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OFFICE OF
PREVENTION, PESTICIDES AND
TOXIC SUBSTANCES

Subject: To Be Presented To The HED Metabolism Committee At The Meeting Of March 9, 1994: Glyphosate/AMPA Regulation

To: The Metabolism Committee

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INTRODUCTION

Glyphosate (N-phosphonomethyl glycine) is a nonselective herbicide and plant growth regulator that includes isopropylamine salt (Chemical Code 103601) and the sodium salt (Chemical Code 103603). It is registered for use on a large number of food and feed crops. Glyphosate is typically applied on these crops as postemergence spray to foliage of the vegetation controlled before planting, and after planting but prior to crop emergence, or as directed spray in established crops. In addition, glyphosate may be used in and around aquatic sites; treated water from aquatic sites may be used to irrigate crops. Codex MRL's are established in terms of glyphosate per se. The glyphosate RED issued September, 1993 and in that document the Agency indicated that AMPA would no longer be included in the tolerance expression for glyphosate.

Monsanto Company has informed the Agency that they have/are developing glyphosate resistant crops which would allow weed control using foliar sprays of glyphosate quite close to harvest. The metabolism of glyphosate in these transgenic crops results in a different ratio of parent compound to AMPA. For non-resistant plants the ratio of glyphosate to AMPA is 9 to 1 but it can approach 1 to 1 in a few cases (e.g., soybeans and carrots). In resistant soybeans however, AMPA ranges up to twice the level of glyphosate. A second consideration of the late post-emergence use of glyphosate on these resistant crops is that residues of parent and AMPA will be higher simply because the herbicide will be

applied foliarly at relatively short PHI's. The Registrant has conducted crop field trials which demonstrate that residues of glyphosate and AMPA will not exceed the present 20 and 15 ppm tolerances for soybean seed and hay respectively. Monsanto has indicated that residues of parent and AMPA will be higher in forage and that they will propose a higher tolerance for this commodity.

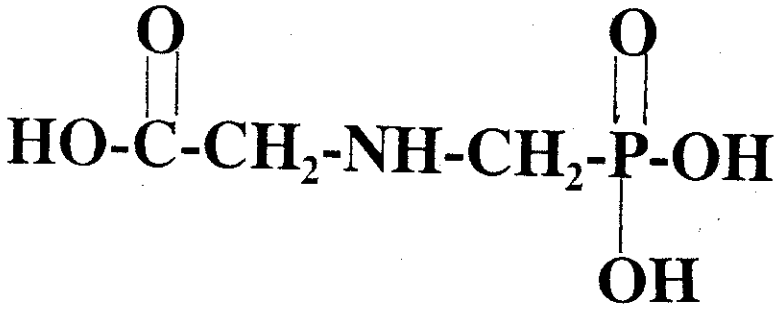
In summary, combined residues of glyphosate and AMPA will not be any higher in soybeans and probably other resistant crops under the new use, but the ratio of AMPA to parent will be somewhat different.

On the attached pages please find the structure of glyphosate and AMPA as well as details of the information summarized above.

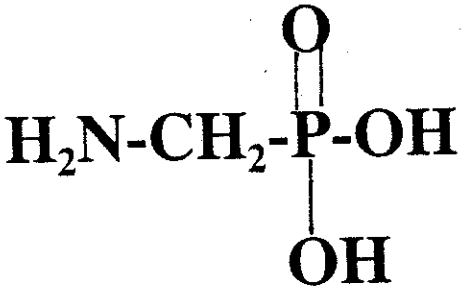
Question To The Committee

The HED Metabolism Committee has previously concluded that AMPA need not be included in the glyphosate tolerance expression.

Considering this new information, and in order to harmonize the U.S. tolerances with Codex MRL's, does AMPA need to be regulated?



GLYPHOSATE



AMINOMETHYL PHOSPHONIC ACID

(AMPA)

METABOLISM OF GLYPHOSATE IN SOYBEANS TOLERANT TO ROUNDUP® HERBICIDE IS THE SAME AS THAT IN PLANTS THAT ARE NOT TOLERANT.

Glyphosate is slowly metabolized to aminomethylphosphonic acid (AMPA):

- **Forage: ~85% glyphosate + ~7% AMPA.**
- **Hay: ~69% glyphosate + ~17% AMPA.**
- **Grain: ~28% glyphosate + ~56% AMPA.**

No other metabolites detected which were greater than 2% of total radioactive residues.

- **Trace level metabolites identified and/or characterized as amides of AMPA.**

Radioactive compounds in hexane extracts (oil) were demonstrated to be naturally occurring fatty acids.

Radioactive compounds not retained on strong anion exchange, cation exchange, and Chelex® Fe^{3+} chromatography have been characterized as natural products.

- **Radiolabeled natural products account for up to ~3.5% of total radioactive residues.**

MAGNITUDE OF RESIDUES STUDIES:

Field residue trials were established in both 1992 and 1993:

- **1992 trials were planted with maturity group V soybeans and focussed on the middle and southern soybean producing states.**

  19 trial locations in 16 states.

- **1993 trials focussed on northern soybean producing states and were planted with maturity group III soybeans.**

  16 trial locations in 10 states.

- **Combined 1992 and 1993 trial locations encompass >90% of harvested soybean acreage.**

- **Magnitude of residues were determined in raw agricultural commodities (1992 & 1993) and processed foods and feed (1992).**

MAGNITUDE OF RESIDUES STUDIES:

STUDY DESIGN:

- Four different treatment types to encompass all expected agronomic uses:

  All treated test plots received a preemergence treatment after planting but prior to crop emergence at an application rate of 5.7 lb a.e./acre.

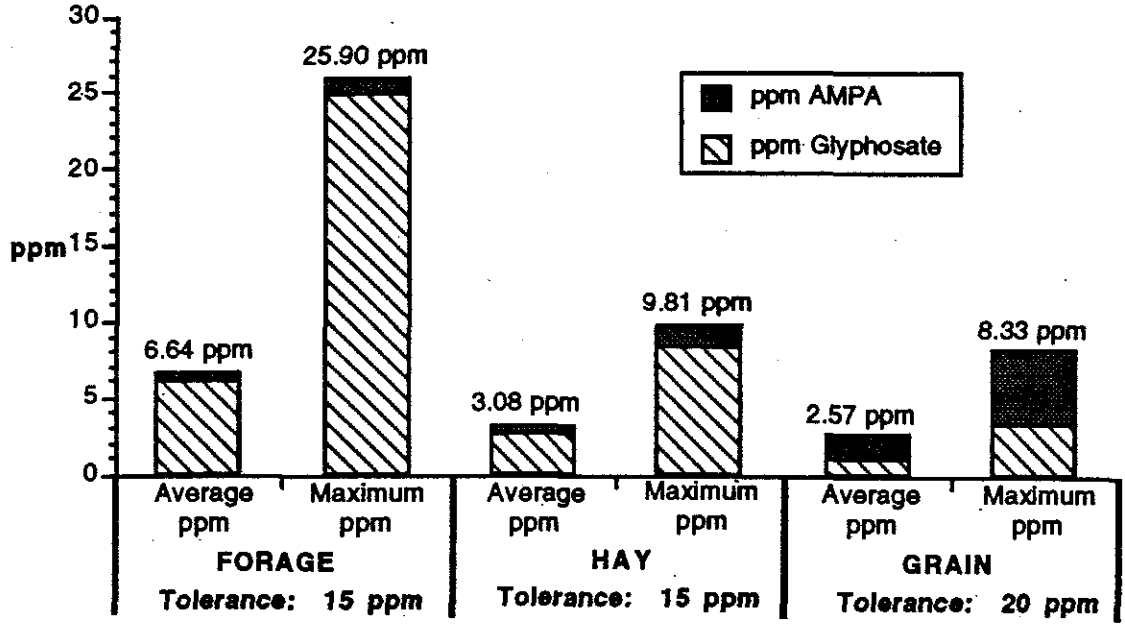
  1. Early postemergence treatment
  2. Late postemergence treatment.
  3. Sequential early postemergence + late postemergence treatments.
  4. Sequential early postemergence + late postemergence + preharvest treatments.

- Early postemergence treatments were made at approximately the V3 growth stage at application rates of 0.56 and 0.75 lb a.e./acre.
- Late postemergence treatments were made just prior to flowering at application rates of 0.75 and 1.50 lb a.e./acre.
- Preharvest treatments were made 10-14 days prior to harvest at an application rate of 0.75 lb a.e./acre.

MAGNITUDE OF RESIDUES IN RAW AGRICULTURAL COMMODITIES:

Sequential Applications:

- **Preemergence + early postemergence + late postemergence (5.7 + 0.75 + 0.75 lb a.e./acre).**

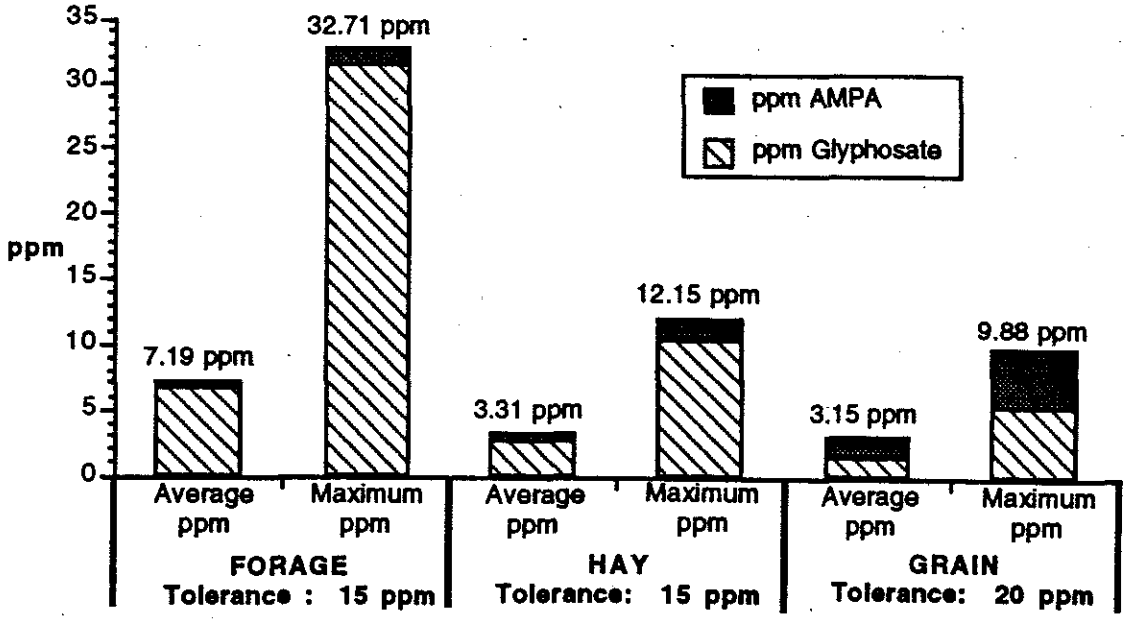


Matrix (Tolerance)	Average PHI (days)	Average ppm Glyphosate (max.)	Average ppm AMPA (max.)	Average ppm Total Residues (max.)
Forage:	10	6.21	0.43	6.64
(15 ppm)		(24.75)	(1.15)	(25.90)
Hay:	54	2.54	0.54	3.08
(15 ppm)		(8.41)	(1.40)	(9.81)
Seed:	94	1.07	1.50	2.57
(20 ppm)		(3.31)	(5.02)	(8.33)

MAGNITUDE OF RESIDUES IN RAW AGRICULTURAL COMMODITIES:

Sequential Applications:

- **Preemergence + early postemergence + late postemergence + preharvest (5.7 + 0.75 + 0.75 + 0.75 lb a.e./acre).**



Matrix (Tolerance)	Average PHI (days)	Average ppm Glyphosate (max.)	Average ppm AMPA (max.)	Average ppm Total Residues (max.)
Forage: (15 ppm)	10	6.74 (31.32)	0.45 (1.39)	7.19 (32.71) ✓
Hay: (15 ppm)	54	2.74 (10.49)	0.57 (1.66)	3.31 (12.15) ✓
Seed: (20 ppm)	15	1.62 (5.34)	1.53 (4.54)	3.15 (9.88) ✓

CONCLUSIONS:

1. The nature of the residues of glyphosate in soybeans tolerant to Roundup® herbicide are the same as those found in non-tolerant crops.

2. The magnitude of the residues of glyphosate following preemergence and postemergence applications of Roundup® herbicide to Roundup-tolerant soybeans following proposed label directions are within existing tolerances for hay, grain and processed fractions.

   - An increase in tolerances for residues in forage will be requested or a feeding/grazing restriction will be imposed.

RAC or Processed Fraction (concentration factor)	Maximum Combined Glyphosate and AMPA Residues (ppm)	Current Tolerance (ppm)
Forage	32.71	15
Hay	12.15	15
Soybeans	9.88	20
Fine Dust (0.65)	6.39*	20
Medium Dust (1.09)	10.73*	20
Course Dust (1.34)	13.24*	20
Hulls (2.68)	26.43*	100
Crude Oil (0.03)	0.26*	20
Refined Oil (0.003)	0.03*	20
Soap Stock (0.15)	1.52*	20

* Calculated by multiplying the concentration factor by the maximum combined residues in soybeans.

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Chemical:	**Glyphosate**
PC Code:	**417300**
HED File Code	**21400 MARC**
Memo Date:	**03/02/94**
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HED Records Reference Center
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