MAR 25 1985

UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON D.C. 20460

MAR 4 1985

MEMORANDUM

OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

SUBJECT: Consensus Review of Glyphosate
Caswell No. 661A

TO: Robert Taylor
Product Manager
Herbicide - Fungicide Branch
Registration Division

On February 11, 1985, a group of Toxicology Branch personnel met to evaluate and discuss the data base on Glyphosate, and in particular the potential oncogenic response of Glyphosate.

A. The following persons were in attendance:

Theodore M. Farber, Ph.D.
Chief, Toxicology Branch

Louis Kasza, D.V.M., Ph.D.
Pathologist

Bertram Litt, Statistician

Herbert Lacayo, Ph.D.
Statistician

Reto Engler, Ph.D.

William Dykstra, Ph.D.
Reviewer

Steve Saunders, Ph.D.

Laurence Chitlik, D.A.B.T.

The signatures above indicate concurrence with this concensus report.

B. The material available for review consisted of a package issued on January 25, 1985 (attached) and a letter from Monsanto (dated February 5, 1985), rebutting the significance of renal mouse tumors.

C. Evaluation of the Facts:

1. Long-term/Pivotal Studies:

a) A 26-month rat study showed a NOEL at 30 mg/kg/day which was the HDT. The oncogenic potential at this level was negative, corroborated by an outside consultant. Although some thyroid tumors were observed in female rats in this study they were generally discounted in their significance, in and of themselves. However, it should be noted that on a mg/kg/day basis the exposure of rats was less than 1/100 of the exposure of mice (4,500 mg/kg/day). Since a toxic, or MTD, level was not reached in this study, the panel raised the conjectural issue that at toxic levels at or close to a MTD, tumors might have been induced.

b) The NOEL in a rat 3-generation reproduction study was 10 mg/kg/day. In separate teratogenicity studies feto toxic effects were noted in rats and rabbits at levels which caused significant maternal toxicity, including death; terata were not observed (ibid). These results were, however, not entered into the discussion on Glyphosate.

2. Mutagenicity Assays:

Glyphosate was tested for mutagenic activity (1) Reverse Mutation in S. typhimurium. and E. coli with and without microsomal activation, (2) Ames Assay with and without activation, (3) CHO cells with and without activation, (4) DNA repair in rat hepatocytes, (5) Rec-assay in B subtilis, and (6) Dominant lethal assay in mice. All these tests were negative, tests 1-3 are fairly well predictive of oncogenic response while 4-6 are less appropriate. An in vivo bone marrow cytogenetics study was also performed. It was negative, but scientifically not acceptable. In summary, several appropriate and scientifically acceptable tests are supportive of non-oncogenic potential of Glyphosate.

3. In the chronic mouse study carried out by Biodynamics (#BD 77-420) renal tubule adenomas were observed in males.

Dose (ppm)	0	1000	5000	30,000
No. Exposed	49	49	50	50
Tumors	0	0	1	3

See review of W. Dykstra (dated 9/4/84).

or even in Charles River CD-1 male mice.

The probability of observing this tumor 4 times or more in 198 mice (the total number of mice examined in the Glyphosate study) is p = 0.0064 when considering the historical control of the same laboratory. Even considering other reported historical controls, the p-value is low, about 0.01 indicating that it is very unlikely that the glyphosate test group is consistent with any historical controls. (See review by Dr. Lacayo).

In addition, the response rate (see above) seems to be related to the dose.

Therefore, it was the concensus of the group that the renal tubular adenomas were related to compound administration, since their frequency was not consistent with the historical controls and there is a trend indicating dose dependency.

3a. The group noted that there were other non-oncogenic, i.e., toxicological changes apparant in the kidney and liver e.g., central lobular hepatocyte hypertrophy and necrosis and chronic interstitial nephritis in males and proximal tubule epithelial basophylia and hypertrophy in females. The group discussed the possibility of kidney irritation and forsulation of crystals but noted that kidney or bladder precipitaters were not reported for this assay. Therefore, a conclusion mitigating the renal tumors could not be reached. (See page 10 of contractor review).

D. Other Considerations:

The review panel recognizes that the exposure of mice was at a very high level 4.5 g/kg/day. Precipitation of Glyphosate in the kidneys might have occurred but none was reported. The panel believes that additional sectioning of new blocks of male kidneys might help in the interpretation of the study results. The kidney tumors as reported, were unilateral (pers. communication by Dr. Dykstra, after the panel meeting); additional histopathology could resolve the issue of whether this is a valid observation or due to not "finding" the tumors in the particular block analyzed.

The panel also believes that realistic exposure assessment, both for dietary and worker exposure are of singular importance. For example, the limit of detecting residue tolerances may overestimate exposure. Particular emphasis also should be given to residues in water, since Glyphosate has been used for aquatic weed control (EUP) and this use may become the subject of a permanent registration.

E. Classification of Glyphosate:

In accordance with EPA proposed guidelines (FR of Nov. 23, 1984) the panel has classified Glyphosate as a Category C oncogen.

ADDENDUM:

The letter by Monsanto (Feb. 4, 1985) has been considered in these deliberations. Several of the issues raised are, in fact, addressed in the above deliberations, although not point by point. A point by point rebuttal, including those points with little merit, will be done in addition to this evaluation.

Attachments

cc: B. Coberly
Caswell No. 661A