



December 16, 2013

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**RE: Comments submitted by Syngenta Crop Protection, LLC. Concerning Chlorothalonil
Nomination to the National Toxicology Program Carcinogen List: National Institutes of
Health: NIH_FRDOC_0001-8332**

Dear Dr. Ruth Lunn:

Again, Syngenta appreciates the opportunity to comment on the nomination of chlorothalonil to the NTP carcinogen list (RoC) as posted in NIH_FRDOC_0001-8332. As mentioned in the letter from Syngenta Crop Protection, LLC. on October 17th, Syngenta is representing its affiliate, GB Biosciences, Inc., as one of the producers of chlorothalonil.

For more than 45 years, as Chlorothalonil continues to be an important grower tool to help manage fungicide resistance, EPA has carefully re-evaluated chlorothalonil's environmental and human safety under the Federal Insecticide, Fungicide and Rodenticide Act (FIFRA), numerous times, sometimes during consideration of a new crop use, sometimes when considering use direction changes on the label and during the scheduled reregistration review cycle. In fact, Chlorothalonil is currently going through its registration review process at EPA (see Appendix 1 for the EPA work plan schedule). Re-evaluation also occurs for registered uses in Canada, Mexico, Brazil and Europe.

During these periods of extensive evaluation, EPA (similar to IARC) concluded the following about chlorothalonil:

- Chlorothalonil induces forestomach and kidney tumors in rodents following chronic daily oral administration at a concentration that is orders of magnitude greater than what a human would be exposed to.
- There is a similar view among USEPA and international agencies that rodent forestomach tumors are not relevant to humans and should not be considered in human health risk assessments.
- The chlorothalonil mode of action leading to tumor formation in the rodent kidney has been extensively studied and is well understood.
- The USEPA has concluded that mechanistic data support a non-genotoxic, threshold-based tumor mode of action in the rodent kidney and uses a margin of exposure (MOE) approach for assessing human cancer risk for chlorothalonil.

Syngenta appreciates the opportunity to provide toxicology data citations that demonstrate the expansive database relevant to determining the carcinogenicity of chlorothalonil and upon which EPA based their conclusions (Appendix 2). Further evaluation or review would consume Governmental resources that duplicate review efforts already performed, or currently are being performed by EPA and would not further inform. Therefore, chlorothalonil should not be considered a candidate for NTP evaluation.

In closing, Syngenta would like to thank NIH, NTP for the opportunity to comment. Please contact me by telephone at 336-632-7477 or by email at adora.clark@syngenta.com if you have any questions.

[Redacted]

Adora Clark, Ph.D.,
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APPENDIX 1 EPA Registration Review Final Work Plan for Chlorothalonil

| Registration Review for Chlorothalonil– Projected Registration Review Timeline | |
|---|---------------------------------|
| Activities | Estimated Date |
| Opening the Docket | |
| Open Docket and 60-day Public Comment Period | 2012 – March - Completed |
| Close Public Comment | 2012 – May - Completed |
| Case Development | |
| Final Work Plan | 2012 – Aug. – Sept. - Completed |
| Issue DCI | 2013 – April – June |
| Data Submission | 2015 – April – June |
| Open 30-day Public Comment Period for Draft Risk Assessments | 2016 – Oct. – Dec. |
| Close Public Comment Period | 2017 – Jan. – March |
| Registration Review Decision | |
| Open 60-day Public Comment Period for Proposed Registration Review Decision | 2017 – April – June |
| Close Public Comment Period | 2017 – July – Sept. |
| Registration Review Decision and Begin Post-Decision Follow-up | 2018 |
| Total (years) | 6 |

APPENDIX 2 Toxicology Data Citations

- 00030286 Campbell, L.A.; Olin, S.S.; Robens, J.F.; et al. (1980) Bioassay of Chlorothalonil for Possible Carcinogenicity. (Unpublished study including letters dated Aug 7, 1979 and Oct 24, 1979 from M.S. Weinberg to Joseph A. Ignatoski, received Feb 19, 1980 under 677-313; prepared by Tracor Jitco, Inc. and others, submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, Ohio; CDL:099243-B)
- 00030288 Kouri, R.E.; Parmar, A.S.; Kuzava, J.M.; et al. (1977) Activity of DTX-77-0033 in a Test for Differential Inhibition of Repair Deficient and Repair Competent Strains of Salmonella typhimurium: Repair Test. Final rept. (Unpublished study received Feb 19, 1980 under 677-313; prepared by Microbiological Associates, submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, Ohio; CDL:099243-D)
- 00030289 Kouri, R.E.; Joglekar, R.; Fabrizio, D.P.A. (1977) Activity of DTX-77-0034 in an in vitro Mammalian Cell Point Mutation Assay. Final rept. (Unpublished study received Feb 19, 1980 under 677-313; prepared by Microbiological Associates, submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, Ohio; CDL: 099243-E)
- 00030290 Kouri, R.E.; Parmar, A.S.; Kuzava, J.M.; et al. (1977) Activity of DTX-77-0035 in the Salmonella/Microsomal Assay for Bacterial Mutagenicity. (Unpublished study received Feb 19, 1980 under 677-313; prepared by Microbiological Associates, submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, Ohio; CDL:099243-F)
- 00030291 Shirasu, Y.; Moriya, M.; Watanabe, K. (1977) Mutagenicity Testing on Daconil in Microbial Systems. (Unpublished study received Feb 19, 1980 under 677-313; prepared by Institute of Environmental Toxicology, submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, Ohio; CDL:099243-G)
- 00044728 Legator, M.S. (1974) Report on Mutagenic Testing with Dac 3701. (Unpublished study including submitter summary, received Dec 8, 1976 under 677-313; prepared by Brown Univ., Div. of Biological and Medical Sciences and Roger Williams General Hospital, submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, Ohio; CDL:095783-G)
- 00047936 Hastings, T.F.; Stemmer, K.L. (1975) 120-Day Dietary Toxicity Study--Rats: Dac-3701: Project No. 24-051. Final rept. (Unpublished study including submitter summary, received Dec 8, 1976 under 677-313; prepared by Bio/Tox Research Laboratories, Inc., submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, Ohio; CDL:095783-A)
- 00047940 Hastings, T.F.; Stemmer, K.L. (1975) 90-Day Toxicity Study-Dogs: Dac-3701. Final report (Unpublished study including submitter summary, received Dec 8, 1976 under 677-313; prepared by Bio/Tox Research Laboratories, Inc., submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, Ohio; CDL:095783-F)
- 00047941 Legator, M.S. (1975) 4-Hydroxy 2,5,6-trichloroisophthalonitrile: Mutagenicity Investigation (Dominant Lethal). (Unpublished study received Dec 8, 1976 under 677-313; prepared in cooperation with Brown Univ., Div. of Biological and Medical Sciences and Roger Williams General Hospital, submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, Ohio; CDL:095783-H)

APPENDIX 2 Toxicology Data Citations (Continued)

- 00114034 Holsing, G.; Voelker, R. (1970) 104-week Dietary Administration-- Dogs: Daconil 2787 (Technical): Project No. 200-206. Final rept. (Unpublished study received Sep 1, 1971 under 1F1024; prepared by TRW, Inc., submitted by Diamond Shamrock Chemical Co., Cleveland, OH; CDL:091899-A)
- 00127846 Price, P.; Killeen, J.; Ignatoski, J. (1980) Cell Transformation Assay with DS-3701: Document No. 041-5TX-80-0015-003. (Unpublished study received Apr 21, 1983 under 677-313; submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, OH; CDL: 071525-F)
- 00127848 Ford, W.; Laveglia, J.; Killeen, J.; et al. (1983) A Two Year Toxicity and Tumorigenicity Study of DS-3701 in Rats: Document No. 100-5TX-80-0016-007. (Unpublished study received Apr 21, 1983 under 677-313; submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, OH; CDL:071527-E; 071528; 071529)
- 00127849 Ford, W.; Killeen, J.; Ignatoski, J.; et al. (1982) A Chronic Dietary Study in Mice with DS-3701: Document No. 098-5TX-78- 0024-001. (Unpublished study received Apr 21, 1983 under 677-313; submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, OH; CDL:071531-A; 071532; 071533; 071534; 071548; 071530)
- 00127850 Wilson, N.; Killeen, J.; Ignatoski, J.; et al. (1981) A 90-day Toxicity Study of Technical Chlorothalonil in Rats: Document No. 099-5TX-80-0200-006. (Unpublished study received Apr 21, 1983 under 677-313; submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, OH; CDL:071535-E; 071536)
- 00127852 Colley, J.; Syred, L.; Heywood, R.; et al. (1983) A 13-week sub-chronic Toxicity Study of T-117-11 in Rats (Followed by a 13- week Withdrawal Period): Diamond Document No. 562-5TX-81-0213- 003. (Unpublished study received Apr 21, 1983 under 677-313; prepared by Huntingdon Research Center, Eng., submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, OH; CDL: 071537-D; 071538)
- 00127853 Mizens, M.; Killeen, J.; Ignatoski, J. (1983) The Micronucleus Test in the Rat, Mouse and Hamster Using Chlorothalonil: Document No. 000-5TX-81-0024-004. (Unpublished study received Apr 21, 1983 under 677-313; submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, OH; CDL:071539-E)
- 00127854 Mizens, M.; Killeen, J.; Ignatoski, J. (1983) The Chromosomal Aberration Test in the Rat, Mouse and Hamster Using Chlorothalonil: Report Document No. 000-5TX-81-0025-004. (Unpublished study received Apr 21, 1983 under 677-313; submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, OH; CDL:071539-F)
- 00127858 Tierney, W.; Wilson, N.; Killeen, J.; et al. (1983) A Chronic Dietary Study in Mice with Technical Chlorothalonil: Document No. 108-5TX-79-0102-004. (Unpublished study received Apr 21, 1983 under 677-313; submitted by Diamond Shamrock Agricultural Chemicals, Cleveland, OH; CDL:071541-E; 071542; 071543; 071544; 071545; 071546)

APPENDIX 2 Toxicology Data Citations (Continued)

- 00137124 Ford, W.; Laveglia, J.; Killeen, J.; et al. (1983) A Two-year Toxicity and Tumorigenicity Study of DS-3701 in Rats: Document Number 100-5TX-80-0016-011. Final rept. (Unpublished study received Jan 10, 1984 under 50534-8; submitted by SDS Biotech Corp., Painesville, OH; CDL:072270-A; 072271; 072272; 072273; 072274; 072275; 072276)
- 00138148 Shults, S.; Laveglia, J.; Killeen, J.; et al. (1983) A 90-day Feeding Study in Mice with Technical Chlorothalonil: Document No. 618-5TX-83-0007-004: Report DS-2787. (Unpublished study received Jan 10, 1984 under 50534-8; submitted by SDS Biotech Corp., Painesville, OH; CDL:072269-A)
- 00146945 Wilson, N.; Killeen, J.; Ignatoski, J. (1985) A Tumorigenicity Study of Technical Chlorothalonil in Rats: Document No. 099-5TX- 80-0234-008. Unpublished study prepared by SDS Biotech Corp. 2369 p.
- 00147946 Mizens, M. (1985) In vivo Bone Marrow Chromosomal Aberration Assay in Mice with a Single Dose of Technical Chlorothalonil: Document No. 625-5TX-83-0029-002. Unpublished study prepared by SDS Biotech Corp. and C.E.R.T.I. 86 p.
- 00147947 Mizens, M. (1985) In vivo Bone Marrow Chromosomal Aberration Assay in Rats with a Single Dose of Technical Chlorothalonil: Document No. 625-5TX-83-0028-002. Unpublished study prepared by SDS Biotech Corp. and C.E.R.T.I. 94 p.
- 00147948 Mizens, M. (1985) Acute and Subchronic in vivo Bone Marrow Chromosomal Aberration Assay in Chinese Hamsters with Technical Chlorothalonil: Document No. 625-5TX-83-0014-003. Unpublished study prepared by SDS Biotech Corp. and C.E.R.T.I. 180 p.
- 00147949 Jones, R. (1984) Salmonella/Mammalian-microsome Plate Incorporation Assay (Ames Test) with and without Renal Activation with Technical Chlorothalonil: Document No. 694-5TX-84-0064-002. Unpublished study prepared by SDS Biotech Corp. and Microbiological Assoc., Inc. 107 p.
- 40243701 Wilson, N.; Killeen, J. (1987) A Tumorigenicity Study of Technical Chlorothalonil in Male Mice: Final Report: Document No: 1099- 84-0077-TX-006; Project ID: 293-134. Unpublished study prepared by Ricerca, Inc. in cooperation with Experimental Pathology Laboratories, Inc. and International Research and Development Corp., Inc. 837 p.
- 40243702 Ford, W.; Killeen, J. (1987) A 90-day Feeding Study in Rats with Chlorothalonil: Supplemental Data: Document No.: 1115-85-0079- TX-006; Project ID: 293-144. Unpublished study prepared by Ricerca, Inc. in cooperation with International Research and Development Corp.; Experimental Pathology Laboratories, Inc.; and Laboratoire d'histopathologie, C.E.R.T.I. 464 p.
- 40559103 Mizens, M. (1988) In vitro Chromosomal Aberration Assay in Chinese Hamster Ovary (CHO) Cells with Technical Chlorothalonil: Document No. 1109-85-0082-TX-002-001. Unpublished study prepared by Microbiological Associates, Inc. 10 p.

APPENDIX 2 Toxicology Data Citations (Continued)

- 43653602 Fillmore, G.; Laveglia, J. (1993) A 90-Day Oral Toxicity Study in Dogs with Chlorothalonil: Final Report: Lab Project Number: 92-3820: 92-0103: 5210-92-0103-TX-003. Unpublished study prepared by Bio/Dynamics, Inc. 438 p.
- 43653603 Mizens, M.; Laveglia, J. (1994) A Chronic (12-Month) Oral Toxicity Study in Dogs with Technical Chlorothalonil: Lab Project Number: 92-135: 92-0457: 5211-92-0457-TX-003. Unpublished study prepared by Pharmaco LSR Inc. and Experimental Pathology Labs, Inc. 546 p.
- 43700601 Kajiwara, Y. (1994) Five-Day Repeated-Dose Chromosomal Abberation (sic) Test in Vivo with SB-341 Using Rats: Lab Project Number: T-3883: K12-0001. Unpublished study prepared by Hita Research Labs. 22 p.
- 43700602 Mizens, M.; Lavegalia, J. (1995) In Vivo Bone Marrow Chromosomal Analysis in Chinese Hamsters Following Multiple Dose Administration of Technical Chlorothalonil: Lab Project Number: 6005-94-0047-TX-003: 1081-92-0458-AS-000: RIC 56/941583. Unpublished study prepared by Huntingdon Research Centre, Ltd. and Ricerca Inc. 117 p.
- 44022201 Mizens, M.; Laveglia, J. (1994) In vitro Mammalian Cytogenetic Test with SDS-3701: Lab Project Number: 94-0048: GS94AS26.332: 6006-94-0048-TX-003. Unpublished study prepared by Ricerca, Inc. and Microbiological Associates, Inc. 89 p.
- 44022202 Mizens, M.; Laveglia, J. (1995) In vivo Bone Marrow Chromosomal Analysis in Chinese Hamsters with SDS-3701: Lab Project Number: 94-0049: 6006-94-0049-TX-003: RIC 57/950142. Unpublished study prepared by Huntingdon Research Centre, Ltd. and Ricerca, Inc. 109 p.
- 44223002 Mizens, M. (1996) A 90-Day Pilot Study for the Evaluation of Cell Proliferation in the Kidneys of Male Rats Following the Oral Administration of Technical Chlorothalonil: Lab Project Number: 6704-96-0010-TX-003. Unpublished study prepared by Ricerca, Inc. 182 p.
- 44240901 Hironaka, M. (1996) Analysis of Hyperplastic Changes in the Stomach and Kidney of Male Rats after 28-Day Induction By Chlorothalonil Technical: Lab Project Number: 2913 (063-002): WCH28469: 3561. Unpublished translation of study prepared by Center for Safety Assessment of Food, Agricultural Chemicals, and Medical Drugs (An-Pyo Center). 209 p.