R.F. 9/10/85

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

SEP 10 1985

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Chlorothalonil - EPA Registration No. 50534-7 [RCB #922]. SDS Biotech's Response of March 28, 1985 to Product Chemistry and Residue Chemistry Data Gaps Cited in the Chlorothalonil Registration Standard Dated September 30,1984 (Accession Numbers 257516 and 257517).

FROM: Michael P. Firestone, Ph.D., Chemist
Tolerance Petition Section II
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

M. P. Firestone

THRU: Charles L. Trichilo, Ph.D., Chief
Residue Chemistry Branch
Hazard Evaluation Division (TS-769)

Richard D. Schmitt for

TO: Henry M. Jacoby, Product Manager No. 21
Fungicide-Herbicide Branch
Registration Division (TS-767)

and

Amy Rispin, Chief
Science Integration Staff
Hazard Evaluation Division (TS-769)

SDS Biotech Corporation has submitted a cover letter dated March 28, 1985 in addition to Product Chemistry (Part 158.120) and Residue Chemistry Data (Part 158.125 - Plant Metabolism Data) as part of its response to Data Gaps cited in the Chlorothalonil Registration Standard (dated 9/30/84).

Currently, tolerances are established for the fungicide chlorothalonil (tetrachloroisophthalonitrile) and its metabolite 4-hydroxy-2,5,6-trichloroisophthalonitrile for residues in/on a wide variety of raw agricultural commodities at levels ranging from 0.1 to 15 ppm.

The data gaps will be detailed below, followed by SDS Biotech's Responses and RCB's Comments/Conclusions.

149

143749

Note: The product chemistry portion of this review covers issues related to product chemistry data gaps for Technical Chlorothalonil Fungicide (EPA Reg. No. 50534-7, Old No. 677-308) only. It does not cover issues relating to any formulated intermediate (FI) products.

Part I - Product Chemistry for Technical Chlorothalonil Fungicide (EPA Reg. No. 50534-7, Old No. 677-308)

Product Identity and Composition

61-2. Description of Beginning Materials and Manufacturing Process

Data Gap:

This topic was not fully addressed for any manufacturing-use product. Therefore, the following data are required:

a. The purities of the intermediates and any quality control measures used for the technical and formulation intermediate (FI) products. In addition, the manufacturing process, purities of starting materials, descriptions of reaction conditions, and any purification steps required for the unregistered 97.5- 98.0% technical used [redacted] and for all FI products (75% FI, EPA Reg. No. 677-293; and 2.88 lb/gal FI, EPA Reg. No. 677-326; 3.0 lb/gal FI, EPA Reg. No. 677-331; and 4.17 lb/gal FI, EPA Reg. No. 677-330).

b. The names and addresses of the manufacturers or producers of the starting materials.

SDS Biotech's Response

A detailed description of the manufacturing process for Technical Chlorothalonil Fungicide/Technical Daconil 2787 is submitted in the present submission, Accession No. 257516 (dated 4/1/85), and is discussed in the Confidential Appendix of this review (see also Confidential Appendix A to the Chlorothalonil Registration Standard).

The names of the suppliers of the starting materials have also been submitted, along with technical specifications (including information concerning impurities) of each starting material (see Accession No. 257516).

PRODUCT INGREDIENT SOURCE INFORMATION IS NOT INCLUDED

RCB's Comments/Conclusions re: 61-2

This data gap has now been resolved with regards to EPA Reg. No. 50534-7 (i.e., technical chlorothalonil).

61-3. Discussion of the Formation of Impurities

Data Gap:

This topic was not previously addressed; the following is required:

a. A discussion of each impurity believed to be present at >0.1% based on knowledge of the beginning materials, all possible chemical reactions, and any contamination.

b. A discussion of all the available data on the impurities in technical chlorothalonil and whether they would be present as residues in the treated raw agricultural commodities.

SDS Biotech's Response

A brief discussion of the formation of impurities is presented in the current submission for Technical Chlorothalonil Fungicide and Technical Daconil 2787 Fungicide (see Confidential Appendix of this review).

RCB's Comments/Conclusions re: 61-3

SDS will need to better define chemically what constitutes the [redacted] and how these chemical(s) may be formed.

With regard to residue data for specific impurities that may be present in technical chlorothalonil, this issue will be discussed in Part II - Residue Chemistry section of this review.

A data gap remains with regard to technical chlorothalonil concerning formation of [redacted] (see Part III of the Confidential Appendix of this review).

PRODUCT IMPURITY INFO IS NOT INCLUDED

ANALYSIS AND CERTIFICATION OF PRODUCT INGREDIENTS

62-1. Preliminary Analysis

Data Gap:

This topic was not fully addressed for technical and formulation intermediate (FI) products. For technical chlorothalonil, the following will be required:

a. The lack of this information for the FI products and for the unregistered technical used [redacted] constitutes a data gap.

b. Additional characterization of the [redacted] is needed.

Note: Part (a) is not relevant to this review since EPA Reg. No. 50534-7 (Technical Chlorothalonil Fungicide) is a registered technical for which the appropriate Section 62-1 data have been reviewed in the Chlorothalonil Registration Standard.

SDS Biotech's Response

None

RCB's Comments/Conclusions re: 62-1

The manufacturer will still need to submit additional information relating to the characterization of the [redacted]

62-2. Certification of Ingredient Limits

Data Gap:

The following data are still required:

a. Upper and lower limits must be provided (and certified) for chlorothalonil and for any intentionally added inert ingredients in the FI and technical products (lower limits were provided for chlorothalonil in two 96% technical products, EPA Reg. Nos. 677-283 and 677-308).

b. Upper limits must be provided (and certified) for each impurity present at >0.1% (w:w) in the unregistered technical used for [redacted] and for all FI products.

c. The unintentional impurities in the 96% technical (EPA Reg. Nos. 677-283 and 677-308) listed as [redacted] must be more specifically identified.

d. The purpose of each intentionally added inert in the 75% FI.

PRODUCT INGREDIENT SOURCE INFORMATION IS NOT INCLUDED

IMPURITY INFO IS NOT INCLUDED

e. Certified limits for the presence of hexachlorobenzene (HCB).

SDS Biotech's Response

The registrant has submitted a "Certification for Ingredient Levels" (see Accession No. 257516) for Technical Chlorothalonil Fungicide and Technical Daconil 2787 Fungicide.

RCB's Comments/Conclusions re: 62-2

The certified limits for technical chlorothalonil (EPA Reg. No. 50534-7) can be found in the Confidential Appendix to this review. QUALITY CONTROL PROCEDURE INFORMATION IS NOT INCLUDED

The registrant has set his lower (min.) certified limit for technical chlorothalonil as [redacted] However, the registrant will need to submit both an upper and lower limit for chlorothalonil (tetrachloroisophthalonitrile) in the technical product. This continues to represent a data gap.

62-3. Analytical Methods to Verify Certified Limits

Methods considered adequate for regulatory purposes are available for analysis of chlorothalonil in the technical product (GLC with a thermal conductivity detector) and for analysis of the impurity hexachlorobenzene to <0.02% (GLC with a flame ionization detector).

The following information is required:

Data Gap:

a. Quantitative methods to detect the remaining impurities present at >0.1% by weight.

b. Methods to enforce the certified limits of pentachlorobenzonitrile (PCBN) and possible other impurities, including data validating the methodology.

SDS Biotech's Response

None

RCB's Comments/Conclusions re: 62-3

The lack of validated analytical methodology for the determination of impurities in technical chlorothalonil present at >0.1% (w/w) remains a data gap.

Each analytical method must be validated by studies of the precision and accuracy of the method. This includes

fortification-recovery data, control (blank) values, submission of representative chromatograms, etc. Complete descriptions for each procedure must be submitted.

Physical and Chemical Characteristics

Listed below are the data gaps involving the physical and chemical properties for technical chlorothalonil and a discussion of whether or not appropriate data have been submitted in the subject (3/25/85) response (see Accession No. 257517) by SDS Biotech to the Chlorothalonil Registration Standard.

63-7. Density, Bulk Density, or Specific Gravity

RCB's Comments/Conclusions re: 63-7

The continued lack of data represents a data gap.

63-8. Solubility

In the Chlorothalonil Registration Standard, it was stated that solubility data, expressed in terms of g/100 ml of solvent or ppm (mg/kg) should be determined at 20°C (68°F). Data generated at 25°C was considered not acceptable.

RCB's Comments/Conclusions re: 63-8

Since the Pesticide Assessment Guidelines-Product Chemist-Subdivision D (§63-8c) now states that solubilities can be determined at 20°C or 25°C, no additional data will be required. Thus, this data gap is now considered resolved.

63-9. Vapor Pressure

Although the Chlorothalonil Registration Standard does not identify topic 63-9 as a data gap (previous data reflected vapor pressure at 40°C - <0.01 mm Hg, and at several other temperatures from 170.4°C - 9.20 mm Hg to 229.5°C - 43.30 mm Hg), the registrant reports the following additional vapor pressure data:

Temperature °C	Torr (mm Hg)
25°	5.72×10^{-7}
35°	2.65×10^{-6}
45°	4.49×10^{-5}

RCB's Comments/Conclusions re: 63-9

No additional data are required for technical chlorothalonil.

63-10. Dissociation Constant

The registrant claims that no data are required since chlorothalonil contains no available acidic or basic groups.

RCB's Comments/Conclusions re: 63-10

RCB concurs that this topic is not applicable to technical chlorothalonil.

63-11. Octanol/Water Partition Coefficient

The registrant reports that Kow = 7.62×10^{-2}

This values represents the average of determinations at chlorothalonil concentrations in water of 10^{-4} (Kow = 9.73×10^{-2}) and 10^{-6} M (Kow = 5.50×10^{-2})

The octanol phase was analyzed neat while the aqueous phase was run through a Sep-Pak column which was then eluted with toluene and analyzed.

Analysis was performed by GLC (3% OV-225 or OV-101) using an electron capture detector.

RCB's Comments/Conclusions re: 63-11

No additional data are required for technical chlorothalonil.

63-12. pH

The registrant claims that this topic is not applicable to technical chlorothalonil.

RCB's Comments/Conclusions re: 63-12

RCB concurs, thus, no additional data are required.

63-14. Oxidizing or Reducing Action

The registrant claims that this topic is not applicable to technical chlorothalonil.

11B's Comments/Conclusions re: 63-14

RCB concurs, thus, no additional data are required.

63-15. Flammability

The registrant reports that technical chlorothalonil is not flammable.

RCB's Comments/Conclusions re: 63-15

No additional data are required on this topic.

63-16. Explodability

The registrant reports that technical chlorothalonil is not potentially explosive.

RCB's Comments/Conclusions re: 63-16

No additional data are required on this topic.

63-17. Storage Stability; 63-18. Viscosity; and 63-19. Miscibility

No data were submitted regarding technical chlorothalonil (EPA Reg. No. 50534-7) for the above three topics (some data re: chlorothalonil containing formulations were submitted).

The Pesticide Assessment Guidelines - Product Chemistry - Subdivision D states that data concerning these three topics (§63-17, 18, 19) must be available for each manufacturing-use product as well as end-use product.

RCB's Comments/Conclusions re: 63-17, 63-18, and 63-19

These data gaps have not been resolved with respect to technical chlorothalonil (EPA Reg. No. 50534-7).

Product Chemistry Summary

The following topics still contain data gaps with respect to technical chlorothalonil (EPA Reg. No. 50534-7, Old No. 677-308]:

61-3: More detailed information regarding the formation of [redacted] must be submitted.

62-1: RCB will require additional information relating to the characterization of [redacted]

PRODUCT IMPURITY INFO IS NOT INCLUDED

62-2 : RCB will require both upper and lower limits for chlorothalonil in the technical product.

62-3 : The registrant will need to supply detailed descriptions of all methods used to quantitate impurities in technical chlorothalonil as well as validation data.

63-7 : Data reflecting the density of technical chlorothalonil.

63-17: Data reflecting the storage stability of technical chlorothalonil.

63-18: Data reflecting the viscosity of technical chlorothalonil.

63-19: Data reflecting the miscibility of technical chlorothalonil.

Part II - Residue Chemistry

Various data gaps exist with respect to plant metabolism, animal metabolism, analytical methodology (only if residues of hexachlorobenzene [HCB] and pentachlorobenzonitrile [PCBN] are included in the tolerance expression for residues resulting from use of chlorothalonil), residue data for raw agricultural commodities and their processed fractions (parent compound, 4-hydroxy-2,5,6-tri-chloroisophthalonitrile, any additional metabolites identified in new metabolism studies, and the technical product contaminants HCB and PCBN), and possibly animal feeding studies.

In the subject (March 28, 1985) submission, the registrant is responding only to the plant metabolism data gaps. SDS Biotech has included the results of a lettuce metabolism study, and reports that additional metabolism studies are also planned for a root crop and a fruiting crop.

In the Chlorothalonil Registration Standard, the following data gaps were identified with respect to adequately understanding the metabolism of chlorothalonil in plants:

a. Studies in which the unidentified water-soluble compounds, which constitute the major portion of the [^{14}C] chlorothalonil residues taken up from treated soil by plants, are characterized along with other possible metabolism of chlorothalonil.

b. Translocation studies involving the application of ring-labeled [^{14}C] chlorothalonil to foliar plant surfaces (one such study was submitted but involved immature plants).

c. Data on whether the impurities in technical chlorothalonil need to be included in the tolerance definition.

Note: Part (c) relating to impurities in technical chlorothalonil (i.e., HCB and PCBN) should ideally be discussed in terms of residue data, not plant metabolism.

Chlorothalonil Metabolism in Lettuce [171-4: Nature of the Residue-Plants (Metabolism)]

SDS Biotech has submitted Report No. 672-3EF-84-0014-001 entitled "A Plant Metabolism Study With ^{14}C-Chlorothalonil (2,4,5,6-Tetrachloroisophthalonitrile) on Lettuce" (see Accession No. 257517).

Lettuce plants received four foliar applications of ^{14}C-chlorothalonil at a rate equivalent to approximately 1.6 lb ai/A/treatment. Plants (mature stage) were harvested at 1, 3, 7, 10, 14 and 21 days following the fourth application.

Residues were extracted with acetone/0.3N HCl (4:1), and following evaporation of acetone, partitioned against diethyl ether.

Identification of the terminal residues was performed by HPLC (Partisil 10 ODS column) and confirmed by mass spectroscopy. The HPLC technique was found to be capable of separating the following five known soil metabolites of chlorothalonil:

1. 4-Hydroxy-2,5,6-trichloroisophthalonitrile (SDS-3701)
2. 3-Cyano-2,4,5,6-tetrachlorobenzamide (SDS-19221)
3. 3-Cyano-2,5,6-trichlorobenzamide (SDS-47524)
4. 2-Hydroxy-5-cyano-3,4,6-trichlorobenzamide (SDS-47525)
5. 3-Carboxy-2,5,6-trichlorobenzamide (SDS-46851)

Regardless of the length of time after the last application, the amount of applied ^{14}C-activity recovered remained constant at approximately 50%. The extractability of the ^{14}C-activity decreased only slightly from 99% at a one-day PHI to 96.4% at 21 days following the last application.

Of the extractable residues, approximately 94% partitioned into the diethyl ether fraction, independent of post-harvest interval (i.e., the aqueous soluble fraction accounted for only about 6% of terminal residues).

The following table summarizes the results of identifying the terminal residues:

PHI (days)	Percentage of the Recovered ^{14}C-Activity Chlorothalonil	SDS-3701	Unidentified
1	89.2	1.5	9.3
3	87.1	0.9	12.0
7	88.2	1.4	10.4
10	89.8	1.5	8.7
14	88.8	1.8	9.4
21	87.1	2.0	10.9

The major terminal residue was found to be the parent compound, chlorothalonil. The relative amount of the metabolite 4-hydroxy-chlorothalonil (SDS-3701) was found to slowly increase with time.

RCB's Comments/Conclusions re: 171-4: Nature of the Residue-Plants (Metabolism)

While the lettuce metabolism study reflecting foliar application shows that the parent compound comprises a majority (>87%) of the terminal residues up to 21-days post-application, the following questions remain with respect to the metabolism of chlorothalonil in lettuce:

1. To what extent can lettuce plants take up the five identified soil metabolites (i.e., should these metabolites be included in the chlorothalonil tolerance expression).

2. To what extent is chlorothalonil translocated across foliar surfaces in mature lettuce plants.

3. What is the nature of the residue at very long PHI's.

The registrant must consider the above questions with respect to the pending root crop and fruit corp metabolism studies.

At this time, data gaps remain with respect to the metabolism of chlorothalonil in plants.

Attachment 1:Confidential Appendix (Copies to MFirestone, TOX, PM#21-Jacoby, RF, PMSD/ISB, Chlorothalonil Reg. Std. Files, George Beusch only)

cc :Chlorothalonil SF, Circu, RF, MFirestone, Chlorothalonil Reg. Std. Files, PMSD/ISB, GBeusch

RDI:JHOnley:8/22/85:RDSchmitt:8/22/85
TS-769:RCB:CM#2:RM810:X7484:MPFirestone:wh:9/4/85

Chlorothalonil

Page_____ is not included in this copy.

Pages 12 through 13 are not included.

The material not included contains the following type of information:

____ Identity of product inert ingredients.

X Identity of product impurities.

X Description of the product manufacturing process.

____ Description of quality control procedures.

____ Identity of the source of product ingredients.

____ Sales or other commercial/financial information.

____ A draft product label.

____ The product confidential statement of formula.

____ Information about a pending registration action.

____ FIFRA registration data.

____ The document is a duplicate of page(s) _____.

____ The document is not responsive to the request.

The information not included is generally considered confidential by product registrants. If you have any questions, please contact the individual who prepared the response to your request.