Monsanto

Glyphosate Correspondence

DMEH CENTRAL FILES

FROM (NAME—LOCATION—PHONE) T.J. Long /C2SK /[redacted]

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SUBJECT : Glyphosate Reregistration Standard

REFERENCE :

TO : F. S. Serdy / C2SC

cc: T.F. Armstrong /C2SC
E.E. Debus /C2SC
T.W. Fuhremann /C2SK
R.L. Harness /C2SB
T.J. Hoogheem /C2SC
R.W. Street /C2SC

After reviewing the referenced document, I would like to make the following suggestions for our response to the requirements for additional testing.

I. Rat and Mouse Oncogenicity Studies

Several approaches could be taken:

1. Present arguments for not repeating either study based upon the principles discussed in the Agency's MTD position paper (Attachment 1). We might also add that repeating these studies will not enable one to evaluate potential human risk any better than with the currently available information. The available studies have already tested dosages which are 1300 to 200,000 times greater than possible human exposures. Even if one were to assume the worst case and conclude that the mouse kidney tumors were treatment-related, when an adequate risk assessment is conducted[1], the risks for man are insignificant.

   If successful, this approach has the following downside: EPA's response may be: "Fine, don't repeat either study. We will just put you into class C."

2. Agree to repeat the rat study and vehemently argue the lack of justification for a repeat mouse study. Again, the reasons for not repeating the mouse would be

   a) Failure to meet any of the criteria stated in the MTD paper that require a repeat study. The only weak link in this argument is at level 2 of the tier scheme. Level 2 states that if the substance was not oncogenic in an acceptable study in another specie, consideration at the next level is required. The EPA does not consider the rat study to be acceptable. However, we have already agreed to repeat the rat, and none of the other criteria necessitating a repeat are met.

UNITED STATES DISTRICT COURT
NORTHERN DISTRICT OF CALIFORNIA
TRIAL EXHIBIT 515
Case No. 3:16-cv-0525-VC
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b) Ted Farber's statement during the SAP hearing that "If in fact there wasn't a remaining MTD issue in regard to the rat study, and the rat study was run at a somewhat higher level and nothing was seen, then basically the whole thing comes out as no evidence of carcinogenicity." If we repeat the rat study at higher levels and see nothing, the issue should be settled.

c) Failure of the proposal to increase the number of animals per group to significantly alter the statistical power of the study. The Agency states that repeating the mouse study with larger numbers of animals per group will increase the statistical power of the study. Attachment 2 graphically depicts the probability (y-axis) of detecting a statistically significant difference between the true control group renal tumor incidence (assumed to be 0.368%, based upon Bio/dynamics historical control data) and the true treated group incidence (x-axis) for groups of different size, using the Fisher exact test (p=0.05). For example, if the true treated group incidence was in fact 6% as observed in the Bio/dynamics mouse study, then there is only a 26% probability of getting treated group incidences which would be declared significantly different from control. If the group sizes are increased to 75 or 100 animals each, then the probability of getting statistically different incidences rises to 44 and 58%, respectively. Thus, even when group sizes are doubled over the 50/group used in the current study, there is still only slightly greater than a 50/50 chance of such a true difference being statistically detectable. Approximately 200 animals/group would be needed to detect a significant difference with 90% probability, at an estimated cost of $1.4 million.

The Agency's argument is even less relevant if the 6% treated group incidence occurred strictly by chance, and the true treated group incidence is closer to the spontaneous background rate of 1.1% (as discussed by Dr. Gaylor on pages 46-47 of the SAP hearing transcript). In such a case it wouldn't matter whether 50, 75, or 100 animals/group are used. No significant gain in statistical power is achieved unless 1000 or more animals/group are employed. Such an experiment would probably cost in excess of $5 million.

Finally, as discussed in point 1) above, the results of detailed risk assessments have already shown that, even if real, the carcinogenic risks for man calculated from the mouse study data are in the range of 10^{-8} to 10^{-14}. Therefore, the risks are insignificant and a new study is not needed to assess potential human risk.

If we decide to take this approach, we should indicate that the maximum dose tested in the repeat 90-day rat study will be 20,000 ppm per the EPA MTD position paper. Dosage levels for the repeat oncogenic rat study will then be selected based upon the 90-day study results, but in any case would not exceed 20,000 ppm in the diet.

3. Repeat only the mouse study, and only to a maximum dosage level of 7,000 ppm. Since the major issue concerning the EPA appears to be the kidney tumors observed in this study, a repeat mouse study will address this question. The current rat study is a valid chronic/oncogenicity study and does not demonstrate any oncogenic potential for glyphosate. None of the criteria described in the MTD position paper which would necessitate a repeat study are met, especially if a new mouse study is conducted. Thus, if we repeat the mouse study and it turns out to be clean, there should be no question that glyphosate is not oncogenic. The only touchy issue is -- how high do we test in the repeat mouse study? Will the Agency require that we test to 30,000 ppm again to specifically address the kidney tumor issue, or can we get them to abide by the 7,000 ppm limit as described in their MTD paper?

4. As a final fall-back position, if necessary, we could agree to repeat the oncogenic rat study as discussed in point 2) above, and agree to a partial mouse oncogenicity repeat. For example, we could conduct a study where only male mice are used and where only the kidneys are evaluated. Furthermore, the highest dose tested should only need to be 7,000 ppm in the diet per the Agency's MTD position paper. I feel this should be the last, and least desirable, position that we should take on the issue of repeat studies.

II. Glyphosate Acute Inhalation Study

Originally, I felt that we could request a waiver of this requirement based upon two points. First, if the percent of glyphosate particles less than 10 microns (respirable size) was relatively low, exposure to toxicologically significant levels would be minimal. Second, since any potential for occupational glyphosate exposure would be to the wet cake, there really is no potential for exposure to dusts since the material is wet.

Based upon preliminary information obtained by Bob Street, it appears that the first argument will not fly. Based upon analyses of six lots of glyphosate, the average particle size

appears to be around 5 microns. Thus, a large part of the glyphosate particles would be respirable. The second point, regarding the physical state of the material, still should be a valid argument.

In addition, the argument could be made that the real potential for occupational exposure, if any exists, is due to applicator/mixer exposure to formulated products. We have already conducted acute inhalation studies with Roundup® herbicide and other formulations with glyphosate concentrations ranging from 0.6 to 30%. Since these concentrations cover the range of expected human exposures, any hazard due to glyphosate exposure has already been adequately assessed.

III. Guinea Pig Dermal Sensitization Study With Glyphosate

A study with glyphosate in guinea pigs has been conducted (BD-83-008). We should inquire as to the reason why this study is listed in tables A and B as a data requirement.

I would be glad to discuss these comments with you if you wish.

Timothy J. Long

/jb

attachments: 1 & 2

References

1. Shipp, A.M., et al. Worst case analysis on forest plantation herbicide use. K.S. Crump and Company, Inc. for the Forest Land Management Division, Dept. of Natural Resources, State of Washington, 1986.