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Verona, 23.08.2004

Spett.
Direzione
MITENI S.p.A.
Trissino (VI)

Report on the meeting held on Friday 20th and Saturday 21st 2004 at the Inn at Montchanin Village (Wilmington, USA) with 3M and DuPont delegations.

1. Participants:

- John Butenhoff	3M, toxicologist
- Geary Olsen	3M, clinical epidemiologist
- Larry Zobel	3M, occupational health physician
- Peter Gillies	DuPont, expert in lipid metabolism
- John Green	DuPont, statistician
- Gerald Kennedy	Dupont, toxicologist
- Robin Leonard	DuPont, epidemiologist
- Robert Rickard	DuPont, toxicologist
- Giovanni Costa	Miteni, occupational health physician

2. Background

On August 9th I have been invited by G. Olsen (3M) to participate in this meeting, organised jointly with P. Gillies (DuPont), aimed at discussing the results of the analysis of the data collected by me at Miteni plant in Trissino, concerning the workers of the PF department.

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As it was been agreed last year in the ambit of the *APME-APFO ad hoc toxicological working group*, I have started a scientific collaboration with them aimed at evaluating the data related to the periodical, biological monitoring of Miteni workers exposed to PFOA.

Despite the small number of workers involved (compared to 3M and DuPont workers), such data were considered very helpful in understanding any possible interaction of PFOA with human physiology, as such cohort of workers has been checked regularly since 1979 by annual medical examinations, integrated by several blood and urine analysis. In the case of 3M workers, some workers (on voluntary basis) have been checked occasionaly (1993, 1996, 2000), whereas DuPont did not carry out regular checks of such kind in the past, but it is now carrying on a general examination of more than 400 workers, the results of which are due by the end of this year.

Therefore, the statistical analysis of Miteni data was considered very useful for checking whether or not any pre-clinical adverse effect could de detected, in order to better address the checks of larger groups at 3M and DuPont plants, and for further more detailed investigations on some specific biological parameters.

So, in December 2003 (after discussion and agreement with Miteni general management in the meeting held in Frankfurt on November 21st) I sent G. Olsen the first database of the biological monitoring of Miteni workers (in anonymous format) and, in February 2004, on occasion of the SOT Conference held in Baltimore, I had a first meeting with them and other 3M and DuPont experts (see my report dated 29.03.04 and abstract below) for a preliminary analysis of the data.

Thereafter, we decided to integrate the dataset with some more specific analysis concerning the lipids metabolism, that I collected during the periodical, annual blood check carried out in Spring this year.

Consequently, two months ago I sent G. Olsen and P. Gillies two updated datasets (still in anonymous format), one concerning the biological data available since 1987 of all exposed workers to PFOA , and the second one concerning the last blood analysis carried out in Spring 2004.

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3. Preliminary results of the statistical analysis

The analysis of the first database was aimed at evaluating any possible abnormality of biological parameters, occurred in the last 17 years, in relation to the PFOA blood levels measured in the last 4 years (2000-2003); the second one was aimed at comparing exposed and non-exposed workers to find out any difference that could be statistically associated to PFOA exposure.

The statistical analysis, carried out by means of appropriate statistical programs by DuPont expert statisticians, confirmed the negative results for almost all the 37 blood parameters considered: in particular no significant effects were detected as concerns haematology, proteins metabolism, immunology, liver, kidney and prostate function.

Only some slight effects on lipids metabolism were detected, which deserve further analysis and proper interpretations.

In fact, a slight increase of total cholesterol in workers exposed to PFOA was observed, which also appeared to show an increasing trend associated with the highest blood PFOA levels.

Table 1 shows the comparison of exposed and non-exposed workers and the slight significant increase of total cholesterol in exposed workers. There is no increase of other lipids, such as tryglicerides in particular, but the fraction of "Non-HDL Cholesterol" seems that concerned.

Figure 1 shows the positive correlation between total cholesterol and PFOA blood levels in the last 4 years (when PFOA was measured): a slight association between PFOA blood level and total cholesterol concentration seems to be consistent over the years. Figure 2 shows the same trend as concerns "Non-HDL Cholesterol".

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Table 1: Comparison of the main lipid components in exposed and non-exposed workers to PFOA

Endpoints	Manufacturing Area		P-value
	Non -PFOA	PFOA	
Serum Lipids			
Total Cholesterol	214 ± 4	233 ± 9	0.03
HDL Cholesterol	53 ± 1	51 ± 2	0.37
LDL Cholesterol	133 ± 3	146 ± 8	0.09
Non-HDL Cholesterol	160 ± 4	182 ± 10	0.03
Non-HDL/HDL	3.3 ± 0.2	3.9 ± 0.3	0.09
Total Triglycerides	141 ± 12	169 ± 19	0.22
Demographic Characteristics			
Age	39.5 ± 1.0	40.7 ± 1.5	0.53
BMI	25.3 ± 0.3	25.7 ± 0.5	0.52
Alcohol Consumption	0.27 ± 0.02	0.36 ± 0.04	0.07

Values are expressed as the mean ± SEM for approximately n = 94 non -PFOA workers and n = 35 PFOA workers.

Data are from a 2004 sample collection

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Figure 1: Correlations between Total Cholesterol (log) and PFOA (log) levels in the 4 years

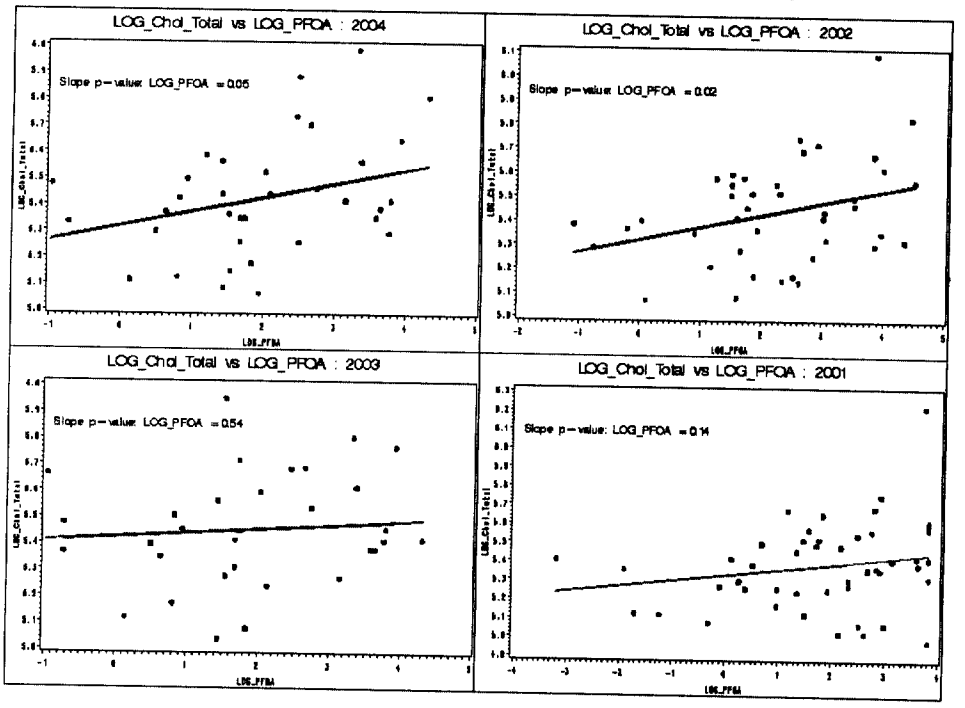
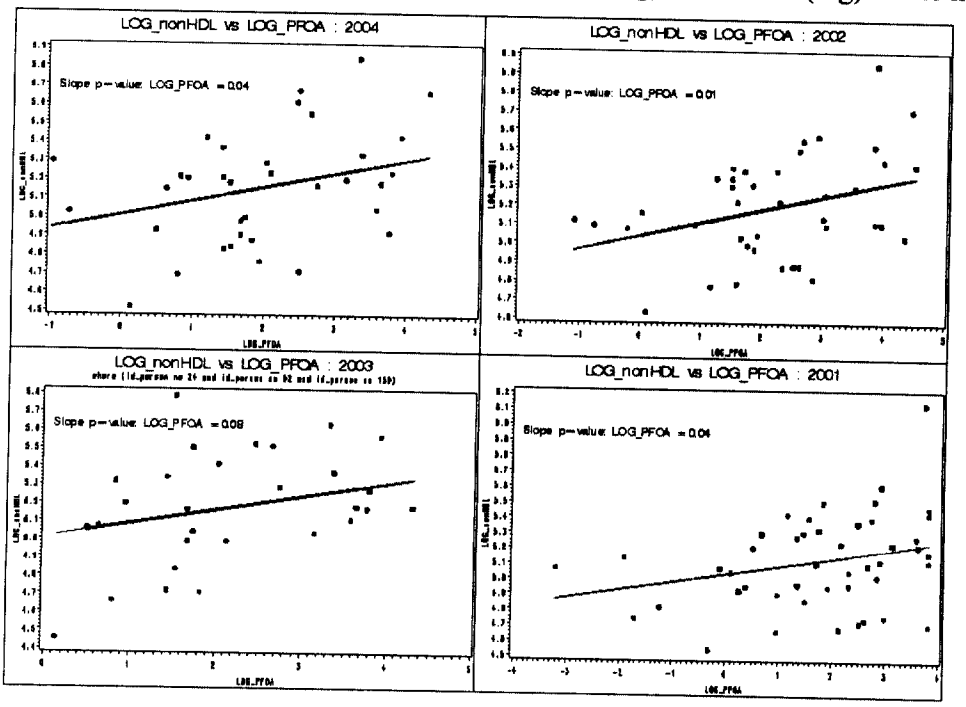


Figure 2: Correlations between non-HDL Cholesterol (log) and PFOA (log) levels in the 4 years



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In the light of these findings, G. Olsen (3M epidemiologist) reviewed the 3M datasets related to their surveys carried out in 1993, 1996 and 2000, and a preliminary analysis concerning cholesterol levels appears to be in agreement with the Miteni data.

In other words, it seems that PFOA (probably only at high blood concentrations) can interfere with metabolism of Cholesterol, in particular by increasing the fraction of "Non-HDL Cholesterol".

Such findings need a precise interpretation, also because they are in contrast with the animal experimental data (rats), where PFOA causes a decrease of cholesterol levels. That can be related to interspecies differences in drug metabolism, which are also raised for the different findings in carcinogenicity (it is carcinogen in rats, but not in primates and humans).

In order to elucidate better the possible mechanisms underlying such effect P. Gillies, DuPont expert on lipid metabolism, made an updated review of the current knowledge on lipids metabolism, trying to make some hypothesis about possible mechanisms. According to his analysis, such effect cannot be mediated by a PPARalfa mechanism (as suggested for rats), bur it is probably due to an interference with a protein (CEPT) able to transfer of cholesterol in blood and liver. He is going to have a deeper insight on such matter both by further discussion with the best academy experts on lipids and by a bio-molecular study concerning the nuclear receptors for such protein.

4. Communication and regulatory aspects.

Robert Rickard (DuPont) said that is going to have a FYI ("For your information") meeting with EPA next Wednesday, August 25th.

According to the TSCA 8e rules he has to report to EPA any new data concerning possible toxicological characteristics of PFOA DuPont may know, with particular reference to human health.

He exposed his agenda, which includes an updating of the recent toxicological studies carried out at the Haskell Lab concerning the exposure of rats and mice to linear, branched

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and mixed (linear/branched) PFOA, as well as the presentation of some ongoing studies, dealing with the health examination of more the 400 workers at DuPont "Washington" plant in West Virginia, and the review of epidemiological data concerning mortality in general population of West Virginia. G. Olsen and L. Zobel (3M) will also communicate their epidemiological data concerning 3M workers at Decatur and Antwerp plants.

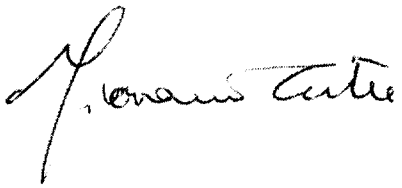
In such agenda he would like to mention also some findings related to the data on lipid metabolism mentioned above, related to Miteni workers, keeping anonymous the source of data. In particular, he would like to report the positive findings of a long lasting medical surveillance of workers exposed to PFOA, showing no effects on general health and also on biological parameters, concerning the main target organs and functions, except for a mild possible interference with lipid metabolism, which deserves further analysis.

So, he asked me whether he can report such data, in particular he would like to show one or two charts related to the lipid parameters (such as figures 1 and 2) in his presentation, without mentioning the source and the name of Miteni, and without giving EPA any written document.

As I replied that I could not deal with such request, but he must ask and get the formal permission from Miteni Management, due to the short time available he asked me to pass you such request in order to get your response (whatever it is) as soon as possible.

With kind regards

Prof. Giovanni Costa



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Abstract of my report dated 29.03.04 concerning the meeting of the APME-APFO ad hoc toxicology groupo, held in Baltimore on March 24.03.04.

5.2. Workers.

The Chairman noted that most of the companies represented in the WG had commenced or were about to embark on a blood level monitoring programme in their current employees (Asahi Glass has just started it and asked me some advice concerning the parameters to be collected from the workers). He encouraged all companies to share their data in the way that Miteni and 3M had done in the past, and he also asked me to co-ordinate the outcomes for the APME group; I gave him my willingness for that.

As also Asahi Glass is sending its sample to the German lab already used by Solvay, I suggested that all European should join this lab, provided that it is quite reliable, in order to limit the factors that can confound the results.

As concerns our data, I informed the group that we analysing them with reference to the interaction with lipid metabolism in collaboration with Geary Olsen (3M) and Peter Gillies (DuPont); see the enclosed report of the meeting held at Marriott hotel on Wednesday morning with G. Olsen and J. Buthenoff (3M) and P. Gillies and G. Kennedy (DuPont).

G. Kennedy confirmed that DuPont is starting its biomonitoring according to the protocol he circulated to the group in the last week. On Wednesday evening I have been invited for a dinner by Larry Jansen (Lawyer) and Robert Rickard (Science Director) of DuPont for exchanging information about the workers' biomonitoring (see attached report).

Attachment 1.

Meeting with G. Olsen and J. Butenhoff (3M toxicologists), Peter Gillies and J. Kennedy (DuPont toxicologists)

On Wednesday 24th morning, I had a 3-hour meeting with with 3M and DuPont toxicologist to discuss the preliminary findings of the data collected in MITENI workers and concerning the possible interference of PFOA with lipid metabolism.

G. Olsen have carried out a preliminary statistical analysis of the biochemical data related to year 2002 and 2003, which showed some possible slight effects on HDL and LDL cholesterol.

P. Gillies (DuPont expert on lipids) described the meaning of the different blood lipid components and their possible interaction with PFOA.

After a long discussion and a careful analysis of the present data, it has been convened to add further data to the dataset, in particular those related to the ongoing biomonitoring which is due to end by April. In this survey further analysis of lipids and proteins (LDL.Cholesterol, APO-A2, APO-B, reactive C-protein) have been added in order to clarify better such interaction.

So, I agreed in sending them such new data by the end of April and then start a deeper statistical analysis.

The results are expected to be sent to a toxicology journal for publication by the end of the year.