Message

**From:** GARNETT, RICHARD P [AG/5040] [/O=MONSANTO/OU=EA-5040-01/CN=RECIPIENTS/CN=107838]
**Sent:** 3/8/2002 8:13:40 AM
**To:** GRAHAM, WILLIAM [AG/8050] [/O=MONSANTO/OU=EA-5040-01/CN=RECIPIENTS/CN=233911]
**Subject:** FW: in vitro dermal study

Bill,
Ruth is planning the following studies with MON 59117, the surfactant in Knock out:
> in vivo dermal absorption
> in vivo gastro intestinal tract absorption

While there is always a risk in doing more studies, I don't see any untoward risk to our EU registration from these studies, and would anyway like to see results which show no GI tract absorption of a surfactant in the tallow/ether amine groups. It will almost undoubtedly be useful here when the Chemical Policy gets implemented. There are other surfactants which we might prefer they use, but I see the logic for MON 59117. In fact, the dermal absorption complements what we are doing on dermal absorption of formulations.

Any more watch outs?

thanks and regards richard

-----Original Message-----
**From:** MCKENNA, RUTH M [AG/1000]
**Sent:** Thursday, March 07, 2002 5:58 PM
**To:** BROECKAERT, FABRICE [AG/5040]
**Cc:** GUSTIN, CHRISTOPHE [AG/1000]; DIRKS, RICHARD C [AG/1000]; GARNETT, RICHARD P [AG/5040]; MARTENS, MARK A [AG/5040]
**Subject:** RE: in vitro dermal study

Dear All,

I've taken a lot of short cuts in explaining what the US team has had 9 months to think about. So I am happy to continue this dialogue via e-mail as long as it is helpful to you or set up a conference call.

But we have to stay focussed. At this stage we do not need alternative suggestions of inerts to test. MON 59117 is our preferred choice. The question is can you live with that choice NOT would you prefer some other inert to be tested. Now I know that reads like a very bold statement but the fact is we will only change our strategy if we endanger EU registrations in some way.

And now I'm going to continue the dialogue on the points you have made Fabrice.The suggestions you make below are appropriate in the Registration process we have today with both EPA and in the EU. But what we are trying to do in the US is CHANGE the EPA Risk assessment process- ideally to an approval process with a timeline of 1-2 years (from the current 3-4 years) and if we can to eliminate or reduce the need a for traditional 90 day data package. Let me say right away that we are not intrinsically against generating the 90 day package (it may be needed for other world areas) but a 90 day data package requires a lot of scientific resource at EPA to review and Inerts get pretty low priority for that resource-one reason for the long approval timeline. This is where the in vivo GI tract study fits in- if we can demonstrate negligible absorption then we can say - this is similar to polymers, no systemic exposure, give us an exemption- you EPA don't need to quantify consumer exposure, set tolerances etc as there is no systemic exposure. Now tactically the first time we run this past EPA it will be helpful to have the 'traditional data' available to reassure EPA that nothing weird is going on and we have sufficient 'traditional data' for MON 59117 to do this.

In essence we are using MON 59117 as a trojan horse to introduce a new risk assessment model to EPA that will deliver inert approvals in a shorter time frame and ideally with reduced data requirements. This is

essential to support the US business strategy of introducing new Glyphosate formulations with Monsanto 'designer surfactants' every 2 years or so.

Ruth

-----Original Message-----
**From:** BROECKAERT, FABRICE [AG/5040]
**Sent:** Thursday, March 07, 2002 9:46 AM
**To:** MCKENNA, RUTH M [AG/1000]
**Cc:** GUSTIN, CHRISTOPHE [AG/1000]; DIRKS, RICHARD C [AG/1000]; GARNETT, RICHARD P [AG/5040]; MARTENS, MARK A [AG/5040]
**Subject:** RE: in vitro dermal study

Ruth,

I understand your strategy and I agree....However, MON 59117 being so similar to AGM 550, why not to use data of AGM 550 to obtain the registration of MON 59117 ?. According to Christophe, we are find with a 10% dermal penetration factor (which was derived by the EPA using a SAR analysis !!!). If we are sure that the systemic absorption of MON 59117 will be very low, we don't know what will be the amounts retained in skin tissues (corrosivity).

Another option would be to test the cocoamine surfactant. This would nicely complete the *in vitro* dermal penetration study that we have launched with MON 35012 and MON 0139 (gly without surfactant).

Let's discuss.

Regards,
Fabrice

-----Original Message-----
**From:** MCKENNA, RUTH M [AG/1000]
**Sent:** Thursday, March 07, 2002 3:38 PM
**To:** BROECKAERT, FABRICE [AG/5040]
**Cc:** GUSTIN, CHRISTOPHE [AG/1000]; DIRKS, RICHARD C [AG/1000]; GARNETT, RICHARD P [AG/5040]; MARTENS, MARK A [AG/5040]
**Subject:** RE: in vitro dermal study

We were initially in the same place as you Fabrice and we thought long and hard about AGM 550 but the effort invested in MON 59117 does give us a possibility of a new use in the USA and according to the Washington office it would be very difficult(impossible) to get EPA's attention for a surfactant that is already approved. So MON 59117 is our preferred option. Remember we are not just trying to get EPA's attention to approve an inert we are trying to introduce a novel approach to Risk Assessment so we need to engage of a lot of busy scientists. We could invest 50K$ in AGM 550 and EPA could say -this is approved don't bother us- we're too busy. It's a big risk we can't take.

So far I'm not hearing anything negative about our strategy affecting the approval of MON 59117 in Europe?

Ruth

-----Original Message-----
**From:** BROECKAERT, FABRICE [AG/5040]
**Sent:** Thursday, March 07, 2002 7:29 AM
**To:** MCKENNA, RUTH M [AG/1000]
**Cc:** GUSTIN, CHRISTOPHE [AG/1000]; DIRKS, RICHARD C [AG/1000]; GARNETT, RICHARD P [AG/5040]; MARTENS, MARK A [AG/5040]
**Subject:** RE: in vitro dermal study
**Importance:** High

Dear Ruth,

For my point of view, it would be more appropriate to test a surfactant which has already been approved, for instance AGM 550. In the exemption of tolerance doc for this surfactant, US EPA determined a dermal absorption factor of 10% by using SAR analysis which rated absorption through the skin as poor. Real dermal absorption is expected to be (significantly) lower than 10%. Furthermore, data from AGM 550 could can be extrapolate to MON 59117 because of:
- similar physico-chemical properties;
- similar chemical structure except that MON 59117 is less likely to penetrate the skin (i.e. systemic availability) due to alkyl chain branching;
- similar tox properties except that MON 59117 is less irritant to the skin than AGM 550 and so less likely to penetrate the skin

Regards, Fabrice

-----Original Message-----
**From:** MCKENNA, RUTH M [AG/1000]
**Sent:** Wednesday, March 06, 2002 7:15 PM
**To:** GARNETT, RICHARD P [AG/5040]; MARTENS, MARK A [AG/5040]; BROECKAERT, FABRICE [AG/5040]
**Cc:** GUSTIN, CHRISTOPHE [AG/1000]; DIRKS, RICHARD C [AG/1000]
**Subject:** FW: in vitro dermal study

Richard, Mark and Fabrice,

As you can see from the e-mail traffic below Christophe has flagged up that the US Inert team should ensure that you are comfortable with the studies we hope to initiate May 2002 with MON 59117 to support the US Inert strategy.

I attach a brief outline of the drivers for the strategy and the choice of MON 59117. Suffice to say we believe that the outcome of the two pivotal studies; in vitro dermal penetration and in vivo absorption are highly unlikely to generate data that would adversely affect approvals in the EU.

Let me know if you wish to discuss this in more detail - I'll set up a conference call. You can also follow all these developments in the Team Space.

Ruth
<< File: Drivers for Inert Strategy in the USA.doc >>

-----Original Message-----
**From:** MCKENNA, RUTH M [AG/1000]
**Sent:** Wednesday, March 06, 2002 10:41 AM
**To:** GUSTIN, CHRISTOPHE [AG/1000]; HEALY, CHARLES E [AG/1000]; DIRKS, RICHARD C [AG/1000]; FARMER, DONNA R [AG/1000]; GOLDSTEIN, DANIEL A [AG/1000]; GRAHAM, JEFF A CROP [AG/1000]; HONEGGER, JOY L [AG/1000]; KIRK, ANNETTE M [AG/1000]; KLEIN, ANDREW J [AG/1000]; KURTZWEIL, MITCHELL L [AG/1000]; MEHRSHEIKH, AKBAR [AG/1000]; WRATTEN, STEPHEN J [AG/1000]
**Subject:** RE: in vitro dermal study

The choice of studies; in vitro dermal penetration and in vivo absorption were discussed in detail with Mark and Fabrice in December last year and the protocols will be circulated to them for comment. However I do agree that the time is right to flag up our choice of inert to develop an alternative EPA inert risk assessment (RA)

I'll send the EU team the rational for the choice of MON 59117 which is included in the minutes of the last meeting. To my knowledge the data we generate plays no role in EU decisions on Inerts-it is not required data and as no risk assessment is conducted on the use of the inert in agricultural use it cannot adversely effect such a RA. If a risk assessment were conducted it would almost certainly include similar conservative assumptions as the EPA RA.

Ruth

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

**From:** GUSTIN, CHRISTOPHE [AG/1000]
**Sent:** Tuesday, March 05, 2002 4:00 PM
**To:** HEALY, CHARLES E [AG/1000]; DIRKS, RICHARD C [AG/1000]; FARMER, DONNA R [AG/1000]; GOLDSTEIN, DANIEL A [AG/1000]; GRAHAM, JEFF A CROP [AG/1000]; HONEGGER, JOY L [AG/1000]; KIRK, ANNETTE M [AG/1000]; KLEIN, ANDREW J [AG/1000]; KURTZWEIL, MITCHELL L [AG/1000]; MCKENNA, RUTH M [AG/1000]; MEHRSHEIKH, AKBAR [AG/1000]; WRATTEN, STEPHEN J [AG/1000]
**Subject:** in vitro dermal study

Dear Ruth et.al.,

I talked with Chuck about the dermal in vitro protocol for the inerts and we decided to go ahead with TNO (The Netherlands).
About the reference compound we want to use: MON 59117, I 'm sure you know that this is an important surfactant in Europe (in MON 78294 and MON 78362).I forgot the rational behind the selection of MON 59117 as reference inert but we need to be careful not to generate data that could compromise European submissions (I'm pretty comfortable that we are not but we need to understand what we are doing...).

best regards,
Christophe