99	95	96
Maternal body wt. gain (%) ⁴	-	-		99	135	78	54	43	43

1980 Study: Hoberman et al. 1980. 1991 Study: Alvarez 1991a. ^a: From USEPA 1981. ^b: From Table 2 in Hoberman et al. 1980, page 19, day 29 data. ^c: From Table 3 of Hoberman et al. 1980, page 19, days 0-29. ¹: From

Table 3 of USEPA 2002a, page 12. ²: From Table 3 of USEPA 2002a, page 12. Fetal viability = live fetuses/total implantations (nidations). ³: From Table 2c of USEPA 2002a, page 9, day 29 data. ⁴: From Table 2b of USEPA 2002a, page 8-9, days 0-29 data.

- b. **HIARC – First Report.** Chlorsulfuron – Report of the Hazard Identification Assessment Review Committee. June 5, 2002 (USEPA 2002b). The HIARC evaluated the new developmental toxicity studies (Alvarez 1991a and 1991b) and concluded that “there is not a concern for pre- and/or postnatal toxicity resulting from exposure to chlorsulfuron.” and that there “is no evidence of increased susceptibility [qualitative and quantitative] following *in utero* exposure to chlorsulfuron in either the rat or rabbit developmental toxicity study.” The USEPA concluded that no other studies were relevant for their evaluation of chlorsulfuron developmental toxicity, including any studies available in the literature. Clearly, the USEPA was no longer considering the original developmental toxicity study in rabbits (Hoberman et al. 1980) as worthy of contributing to the Agency’s risk assessment of chlorsulfuron.

For both the rat and rabbit developmental toxicity studies, the USEPA concluded that significant maternal toxicity was evident at lower doses than observations relating to developmental toxicity. Maternal NOAEL and Developmental NOAEL for rabbits were set at 75 mg/kg/day and 200 mg/kg/day, and for rats the levels were set at 165 mg/kg/day and 500 mg/kg/day. Maternal toxicity included significant systemic effects, such as decreased body weight gain and food consumption at 500 and 1500 mg/kg/day, 2 treatment-related deaths at the high dose (1500 mg/kg/day), and clinical signs such as vaginal discharge and alopecia in the rat, and decreased body weight gain at 200 and 400 mg/kg/day along with 8 deaths out of 20 test animals in the high dose group (400 mg/kg/day) in the rabbit.

- c. **HIARC – Second Report.** Second Report of the Hazard Identification Assessment Review Committee. July 17, 2002 (USEPA 2002c). In this second HIARC report, the Agency reevaluated the 1981 3-generation reproductive toxicity study on chlorsulfuron in rats because, in the Agency’s first HIARC on chlorsulfuron, the wrong reproductive toxicity study was evaluated, a study on “**bensulfuron**”. However, all other conclusions in the Second HIARC Report remained the same as those in the First Report. The Agency reiterated that “there is not a concern for pre- and/or postnatal toxicity resulting from exposure to chlorsulfuron.” and that there “is no evidence of increased susceptibility [qualitative and

quantitative] following *in utero* exposure to chlorsulfuron in either the rat or rabbit developmental toxicity study.”

Note that the Executive Summary in the Second HIARC Report for the original 3-generation reproductive toxicity study (USEPA 2002c, page 5), states incorrectly that the reproductive NOEL is 100 ppm (5 mg/kg/day). On page 6 of the Second HIARC Report, under “Degree of Concern Analysis and Residual Uncertainties” the NOEL is correctly summarized as being 25 mg/kg/day, based on minimal decreased fertility index in the F3 generation, with the USEPA concluding that the NOAEL could be 125 mg/kg/day, the high-dose level tested. We have enclosed the 1982 DER for the original 3-Generation reproductive toxicity study (USEPA 1982).

- d. **FQPA Safety Factor Committee.** Chlorsulfuron – Report of the FQPA Safety Factor Committee. July 18, 2002 (USEPA 2002d). The 2002 meeting of the Safety Factor Committee came to conclusions regarding the developmental and reproductive effects of chlorsulfuron that are fully consistent with the conclusions of the HIARC. The Committee reiterated the HIARC’s position that the developmental toxicity studies provided no indication that there is a susceptibility to rats or rabbits *in utero* to chlorsulfuron. The hazard-based safety factor was removed (i.e., changed to 1X) as a consequence of this lack of concern. The inadequacies of the old 3-generation reproductive toxicity study (Wood et al, 1981) were balanced by the reasonable anticipation, in the Committee’s mind, that the results of a new reproductive toxicity study would be within 3-fold of the original study.

- e. **Toxicology Chapter for Chlorsulfuron.** USEPA Health Effects Division (HED). July 17, 2002 (USEPA 2002e). Based on the USEPA’s Data Evaluation Records, their HIARC Reports, and the Report of the FQPA Safety Factor Committee, the Health Effects Division (HED) completed their “Toxicology Chapter” for Chlorsulfuron, one of the primary precursors to the USEPA’s ultimate summary document, the RED. The Toxicology Chapter does not conclude that chlorsulfuron is a developmental toxicant, a specific developmental toxicant, a fetotoxic compound, or either a male or female reproductive toxicant. These conclusions are absent for the compound based on the USEPA’s assessment of the studies. The general (non-quantitative) summary of the developmental effects of chlorsulfuron is found on page 12 of the Chapter (USEPA 2002e). It states:

“Adequacy of data base for Developmental Toxicity.: The data base for developmental toxicity is considered complete. In the rat, developmental toxicity was observed at the highest dose tested, 1500 mg/kg/day, based on decreased fetal body weight. Maternal toxicity was observed as an increased incidence of clinical signs [vaginal discharge with associated alopecia]. In the rabbit, maternal toxicity was observed as decreased body-weight gain. Developmental toxicity was indicated by decreased fetal body weight. Mortality was observed in both species at their respective high-dose levels, which were at or above the limit dose, and treatment-related abortions were observed in the rabbit study at the highest dose level also.”

The more detailed Executive Summaries that follow this non-quantitative overview reiterate the conclusions of the Data Evaluation Records and the HIARC Reports; that the Maternal NOELs for the rat and rabbit are lower than the Developmental NOELs (USEPA 2002e, page 13). The Toxicology Chapter reiterates that there is no indication of increased susceptibility following *in utero* exposure to chlorsulfuron (USEPA 2002e, page 4), consistent with previous HED conclusions (e.g., USEPA 2002a, 2002b, 2002c, 2002d), but also expands on the significance of the conclusions, and the relevance of the significant levels of maternal toxicity, in their paragraph on the “Special Sensitivity to Infants and Children” (USEPA 2002e, page 18, emphasis added):

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

The Chapter found the original 3-generation reproductive toxicity study (Wood et al 1981) to be unacceptable, and required the production of a new study, as detailed below. A new reproductive toxicity study on chlorsulfuron was subsequently completed (Mylchreest 2005) and the

USEPA's evaluation of this study in 2007 concluded that there were no specific effects on reproduction (USEPA 2007).

Finally, the Toxicology Chapter establishes the endpoints to be used in the Agency's risk assessments on chlorsulfuron. Several of the "Exposure Scenarios" use the *maternal toxicity* endpoint from the rabbit developmental toxicity study (Alvarez 1991a). This endpoint was selected because the rabbit study had the lowest NOEL of the short-term studies on chlorsulfuron, the *maternal toxicity* NOEL. No concerns were raised about *developmental toxicity* in the selection of the toxicological endpoints for chlorsulfuron.

- f. **Toxicological Summary in Federal Register.** Chlorsulfuron: Pesticide Tolerance. August 14, 2002 (Fed. Reg. 67, No. 157, Pg. 52866 et seq.) (USEPA 2002f). This Federal Register Final Rule summarizes the findings reached in by the USEPA evaluators and committees that we have detailed above (USEPA 2002a, 2002b, 2002c, 2002d, 2002e). Again, the USEPA does not conclude in any way that chlorsulfuron is a developmental or reproductive toxicant or that it is fetotoxic.

2. **USEPA RED in 2005, a Formal Decision Document, Does Not Conclude that Chlorsulfuron is a Developmental or Reproductive Toxin.** The 2005 RED on chlorsulfuron reiterates and is fully consistent with the conclusions and decisions made by the Agency in the 2002 documents listed above. The USEPA's REDs are clearly the "authoritative body's" ultimate decisions on pesticide active ingredients such as chlorsulfuron. The key 2005 document is:

RED. Reregistration Eligibility Decision for Chlorsulfuron. May 20, 2005 (USEPA 2005).

The RED reiterates the conclusions of the 2002 preparatory documents, summarized above. As expected, the RED uses the *maternal toxicity* endpoint from the rabbit developmental toxicity as the lowest effect for short term exposure scenarios. Developmental and reproductive toxicity are not emphasized or even discussed in the RED. The RED refers to the decisions reached in the 2002 documents, summarized above, and refers to the August 14, 2002 Federal Register Summary (USEPA 2002f), as their reference in the RED for the details (USEPA 2005, page 7).

3. **USEPA Evaluation of New Reproductive Toxicity Study Concluded that Chlorsulfuron did Not Result in Reproductive or Developmental Effects.** The USEPA evaluated the new 2-Generation Reproductive Toxicity Study in Rats

(Mylchreest 2005), a process which resulted in a formal, signed Data Evaluation Record (DER) dated June 14, 2007 (USEPA 2007). The DER concludes that the study was acceptable (Guideline) and that there were no significant effects of chlorsulfuron on either F1 or F2 offspring or reproduction and, accordingly, the NOAEL for offspring effects and reproductive effects were both set at the highest dose tested, 7500 ppm. The high dose did result in parental effects (decreased body weight, body weight gain, and food efficiency), but no effects on offspring or reproduction.

Table 2 compares the results of the two reproductive toxicity studies on rats with chlorsulfuron. The Table summarizes the data behind the USEPA's conclusion that there were no effects of chlorsulfuron on the Fertility Index. The Fertility Index is the parameter from the original, non-guideline reproductive toxicity study on rats (Wood et al. 1981) that the Tox Onliners (USEPA 1990) cited and was subsequently used as the basis of the reproductive effects statement in the 1994 TRI process (USEPA 1994a, 1994b), but is no longer used or cited by the USEPA. The 2007 DER by the USEPA was prepared after the 2005 RED on chlorsulfuron, satisfying the final data requirement for assessing chlorsulfuron developmental and reproductive effects and capping the USEPA's conclusion that chlorsulfuron is neither a reproductive or developmental toxicant.

Table 2. Comparison of Results Obtained From 1981 and 2005 Reproductive Toxicity Studies on Rats with Chlorsulfuron

Dose (ppm)	0	100	500	2500	7500
1981 3-Generation Study					
CD® Rats					
Body Weight – Males (g)					
Week 0	119.5	119.5	119.4	119.4	
Week 6	361.9	362.3	349.1 *	344.1 *	
Week 13	491.3	493.0	481.8	471.8 *	
Week 26	580.3	578.9	572.7	554.2 *	
Week 52	695.2	677.1	669.2 *	637.8 *	
Week 76	768.9	748.8	730.5 *	702.9 *	
Week 104	751.1	754.9	710.5	721.2	
Fertility Index					
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	
2005 2-Generation Study					
CrI:CD®(SD)IGS BR Rats					
Body Weight – Males (g)					
Week 0	293.1	294.2	290.6	289.9	291.0
Week 1	339.2	339.9	334.4	332.4	328.0
Week 2	381.1	377.9	370.5	367.3	360.0 *
Week 3	418.0	412.8	406.3	401.4	392.5 *
Week 10	557.7	554.8	544.1	535.4	523.2 *
Fertility Index					
P1	88.5	89.3	93.3	96.7	93.3
F1	81.5	88.5	92.6	96.6	78.6
Mating Index					
P1	86.7	93.3	100	100	100
F1	90.0	92.9	90.0	96.7	93.3

1981 Study: Wood et al. 1981. 2005 Study: Mylchreest 2005. *: Different from control at P ≤ 0.05 level of significance. Fertility Index = (# pregnant/# copulated) x 100. Mating Index = (# copulated/# cohabited) x 100.

CONCLUSIONS

Request to Remove Chlorsulfuron from Proposition 65 List. For the reasons detailed above, we request that OEHHA initiate the process under California Code of Regulations (CCR) Title 22, Subsections 12306(j) and 12306(h) that will ultimately remove chlorsulfuron from the Proposition 65 list for all three developmental and reproductive toxicity (DART) endpoints.

Request for a Meeting. We would like to meet with OEHHA staff to discuss the details of our request and any further information that OEHHA may need to proceed with the delisting process.

Please contact me if you have any questions or need further information.

Sincerely,



Enclosures

ALL:/DuPont Chlorsulfuron Delisting Request 9-10-09.doc

cc: Jacob J. Vukich, DuPont Crop Protection
Jay Schreider, DPR
Files

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