2-16-77

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UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

SUBJECT: Glyphosate, N-phosphonomethyl glycine, and its metabolite, aminomethylphosphonic acid, tolerances requested at 0.05 ppm in or on sugarcane and at 0.5 ppm for sugarcane molasses, TB evaluation of.

DATE: FEB 16 1977

FROM: Mary L. Quaife, Ph.D. TB/RD

TO: PM R. J. Taylor

PP No. 6F1758
FAP No. 6H5126

Monsanto Agr. Prods. Co.
St. Louis, No. 63166

CONCLUSIONS:

1. The "no-effect level" of the rat reproduction study on glyphosate is now considered to be 100 ppm (not 300 ppm) because of impaired fertility which occurred in a significant number of F2a and F3a dams.

2. The "no-effect level" of the 2-year rat feeding study on glyphosate is judged not determined, pending Petitioner's providing further information regarding the study. Petitioner should be asked to provide details of microscopic examinations which were made of livers of T-I and T-II (30-ppm and 100-ppm) rats for liver lipid (in the study, IBT No. B564, 1/14/74, Part N. Sec. C, PP No. 5F1536). Specifically, he should identify the T-I and T-II rats which were examined with respect to lipid in the liver and specify findings made in each such rat. By whom and when were the examinations made, and where are these specific findings recorded?

3. Since the plant metabolite of glyphosate, aminomethylphosphonic acid, is not formed in mammalian (rat) metabolism from glyphosate, TOX data on it are needed, e.g., minimum of rat 90-day feeding study.

RECOMMENDATION:

TB recommends that requested tolerances of this PP not be established because of deficiencies noted in Conclusions 2 and 3 (above).

INTRODUCTION:

Petitioner requests tolerances (memo title) noted for glyphosate for use as a herbicide.

Permanent tolerances exist at 0.1 ppm on grain crops; at 0.2 ppm on forage grasses and soybeans; and at 0.4 ppm on soybean forage and soybean hay (CFR 40:180.364 - cf. PP No. 5F1536).

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Requested tolerances at 0.2 ppm on citrus crop groups and at 0.4 ppm on dried citrus pulp were approved by TB (memo of Dr. D. Reisa, 3/17/76, PP No. 6F1733 and FAP No. 6H5115), but they are not yet established.

Temporary tolerances have been set at 5 ppm on cottonseed; at 10 ppm on soybean grain, soybean forage and hay; at 20 ppm on cotton forage; and at 0.1 ppm each in the liver and kidney of cattle, goats, hogs, horses, poultry, and sheep (ltr., Mr. J. B. Ritch, Jr. - Mr. L. H. Hannah, Monsanto, 9/7/76, PP No. 6G1757).

A temporary tolerance for sugarcane is pending (PP No. 6G1826).

The formulation, Roundup, EPA 524-308, is to be used in Hawaii only. It is to be applied at 3-3.75 lbs acid equivalent/acre before cane emergence or by spot treatment around the field. It contains 4 pounds of the amine salt or 3 pounds of the acid glyphosate per gallon. According to CB (memo of Mr. D. Duffy, 1/17/77, these petitions), adjuvants are cleared under Sec. 180.1001, and other inerts [redacted] will not cause residue problems.

The CB memo notes that metabolism of glyphosate in plants and animals (mammals) is adequately defined. In plants, C-N cleavage yields aminomethyl phosphonic acid and glyoxalate, fragments of which are incorporated into natural plant constituents. Mammals excrete most of administered C^{14}-glyphosate (90% in 5-7 days) in feces (75%) and urine. The major component of the residue is the parent compound.

The CB memo calls for following tolerances (instead of those noted in the title of this memo): 0.1 ppm, sugarcane; 2 ppm, sugarcane molasses; and 0.1 ppm each for liver and kidney of cattle, goats, horses, hogs, poultry, and sheep. Assurance is required that there are no nitrosamine-type impurities in the formulation. And the proposed enforcement analytical method, A gas-liquid chromatographic one, is now called acceptable despite rather low recovery values for reasons noted in the memo. On 1/21/77, Petitioner amended Sec. F. to reflect these changes.

TOX DATA:

No new TOX data are submitted herewith. Sec. C of current submission incorporates "Masterfile for EPA 524-398" by reference. As we lack access to such masterfile, pertinent TOX data of previous petitions, including animal metabolism data, are noted by this reviewer.

INERT INGREDIENT INFORMATION IS NOT INCLUDED

A TOX review of 2-year rat and dog feeding studies on glyphosate by Dr. D. Reisa (1/28/75, PP No. 5F1536) finds respective "no-effect levels" for these to be 100 ppm (with liver lipid inclusions shown at 300 ppm) and 300 ppm (highest level fed), respectively. The rat study was negative for tumorigenicity. That review includes copy of early summary of pertinent TOX data compiled by Mr. R. Landolt. Further acute TOX data are included in Mr. L. Chitlik's review of 5/17/76 in PP No. 6F1757. Studies on it for cholinesterase effects and delayed neurotoxicity are contained in PP No. 6G1679.

EVALUATION:

We have checked original accounts of pertinent glyphosate TOX studies, and we agree with previous reviewers as to significance of results and on "no-effect levels," as follows: Ninety-day dog feeding (2,000 ppm); 90-day rat feeding (2,000 ppm); mouse mutagenicity (dominant-lethal) (10 mg/kg); rabbit teratologic (30 mg/kg); 18-month mouse carcinogenicity (negative at top level, 300 ppm); 2-year dog feeding study (300 ppm).

We find the rat reproduction "no-effect level" is 100 ppm (rather than 300 ppm); since, according to the study report (IBT No. B566, 7/26/73 - Part K, Sec. C, PP No. 5F1536, p. 2), "Animals fed 300 ppm CP 67573 (glyphosate) exhibited reduced mating, fertility, and pregnancy indices during the first litters of both the second and third generations (F2a and F3a litters) (and)....all apparently non-fertile dams (were) omitted from the second mating trials (5 (from) F2b and 6 (from) F3b)" - which is not acceptable practice.

In the rat 2-year feeding study, according to the report (Part N, Sec. C, PP No. 5F1536, IBT No. B564, 1/12/74), "Livers of animals in the 2 lower dosage groups (T-I and T-II) were examined particularly for lipid," (p. 6), and, "The amount of lipid in the livers of the control, T-I and T-II animals appeared to be comparable," (p. 39). Yet the report of the Pathologists, Drs. W. R. Richter and D. E. Gordon (pp. 40-55), neither specifically mentions examining livers of rats from these groups for lipid content nor tabulates any findings on liver lipid in such rat livers; although it does tabulate findings on liver lipid in T-III-group (300-ppm) rats.

We note that the 100-ppm "no-effect level" for this study is based on presumed lack of occurrence of lipid in liver of these 100-ppm (as well as 30-ppm) rats. Therefore, we ask Petitioner to supply details of examination of livers of T-I and T-II rats for lipid - specifically, to identify rats whose livers were examined and to specify findings in each one. By whom and when were the examinations made, and where are specific findings with regard to liver lipid recorded?

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Pending receipt of above data, we consider that a "no-effect" level is not established for this (2-year) rat study.

Mr. R. Landolt reviewed animal metabolism data on glyphosate and related compounds in detail in his review of 5/15/74, PP No. 4G1444. Metabolites of labeled-(C^{14})-glyphosate of rats which received it either by stomach tube or, ip, at 6.7 mg/kg or by 21-day dietary feeding at 100 ppm were identified in both urine and feces. The ca. 7% each of aminomethyl phosphonic acid and methylaminomethyl phosphonic acid found in fecal extracts was determined to result from impurities in the glyphosate, rather than from animal metabolites. "N-phosphonomethyl-^{14}C-glycine (glyphosate) remains unchanged in the rat through three different types of treatment and is excreted in urine and feces as the parent compound."

Thus, aminomethyl phosphonic acid, the chief plant metabolite of glyphosate, is not a mammalian (rat) metabolite of glyphosate. Therefore, its toxicity would not be evaluated in feeding studies on parent compound, glyphosphate. Accordingly, toxicity testing of the aminomethyl phosphonic acid (minimum of rat 90-day feeding study) is judged needed.

In PP's Nos. 6G1757 and 6G1862, TB memos (of 5/17/76 and 11/18/76, respectively), have called for both cholinesterase inhibition data and delayed neurotoxicity test (hen) on glyphosate. However, since glyphosate has unsubstituted hydroxy (OH) groups on the phosphorus atom (as does its plant metabolite, aminomethyl phosphonic acid), it would appear theoretically not possible for either of these compounds to inhibit cholinesterase. (cf., e.g., D. F. Heath's "Organophosphorus Poisons - Anticholinesterases and Related Compounds," Pergamon Press, Oxford, London, New York, and Paris, 1961, p. 5.) If so, neither cholinesterase inhibition nor delayed neurotoxicity tests are needed.

Nonetheless, test data on effect of acute oral administration of glyphosate on inhibition of cholinesterase of plasma, RBC's, and brain of rats (IBT No. 301 06527, 3/7/75) and on delayed neurotoxicity in hens (IBT No. 8580-09117, 12/22/76), supplied by Petitioner, show glyphosphate to be negative for either effect in systems tested (for details, cf. TB review of Mr. R. Landolt, PP No. 6G1679).

We do not find either cholinesterase or delayed neurotoxicity studies needed on the glyphosate plant metabolite, aminomethyl phosphonic acid, for reasons noted above.

MLQ. 4/25/77

Mary L. Quaife, Ph.D., TB/RD
January 25, 1977

Reviewed 2/16/77

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