

Date: June 4, 2004

SUBJECT: Product Chemistry Review of Glyphosate Technical

FROM: Shyam B. Mathur, Ph.D  
Product Chemistry Team Leader  
Technical Review Branch/RD (7505C)

*S.B. Mathur*  
*6/4/04*  
*SM*

TO: James Tompkins / Vickie Walters, RM 25  
Herbicide Branch / RD (7505C)

DP BARCODE: D302213  
EPA REG. NO.: 70829-5  
PRODUCT: Glyphosate Technical  
PCC : 417300  
REGISTRANT: Chemical Products Technologies, L.L.C  
USE: Herbicide

INTRODUCTION:

The registrant has submitted the product chemistry data in support of the amended registration application of an additional manufacturing site for Glyphosate technical produced by [REDACTED] China. The other registered site of production by [REDACTED] also in China (Basic CSF dated July 7<sup>th</sup>, 2003). In support the applicant has included a CSF for alternate formulation (dated 04-21-04), the product label and the Subgroup A data. The data were submitted under MRID Nos. 462591-01, 462591-02, and 462591-03. No Subgroup B (physical-chemical properties) data was submitted, since the average purity of the technical glyphosate (97.5%, as determined by the five batch analysis), falls with in the upper and lower certified limits of the nominal concentration (96.7%) of the glyphosate technical in basic formulation. The product label claim is 96.7%. The TRB has been asked to evaluate the product chemistry data submitted for the Glyphostae technical produced by [REDACTED] province of China.

SUMMARY OF FINDINGS:

1. The registrant has submitted a Confidential Statement of Formula for alternate formulation (dated 04-21-04) for glyphosate technical. The average purity of the technical glyphosate (97.6%, as determined by the five batch analysis), falls with in the upper and lower certified limits of the nominal concentration (96.7%) of the glyphosate technical in basic formulation. The product label claim is 96.7%. The product chemistry data submitted corresponding to guideline reference 830.1550 (product identity & composition) and 830.1750 (certified limits) satisfy the data requirements of 40CFR§158.155 and 158.175 respectively. [MRID No. 462591-01]
2. The product chemistry data submitted corresponding to guideline reference 830.1600 (description of material used to produce the product) satisfy the data requirements of 40CFR§ 158.160. The registrant has provided product specifications data on all the starting materials used for the production of this technical. [MRID No. 462591-01]
3. The product chemistry data submitted corresponding to guideline reference 830.1620 (description of production process) satisfy the data requirements for 40CFR§158.162. The manufacturing process for the Glyphosate technical has been described in details. [MRID No. 462591-01]

PRODUCT INGREDIENT SOURCE INFORMATION IS NOT INCLUDED

4. The product chemistry data submitted corresponding to guideline reference 830.1670 (discussion on the formation of impurities) satisfy the data requirements for 40CFR§158.167. The registrant has described the mechanism of formation of impurities present in the technical and also discussed the possibilities of the formation of other impurities during the synthesis of this technical. The five batch analysis concurs with the discussion provided on the formation of impurities. The presence and formation of any impurity of toxic concern during the synthesis of Glyphosate technical was not indicated during the discussion. [MRID No. 462591-01]

5. The data submitted corresponding the guideline reference 830.1700 (preliminary analysis) satisfy the data requirements of 40CFR§158.170. Five representative batches of the technical were analyzed for percent active ingredient by HPLC/UV (195 nm). One of the impurity was determined by cation-exchange chromatography and measured by post-column fluorescence derivatization. The inorganic ions were analyzed by ion chromatography. The five batches were found to have the AI content in the range of 96.1% to 98.3% (with mean of 97.2% w/w).

The identities of glyphosate and impurities (where possible) in the test substance were confirmed by matching the retention time and UV spectra of the test substance to each reference substance. In addition, LC/MS/MS identification was performed. [MRID No. 462591-02]

6. The data submitted corresponding the guideline reference 830.1800 (enforcement analytical method) satisfy the data requirements of 40CFR§158.180. The method described in item # 5 above was used to assay the active ingredient in the technical product and was non-confidential. The method was validated for accuracy, linearity, and precision. [MRID No. 462591-02]

#### CONCLUSIONS:

The TRB has reviewed the product chemistry data submitted for Glyphosate technical and has concluded that:

1. All the product chemistry data submitted corresponding to 830 Series Subgroup A satisfy the data requirements of 40CFR§158.155 to 158.180 and are acceptable.
2. The CSF for alternate formulation (dated 04-21-04 ) is acceptable.

**BARCODE:** D302213; **Reg. No.:** 70829-5 **PRODUCT:** Glyphosate Technical

830.1550 **Product identity & Composition:** (MRID No. ~~461605-01~~)

Common Name: Glyphosate

Chemical name: N-(Phosphonomethyl)glycine

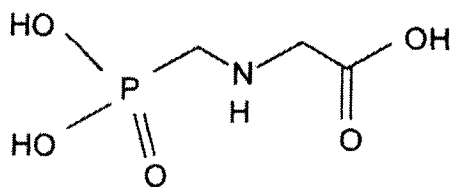
CAS No.: 1071-83-6

PC Code No.: 417300

Empirical formula:  $C_3H_8NO_5P$

Molecular Weight: 169.1

Structural formula:



Glyphosate

REVIEW OF PRODUCT CHEMISTRY, OPPTS 830 SERIES

Chemical Name (IUPAC, CAS)	N-(Phosphonomethyl)glycine	
Chemical Number (CAS; PC Code)	CAS No. 1071-83-6	PC Code: 417300
Registration/Symbol No.	70829-5	
Type of Product (T, MP, EP)	97.2% TGAI/ MP	
DP Barcode	D302213	
Reviewer	Shyam B. Mathur	
Branch Chief	Deborah McCall	

Table 1: Manufacturing and Impurity Data for Metribuzin Technical

GLN	Requirement	MRID	Status	Details and/or Deficiency
830.1550	Product identity and composition	alternate CSF (04-21-04)	A	The NC of AI (97.2%) is supported by 5 batch analysis & falls with in the certified limits of the NC ( 96.7%) of the basic formulation.
830.1600	Description of materials used to produce product	462591-01	A	The product specification sheets(MSDS) for all the starting materials have been provided by registrant.
830.1620	Description of production process	462591-01	A	The production process has been described in full details. The reaction conditions are given, and the amounts of the reagents used in each step have been provided.
830.1670	Discussion of formation of impurities	462591-01	A	The registrant has provided the complete mechanisms of formation, quantification and identification of all the impurities . No toxic impurity was reported during the synthesis of the TGAI/MUP.
830.1700	Preliminary analysis	462569-02	A	Registrant has provided 5 batch analysis for the TGAI. The AI was assayed by using capillary HPLC/UV(195 nm). The ion chromatography, HPLC/RI & HPLC/UV were used for the identification of the impurities. LC/MS/MS was additionally used for identification purposes. The titration method with bismuth volumetric solution was also used for the determination of one of the impurity. The analytical methods have been validated for precision, linearity & accuracy.
830.1750	Certified limits	Basic CSF (04-21-04)	A	The proposed certified limits for the AI were with in standard certified limits. The NC & UCL for the impurities have been provided on the CSF
830.1800	Enforcement analytical method	462569-02 462569-03	A	The HPLC/UV(195 nm) method was used for the assay of the AI in technical. The method validated for linearity, accuracy and precision.

A = Acceptable; N = Unacceptable (see Deficiency); N/A = Not Applicable.; G = Data gap; I = In progress or need upgrade;  
U = Up-grade(additional information required)

**BARCODE:** D302213; **Reg. No.:** 70829-5 **PRODUCT:** Glyphosate Technical

830.1800. Enforcement analytical method: (MRID No. 462591-02)

The HPLC/UV method was used for the estimation of the glyphosate in the TGAI. The test sample was grinded in a mortar pestle and the solution was made in the mobile phase and sonicated for about 30 minutes to completely dissolve the test substance and analyze by HPLC under the following parameters:

Instrument: HPLC equipped with an UV detector

Detector wavelength: 195 nm

Column: Partisil 10 SAX, 250 x 4.6 mm

Column temperature: Ambient

Injection volume: 50  $\mu$ L

Flow rate: 2.3 ml/min

Mobile phase: 96:4 (0.0062 M  $\text{KH}_2\text{PO}_4$  buffer : MeOH, pH 1.9-2.0)

The analytical method was validated for precision, accuracy, and linearity.

Chemical	Glyphosate Technical		Registration Number	70829-5	DP Barcode	D302213
CB Number			Product Type	97.2% T/MUP	Test Substance	TGAI / MUP

Group A - GLNs 830.1550, 830.1600-1650, 830.1670, 830.1700, 830.1750, 830.1800: Composition (CSF), Impurities, Preliminary Analysis, and Analytical Methods.

Compound/Component <sup>1</sup>		Type <sup>2</sup>	Nominal Concentration (% w/w)	Lower Certified Concentration (w/w)	Upper Certified Concentration (% w/w)	Preliminary Analysis Mean $\pm$ s.d. (% w/w)
	Name					
	Glyphosate acid CAS No. 1071-83-6	AI	97.2	94.3	99.9	
	Manufacturing impurities					
1	Aminomethyl phosphoric acid CAS no. 1066-51-9	I	0.05		0.07	
2	Water CAS No. 7732-18-5	I	0.15		0.21	
3	Other impurities < 0.1% in acid	I	1.0		1.2	
4		I				
	Total		100			

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The material not included contains the following type of information:

\_\_\_\_\_ Identity of product inert ingredients.

\_\_\_\_\_ Identity of product impurities.

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.

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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.

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~~CONFIDENTIAL APPENDIX~~

BARCODE D302213; Reg. No. 70829-5 PRODUCT: Glyphosate Technical

830.1670. Discussion on the formation of impurity: (MRID N. 462591-01)

The registrant provided the following information on this topic:

The potential impurities present in the reaction are generally carry over materials used in the production of the Glyphosate technical, unreacted intermediates, minor contaminants found in the raw materials and may include:

830.1700. Preliminary analysis: (MRID No. 46259-02)

Five representative lots of glyphosate acid technical were analyzed for the percentage active ingredient glyphosate and impurities. The % of the AI was determined by HPLC/UV. The impurities were determined by using the following methods:

- The amounts of anions were obtained by using Ion chromatography method (HPLC equipped with the conductivity detector).
- The aminomethyl phosphonic acid (AMPA) was determined by the HPLC method utilizing post-column derivatization and fluorescence detection.
- A screen of miscellaneous impurities was conducted by HPLC/RI (refractive index detector) and HPLC/UV.
- The identities of glyphosate and impurities in the test substance were confirmed by matching the retention time and UV spectra of the test substance to each reference substance. In addition LC/MS/MS identification was performed.
- The water content was determined by Karl Fisher moisture method.

Determination of the active ingredient by HPLC/UV method

The HPLC/UV method was used for the estimation of the glyphosate in the TGAI. The test sample was grinded in a mortar pestle and the solution was made in the mobile phase and sonicated for about 30 minutes to completely dissolve the test substance and analyze by HPLC under the following parameters:

Instrument: HPLC equipped with an UV detector

Detector wavelength: 195 nm

Column: Partisil 10 SAX, 250 x 4.6 mm

Column temperature: Ambient

Injection volume: 50 µL

Flow rate: 2.3 ml/min

Mobile phase: 96:4 (0.0062 M KH<sub>2</sub>PO<sub>4</sub> buffer : MeOH, pH 1.9-2.0)

The analytical method was validated for precision, accuracy, and linearity.



**CONFIDENTIAL APPENDIX**

**BARCODE:** D302213; **Reg. No.:** 70829-5 **PRODUCT:** Glyphosate Technical

Determination of Aminomethylphosphonic acid (AMPA) in Glyphosate TGA

Glyphosate and AMPA were separated by cation-exchange chromatography and measured by post-column fluorescence derivatization. The samples were analyzed by HPLC under following operating conditions.

Instrument: HPLC equipped with Fluorescence Detector

Detector setting: Excitation at 330 nm  
Emission at 465 nm

Column: Potassium cation Exchange Column (PCE-Pickering Lab., Inc., column for glyphosate analysis)

Column temperature: 55°C

Injection volume: 10 µL

Flow rate: 0.4 ml/minute

Mobile phase: A. K200 and B. RG019

1. Isocratic 100% A for 15 min
2. Change to 100% B, hold for 2 minutes
3. Change to 100% A
4. Finish run at 30 minutes (include equilibration step for at least 10 minutes)

Oxidant flow rate: 0.3 ml/min

OPA-MERC Flow rate: 0.3 ml/min

Method validated for precision, linearity, and accuracy.

~~CONFIDENTIAL-APPENDIX~~  
BARCODE: D302213; Reg. No. 70829-5 PRODUCT: Glyphosate Technical

Determination of ions (chloride, bromide, fluoride, nitrite, nitrate, phosphate, and sulfate) by HPC/Conductivity (detector).

The HPLC method with conductivity detector was used for the determination of inorganic ions. The HPLC was operating under the following parameters:

Pump: Alltech 325 HPLC pump  
Autoinjector: Perkin-Elmer, ISS-100  
Column: Alltech, Allsep, 10 cm x 4.1 mm  
Temperature: 40°C  
Mobile phase: 0.7 mM NaHCO<sub>3</sub> / 1.2 mM Na<sub>2</sub>CO<sub>3</sub>  
Flow rate: 1.4 ml/min  
Detector: Alltech 350 Conductivity detector  
Injection volume: 20 µL

Method validated for precision, linearity, and accuracy.

Confirmation of Glyphosate by LC/MS/MS method:

The test and standard samples were analyzed using the following LC/MS/MS chromatographic conditions:

#### **HPLC conditions**

Instrument: HPLC equipped with UV detector  
Detector wavelength: 195 nm  
Column: Partisil 10 SAX 250 x 4.6 mm  
Column temperature: 27°C  
Injection volume: 30 µL  
Flow rate: 1.0 ml/min  
Mobile phase: 96 : 4 (0.0062 M KH<sub>2</sub>PO<sub>4</sub> buffer : MeOH, pH = 1.9)

#### **MS conditions**

Electrospray ionization was used in positive  
Electrospray capillary voltage : 3.75 kV  
Cone voltage: 30V  
Extractor voltage: 2 V  
Ion source temperature: 90°C  
Desolvation temperature: 200°C  
Desolvation gas flow: approximately 500 l/h  
Nebulizer gas flow: approximately 200 l/h  
Collision energy: 15 eV

~~CONFIDENTIAL-APPENDIX~~

~~BARCODE D302213, Reg. No. 70829-5, PRODUCT: Glyphosate Technical~~

A daughter scan of the protonated parent compound (m/z 170) was performed. The resulting daughter ions were compared to known standards. The split ratio was 1:5. The flow from HPLC was split before entering MS.

The analysis was done to determine N-(phosphonomethyl)iminodiacetic acid in glyphosate acid at the LOD at 0.5%. The method of analysis was based on the published analytical method, "Repasi, J. (1993) Selective Complexometric Determination of Glyphosate and Related Compounds. Pesticide Sciences, 39:287-292."

An aliquot from each lot of the test substance was dissolved in a total of 250 ml of water with 5 ml of 1M NaOH. Four replicates (50 ml each) were transferred to 250 ml erlenmeyer flasks, then 1 ml of 10% w/w nitric acid was added followed by 30 mg of methylythymol blue mixture to each flask. The solution was mixed then titrated with bismuth volumetric solution to a bluish-purple color.

The method was validated for accuracy, linearity, and precision.

The analytical results are provided in the following table:

Lot Number	20010701	20010702	20010703	20010704	20010705
Compound					
Glyphosate	96.4%	97.3%	98.1%	98.3%	96.1%
AMPA	< 0.100(0.066)	< 0.100(0.034)	< 0.100(0.027)	< 0.100(0.058)	< 0.100(0.045)
Fluoride	< 0.100	< 0.100	< 0.100	< 0.100	< 0.100
Chloride	< 0.100	< 0.100	< 0.100	< 0.100	< 0.100
Bromide	< 0.100	< 0.100	< 0.100	< 0.100	< 0.100
Nitrite	< 0.100	< 0.100	< 0.100	< 0.100	< 0.100
Nitrate	< 0.100 (0.010)	< 0.100 (0.014)	< 0.100 (0.016)	< 0.100 (0.015)	< 0.100
Sulfate	< 0.100 (0.011)	< 0.100 (0.018)	< 0.100 (0.019)	< 0.100 (0.018)	< 0.100 (0.020)
Phosphate	< 0.100 (0.054)	< 0.100 (0.057)	< 0.100 (0.064)	< 0.100 (0.067)	< 0.100 (0.077)
Water	0.017	0.212	0.149	0.114	0.186
Total	96.6	97.6	98.4	98.6	96.4