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Report on the APME APFO *ad hoc* Toxicology Working Group – Meeting held on Thursday/Friday 28/29th October 2004 at APME, Brussels, Belgium

Participants:

- David Farrar (chairman) Ineoschlor, Asahi Glass

- John Butenhoff 3M

- Giovanni Costa Miteni

- Ilaria Colombo Solvay

- Watze de Wolf Dupont

- Cliff Elcombe University of Dundee, CXR Biosciences

- Reinhardt Jung Clariant

- Gerry Kennedy Dupont

- Giuseppe Malinverno Solvay

- Mike Neal APME

- Bruno Schmit Solvay

- George Ransbotyn APME

- Sandy Murphy Atofina (teleconference)

- Hiro Hiwai Daikin (teleconference)

1. Introduction

G. Ransbotyn introduced the new APME representative (Mike Neal) who is going to take his place in supporting the activities of the Fluoropolymers Group after his retirement.

The Chairman reviewed the actions from the previous meeting. Several ongoing actions were identified and reminded to the members.

2. Proposal to engage a third party scientific expertise to assist in the external communication process

Awni Sharif (DuPont) presented a proposal for a scientific forum on APFO under the auspices of Plastics*Europe*. The purposes are: a) to create an external panel of recognized European scientists regarding the health and toxicity issues surrounding APFO; b) the external panel would act as an

Europe.

These scientists should be expert in these areas: risk assessment; carcinogenesis; developmental toxicity; reproductive toxicity; molecular mechanisms; epidemiology.

The expected benefits are: independent voice; fill remaining gaps; pre-empt some future discussions/issues; better prepared talking points on PTB and other endpoints; potential use of external experts with some regulators. The risks are: additional costs associated with new studies and research; independent voice (e.g. different opinions, no consensus); additional studies can bring unexpected results.

He proposed also a very strict timeline, aimed at having the approval from this scientific committee in few days, in order to contact the selected primary candidates by November and sign the contracts by December; thereafter they should organize some meetings and workshops in the first semester of 2005.

A long discussion took place between those in favour and those having some perplexities. Those in favour (mainly DuPont and 3M) said that the companies should act as a group in responding to any question coming form external groups (e.g. populations, ONG) and institutions; in their opinion, that can be better met and applied (in terms of external credibility) by a mix group of experts than by scientists strictly connected with the industrial groups. So, they stressed the opportunity to have a unique authoritative representative, as a group, in the external communication processes.

Others expressed some perplexities and emphasized the different situations actually present in USA and Europe both in terms of approach and institutions involved in APFO related issues (e.g. in USA only EPA refers to it, whereas in Europe any country has its own institution with different approaches). G. Malinverno (Solvay) also said that a "Communication ad hoc working group of Plastics*Europe* on FluoroPolimers related issues already exists [members are: J. de Gerlache (chairman-Solvay), G. Malinverno (Solvay), C. Muller (Dyneon), S. Re (Daikin), E. van Wely (DuPont), G. Ransbotyn (Plastics*Europe)]*, and then there is no need for another group. In any case, such proposal should be referred to that group and not to the scientific APFO ad hoc scientific group. He also pointed out that the proposal reflects mainly north American methods and procedures; therefore, in case they intend to present it to APME it should be reformulated taking into account the European situation.

At the end of a long discussion A. Sharif (DuPont) has been asked to represent the proposal to the "Communication ad hoc working group" in the forthcoming meeting, to be held in November 18th (see in attachment the revised proposal).

3. Update on activities in Germany

R. Jung (Clariant) said that UBA (the German authority dealing with environmental issues) is preparing a report concerning the biomonitoring of PFOA and PFOS blood levels in the general population by using blood banks; they have 7 time points between 1982 and 2004; in each time point there are 8 males and 8 females aged 20-30 years. From preliminary information the mean levels are similar to those found in the USA population (5-7 ppb; range up to 100 ppb) and the concentration seems to be quite stable over the time period.

UBA has also started an environmental risk assessment; the industries have been invited to a meeting in December for discussing it.

R. Jung also informed the group that the German Ministry of Environment wants to proscribe PFs, putting them in a restriction list; PFOA is the next substance that will be considered. D. Farrar pointed out that European manufacturers (and also users) have to be involved in this process. He should have contacted Dr. Gloria about that.

R. Jung also updated about German MAK Commission: the MAK value has not yet benn decided, but it seems that they are going to set the valute below the existing one (.01 mg/mc), due to its persistency. The classification as carcinogen should be A3.

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W. de Wolf said that a meeting on environmental monitoring and exposure assessment of potential users of PFs will be held in December. He was pleased that Miteni joined the last conference call.

5. Update on the European activities

Danish EPA has just issued a report on assessment environmental friendly alternatives to perfluorinated sulfonate and acid in environment. Those who read the report said it is rather "poor" in data and science; it makes many misunderstandings in chemistry of the different substances and says that all PFs bioaccumulate. W. de Wolf will prepare a short report explaining why PFOA is persistent but not bioaccumulating.

D. Farrar (IneosChlor) reported that UK Technical Committee on existing chemical substances has completed its environmental evaluation on PFOS; it has been labeled as PTB and they are starting the development of a risk reduction strategy in UK (list of PFOS deriving materials). However, they do not intend to submit such report to EU authorities.

As concerns OSPAR, nothing new is going on.

6. APME Food Contact Dossier

The dossier is in progress. It has been rejected twice as it was not drawn according to OECD guidelines and because no mutagenicity test was reported. The last issue has been now delayed due to need for further information concerning analytical methods and references, asked by some public authorities (e.g. Italian Istituto Superiore di Sanità).

Now the APME responsible group (consumer's products) has to approve the final version: that can take some time.

D. Farrar will check the report as concerns the toxicological aspects.

7. Update on interactions with the US EPA

G. Kennedy (DuPont) reported about the last meeting with EPA, in which C. Elcombe (Dundee University) did a very good presentation of the preliminary results of his ongoing study about mechanisms of pancreatic tumours in rats (see point 9.). EPA appreciated the approach that has been taken.

EPA has just published in the Federal Register the call for nomination of the SAB (Science Advisory Board) for the IRIS Risk Assessment on APFO. G. Kennedy said that SPI has already nominated some scientists. Probably the Board will start working on January 2005.

8. PFOS/PFOA comparison

Following the last meeting with EPA, D. Farrar (Ineoschlor), J. Butenhoff (3M) and G. Kennedy (DuPont) agreed on updating a paper emphasizing differences and similarities between the two compounds. The draft will be circulated soon.

J. Butenhoff will circulate a recent paper by Giesy concerning the effects of PFOS on testis (no mention to PFOA).

9. Mechanisms of APFO-induced pancreatic tumour formation (CXR Biosciences) - Update on ongoing research

Cliff Elcombe (University of Dundee and CXR Biosciences) showed the preliminary data comparing the genes expression of rats exposed to DEHP (a peroxisome proliferator but not carcinogen to pancreas) and Wyeth 14043 (both peroxisome proliferator and carcinogen to pancreas).

This is the first step of a project aimed at identifying possible similarities/dissimilarities with PFOA exposed rats in the genes expression changes which may serve as biomarkers of a pre-carcinogenic potential activity.

- The microarray analysis identified 12, 22 and 20 genes that were uniquely ‘regulated’ (p<0.01) by="" greater="" than="" 2-fold="" following="" dietary="" treatment="" of="" SD="" rats="" with="" Wyeth="" 14643="" at="" 50="" ppm="" (compared="" to="" DEHP="" 12,000="" ppm)="" at="" 24="" hr,="" 7="" days="" and="" 28="" days,="" respectively.="">

- There were 9, 3 and 7 genes uniquely ‘regulated’ following treatment with Wyeth 14643 at 50 ppm (compared to DEHP 12,000 ppm) that were altered in a dose-dependent fashion.

- EGR-1, a gene induced by APFO following 28 day dietary treatment with APFO (CXR0183 study) was up-regulated by Wyeth 14643 50 ppm treatment at 28days, up-regulated by DEHP 12,000 ppm treatment at 7 days, and commonly down-regulated by both Wyeth 14643 and DEHP treatments at 24 hrs.

- Thymine-DNA glycosylase, a DNA repair gene found to be down-regulated by APFO in our preliminary study (CXR0183), was uniquely down-regulated by Wyeth 14643 50ppm at 28 days.

- No regulated genes that were uniquely altered following treatment with Wyeth 14643 50 ppm (compared to DEHP treatment) were found to be commonly altered at all time points.

- There was a time–dependent induction of genes associated with a proliferative- and DNA-damage-response and a time-dependent repression of the DNA repair gene thymine glycosylase following dietary treatment with Wyeth 14643 at 50 ppm .

According to these results the group agreed in completing the first phase of the study by repeating the same experiment and analysis in rats exposed to APFO, according to the Elcombe’s proposal approved in the previous meetings.

10. Miteni TSCA 8e concerning findings in exposed employees

The group wanted to be informed about the recent communication given by Miteni to EPA concerning the findings on possible interference by APFO on lipids metabolism. I reported very shortly about the results of the statistical analysis carried out together with 3M and DuPont specialists and discussed about the reliability of the results and the possible hypothesis of interaction. I told the group that such data are still under processing and in the next months further analysis will be carried out in order to better clarify whether or not such interaction exists and in which terms.

11. Levels of APFO in blood

G. Kennedy (DuPont) reported that the study on the health status of DuPont employees at their Parkersburg facility is ongoing. Blood levels of PFOA would also be measured. 1142 volunteers were participating and the data would be fully reported at the year-end.

I reported about he last annual check on PFOA blood levels of Miteni workers, which shows a further decrease of about 19% on average from 2003 to 2004 (see specific report) in exposed workers.

12. Date and location of next meeting

The next meeting of the APFO *ad hoc* Toxicology group will be held on February 2-3, 2005 in Brussels.

With kind regards

Prof. Giovanni Costa

Prof. Giovanni Costa

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