UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
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OFFICE OF
PESTICIDES AND TOXIC SUBSTANCES

MEMORANDUM

SUBJECT: Glyphosate - Monsanto Comments to Glyphosate Guidance Document

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THRU: Edwin Budd, Section Head
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and

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Requested Action

Review Monsanto's comments relative to Glyphosate Guidance Document (Registration Standard). Monsanto specifically requests a waiver of the inhalation LC_{50} with glyphosate and a waiver of a repeat mouse oncogenicity study with glyphosate.

Conclusions and Recommendations

1. TB concurs with Monsanto's waiver request regarding the acute inhalation study with glyphosate technical. The study is not required.

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2. TB does not concur with Monsanto regarding the waiver of the repeat mouse oncogenicity study (see discussion in review section).

TB requires that the mouse oncogenicity study be repeated in males only, using larger numbers of animals for each dose level to increase the statistical power of the bioassay. Possibly 200 mice per group may be needed.

For the repeat study the HDT should be 30,000 ppm since, at that dose level, the "equivocal" increase in kidney tumors was observed in the previous study. Additional doses of 15,000 and 7500 ppm are also recommended, which may provide an indication of a possible dose-response relationship.

Other experimental variables should be the same, as much as possible, as the previous mouse oncogenicity study.

A "tier approach" to histopathological examination of tissues/organs will be acceptable. Specifically, sections of kidney and liver should be examined from all high dosage level and control animals. In addition, all grossly observed findings suggestive of possible tumors should also be examined from all animals in all groups in the study. If the above examinations do not suggest a potential oncogenic response, then additional histopathological examinations will not be necessary.

The registrant should provide a protocol of the repeat study before the experimental work is initiated.

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Review

Issue Number I: Acute Inhalation LC_{50} Study With Glyphosate

In the Glyphosate Guidance Document, EPA stated that an acute inhalation study with glyphosate technical has not been submitted and is required.

Monsanto's Response

"There appears to be no justification for an acute inhalation study with glyphosate because: (a) People are not exposed to glyphosate. If any exposure does occur, it is either to the isopropylamine or sodium sesqui salts of glyphosate. Adequate inhalation toxicity studies have been or are being conducted with these end-use materials. The results of available studies indicate a relatively low degree of acute inhalation toxicity; (b) glyphosate is a nonvolatile solid material which is handled in manufacture as a wet cake (10-15% moisture) which precludes any inhalation exposure. We therefore request the Agency concur with Monsanto's opinion that this acute inhalation study is not required per Section 158.135, 81-3 Guidelines since glyphosate is not an inhalable material."

TB Conclusion and Recommendation

TB concurs with the Monsanto waiver request regarding the acute inhalation study with glyphosate technical. The study is not required.

Issue Number II: Repeat of the Mouse Oncogenicity Study

In the Glyphosate Guidance Document, the Agency requested a repeat of the chronic feeding/oncogenicity study in mice to fully address the question of ". . . whether the apparent effects noted in the mouse study (renal tubular adenomas) are biologically relevant."

Monsanto's Response

"The results of the mouse bioassay do not provide positive, or even suggestive, evidence of carcinogenicity. The most that can be said is that the results were equivocal as, in fact, the Scientific Advisory Panel stated. Furthermore, the SAP pointed out the fact that this equivocal finding occurred only at a dose level that exceeded the MTD. Quoting from the SAP report, '. . . no oncogenic effect is demonstrated using concurrent controls' and '. . . the level of concern raised by historical control data was not great enough to displace putting primary emphasis on the concurrent controls.'

There appears to be no justification for requiring the repeat of a study with equivocal findings at a single site, only at dosage levels exceeding the MTD."

"Several expert toxicologists intimately familiar with the glyphosate chronic/oncogenic mouse study results, and personally involved in the SAP hearing on this issue, were asked to evaluate the need for a repeat study. All experts agreed that additional testing is not justified since the current study was conducted at levels exceeding the MTD and failed to demonstrate a treatment-related oncogenic effect. Their evaluations are enclosed in this part."

"As discussed previously, the fact Monsanto has agreed to repeat the chronic/oncogenic rat study with glyphosate diminishes even further the justification for a repeat mouse study."

"The results of the current rat and mouse studies, along with results to be obtained from a repeat rat study, should be sufficient to assess the oncogenic potential of glyphosate. A repeat mouse study is not necessary."

"Finally, based upon a review of the principles expressed in the Agency's draft 'Position Paper on Maximum Tolerated Dose (MTD) in Oncogenicity Studies,' it is clear that the chronic/oncogenic mouse study was conducted at dosage levels which greatly exceeded the upper limit of 7000 ppm required for mouse studies. Furthermore, none of the requirements listed in that document which would necessitate a study are fulfilled for the mouse study (see Attachment 1)."

TB Conclusion and Recommendations

Regarding the need to repeat the mouse oncogenicity study with glyphosate, TB fully concurs with the conclusion and recommendation of the Scientific Advisory Panel (SAP) viz "The Panel proposes that Glyphosate be categorized as Group D (not classified) and that there be a data call-in for further studies in rats and/or mice to clarify unresolved questions." In view of the equivocal oncogenic response in the first mouse study, TB believes the oncogenic potential of glyphosate in mice still remains unresolved and that a repeat mouse study is necessary to fully and adequately assess this potential.

TB would also point out that the "Position Paper on Maximum Tolerated Dose (MTD) in Oncogenicity Studies," referred to by Monsanto, is a discussion of general principles that may be useful in the interpretation of oncogenic studies and as an aid in determining the need to repeat studies. As such, it is intended to provide guidance rather than rigid rules.

When the circumstances of a particular situation indicate a strict application of the document may be inappropriate, TB will give precedence to what it believes is most prudent for the specific case at hand.

In the case of glyphosate it is recommended that the mouse oncogenicity study be repeated and that the highest dosage level tested be 30,000 ppm, as in the first study, rather than 7000 ppm (or 1000 mg/kg/day) as "suggested" in the MTD document. This dosage level requirement is being imposed to clarify the equivocal results observed at this same dosage level in the first study and in so doing to assess the full potential of glyphosate to induce tumors in mice. It is noted that at this dosage level (30,000 ppm) in the first mouse study, survival of male mice at 24 months was increased compared to male control mice; therefore, this dosage level is not a life-shortening level. It is also recommended that the mid and low dosage levels in the repeat mouse study be 15,000 and 7500 ppm, respectively, rather than 5000 and 1000 ppm as in the first study. The reason for this is to provide an adequate experimental basis for establishing a dose-response relationship if, in fact, a positive oncogenic response came to occur in the repeat study.

In addition, TB recommends that only male mice be tested in the repeat study because the tumors of particular concern, renal tubule adenomas, were only observed in male mice in the first study. However, since renal tubule adenomas are so rare (or at least infrequently observed), TB also recommends that larger numbers of animals be used for each dosage level to increase the statistical power of the bioassay. Possibly, 200 male mice per group may be needed.

TB, then, considers the repeat mouse study to be a specially designed study for the specific purpose of clarifying certain unresolved questions relating to the potential oncogenicity of glyphosate. Hence, the recommendations are that the study be performed at dosage levels of 30,000, 15,000, and 7500 ppm; that only male mice need be tested; and that 200 mice per group may be needed. Similarly, because of the limited nature of the concerns prompting this repeat study, TB will accept a "tier approach" to the pathological examinations in this study. First, a very thorough and complete gross necropsy should be performed on all animals in this study, particularly noting all findings suggestive of possible tumors. Second, a full and complete set of tissues/organs should be excised and fixed from each animal in the study (for possible future need). Third, it will only be necessary in the "first tier" to do the following:

1. Process and examine multiple sections of kidney and liver from all high dosage levels and control animals in the study.

2. Process and examine all grossly observed "findings" suggestive of possible tumors from all animals in all groups in the study.

If the "first tier" examinations do not suggest a potential oncogenic response, then additional histopathological examinations will not be necessary.

The registrant should be requested to submit a proposed protocol for the repeat mouse study to the Agency for comment before the experimental work is initiated.

Regarding the comments of Monsanto's experts (Drs. Squire, Goodman, and Stemmer), the SAP considered their opinions but nevertheless believed the mouse kidney tumors to be "equivocal" and recommended further studies in rats and/or mice. TB concurs with the viewpoint expressed by the SAP.