

Message

From: CARROLL, MICHAEL J [AG/8050] [/O=MONSANTO/OU=EA-8050-01/CN=RECIPIENTS/CN=14038]
Sent: 5/22/2003 8:10:08 AM
To: HEYDENS, WILLIAM F [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=230737]; KRONENBERG, JOEL M [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=501517]; GUSTIN, CHRISTOPHE [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=83930]; BROECKAERT, FABRICE [AG/5040] [/O=MONSANTO/OU=EA-5040-01/CN=RECIPIENTS/CN=591489]; HEALY, CHARLES E [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=297008]
CC: MARTENS, MARK A [AG/5040] [/O=MONSANTO/OU=EA-5040-01/CN=RECIPIENTS/CN=21606]; MORAN, SHARON J [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=119190]; DIRKS, RICHARD C [AG/1000] [/O=MONSANTO/OU=NA-1000-01/CN=RECIPIENTS/CN=214797]
Subject: RE: Dermal penetration studies
Attachments: dermal.pdf

Here are my comments from a registration perspective:

1. The characteristics of sithiofam require that a dermal penetration study be carried out - see Guidance Document on Dermal Absorption attached.
2. If we do not have a dermal penetration study the operator exposure calculation will use a 100% default value instead of 10%.
3. In the EU, operator exposure assessments are carried out using 90-95 percentile values and I think this will put us over 100% of the AOEL.
4. Annex I listing will not be possible with an unacceptable operator exposure.
5. We further risk our existing approvals if the Member States who have already granted registrations suddenly realise that the product could be unsafe and that would be very embarrassing as the season is almost upon us.
6. The silthiofam formulation Latitude(MON 65507) contains certain co-formulants like humectants that will make it highly likely we will get large amounts penetrating the skin.
7. It is unlikely that the operators, workers and applicators will be exposed to the liquid formulation as Latitude is supplied in closed transfer containers for direct connection to the seed treatment equipment.
8. The most likely route of exposure is through contact with the dried formulation that coats the seed, that is, operators, workers and applicators touching the treated seed, handling the bags of seed and unpacking the seed for planting.
9. I understand the concern of carrying out dermal penetration studies, the inherent variability in the results and the concerns with TNO. However, we need a dermal penetration study and we need it fast.
10. By carrying out the study with the dried formulation that actually coats the seed we minimise the chances of getting a massive dermal penetration value and thus exceeding the AOEL. In addition we mimic the real exposure scenario.

Kind regards,

Mike.

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

From: HEYDENS, WILLIAM F [AG/1000]
Sent: 21 May 2003 23:24
To: KRONENBERG, JOEL M [AG/1000]; GUSTIN, CHRISTOPHE [AG/1000]; BROECKAERT, FABRICE [AG/5040]; HEALY, CHARLES E [AG/1000]
Cc: MARTENS, MARK A [AG/5040]; MORAN, SHARON J [AG/1000]; CARROLL, MICHAEL J [AG/8050]; DIRKS, RICHARD C [AG/1000]
Subject: RE: Dermal penetration studies
All,

We need a phone conference to discuss all this. There are obviously several questions needing discussion & resolution before we can proceed.

Second, I too would like to see the silthiofam AOEL calculations.

And last but certainly not least, I am still wary of proceeding at TNO. For the unsuccessful glyphosate formulation study that was conducted there previously, I have not heard that they ever identified the problem or implemented a solution. (And I have always wondered about the highest -chlor DP value ever recorded that was generated at TNO). So I'm not real keen on rolling the dice with them again without some good explanation/reassurances.

Bill

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

From: KRONENBERG, JOEL M [AG/1000]

Sent: Wednesday, May 21, 2003 12:50 PM

To: GUSTIN, CHRISTOPHE [AG/1000]; BROECKAERT, FABRICE [AG/5040]; HEALY, CHARLES E [AG/1000]

Cc: MARTENS, MARK A [AG/5040]; HEYDENS, WILLIAM F [AG/1000]; MORAN, SHARON J [AG/1000]; CARROLL, MICHAEL J [AG/8050]

Subject: RE: Dermal penetration studies

I still don't understand what risk assessment we are trying to refine (seed treatment facility or farmer)? Is testing dried formulation by itself realistic or should it be on the seed? Also, I agree with Christophe that we may pass with just diluted and concentrated and thus could avoid the more complicated dry testing. However, if we are going to run a study anyway, why not run it the normal way, with concentrated, diluted and, if necessary, dried product? The extra cost would probably be relatively low compared to the hassle and expense of possibly doing it again later.

Joel

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

From: GUSTIN, CHRISTOPHE [AG/1000]

Sent: Wednesday, May 21, 2003 10:00 AM

To: BROECKAERT, FABRICE [AG/5040]; HEALY, CHARLES E [AG/1000]; KRONENBERG, JOEL M [AG/1000]

Cc: MARTENS, MARK A [AG/5040]; HEYDENS, WILLIAM F [AG/1000]; MORAN, SHARON J [AG/1000]; CARROLL, MICHAEL J [AG/8050]

Subject: RE: Dermal penetration studies

All,

I agree we have to follow the recommendations of the authorities but I'm still puzzled why the dried formulation is the most critical form to test.

1) it's not a worst case

2) the exposure to dried formulation is limited (just during bagging and loading the seed driller) and inhalation exposure is more critical here

3) the exposure to liquid formulation or diluted formulation is more real and should yield more conservative results (calibration, M&L of seed treating equipment, cleaning)

An alternative approach would be to test the diluted formulation and argue that dermal uptake of other forms of the formulation will be lower. This way you can refine all steps in the risk assessment process rather than just bagging and drilling. As I understood this would simplify the experimental preparations as well.

I'm also not convinced we exceed the AOEL with 100% dermal uptake but I haven't seen the Dutch assessment yet. With our assessment including some PPE recommendations during seed treatment we can present a case we are more than OK.

just my two cents, regards
Christophe

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

From: BROECKAERT, FABRICE [AG/5040]
Sent: Wednesday, May 21, 2003 9:23 AM
To: HEALY, CHARLES E [AG/1000]; KRONENBERG, JOEL M [AG/1000]; GUSTIN, CHRISTOPHE [AG/1000]
Cc: MARTENS, MARK A [AG/5040]; HEYDENS, WILLIAM F [AG/1000]; MORAN, SHARON J [AG/1000]; CARROLL, MICHAEL J [AG/8050]
Subject: RE: Dermal penetration studies
Joel/Chuck,

1. "dried" formulation means that a solid form of MON 65507 will be made by freeze-drying the formulation. The formulation will be moistened on the skin but this step needs to be discussed further. I already planned to go there during the process.
2. I cannot ask them the same question all the time about their experience. TNO is the only lab doing these type of studies and I'm not sure the answer will be satisfactory enough from your side. For my point of view, only one study could be enough to gain experience.
3. as suggested by Chuck, let's have a look at the protocol.

Best regards,
Fabrice

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

From: HEALY, CHARLES E [AG/1000]
Sent: Wednesday, May 21, 2003 3:58 PM
To: KRONENBERG, JOEL M [AG/1000]; BROECKAERT, FABRICE [AG/5040]; GUSTIN, CHRISTOPHE [AG/1000]
Cc: MARTENS, MARK A [AG/5040]; HEYDENS, WILLIAM F [AG/1000]; MORAN, SHARON J [AG/1000]; CARROLL, MICHAEL J [AG/8050]
Subject: RE: Dermal penetration studies
Fabrice:

I agree with Joel's questions below. He and I discussed this briefly after our call a few days ago and it appears that this could be more complicated than a first look might indicate. Let's have a look at the protocol and then talk.

Chuck Healy

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

From: KRONENBERG, JOEL M [AG/1000]
Sent: Wednesday, May 21, 2003 8:54 AM
To: BROECKAERT, FABRICE [AG/5040]; GUSTIN, CHRISTOPHE [AG/1000]; HEALY, CHARLES E [AG/1000]
Cc: MARTENS, MARK A [AG/5040]; HEYDENS, WILLIAM F [AG/1000]; MORAN, SHARON J [AG/1000]; CARROLL, MICHAEL J [AG/8050]
Subject: RE: Dermal penetration studies

What type of "dried" formulation are you considering? Will you use coated intact seed, dust of coated seed, dried formulation itself, etc? Will you moisten? What is objective of study? Testing dried materials is much more complicated than liquids. Knowing that TNO "has experience" with dried/solid formulations is not enough. How much experience? What type of formulations? What was their recovery? I suggest further discussion before proceeding.

Joel

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

From: BROECKAERT, FABRICE [AG/5040]

Sent: Wednesday, May 21, 2003 8:42 AM

To: KRONENBERG, JOEL M [AG/1000]; GUSTIN, CHRISTOPHE [AG/1000]; HEALY, CHARLES E [AG/1000]

Cc: MARTENS, MARK A [AG/5040]; HEYDENS, WILLIAM F [AG/1000]; MORAN, SHARON J [AG/1000]; CARROLL, MICHAEL J [AG/8050]

Subject: Dermal penetration studies

Dear all,

Following the conf call of Friday last week:

Acetochlor/MON 13900:

A comparative dermal penetration of acetochlor in MON 69447 & MON 8448 will be conducted to combine replicates of the biomonitoring study (respectively 10 + 5 in open cab or closed cab). Dermal penetration of MON 13900 will also be conducted in parallel to allow for kinetic comparisons (separate study reports but same skin donors). Protocols are under discussion and will be sent to you soon.

Silthiofam:

Mike discussed with the Irish authorities yesterday. It appears that we have to conduct the study to comply with regulations (see below) as pointed out by The Netherlands. Mike also discussed the type of formulation which should be tested. The authorities agreed that the dried formulation is the most appropriate way to test silthiofam. Since we don't want to delay Annex I listing of silthiofam, a dermal penetration study will thus be conducted. TNO has experience with dried/solid formulations. The protocol is under discussion and will be sent to you soon.

Best regards,

Fabrice

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

From: CARROLL, MICHAEL J [AG/8050]

Sent: Tuesday, May 20, 2003 10:53 AM

To: MOLL, STEVE [AG/5040]; VOSS, MARTIN C [AG/5040]

Cc: MARTENS, MARK A [AG/5040]; BROECKAERT, FABRICE [AG/5040]; WATERS, STEPHEN P [AG/5040]; GARNETT, RICHARD P [AG/5040]

Subject: Silthiofam Annex I Update

The Netherlands have requested a dermal penetration study as part of the Annex I listing review process for silthiofam. Under the conditions laid down by the Dermal Penetration Guidance document a dermal penetration study is required if the parent molecule has certain characteristics. Silthiofam qualifies for this requirement. The result of the dermal penetration study is used to obtain an estimate of operator exposure. Currently we will have to use a default of 100% penetration and this means the AOEL will be exceeded. In order to rectify this we will carry out a dermal penetration study as soon as possible at TNO. We will use the formulation as it coats the seed not the formulation as it is sold in the container. This best reflects the route of exposure to the skin of operators. The results should be available by June and allow a decision to be taken on silthiofam Annex I listing before the summer.

Kind regards,

Mike.