

Message

From: MARTENS, MARK A [AG/5040] [/O=MONSANTO/OU=EA-5040-01/CN=RECIPIENTS/CN=21606]
Sent: 8/11/2003 8:27:04 AM
To: HEYDENS, WILLIAM F [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=230737]; WEBSTER, SUSAN [AG/5040] [/O=MONSANTO/OU=EA-5040-01/CN=RECIPIENTS/CN=127676]; FARMER, DONNA R [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=180070]
CC: GARNETT, RICHARD P [AG/5040] [/O=MONSANTO/OU=EA-5040-01/CN=RECIPIENTS/CN=107838]; DIRKS, RICHARD C [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=214797]; BROECKAERT, FABRICE [AG/5040] [/O=MONSANTO/OU=EA-5040-01/CN=RECIPIENTS/CN=591489]
Subject: RE: K-salt of glyphosate - MON 78623

Bill,

I understand what you are saying.

The regulatory toxicologist I was in contact with first wanted to have us done a 28-day inhalation study. I managed to convince him that this doesn't make any sense. The reason why they insist on having a clear view on the real toxicity of the K-salt are the read-across (in other words structure activity relationship) rules of the new substance notification procedure in the EU. That means that we are allowed to borrow data from a similar substance (in this case the acid) for notification reasons if we can prove through a couple of simple tests that the toxicity is the same. These simple tests are an acute tox study, and Ames test and a Daphnia tox test. Since we are in the possession of the inhalation tox study we had to notify them of that study. As you know the results of this study are quite different from those of the acid and that brings them in embarrassment to declare the glyphosate acid similar to the K-salt. In other words they may reject the complete glyphosate acid database.

In the meantime, the notification procedure within the framework of the dangerous substances directive has become redundant (because of the Annex I inclusion of 91/414) and the authorities are willing to take this into consideration.

Nevertheless, they want to know whether the three death are due to an experimental incident or to real substance related toxicity. The most obvious acute toxicity that would be expected is that of the potassium (leading to heart fibrillation). Another possibility is that the animals died of the osmotic effect of the inhalation of an aerosol of a concentrated salt solution, but this would have caused fluid retention in the lungs which was not observed in gross necropsy. We eyeballed through the MON 21200 studies and couldn't find a reason why potassium could have been the origin of the deaths. We are going to have a closer look to all this and Fabrice will get back to you with a more detailed report.

If we can show that the in a repeat test there are no deaths anymore of the same kind (occurred during the exposure period) I believe that they will get off our back. A single dose level test at 2.0 mg/L using 10 animals would do (preferable 5 males and 5 females).

The Ames test (I presume executed according to OECD protocol and GLP) for Brazil will do.

Regards, Mark.

-----Original Message-----

From: HEYDENS, WILLIAM F [AG/1000]

Sent: Friday, August 08, 2003 6:11 PM

To: WEBSTER, SUSAN [AG/5040]; FARMER, DONNA R [AG/1000]

Cc: MARTENS, MARK A [AG/5040]; GARNETT, RICHARD P [AG/5040]; DIRKS, RICHARD C [AG/1000]

Subject: RE: K-salt of glyphosate - MON 78623

Susan,

First, the easy part. Terry tells me that we have an Ames test on a K-glyphosate formulation done for Brazil. Could we use that? Terry will send out the composition of that formulation.

Regarding acute toxicity, Terry, Donna and I reviewed mortality data from the inhalation database for IPA-, NH4-, MEA- and K-glyphoste formalations. Based on the mortality data seen in those studies, it is not outside the realm of possibilities that the 3 deaths were treatment-related. That having been said, we are willing to reconsider running another exposure that targets 2.0 mg/L. We would suggest males only, and increase "n" to 10. This would cost about \$14,000. But first, I have 2 questions for you & Mark:

1) Do you feel confident that you can get the regulators to totally ignore the 3 deaths in the previous study if we get no deaths in a follow-up study?

In the US, we have had a very difficult time getting EPA to ignore previous data no matter how good the subsequent study(ies) is (are).

2) What if we get 1 or 2 deaths in a follow-up study - what would be your message to the regulators, and would this get us to a better regulatory position?

Again, we feel this scenario is a real possibility.

Best regards,

Bill

-----Original Message-----

From: WEBSTER, SUSAN [AG/5040]

Sent: Friday, August 08, 2003 2:54 AM

To: FARMER, DONNA R [AG/1000]; HEYDENS, WILLIAM F [AG/1000]

Cc: MARTENS, MARK A [AG/5040]; GARNETT, RICHARD P [AG/5040]; GOLDSTEIN, DANIEL A [AG/1000]

Subject: K-salt of glyphosate - MON 78623

Donna and Bill,

I discussed briefly at one of our CSWG meetings the problems we are having with our New Substance Notification for the K-salt of glyphosate and we would like your support with some issues that have not yet been resolved. The ministry in charge has come back to us several times and they are not moving our file forward until they get clarification on a couple of toxicology points. We were finally able to get the name of their toxicology expert working on our file and Mark has been in contact with him a couple of times already.

Here are the issues that we need to address:

Data bridging: most of our file relies on the bridging of data between the K-salt and either glyphosate acid or other salts. The authorities here use specific guidelines to assess whether a 'read-across' of data is acceptable, and this specifies a minimum tox battery that includes comparing Mutagenicity potentials. They are therefore requesting an

Ames test on the K-salt before they can feel comfortable with the bridging. We do not have an Ames test in our files here and are therefore assuming it is not available. Please tell me if this is wrong. If not, is it our intention to run this test or not- or could we consider doing this?

Inhalation toxicity: the problem is still around the 3 unexplained deaths in the acute inhalation test. This raises alarms as to the reliability of the bridging we just discussed. They wanted us to run an additional 28-day inhalation test but, after discussion with Mark, they are now asking that we repeat the acute inhalation test, in order to verify whether the deaths during the exposure phase repeat themselves. As we have no explanation to give around these 3 deaths, we feel that all regulatory authorities will come up with the same question. Here is an excerpt from a message I just received from Mark :

"Fabrice and I looked into the possibility of K-induced cardiac toxicity in the rats exposed to K-salt by inhalation. The key for the interpretation of this are the serum levels of K as a result of K-salt exposure. In order to get an idea what the relationship is between ingested K and serum levels in rats we had a look at the toxicology database of MON 21200 which is a K-salt. We discovered that the total daily dose of the rats in the acute K-salt study is not enough to overrun the homeostatic correction of serum K levels. In other words the K serum levels of the exposed rats would have been normal and thus of no influence to cardiac function. In conclusion, the three deaths during the exposure period may have been due to an experimental error rather than to compound related toxicity. Fabrice will produce a more detailed report next week."

It therefore seems that the exposure numbers don't make it likely that the salt concentration was high enough to induce condensation in alveoli and an osmotic effect, with extraction of liquids that could lead to chemical pneumonitis. We are therefore left with an unexplained toxic effect and we feel we may want to choose to re-run the test to explore this further.

The New Substance Notification is the first regulatory process for us in Europe. The fact that we have not been given the green light may affect our ability to do test batches of MON 78273 formulations- which were already postponed from August to the Fall. In the meantime, we have submitted a registration file for the formulation MON 78273 in the UK- based on results on the similar US formulation MON 78270. We therefore expect that we'll have to report on this inhalation effect in several instances and would like to be prepared to argue our case when authorities (like the Belgian Ministry today) do not accept the irrelevance of inhalation aerosol testing for liquid formulations which do not give rise to any inhalation risk for the user. As we are hoping for a UK registration in February, and to have had the formulation production and stability tested before that in order to sell as soon as we get the registration, all of this is rather urgent today.

One other point of importance: The new formulation MON 79531 is planned to be a G3 replacement with a clean hazard label. We do not plan to run an inhalation study on the formulated product, but:

- if the K salt tech is classified for inhalation, then the content in MON 79531 is sufficient to cause the formulation to be classified as well.
- we might then have to undertake an inhalation study on this formulation to try to remove this classification

My questions to you are as follows:

- When could we expect to get results of an Ames test if you agree to run it?
- What is your expert assessment of the acute inhalation test results?
- If there is no explanation today for the deaths that occurred during the exposure, do you agree that we should re-run an inhalation test and try to get more information in case the deaths do repeat themselves? If so, how quickly could we hope to get these results?

Many thanks for your guidance and best regards,

Susan

MONNET [REDACTED]

[REDACTED] [REDACTED] [REDACTED]
[REDACTED] [REDACTED]
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