

Message

From: [Redacted]
Sent: 6/8/2009 8:42:29 AM
To: GOLDSTEIN, DANIEL A [Redacted]
CC: FARMER, DONNA R [Redacted] ADAMS, STEPHEN A
[Redacted]
Subject: RE: Draft Glyphosate paper
Attachments: glyphosate case series May 5- DAG + AM + MB.DOCX

Dan,

After a quick scan, just 3 comments on the attached. Looks good!

Regards

[Redacted]

From: GOLDSTEIN, DANIEL A [Redacted]
Sent: 02 June 2009 21:30
To: Darren Roberts; [Redacted] 'Nick Buckley'; 'michael eddleston'
Cc: FARMER, DONNA R [Redacted] ADAMS, STEPHEN A [Redacted]
Subject: RE: Draft Glyphosate paper

Darren and all-

Sorry about the delay- I was called off on a short term project and it has thrown a wrench in the timing for everything. You have been more than patient regarding our responses.

Here is my current proposal for revisions. As I noted before- I do not think we have meaningfully changed content. These changes incorporate suggestions from myself and from Marian Bleeke and Akbar Mehrsheik as well as my editorial changes based on verbal comments from Donna Farmer and others.

Now that I am getting caught up, I realized that I have not gotten editorial comments from Donna, Steve, and

[Redacted]

DONNA / [Redacted] / STEVE

I WOULD REQUEST THAT YOU REVIEW THIS BY JUNE 15 AT LATEST TO PROVIDE ANY ADDITIONAL COMMENTS TO DARREN. IF THIS IS NOT POSSIBLE, PLEASE LET ME KNOW SO WE CAN SET A DATE FOR FINAL COMMENTS.

ks! Dan

Than

From: Darren Roberts [Redacted]
Sent: Monday, April 20, 2009 6:42 AM
To: GOLDSTEIN, DANIEL A [Redacted]; 'Nick Buckley'; 'michael eddleston'
Cc: FARMER, DONNA R [Redacted]; ADAMS, STEPHEN A [Redacted]
MEHRSHEIKH, AKBAR [Redacted]; BLEEKE, MARIAN S [Redacted]
Subject: RE: Draft Glyphosate paper

Hi Dan,

Thanks for the detailed comments on the draft glyphosate paper. I enjoyed reading them and feel they have improved the quality of the draft.

I have responded to each of your comments below in bold type and considered all of your comments within the manuscript. Please find attached an updated manuscript that uses track changes to highlight all changes to the first version of the manuscript I sent to you. Many changes are those that you proposed.

Could Akbar (or another delegate) please confirm that the glyphosate analysis methodology as reported is correct. The current text was my summary of the detailed methodology.

I look forward to your feedback on the latest version.

Best regards, Darren

- 1) The US data are almost exclusively NOT suicide attempts. While there are between 400 and 5000 exposure events each year (half of which I personally have involvement in reviewing- Monsanto reports 2000 – 2500 cases a year to the AAPCC from our contracted poison center), only about 12 cases a year (invariably less than 20) are in the moderate category. These consist almost exclusively of corneal abrasions (usually in kids with incidental eye exposure) and contact dermatitis (which may be due to plants) which require topical medications. We see perhaps 2 or 3 documented intentional ingestions per year in the US. The TESS 2007 dataset contains 3 severe cases and 2 deaths. In over 4000 cases. You state that the case-fatality rate for these ingestions is 11.8%, and I cannot see where this came from, as there is source for a denominator in the data you are working from. If this number came from some other case ingestion series, it is not applicable to the 4000 cases or 800 medical facility evaluations, or even to the moderate cases. There really is not equivalent denominator for the US data which is legitimately comparable to your denominator of ingestions in Sri Lanka. We do not object to citing the US data at all- but we need to be clear that these cases are almost without exception TOPICAL exposures and that the case fatality rate overall is miniscule. We are NOT seeing 480 fatalities a year (12% x 4000)- typically 0-2 per year fatalities, and I cannot recall a year with over 3 fatalities recently in the US.

I agree with these comments, however, you will notice that the original draft stated that the denominator was n=373. This is the number of intentional exposures to glyphosate-containing herbicides reported in the TESS data during the same period. An earlier version of this paper stated this qualifier, however it was subsequently removed (can't remember why). I have now clarified this in the draft. I think it is necessary to include this information to highlight to clinicians and journal editorial staff that this is an important topic. I have added another sentence about limitations of this data (although, unfortunately, previous experience suggests that TESS data usually under reports deaths!).

- 2) We have been debating the use of a nomogram approach for as long as I have been at Monsanto- so my thoughts here reflect long consideration and consultation with many toxicologists.

All very important points and I agree with most of them. A lot of your comments seem to have arisen from use of the term 'nomogram' which is probably inappropriate in this context. I will use the term 'figure 3' from here on. As with any study, the results must be interpreted in the context of the study that produced them. In the text I have removed the term nomogram and also removed the controversial line. As mentioned in the original manuscript, this was 'for illustrative purposes only'. Based on some of the other comments listed below we have further modified the draft.

- a. You have an insufficient number of fatal cases with levels to produce any reliable nomogram

- b. There is good evidence that glyphosate is not the toxin involved in fatalities. I will concede that some data suggest a possible synergistic interaction of the IPA salt in particular with the surfactant- but this only makes the problem below worse- not better.

- c. The formulations of glyphosate vary from ZERO to nearly 35% surfactant. Further, while most of the formulations in Sri Lanka are 41% glypho+15% surfactant as best we can tell (copies of the original formula from Monsanto), the majority of concentrate formulations in the global agricultural markets today from Monsanto are NOT THIS ORIGINAL FORMULATION.

- d. Given this- we have considered producing multiple nomograms or a more complex nomogram that takes into account both surfactant concentration and glyphosate- but concluded that we have insufficient data to support it.

- e. I believe that the "nomogram" you have put forth is potentially misleading and may in fact be a hazard in both directions, i.e. — someone with a low or zero surfactant load will get over-treated and someone with a high load product may get undertreated based on glyphosate levels.

- f. I will CONCEDE THAT YOU RECOGNIZE AT LEAST SOME OF THE LIMITATIONS- but you have failed to recognize others. I will even concede that the nomogram may accurately represent CASES IN SRI LANKA.

 - g. HOWEVER- I cannot justify the presentation you have made suggesting that this has global predictive value for multiple formulation types. This will encourage people to get levels of dubious value, and may encourage the development of analytical capacity at considerable cost with little benefit to the patient.

 - h. Please remember the “ibuprofen nomogram”- an entirely useless nomogram that became widely used because it looked like an acetaminophen nomogram. IF YOU PRESENT THIS THE WAY YOU HAVE- PEOPLE WILL USE IT INAPPROPRIATELY, and I think the data need to be presented in a substantially more circumspect manner. You are gonna kill someone with this thing (but probably not in Sri Lanka)!!
- 3) The Receiver-Operator curve for serum levels is NOT an ROC- this is circular reasoning. It is factually based on the lowest detected level in your population, it is not a curve at all, and cannot be said to represent the statistical performance of serum levels drawn from a future random population. This is a technical fine point, and I agree that the reader will take the value in an appropriate manner- so I defer to you on whether to make changes to the presentation.

I'm not sure I agree, see below.

- 4) Similarly, the statement that level above 734 are the “best predictor of mortality” are circular. As this is the lowest level found in fatal cases, it is GUARANTEED to be 100% sensitive. I will agree that the apparent specificity seems to be satisfactory- but the number of cases with levels in this range is very small, and the specificity likely to be non-robust in a larger data set (not that anyone will ever do a bigger one!!)

The cut-offs are derived from our data, of which there were few deaths. It is possible that with more data another concentration would perform better, but that doesn't necessarily mean our data is not informative. The comment “best predictor of mortality” was used for describing its performance relative to other measures.

- 5) While I would argue that the “nomogram” line is drawn at some peril and should probably not be drawn at all, the line you have drawn does NOT have a half-life per-se. Neither does the one in the acetaminophen nomogram. You need to look back at the predictive value of single point nomograms and the underlying partial differential equation that relates V_d , K , and C_o , and recognize that the predictive value for the actual C_o is maximal at $1.5 \times$ the mean serum half life. Beyond this point, scatter of data points increases rapidly as reflects differences in underlying true V_d and variability in $T_{1/2}$. The line on the nomogram is just “a line drawn above all the non-fatal data points, does NOT reflect an exponential decay process, and CANNOT and SHOULD NOT be compared to the determined mean half life. The “discrepancy” between the $T_{1/2}$ and the “nomogram line” is an EXPECTED FINDING and does NOT require an explanation.

Agree that the line should be deleted and that we might be over-interpreting its meaning.

- 6) Specifically- the “discrepancy” between the “nomogram line” and $T_{1/2}$ does NOT inherently suggest anything at all regarding possible saturation/longer half lives or a change in the volume of distribution. It does not rule them out either of course- and it is not unreasonable to discuss this- but the document should not reflect a belief that the “discrepancy” inherently necessitates some additional biological explanation.

OK

- 7) You need to consider that the peak of a kinetic curve reflects the point at which the instantaneous rate of absorption equals the instantaneous rate of excretion. Lacking a full set of kinetic parameters, it does NOT follow from an early peak that the K_a is large ($T_{1/2}$ is small)- a compound may just be well excreted even if slowly absorbed, with the peak (whatever it may be) defined by the apparent V_d and/or $V_{central}$, depending upon distribution time. Again, this is a technical fine point- I agree that the absorption of glyphosate orally must be fairly rapid and complete given the overall rapid time course. (Whether K_a actually exceed K_e is not known, and in fact your terminal phase is defined by the slowest exponential rate in the system- and it is perfectly possible that you are seeing K_a as the terminal phase.) We need to rephrase the document in several places, as the statement that an early peak necessitates a rapid K_a is not pharmacokinetically correct.

I have removed comments about the k_a

TO REITERATE MY PRIMARY CONCERNS:

The US data are not accurately reflected in the introduction. This is an easy fix, and I will propose language. I am not trying to “hide” glyphosate toxicity here or plan any kind of games with the data- the US data are simply NOT suicides, save for 2 or 3 out of every 4000 cases.

Agree this needs clarification, see above.

The nomogram CONCERNS ME IMMENSELY given the variety of glyphosate formulations, limited data, and the propensity for such devices to be grossly misapplied. While you do have final editorial authority, and would implore you to reconsider drawing the line very carefully. Personally, I would not even draw the line and would not call the graph a nomogram- although I have no objection to discussing a “theoretical cut-off line” above the data- provided that you restrict the application to formulations substantially similar to those available in Sri Lanka.

Agree with many of these comments. It has been re-labelled and the line has been removed.

OTHER COMMENTS IN THE MANUSCRIPT:

Could this be affecting glyphosate levels, even if it did not change outcome?? This may be a particular issue here as the glyphosate is not the primary toxin and AC may work very poorly for surfactants. I am confused- do you mean that no subjects were enrolled in the kinetic study until you were done with the charcoal study- or do individual patients from the charcoal study get moved into the kinetic study, despite having charcoal onboard??

The AC study preceded the kinetic study. Once the AC study was completed, the kinetic study was set up to allow collection of serial samples. Ie, patients were not transferred from one study to another. It is difficult to know how to deal with the issue of AC adsorbing glyphosate and the impact on the observed concentration-time graphs.

It looks like all of these must have been AFTER the charcoal study. We need to state that clearly IF it is correct (I am questioning my understanding- not your veracity- whatever you tell me is correct just needs to be reflected clearly.)

These were after the AC study. I hadn't mentioned this before in an effort to decrease the word count and because I wasn't aware of data suggesting that AC (eg MDAC?) altered the kinetics of glyphosate. I have now clarified this in the text.

Suggest re-plotting this with just the regression line for the kinetic data. Can related points be connected with lines?? This might be too noisy to see- I would have to try it to know, and you may have already decided it is not workable.

This was the intention of figure 4 which was messy. We could plot the regression line on this, the problem is knowing what initial concentration to start it at. The median of the others? I felt that it messed up the figure too much so omitted it. Is this ok?

A bit confusing- as this accounts for only 5 patients- what happened to the rest, and if only 5 had hypotension, the general statement above is not justified.,

Agree, I have probably over-generalised. On initial review of the data (and clinical experience with some of these deaths), I had the impression that this clinical progression occurred. But when I was extracting the exact information from the database and clinical records (when available) this progression was less well described so I only listed patients for which we had specific data. A limitation of the available data is that in some patients there were limited details documented, which reflects staff resources to a degree (so some of the numbers are likely to underestimate the true occurrence). So the general comment cannot be sufficiently backed up. I have modified this.

Sorry- I don't get the point here- are you talkinga bout measureing isopropylamine, or the IPA salt- which is usually measeured as the parent compound and then REPORTED as the IPA salt....

I have just deleted the comment and reference, it is not core to our data. I mentioned it to show that forensic groups have asked this question before.