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Arthur L. Lawyer, Ph.D.
President



February 25, 2014

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

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

Dear Dr. Alexeeff,

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). Based on the guidance we have recently received from OEHHA on this matter, we are basing our request on the criteria of Subsection 26306(j)(2) of Title 27 – “the chemical is no longer identified as causing cancer or reproductive toxicity by the authoritative body.” As we have discussed, we are requesting that this request be processed by OEHHA so that it can be considered by the Developmental and Reproductive Toxicant Identification Committee (the DART-IC) during their scheduled meeting of May 21, 2014.

Chlorsulfuron was added to the Proposition 65 list on May 14, 1999 via the “Authoritative Bodies” listing mechanism based on the 1994 classification of chlorsulfuron by the USEPA under the Agency’s Toxic Release Inventory (TRI). The listing of chlorsulfuron under Proposition 65 is as a developmental and female reproductive toxicant.

The same USEPA authority has recently reevaluated chlorsulfuron under the TRI program. The Agency has now concluded that chlorsulfuron is neither a developmental toxicant nor a female reproductive toxicant. The USEPA’s formal conclusion published on December 9, 2013 states that “Based on EPA’s review of the available data, there is no compelling evidence of the acute toxicity, carcinogenicity, reproductive or developmental toxicity, mutagenicity, or other serious chronic toxicity of chlorsulfuron.” Accordingly, the criteria for delisting a compound under Proposition 65 have been satisfied because “the chemical is no longer identified as causing

cancer or reproductive toxicity by the authoritative body.” Further, no other authority body has classified chlorsulfuron as a developmental or reproductive toxicant.

It is our understanding that the DART-IC will be provided copies of the recent USEPA conclusion on chlorsulfuron, the scientific studies used by the USEPA to develop their conclusions, and summary tables of the key studies, using the templates that have recently been established by OEHHA. OEHHA will not be preparing a de-novo Hazard Identification Document for chlorsulfuron.

The purpose of this letter is to request that the delisting process be initiated and, as we have discussed, to provide OEHHA staff with the documents and relevant scientific studies that will be needed for the evaluation of chlorsulfuron by the DART-IC. These documents are being provided in an electronic manner that, hopefully, will be convenient for referencing by DART-IC members, and OEHHA staff alike.

Brief Background of USEPA Conclusions:

Original USEPA Conclusion (1994). The 1994 classification of chlorsulfuron as a developmental and reproductive toxin under the USEPA’s TRI program was based on the USEPA’s “one-liner” evaluations of the old 1980 rabbit teratology and 1981 3-generation reproductive toxicity studies for chlorsulfuron. This TRI classification triggered California’s administrative addition of chlorsulfuron onto the Proposition 65 list as a developmental and female reproductive toxicant.

The totality of the conclusions generated by the USEPA in 1994 was the following statements:

“Chlorsulfuron (2-chloro-N-[[[4-methoxy-6-methyl-1,3,5-triazin-2-yl)amino]carbonyl]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 1994)

The USEPA’s TRI conclusions were based on a cursory evaluation of “one-liner” summaries that were available to a contractor to the USEPA at that time. 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)” USEPA (1993)

This cursory assessment did not consider more appropriate studies on developmental toxicity that had already been generated by DuPont and submitted to the USEPA by 1993.

The above classification of chlorsulfuron under the TRI program stood until the Agency reevaluated chlorsulfuron for this program in 2013.

New USEPA Conclusion (2103). The USEPA’s TRI staff have recently completed a new, comprehensive assessment of chlorsulfuron for TRI classification (USEPA 2013). As a result of this assessment, they have changed their bases for listing chlorsulfuron under the TRI. They have concluded that chlorsulfuron is neither a developmental toxicant nor a reproductive toxicant. Further, they have concluded that chlorsulfuron is not reasonably anticipated to cause any acute or chronic toxicity in humans. The new evaluation by the USEPA concludes:

“Based on EPA’s review of the available data, there is no compelling evidence of the acute toxicity, carcinogenicity, reproductive or developmental toxicity, mutagenicity, or other serious chronic toxicity of chlorsulfuron. While treatment-related body weight changes were observed in some studies, the evidence for these changes is not sufficient to conclude that chlorsulfuron is expected to cause serious or irreversible systemic toxicity. Therefore, chlorsulfuron is not reasonably anticipated to cause acute or chronic toxicity in humans.” (USEPA, 2013)

The USEPA further explained why their new (2013) conclusions regarding chlorsulfuron toxicity to humans differed from the original (1994) conclusion as follows:

“Based on previous EPA hazard characterizations (Refs. 2 and 3; 67 FR 52866, August 14, 2002), there is sufficient evidence to support a low concern for human toxicity from exposure to chlorsulfuron. A more recent guideline (Ref. 14)

study (Ref. 15) was not able to replicate findings from one of the studies upon which the addition of chlorsulfuron to the list of toxic chemicals subject to reporting requirements of EPCRA section 313 and section 6607 of the PPA was based (Ref. 13). Additionally, recent assessments of the studies cited in the listing of chlorsulfuron (Refs. 11 and 13) question the validity of these studies' methods and conclusions (Ref. 2; 67 FR 52866, August 14, 2002)."

"Additionally, no studies that strongly suggest either acute or chronic toxicity of chlorsulfuron were identified in the literature since the publication of the RED for chlorsulfuron (Ref. 3). A relatively recent guideline (Ref. 14) study (Ref. 19) was not able to replicate findings from another one of the studies upon which the addition of chlorsulfuron to the EPCRA section 313 toxic chemical list was based (Ref. 11). The reported findings from the other additional studies (Refs. 20, 21, and 22) were of very limited use in the determination of hazard for chlorsulfuron due to the study deficiencies previously outlined. While treatment-related body weight changes were observed in the Mylchreest study (Ref. 19), these changes were observed at a relatively high dose level (close to 500 mg/kg/day) and were observed in the absence of any other treatment-related effects." (USEPA, 2013)

Note that the new evaluation of chlorsulfuron by USEPA under the TRI program (USEPA, 2013) cites the analogous evaluation and conclusions drawn by the USEPA's Office of Pesticide Programs (USEPA, 2005; cited as "Ref. 3" in the new USEPA evaluation document). Both USEPA documents come to similar conclusions regarding the developmental and reproductive toxicity of chlorsulfuron.

Finally, it is also worth noting that this reevaluation and conclusion were generated in response to a Petition to the USEPA by DuPont Crop Protection, requesting that the Agency delete chlorsulfuron from the TRI list altogether. And though the USEPA agreed that the original criteria for listing – the potential toxicity to humans by development and reproductive effects – was no longer scientifically reasonable, chlorsulfuron was retained on the TRI list, nonetheless, due to the toxicity of chlorsulfuron to aquatic plants (which is not surprising given that chlorsulfuron is used commercially as a herbicide). The USEPA conclusions regarding aquatic plant toxicity are as follows:

"Chlorsulfuron has low toxicity to most aquatic and terrestrial animals. However, chlorsulfuron is highly toxic to some species of aquatic plants."

"EPA is denying the petition to delete chlorsulfuron from the EPCRA section 313 list of toxic chemicals. This denial is based on EPA's conclusion that chlorsulfuron can reasonably be anticipated to cause toxicity to aquatic plants. Chlorsulfuron has been shown to have an adverse effect on aquatic plant growth at very low

concentrations with an EC50 of 3.5×10^{-4} mg/L for duckweed and an EC50 of 0.05 mg/L for green algae as well as EC50 of 0.609 mg/L for blue green algae. Therefore, EPA has concluded that chlorsulfuron meets the EPCRA section 313(d)(2)(C) listing criteria based on the available environmental toxicity data.” (USEPA, 2013)

Relevant Documents on the Developmental and Reproductive Effects of Chlorsulfuron, Including Those Cited by USEPA in their 2013 Evaluation of Chlorsulfuron:

For the convenience of the members of the DART-IC and OEHHA staff, we have enclosed two searchable CDs. The CDs contain all the documentation and studies that will be relevant to the DART-IC evaluation of chlorsulfuron during the May 21 2014 meeting. The two CDs have the following material:

- **CD-1: Public Documentation:** This includes the documents, evaluations, and decisions produced by the US EPA, published scientific literature cited by US EPA that are relevant to developmental and reproductive toxicity, and this letter. For your convenience, all enclosed references can be “clicked” to within the cover letters and EPA decision documents.
- **CD-2: Proprietary Scientific Studies.** This disc includes the 5 key studies on chlorsulfuron developmental and reproductive effects, in their entirety. The EPA decision document and this letter are also enclosed so the members of the DART-IC and OEHHA staff can easily “click” onto the studies and supplements that they want to further assess.

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. These proprietary studies are noted in the following reference list.

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.

CD-1: Public Documentation.

USEPA, 2013. Chlorsulfuron; Community Right-to-Know Toxic Chemical Release Reporting. Federal Register 78:73787-73793. *[NOTE to DART-IC: Publically available references that are relevant to the development and reproductive toxicity of chlorsulfuron are “clickable”.]*

DuPont Crop Protection, 2012. Petition to Delete Chlorsulfuron from TRI List. DuPont Crop Protection (DuPont), Technology Sciences Group Inc. (TSG). May 18, 2012. *[NOTE to DART-IC: Publically available references that are relevant to the development and reproductive toxicity of chlorsulfuron are “clickable”.]*

USEPA Documents Utilized in USEPA’s 2013 Reevaluation of Chlorsulfuron:

USEPA, 2002a. Toxicology Chapter for Chlorsulfuron. Health Effects Division, Office of Pesticide Programs. July 17, 2002.

USEPA, 2002b. Data Evaluation Record. Prenatal Developmental Toxicity Study – Rabbits. Citation: Alvarez, L. (1991). Teratogenicity study of DPX-W4189-165 (Chlorsulfuron) in Rabbits. Haskell Laboratory for Toxicology and Industrial Medicine. No. HLR 306-90. August 12, 1991. Evaluation Date: May 2, 2002. Reviewer: Linda Taylor. TXR#: 0050460. P.C. Code: 118601.

USEPA, 2005. Reregistration Eligibility Decision for Chlorsulfuron. Office of Pesticide Programs. May 20, 2005.

USEPA, 2007. Data Evaluation Record. Reproduction and Fertility Effects Study – Rat. Citation: Mylchreest, E. 2005. Chlorsulfuron (DPX-W4189) Technical: Multigeneration Reproduction Study in Rats. DuPont Haskell Laboratory for Health and Environmental Sciences. Project No. DUPONT 13495, 14601, 904. Reviewer: Linda L. Taylor. Evaluation Date: June 14, 2007. MRID 46493201.

USEPA – OEI, 2013. Memorandum from Jocelyn Hospital, Toxicologist, Analytical Support Branch to Daniel Bushman, TRI Petitions Coordinator and Chemical List Manager, Analytical Support Branch. April 24, 2013. Subject: Review of Chlorsulfuron Studies Published Since Publication of the Reregistration Decision for Chlorsulfuron.

Other Public Documents Utilized in USEPA's 2013 Reevaluation of Chlorsulfuron that are Potentially Relevant to Developmental and Reproductive Effects:

Rakitsky, V.N. and Beloyedova, N.S. 2009. Toxicity and Hazardousness of Sulfonylurea Herbicides. *Toxicology Herald* 4: 25 – 30. *Translated from Russian.*

Rudaya, P.L., and Zhminko, P.G. 2009. Toxic Properties of Chlorsulfuron Potassium Salt Herbicide Administered Once Orally to Mammals. *Modern Problems of Toxicology* 2: 59 – 65. *Translated from Ukrainian.*

Rudaya, P.L., Zhminko, P.G., Povyakel, L.I., and Reshavska, O.V. 2010. Toxicodynamics of Chlorsulfuron Potassium Salt Given Orally In Long-Term Experiment on White Rats. *Modern Problems of Toxicology* 1: 59 – 63. *Translated from Ukrainian.*

Other USEPA Historical Documents Relevant to the Original Listing of Chlorsulfuron Under Proposition 65

USEPA, 1993. Support Document for the addition of chemical from Federal Insecticide, Fungicide, Rodenticide Act (FIFRA) active ingredients to EPCRA Section 313. Prepared by ICF, Inc and Clement International Corporation. EPA Contract No. 68-D2-0064.

USEPA, 1994. TRI Final Rule. Addition of Certain Chemical; Toxic Chemical Release Reporting; Community Right-to-Know. Final Rule: Federal Register 59(229):61432-61485. November 10, 1994.

CD-2: Proprietary Scientific Studies.

USEPA, 2013. Chlorsulfuron; Community Right-to-Know Toxic Chemical Release Reporting. Federal Register 78:73787-73793. *[NOTE to DART-IC: Proprietary scientific studies that are relevant to the development and reproductive toxicity of chlorsulfuron are "clickable".]*

DuPont Crop Protection, 2012. Petition to Delete Chlorsulfuron from TRI List. DuPont Crop Protection (DuPont), Technology Sciences Group Inc. (TSG). May 18, 2012. *[NOTE to DART-IC: Proprietary scientific studies relevant to the development and reproductive toxicity of chlorsulfuron are "clickable".]*

1980 Developmental Toxicity Study in Rabbits (including Supplements)

Hoberman AM, Wolfe GW, Durluo RS, 1980. Chlorsulfuron (DPX-W4189) Technical: Teratology Study in Rabbits. Laboratory ID HLO-534-80. Original Date July 17, 1980.

Hoberman AM, Wolfe GW, Durloo RS, 1980, Supplement 1, 2010. Chlorsulfuron (DPX-W4189) Technical: Teratology Study in Rabbits. Laboratory ID HLO-534-80. Original Study Date: July 17, 1980. Supplement 1 Date: June 16, 2010.

Hoberman AM, Wolfe GW, Durloo RS, 1980, Supplement 1, Revision 1, 2011. Chlorsulfuron (DPX-W4189) Technical: Teratology Study in Rabbits. Laboratory ID HLO-534-80. Original Study Date: July 17, 1980. Supplement 1, Revision 1 author: S. M. Munley. Supplement 1, Revision 1 date: October 27, 2011.

Hoberman AM, Wolfe GW, Durloo RS, 1980, Supplement 1, Revision 2, 2014. Chlorsulfuron (DPX-W4189) Technical: Teratology Study in Rabbits. Laboratory ID HLO-534-80. Original Study Date: July 17, 1980. Supplement 1, Revision 2 author: S. M. Munley. Supplement 1, Revision 2 date: February 24, 2014.

1981 Reproductive Toxicity Study (including Supplements)

Wood CW, Wollenberg EJ, Turner DT, 1981. Long-Term Feeding Study with 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl]benzenesulfonamide (IN-W4189) in Rats. Laboratory ID: HLR-557-81. Original Study Date: October 8, 1981.

Wood CW, Wollenberg EJ, Turner DT, 1981, Supplement 3, Revision 1, 2011. Long-Term Feeding Study with 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl]benzenesulfonamide (IN-W4189) in Rats. Laboratory ID: HLR-557-81. Original Study Date: October 8, 1981. Supplement 3, Revision 1 author: SM Munley. Supplement 3, Revision 1 date: January 14, 2011.

Wood CW, Wollenberg EJ, Turner DT, 1981, Supplement 3, Revision 2, 2012. Long-Term Feeding Study with 2-Chloro-N-[(4-methoxy-6-methyl-1,3,5-triazin-2-yl)aminocarbonyl]benzenesulfonamide (IN-W4189) in Rats. Laboratory ID: HLR-557-81. Original Study Date: October 8, 1981. Supplement 3, Revision 2 author: SM Munley. Supplement 3, Revision 2 date: February 1, 2012.

1991 Developmental Toxicity Study in Rabbits (with Supplements)

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.

Alvarez L, 1991a. Supplement 2, 2008. Teratogenicity study of DPX-W4189-165 (Chlorsulfuron) in Rabbits. Supplement 2. DuPont Haskell Laboratory for Toxicology and Industrial Medicine. Study ID No.: HLR 306-90. Supplement 2 author: Joseph M. Lewis. Completion Date: August 23, 2008.

Alvarez L, 1991a. Supplement 3, 2012. Teratogenicity study of DPX-W4189-165 (Chlorsulfuron) in Rabbits. Supplement 3. DuPont Haskell Laboratory for Toxicology and Industrial Medicine. Study ID No.: HLR 306-90. Supplement 3 Author: S. M. Munley. Completion Date: February 1, 2012.

1991 Developmental Toxicity Study in Rats

Alvarez L, 1991b. Teratogenicity study of DPX-W4189-165 (Chlorsulfuron) in Rats. DuPont Haskell Laboratory for Toxicology and Industrial Medicine. Study ID No. HLR 734-90. MRID 41976406.

2005 Reproductive Toxicity Study in Rats

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

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,



Enclosures
ALL:/DuPont Chlorsulfuron Delist Ltr to OEHHA – Feb 25 2014.docx

CC: C. Oshita, OEHHA
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