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

SEP 1 1987

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

Memorandum:

SUBJECT: PP#6F3380/FAP#6H5502. Glyphosate in/on Soybeans (RCB#'s 2346 and 2347). Amendment from Monsanto dated 2/20/87.

Glyphosate Registration Standard. Product chemistry for isopropylamine and sodium sesqui salts; nitrosamines. Response by Monsanto (letter dated 3/24/87) to the 3(c)2(B) letter of 8/11/86. (MRID#'s 401548-01, -02, -03, -01C, -02C, -03C, and Acc#263795)

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THRU: Philip V. Errico, Section Head
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TO: Robert J. Taylor, PM-25
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and

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Monsanto Agricultural Products Company has proposed to increase the tolerances (PP#6F3380/FAP#6H5502) for the combined residues of the herbicide glyphosate, (N-phosphonomethyl) glycine and its metabolite aminomethylphosphonic acid (AMPA), in/on soybeans from 6 to 20 ppm and soybean hay from 15 to 200 ppm as established under 40 CFR 180.364, and in/on soybean hulls from 20 to 100 ppm as established under 21 CFR 561.253 based on preharvest applications.

Deficiencies were cited with the original petition (See memo of 10/24/86, W. T. Chin, PP#6F3380). Several of these deficiencies have been addressed in previous submission by petitioner. (See memo of 7/6/87, W. T. Chin, PP#6F3380). In response to still outstanding deficiencies (See above memos of 10/24/86 and 7/6/87), the petitioner has submitted a cover letter (2/20/87, K. F. Cannon, Senior Reg. Spec., Monsanto), and addenda to Section B and D.

Monsanto Agricultural Products Company has also submitted data to support the continued registration of the product used in this petition, the isopropylamine salt of the herbicide glyphosate, (N-phosphonomethyl) glycine.

In response to data gaps in product chemistry for the isopropylamine salt (See Guidance Package for Glyphosate Registration Standard, 8/11/86, p. 52), the registrant has submitted a cover letter (3/24/87, K. F. Cannon, Senior Reg. Spec., Monsanto). In regard to the unregistered technical sodium sesqui salt of glyphosate, the cover letter (dated 3/24/87) does not refer to the sodium sesqui salt or the data (MRID#'s 401548-01C, -02C, and -03C) that has been submitted to RCB for review. In addition this product is registered for use as a plant growth regulator on sugar cane, and is not used on soybeans. However, since the preparation of the sodium sesqui salt only involves a simple acid-base neutralization, RCB can easily also discuss the product chemistry data gaps for the sodium sesqui salt here. RCB has previously reviewed submitted product chemistry for technical glyphosate (TGAI) (See memo of 7/6/87, W. T. Chin).

Note: Only one tracking sheet was sent to RCB for both actions. Although the sodium sesqui salt is not used in this petition, the submitted product chemistry can easily be discussed here.

The data gaps cited in the Glyphosate Registration Standard (8/11/86) are restated, followed by the registrant's response and RCB's comments. These deficiencies cited in memo of 10/24/86 (W. T. Chin) are restated, followed by the petitioner's response and RCB's comments.

Conclusions:

1a. Registrant has supplied detailed application rates and instructions on revised label. Deficiency 2(a) is resolved.

1b. RCB considers the nature of the residues understood for the proposed use. Deficiencies 3(b) and 6(a) are resolved.

1c New analytical methodology has been submitted to BUD, COB, for MTO. Deficiency 4(a) is resolved.

1d. Storage stability data submitted by the registrant is adequate. The residue data will support the proposed tolerance increases. Deficiency 5 is resolved.

1e. RCB has requested a revised Section B in regards to modification of a livestock grazing and feeding restriction. RCB considers deficiency 2(b) still unresolved.

1f. RCB has requested a revised Section F in regards to clarification of term "soybean straw" and subsequent proposed tolerance. RCB considers deficiency 2(c) still unresolved.

2a. RCB considers the product chemistry data gaps, §61-1 and §61-3, in reference to the isopropylamine and sodium sesqui salts of glyphosate resolved.

2b Nitrosamine levels (data gap, §62-1) in the technical glyphosate have exceeded the 1.0 ppm level in the manufacture of the TGAI in approximately [redacted] registrant's submitted runs (1983-1985). TOX has been asked to comment on the presence of N-nitrosoglyphosate >1 ppm in technical glyphosate.

2c. According to prior arrangement, RD will address the physical/chemical properties of isopropylamine and sodium sesqui salts, and the 41.04% and 53% FI's.

2d. Registrant has provided certification of ingredient limits (§62-2) and analytical methods to verify certified limits (§62-3) for isopropylamine and sodium sesqui salts.

Recommendations:

RCB continues to recommend against the proposed tolerance increases for the combined residues of the herbicide glyphosate, (N-phosphonomethyl) glycine and its metabolite aminomethylphosphonic acid (AMPA), in/on soybeans; deficiencies 2(b) and 2(c) are not resolved. RCB defers data gap 62-1, the nitrosamine concentration in the TGAI, to TOX for evaluation.

Product Identity

§61.1 Description of Beginning Materials and Manufacturing Process

"Details of the manufacturing process, including the relative amounts of beginning materials, a description of equipment used to produce the product, reaction conditions, the duration of each step of the process and purification procedures and quality control measures for 41.04% formulation intermediate (FI), the 53.5% FI, the 62% FI, the unregistered technical isopropylamine glyphosate salt product used to produce the FI's, and the unregistered technical trisodium sesqui salt are required

The name and address of the manufacturer, producer, or supplier of each beginning material used to manufacture the 41.04% FI, the 53% FI, the unregistered technical products to produce the FI's and the unregistered trisodium sesqui salt are required. Also, a copy of all available technical specifications, data sheets, and other documents in which the manufacturer, producer, or supplier of the beginning material describes the composition and properties must be submitted."

Petitioner's Response:

Monsanto has submitted Study No.'s MSL-6196 (MRID#401558-01) and MSL-6197 (MRID#401558-02) in support of the continued

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registration of the isopropylamine salt of glyphosate, and Study No.'s MSL-6265 (MRID#401548-01C) and MSL-6266 (MRID#401548-02C) in support of the continued registration of the sodium sesqui salt of glyphosate.

RCB Comments:

Note to PM The 62% FI should be more correctly be referred to as the technical isopropylamine salt; the 41.04% FI and 53% FI are actually end-use products (EP) and are prepared from the technical (62%) isopropylamine salt. According to prior arrangement, RD will address EP's physical/chemical properties of manufacturing-use products (MP).

The manufacturing process equipment used composition of reactants, reaction conditions, purification procedures, and quality controls measures are adequately understood for the for the continued registration of the technical isopropylamine and sodium sesqui salts of glyphosate RCB considers this data gap resolved for both the isopropylamine (62%) and sesqui sodium salts.

§61-3 Discussion of Formation of Impurities

"A discussion of each impurity believed to be present at 0.1% or more based on knowledge of the beginning materials, all possible chemical reactions and any contamination are required for the 41.04% FI, the 53% FI, the 62% FI, and the technical trisodium sesqui salt."

Petitioner's Response:

Monsanto has submitted Study No.'s MSL-6196 (MRID#401558-01) and MSL-6197 (MRID#401558-02) in support of the continued registration of the isopropylamine salt of glyphosate, and Study No.'s MSL-6265 (MRID#401548-01C) and MSL-6266 (MRID#401548-02C) in support of the continued registration of the sodium sesqui salt of glyphosate.

RCB Comments.

RCB has reviewed the impurities in the technical glyphosate (See memo of 7/6/87, W. T. Chin, PP#6F3380/FAP#6H5502). The preparation of the technical isopropylamine (62%) will not increase levels of impurities already present in technical glyphosate. Formation of any new impurities will only be a reflection of the purity of the reactant; [redacted] Likewise, the preparation of the sodium sesqui salt involves simple acid-base neutralization and will not result in either an increase of impurities or formation of new impurities in glyphosate products. RCB considers this data gap resolved for the isopropylamine and the sodium sesqui salts.

MANUFACTURING PROCESS INFORMATION IS NOT INCLUDED

Analysis and Certification of Product Ingredients

§62-1 Preliminary Analysis

"Five or more representative samples of the 41 04% FI, the 53% FI, the 62% FI, and the unregistered technical sodium sesqui salt analyzed for the amount of active ingredient and each impurity present at 0.1% (w/w) (including any nitrosamines which may be present at ca. 0.1 ppm) are required."

Petitioner's Response:

Monsanto has submitted Study No.'s MSL-6196 (MRID#401558-01) and MSL-6197 (MRID#401558-02) in support of analytical methods for analyses of the isopropylamine salt of glyphosate, and Study No.'s MSL-6265 (MRID#401548-01C) and MSL-6266 (MRID#401548-02C) in support for analyses of the sodium sesqui salt of glyphosate. The registrant has also submitted Study No. MSL-5808 (Acc#263795, PP#6F3380/FAP#6H5502).

RCB Comments:

RCB has reviewed analyses of the technical glyphosate (See memo of 7/6/87, W. T. Chin, PP#6F3380/FAP#6H5502). The preparations of the technical isopropylamine (62%) and sodium sesqui salts were analyzed by identical methods used for the technical glyphosate. (See Acc#263795, MSL-5808). Analyses of 19 samples of the isopropylamine salt yielded a range of [redacted] glyphosate, Analysis of 8 samples of the sodium sesqui salt yielded a range of [redacted] glyphosate.

In accordance with the Federal Register, Vol. 45 6/25/80, the registrant has provided validated nitrosamine analyses of representative samplings of the isopropylamine (19 samples) and sodium sesqui (8 samples) salts of glyphosate. Samples of the technical isopropylamine salt contained <200 ppb N-nitros-glyphosate. Samples of the sodium sesqui salt ranged from [redacted] ppb N-nitrosoglyphosate. Although the registrant has submitted data for nitrosoglyphosate levels in the manufacturing-use products isopropylamine and sodium sesqui salts, data submitted in support for the continued registration of technical glyphosate revealed that from a total of 2191 runs the N-nitroso-glyphosate levels exceeded 1 ppm [redacted] certification limit. Production of the isopropylamine and sodium sesqui salts require use of technical glyphosate (wetcake) which can contain a maximum of [redacted] concentration of >1.0 ppm nitrosamine Eleven samples of the

2191 runs fall into this category. However the production of the sesqui sodium salt gives no dilution of any N-nitrosoglyphosate Theoretically the final concentration of any nitrosamine will be the same as that present in the wetcake. This could involve a maximum [redacted] of the technical product.

NOTE: EPA policy, in accordance with Section II. B. of the Federal Register notice, requires a risk analysis of any product which contains at least 1.0 ppm or above of nitrosamine Therefore RCB requests that TOX review the N-nitrosoglyphosate levels in the technical wetcake and determine if this is of toxicological concern in the technical glyphosate and any manufacturing-use or end-use products.

Other Considerations:

The registrant has provide certification of ingredient limits (§62-2), and as forementioned, analytical methods to verify certified limits (§62-3).

§62-2 Certification of Ingredient Limits

Isopropylamine salt

Glyphosate acid: 45.5 - 47.5%
Isopropylamine: 15.0 - 22.0%
[redacted]

INERT INGREDIENT INFORMATION IS NOT INCLUDED

Sodium salt

Glyphosate acid: 79.0 - 83.7%
Sodium: 15 - 18%
[redacted]

§62-3 Analtyical Methods to Verify Certified Limits

Analytical methods used for major components and impurities are provided in submitted reports:

Study No.'s MSL-6196 (MRID#401558-01), MSL-6197 (MRID#401558-02), MSL-6265 (MRID#401548-01C), MSL-6266 (MRID#401548-02C), and MSL-5808 (Acc#263795, PP#6F3380/FAP#6H5502).

Deficiency 2(a), memo of 10/24/86:

"Detailed information regarding specific rates and application instructions for the current petition are needed."

Petitioner's Response:

Monsanto has submitted copy of proposed new label which includes soybean preharvest applications. Detailed information in this regard

are found on pages 94-95 of the current 1986-1 label approved by the Agency on May 28, 1986.

RCB Comments:

RCB considers this deficiency resolved

Deficiency 3(b), memo of 10/24/86:

"As indicated by the Glyphosate Registration Standard metabolism studies using ruminants and poultry are required."

Petitioner's Response:

Mosanto has agreed to submit these studies. However, Monsanto believes the Agency has sufficient metabolism data to approve this new use and requests the Agency grant the new tolerances and preharvest application pending outcome of these studies.

RCB Comments:

For the proposed purpose in this petition, the nature of the residues in/on soybeans is adequately understood. Residue data submitted by the registrant supports the proposed increases for the established tolerances under 40 CFR 180.364 and 21 CFR 561.253. Monsanto has agreed to submit additional data (See letter of 11/7/86 Monsanto response to Glyphosate Guidance Document) within a 18-24 month projected timeline. Although the Agency has not yet received the requested studies, RCB can accept the proposed increases for the purposes of this petition only. If the requested metabolic studies show additional residues of toxicological concern, other than the parent and its metabolite, AMPA, then additional residue will be needed, with validated analytical methodology. Such components must be included in the tolerance expression. RCB considers this deficiency resolved.

Deficiency 4(a), memo of 10/24/86:

"RCB concludes that the new residue method submitted with this petition is better and faster than the old enforcement method published in PAM II and that a method trial for this new method will be needed. The tolerance recommendation will not be held up for this method trial. For method trial purposes, the petitioner is requested to resubmit this method without the 'Confidential' label."

Petitioner's Response:

Monsanto submitted a document (5/19/86) entitled 'Validation of New Residue Method' (Part A), and 'Reanalysis of Glyphosate Residues in Water' (Part B) (R.D. No. 677 EPA Acc#262896). Appendix C, 'Analytical Method' page 76 through 98 part A, entitled 'HPLC-Flurometric Method for the Analysis of Glyphosate and Aminophosphonic Acid in Raw Agricultural Commodities and Water'. Monsanto asks

the Agency to confirm their observation that this method was not stamped as confidential business information, and thus available for MTO.

RCB Comments:

RCB concurs with the petiioner's observation. Monsanto has given the Agency permission for this new method to be made available in PAM for enforcement purposes (method sensitivity 0.05 ppm). This method will be submitted for MTO. RCB also reiterates that any tolerance recommendations in these petitions (PP#6F3380/FAP#6H5502) will not be delayed while MTO is run.

Deficiency 5, memo of 10/24/86:

"Since the field trials were conducted in 1979 and the dates of analysis of the samples are not given, RCB cannot determine the storage periods of the samples analyzed. Therefore, RCB is unable to determine the adequacy of the residue data submitted for the requested tolerance changes without the support of adequate storage stability data. The petitioner should submit information on the conditions and period of sample storage."

Petitioner's Response:

The petitioner has submitted a listing of sample and analyses dates, and pesticide recovery of such samples. Monsanto stated that company report (FR-469) indicated storage stability in soybean hay for up to 21 months and in soybean grain for up to 8 months. Soybean samples from the preharvest treatment (Acc#261638) were in frozen storage at zero degrees Fahrenheit (-20°C) for approximately four years before the final report analyses. Preliminary analyses were performed approximately one year after sampling. Variations in data, preliminary vs. final, could reflect the use of a glc method for 1979 analyses vs. hplc method for 1983 analyses.

RCB Comments:

Monsanto has submitted storage stability data for soybean grain from 9 to 45 months and for soybean hay from 9 to 46 months. Samples were collected from field trials run in 1979, and stored frozen at temperature of minus 20 degrees centigrade, for approximately four years before the final report analyses. Preliminary data were collected 9 to 15 months from harvest (PHI ranged from 6 to 13 days). The preliminary sample analyses were run with a glc method while the final analyses were performed with a hplc method. Validation data submitted by Monsanto (Acc#262896, PP#6F3380) showed good recovery for fortified samples, although several values seemed to go over 100% recovery. In comparsion to the glc method, the hplc method is faster and gives better recovery, e.g., average recovery hplc method, 97% for 20 fortified samples, and average recovery glc method, 65% for 12 fortified samples. Hplc analysis in 1983 of field samples from 1979 trials (stored for four years), showed slightly higher glyphosate (and AMPA)

residues than recorded in 1981 glc analyses. However, in general, the submitted results show good storage stability of glyphosate (and AMPA) in/on soybean grain and hay. Thus the residue data submitted in this petition will support the request for the tolerance increases. RCB considers this deficiency resolved.

Deficiency 6(a), memo of 10/24/86:

"Previous feeding studies on cattle, poultry, and swines using a 3:1 ratio of glyphosate and AMPA at dietary levels of 10 30, and 100 ppm indicated that no detectable (<0.025 ppm) residues of glyphosate and AMPA were found in milk oe eggs and none (0.05 ppm) were found in muscle or fat of cattle, swine, or poultry from the 100 ppm feeding level (PP#5F1536). However, if additional studies requested in conclusion "3b" above identify additional residues of toxicological concern, new feeding studies may be needed."

Petitioner's Response:

Mosanto has agreed to submit these studies. However, Monsanto believes the Agency has sufficient metabolism data to approve this new use and requests the Agency grant the new tolerances and preharvest application pending outcome of these studies.

RCB Comments:

RCB reiterates its comments forementioned under discussion of deficiency 3(b). Although the Agency has not yet received the requested studies RCB can accept the proposed increases for the purposes of this petition only. If the requested metabolic studies show additional residues of toxicological concern other than the parent and its metabolite, AMPA, then additional residue will be needed, with validated analytical methodology. Such components must be included in the tolerance expression. RCB considers this deficiency resolved.

cc: R.F.; S.F.; Circu; PMSD/ISB; PM-25; PP#6F3380/FAP#6H5502; Glyphosate Reg. Std.; J. Stokes
RDI: JGarbus:7/24/87:PVErrico:8/31/87:RDSchmitt:8/31/87
TS-769:RCB:J. Stokes:js:Rm 805:CM#2:8/31/87