FIND

From:	"Giovanni Costa" <giovanni.costa@unimi.it>
Sent:	25/09/2007 08:14:55
To:	"Gloria Carlo" <carlo.gloria@miteni.it>
CC:	<yuji.suetsune@mitsubishi.com>, <brian.mcglynn@miteni.it>, <davide.drusian@miteni.it>, "Mario Mistrorigo" <mario.mistrorigo@miteni.it>
Subject:	Fw: PE APFO ad hoc WG
Attachments:	Proposall for further studies.doc

Mi scuso, ma non Ã¨ partito l'attachment.
----- Original Message -----
From: Giovanni Costa
To: Gloria Carlo
Cc:yuji.suetsune@mitsubishi.com ; brian.mcglynn@miteni.it ; davide.drusian@miteni.it ; Mario Mistrorigo
Sent: Tuesday, September 25, 2007 10:05 AM
Subject: PE APFO ad hoc WG

Caro dr. Gloria,
Trasmetto per opportuna conoscenza i testi di alcune e-mail pervenutemi nei giorni scorsi relative alla proposta di ulteriori studi sperimentali sul ratto.
Come si puÃ² leggere, noto che da un lato Farrar segnala l'assenza di Miteni ad una recente riunione in merito e, dall'altro, colgo una netta opposizione di Solvay.
Devo confessare che la mia opinione in merito non Ã¨ del tutto precisa.
Se da un lato posso accettare la necessitÃ di chiarire fino in fondo i meccanismi di supposta tossicitÃ (o non tossicitÃ) dell'APFO sul fegato, dall'altro devo anche convenire che forse questa non Ã¨ una prioritÃ assoluta. Tale mia opinione puÃ² essere certamente dettata dal mio particolare punto di osservazione, in qualitÃ di medico del lavoro piuttosto che tossicologo puro, ma Ã¨ anche conseguenza del fatto che mi sfuggono a volte le reali finalitÃ del gruppo di lavoro, o forse di alcuni membri dello stesso.
Lascio pertanto a Lei, che cettamente conosce meglio di me tutti i vari risvolti e condizionamenti (anche in prospettiva REACH), di valutare le decisioni piÃ¹ opportune da prendere.
Cordiali saluti
Giovanni Costa

From: david.farrar@ineoschlor.com david.farrar@ineoschlor.com

To: PE APFO ad hoc wWG
giovedì 20 settembre 2007 17.38

You will recall that I had an action to prepare, for members of the Plastics Europe Fluoropolymers Main Committee, a summary of the basis of our recommendation to conduct further studies (in the guinea pig and in-vitro) to further characterise the peroxisome proliferating potential of APFO. The summary that I prepared is at the end of this e-mail.

The Main Committee met on Tuesday 18th January. They did not reach a consensus on the need for further testing in this regard and, as a consequence, did not accept our recommendation. In detail, we received support from Asahi Glass and DuPont. However, neither Daikin, Solvay Solexis nor Arkema were
prepared to support our recommendation. Neither Dyneon nor Miteni were present at the meeting and I understand that they will be approached to ascertain their opinion on the matter. The Chairman of the meeting asked those companies that did not support our proposal to brief their members of
the APFO Ad-hoc Toxicology WG on the reasons for their lack of support, so that we can understand their thinking on this matter.

I intend to come back to this issue at our next meeting on 7th November in Cheshire, when I hope that Iwai-san and Ilaria will be able to explain to us the thinking in their company. If you should feel that we need to discuss this matter more urgently, please let me know and we will try to arrange a teleconference to discuss this item specifically.

I am sure that you are aware that this is the first time that the Main Committee has not accepted a recommendation from our group to conduct further testing. I personally think that this development has broader implications for the work of our group and I am inclined to seek clarification from the Main Committee of their perception of our role in the toxicology debate on APFO. I would appreciate your thoughts on this suggestion before I proceed further. DGF.

Recommendation of the APFO Ad-hoc Toxicology WG.

The WG has recommended that a further study is conducted on APFO in guinea-pigs. The purpose of the study is to gather further information in support of the hypothesis that APFO exerts its toxicity to the liver in rat, in part, because it is a peroxisome proliferator. This understanding is important because it is generally accepted that liver tumours seen in rats and mice exposed to peroxisome proliferators are not relevant for human health risk assessment.

Liver tumours were seen in the two carcinogenicity studies that have been conducted on APFO by 3M and DuPont, along with testicular tumours and pancreatic acinar cell tumours. In the absence of sound mechanistic arguments, regulatory authorities tend to assume that such findings are relevant for human health risk assessment.

We have managed to promulgate arguments that the testicular tumours seen with APFO are of no concern for humans. This position is re-inforced by a general belief that these specific tumours (benign Leydig cell tumours), when seen in the rat, are not relevant for humans. Consequently our research programme has not focussed on these tumours.

We have no understanding of the mechanism of induction of the APFO-induced pancreatic acinar cell tumours in the rat, hence our recommendations to conduct research into their aetiology

Concerning the liver tumours, we have argued that these tumours are not relevant for human health risk assessment because APFO is a peroxisome proliferator. This argument has been generally accepted by the regulatory authorities in Europe and, as a consequence APFO is only classified as a category 3 carcinogen in the EU scheme (based on the pancreatic tumours). The argument is also supported by the US EPA experts, who have reflected their opinion in draft EPA Health Hazard Assessment on APFO. However, the EPA Science Advisory Panel did not accept the argument on the basis that there was insufficient evidence to conclude with certainty that APFO is a peroxisome proliferator. As a consequence, they have requested that a further evidence in support of the hypothesis that APFO is a peroxisome proliferator is required before they would accept it. Otherwise they would consider that the liver tumours seen in APFO-exposed rats were of relevance for human health risk assessment and that they would recommend that any health risk assessment was conducted on that basis

In response to the EPA SAP opinion, we have been collecting further evidence in support of our hypothesis. As a guide, we are using the WHO International Agency on Cancer (IARC) Criteria and Recommendations for characterising a peroxisome proliferator.

1. The peroxisome proliferator phenomenon has been clearly demonstrated in rodents. Our most recent study added to

the existing data and allows us to conclude, with certainty, that this criterion is now met for APFO.

2. That no-effect is seen in a non-responding species (eg a guinea-pig).

3. Duplication of the peroxisomal response and non-response in in-vitro hepatocyte cultures from relevant species (ie rat and guinea-pig).

4. Demonstration of a lack of response in human hepatocytes in-vitro.

Criterion 2 is the basis for the current proposal. Should this study be successful, we would recommend that we proceed to fulfil criteria 3 and 4.

The cost of the guinea-pig study is £135,000 (criteria 2). The cost of the in-vitro studies is £77,000 (criteria 3 and 4).

The Ad-hoc WG recommend that these studies are conducted. If they are not conducted, we feel that it would be highly unlikely that we would be able to persuade the SAP to change their opinion on this matter.

David Farrar.

On behalf of the Plastics Europe APFO Ad-hoc Toxicology Working Group.

Replies

David,

Just a clarification for the benefit of the good understanding for the group.

I am a member of this group since its foundation , I am a Toxicologist and even I am now the General Secretary of EUROTOX.

Having said I think that I can be considered qualified for give and substantiate a technical and scientific position towards this issue .
More than that in this position and also in the position of Executive Manger of Solvay SA to which Solvay Solexis is part of I already expressed at the last two meetings of the Main Committee the Solvay SA our position and the Scientific and Regulatory motivation behind.
We consider that our motivation is well balanced especially towards the EU Scenario and the New Regulatory Framework we are going to deal after the entry into force of REACH.
Of course we stated many time that from a pure and solely Scientific point of view we cannot have anything against the "Academic" validity of the proposed studies. Simply today we do not considered them anymore a priority .
We certainly have proposed at the last Main Committee to pragmatically reconsider the whole role and responsibilities of the Tox group (including the ads hoc APFO Tox Committee) to include a more consistent and through Regulatory point of view as well as to identify priorities .
We are certainly open to discuss our thoughts in the next coming future with all the relevant stakeholders.
I will be present at the next Tox Committee and together with my colleagues Ilaria and Bruno we could repeat and restate our position, if necessary.
Ciao and all the best to all of you.

Giuseppe Malinverno - General Secretary EUROTOX
Governmental and Public Affairs
EU and Italian Manager - Solvay SA
Via Turati 12- 20121 Milano - Italy
Tel 0039 02 2909 2393
GSM 0039 348 55 09 357

-----Original Message-----
From: david.farrar@ineoschlor.com [mailto:david.farrar@ineoschlor.com]
Sent: jeudi 20 septembre 2007 17:39
To: gerald.l.kennedy@usa.dupont.com; jlbutenhoff@mmm.com; giovanni.costa@unimi.it; hiwai@notes.che.daikin.co.jp; reinhard.jung@clariant.com; Colombo, Ilaria; Schmit, Bruno; sandi.murphy@arkemagroup.com; Seiji-Shinya@agc.co.jp; Watze.de-Wolf@bel.dupont.com; phoff@mmm.com; Malinverno, Giuseppe
Cc: les_hoy@agcce.com; mike.neal@plasticseurope.org
Subject: Further studies on the characterisation of APFO as a peroxisome proliferator

David,

Just a comment or two.

First, I can't help but rememebr a certain someone with initials JLB recommending a GP study before we launched into Cynos. So, even though I may have been somewhat ridiculed at the time from some quarters, of course you have my support. Reinhard and I will need to sort out the Dyneon position.

Point of factual correction - liver "tumors" and pancreatic acinar cell "tumors" were not elevated in the 3M cancer study in SD rats; although, hyperplasia was there, it did not reach adenoma status.

On study 4, I may actually be in position to contribute some of that rat vs human hepatocyte data fairly soon, based on work currently on-going at the University of Minnesota.

Looking forward to the 7th.

By the way, Mel Andersen is planning to join us, at least for the early part of the meeting.

We should also table a presentation from Geary on the latest Epi/biomonitoring.

All the best, John

John L. Butenhoff, Ph.D., CIH, DABT
Medical Department
3M Center, Building 0220-06-W-08
St. Paul, Minnesota 55144-1000
651-733-1962 Office
651-733-1773 Fax
jlbutenhoff@mmm.com

David,

Do not doubt that Solvay / Solexis appreciates the effort to elucidate the mechanism of action of APFO by any scientific , well founded research.

In this case however, the proposed protocol on guinea pigs has following potential shortcomings:

1)it will look at liver effects only in a short term study (28 days): this may yield either "no effects" or "functional/structural effects" mediated by other mechanisms than PPAR activation.

In case we find "no effect": we answer only partially our hypothesis: effects seen in rat LIVER are mainly attributable to PPAR activation. (We would only know that APFO has no short term effect in guinea pig liver and we have no real argument for the pancreatic effects seen in rats)
In case we find a "functional/structural effect" : we have then indicated that APFO can cause liver effects in PPAR non-responsive species, which will raise further questions and cripple our PPAR argument.

2) this short term study, whatever the outcome, will most probably not be able to change the REACH classification that hangs as a (already fallen?) sword of Damocles over APFO's head.(think e.g. of the apelman and fei study that will influence the reprotox classification...)

Therefore Solvay/Solexis considers that this budget may better be reserved for actions that can yield more direct and pragmatic beneficial results for the industries concerned.

This brings me to your next question:
I personally think the main challenge of the PE APFO ad hoc Tox WG remains to find out what efficient and pragmatic scientific actions we may take to counteract/minimalise the REACH impact on APFO .
It is just therefore that I would suggest to keep this WG alive and seriously review our further actions.

Best regards

Bruno Schmit

Solway

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Revision number:	1
Application:	Microsoft Office Word
Total editing time:	00:12:00
Created:	2007/09/25 07:27:00
Last saved:	2007/09/25 07:39:00

From:	"Giovanni Costa"
To:	"Gloria Carlo"
CC:	, , davide.drusian@miteni.it>, "Mario Mistrorigo"
Subject:	Fw: PE APFO ad hoc WG
Date:	Tue, 25 Sep 2007 10:14:55 +0200

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Subject: Fw: PE APFO ad hoc WG
Date: Tue, 25 Sep 2007 10:14:55 +0200
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Governmental and Public Affairs
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Via Turati 12- 20121 Milano - Italy
Tel 0039 02 2909 2393
GSM 0039 348 55 09 357

-----Original Message-----
From: david.farrar@ineoschlor.com [mailto:david.farrar@ineoschlor.com]
Sent: jeudi 20 septembre 2007 17:39
To: gerald.l.kennedy@usa.dupont.com; jlbutenhoff@mmm.com; giovanni.costa@unimi.it; hiwai@notes.che.daikin.co.jp; reinhard.jung@clariant.com; Colombo, Ilaria; Schmit, Bruno; sandi.murphy@arkemagroup.com; Seiji-Shinya@agc.co.jp; Watze.de-Wolf@bel.dupont.com; phoff@mmm.com; Malinverno, Giuseppe
Cc: les_hoy@agcce.com; mike.neal@plasticseurope.org
Subject: Further studies on the characterisation of APFO as a peroxisome proliferator

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All the best, John

John L. Butenhoff, Ph.D., CIH, DABT
Medical Department
3M Center, Building 0220-06-W-08
St. Paul, Minnesota 55144-1000
651-733-1962 Office
651-733-1773 Fax
jlbutenhoff@mmm.com

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Last saved:	2007/09/25 07:39:00

Sender:	"Giovanni Costa"
Recipient:	"Gloria Carlo "; ""; " "; " davide.drusian@miteni.it>"; " Mario Mistrorigo "
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