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Interoffice Correspondence: July 10, 1980

cc: J.W. Belisle
J.D. LaZerte
R.A. Nelson/T.L. Kerley
F.A. Ubel

TO: R.A. Prokop

FROM: R.E. Ober

Jon Belisle brought by for my comments on Tuesday of this week a copy of the already cleared manuscript on Serum Organic/Inorganic Fluorine Levels of Rural Chinese. My overall thoughts and comments are outlined below; additional points - mostly more specific - are written on the attached copy of the manuscript.

I agree that the data from China are worth publishing. They are novel, probably unique and make an interesting contribution to this research area. However, my impression beyond that is that an unnecessary and potentially counter productive effort is made to reach an interim conclusion about the source of the trace amounts of serum organic fluorine in humans. As Jon goes to some length to illustrate, the available data are difficult to interpret, primarily because of analytical uncertainties. I suggest that the long range interests of both the individuals involved and 3M would be better served by deleting most of pp. 4 and 5 and viewing the paper as a useful, interesting and novel scientific contribution to information in this area; but don't attempt to use the paper defensively on the question of industrial sources of serum organic fluorine. As I have mentioned on numerous past occassions, I think maintaining credibility particularly on "scientific" questions like "what is the source of organic fluorine in human serum," should be a primary goal of 3M as we continue into this rapidly expanding area of subtle potential effects of industrial chemicals. One way to help maintain credibility is to not make unnecessary and technically uncertain defensive efforts.

Thanks for the opportunity to comment. I hope my input has been helpful.

Bob

REO:mho

Attachment

PS: Since this memo was typed, I have learned from you and Jon that a specific goal of this paper was to refute the statement (probably overstatement) of Guy and Taves regarding the specific identity of some of the fluorochemicals which he claims to have found in the serum of the general population. While on yet another reading of the paper I could detect the message re Guy and

DFS-128

Exhibit
1234
State of Minnesota v. 3M Co.,
Court File No. 27-CV-10-28862

3MA10034975

1234.0001

Taves, I'm afraid that message did not and does not come thru very clearly and cogently to me. Is there any other way or any more cogent data (appropriate for release) that would make point more clearly and directly? As I mentioned on the phone, countering Guy's overstatement with an overstatement of our own probably won't be too helpful in the long run.

SERUM ORGANIC/INORGANIC FLUORINE LEVELS OF RURAL CHINESE

Jon Belisle

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WITH THE OBSERVATION[1] THAT THERE ARE TWO FORMS OF FLUORINE IN HUMAN SERUM (EXCHANGEABLE AND NON-EXCHANGEABLE TOWARDS $^{18}F^-$), RESEARCH[2] HAS BEEN DIRECTED AT IDENTIFYING THE NON-IONIC (ALSO REFERRED TO AS THE NON-EXCHANGEABLE, BOUND, OR ORGANIC) FORM. FURTHER STUDIES INDICATED THE WIDESPREAD PRESENCE IN HUMAN PLASMA[3] OF ORGANIC FLUORINE WHICH WAS NOT DETECTABLE IN THE SERUM OF ANIMALS[4] THOUGH OTHER STUDIES REPORT THE FINDING OF ORGANIC FLUORINE IN BOVINE[5] AND RAT[6] SERUM. SINCE THE WIDE-SPREAD OCCURRENCE IN HUMAN BLOOD OF TRACE AMOUNTS OF ORGANIC FLUORO-COMPOUNDS DERIVED FROM COMMERCIAL SOURCES HAS BEEN SUGGESTED[2], WE DECIDED TO OBTAIN BLOOD SERUM FROM HUMANS LIVING IN A NON-INDUSTRIALIZED AREA; OUR ANALYSIS INDICATES DETECTABLE ORGANIC FLUORINE IN THESE PEOPLE AS WELL.

[The journal (NATURE) requires the first paragraph to be a brief background and conclusion to the research, therefore in capital letters.]

Several methods of analysis have been used for total fluorine in serum/plasma. Most samples have been analyzed by open ashing which is known to give a variable loss of fluorine[5]. For example, only 21% of available fluorine from perfluorooctanoic acid is recovered as inorganic fluoride (sample size not specified)[2]. The use of the closed oxygen bomb technique[5,6,7] avoids most of these losses and our further work indicates 90+ % recovery for perfluorooctanoic acid (1-5 ug)[7].

With the kind cooperation of the medical authorities from the People's Republic of China, eight human serum samples were obtained from Chinese donors who live in a rural commune with little chance for exposure to industrial fluorochemicals. The samples were analyzed for fluorine by the oxygen bomb method[7] which is known to be more reliable than the other methods involving ashing[5].

Table 1 Organic/Inorganic fluorine levels of rural Chinese

Person	Organic Fluorine	Inorganic Fluoride
1	0.008 ppm	0.051 ppm
2	0.013	0.054
3	0.011	0.046
4	0.014	0.046
5	0.009	0.044
6	0.009	0.049
7	0.004	0.046
8	0.017	0.076

All the samples (Table 1) had detectable organic fluorine levels. A brief review of the literature indicates that the determination of organic fluorine (ashing) in 65 plasma samples of persons residing in the state of New York gave an average value of 0.03 ppm organic fluorine with the lowest value at the 0.005 ppm level[3]. In a later study involving 106 individuals living in five different cities in two different states, a mean plasma organic fluorine value of 0.025 ppm (ashing) was observed with 2 people estimated at less than 0.005 ppm[2]. In a recent study of 264 people living in one Minnesota community, an average organic fluorine value of 0.045 ppm (ashing) was reported with the lowest person having non-detectable organic fluorine (0 00 ppm)[8]. In a current report from Argentina, analysis of a pooled serum sample indicates an organic fluorine level (ashing) of 0.085 ppm[6]. Analysis of 9 individuals (Minnesota residents) gave an average or 0.02 ppm organic fluorine (oxygen bomb) with the lowest person at 0.01 ppm[7].

From Table 1 and the above cited literature, the organic fluorine levels of this rural Chinese group are at the low end of the range when compared to a group representing a more urban environment.

The inorganic fluoride levels were slightly higher than the levels in the case of our previous (0.02 ppm) Minnesota group[7] although in another work[8], an average value of 0.058 ppm was reported. Guy[3] reported a mean of 0.015 ppm inorganic fluoride and later showed the plasma inorganic fluoride level to be dependent on the level of F^- in the drinking water. Therefore, the slightly higher Chinese inorganic F^- levels may be due to the fluoride in diet and drinking water.

As the conjecture to the source and identity of the organic fluorine in blood continues, it would seem helpful to compare ashing and bomb results. While a fluorochemical has been isolated from plasma[2] and suggested to be perfluorooctanoic acid, that compound is recovered by the same researcher only to the extent of 20 % (ashing), yet the bomb (90+ % recovery[7]) and ashing results of serum/plasma are quite comparable; for example, 0.026 ± 0.016 ppm SD (n = 106, ashing)[2] to 0.022 ± 0.007 SD (n = 9, oxygen bomb)[7]. This good agreement between the two methods suggests that a significant portion of the serum/plasma organic fluorine is not perfluorooctanoate since one would then expect higher values by the bomb than open ashing. In fact, the most recent results[8] by ashing give a organic fluorine level twice that previously reported[2,3,7]. These researchers[8] further conclude that the range of total fluorine in plasma has not changed in the past 20 years and that there is no evidence for environmental contamination with organic fluorine. In considering these conclusions, it is necessary to realize that one is comparing the results of different researchers using a variety of methods. Perhaps the most important concern here is the comparison of open ashing to closed oxygen bomb results. It is known that open ashing is prone to contamination with inorganic[10] as well as organic (FREONS^R)[3] fluorine and that fluorine results are method dependent[10,11]. In addition, as stated above, open ashing is susceptible to low recovery of organic fluorine due to loss (volatility) of organic compound prior to decomposition; thus open ashing has both positive and negative errors. Due to the paucity of values determined with the oxygen bomb, it is necessary to use open ashing results of questionable value for purposes of comparing organic fluorine blood levels.

Compounds containing organic fluorine have a number of useful industrial and medical applications[12]. The wide use of these compounds gives a number of sources for exposure to organofluorine compounds. A review on organic fluorine covers biochemistry[13], another gives special emphasis to the field of psychiatry[14], while others present toxicology data[15,16]. The fluoroorganic compounds methoxyflurane and halothane are anesthetics[17] while artificial blood contains perfluorocarbons[18,19]. In addition, several natural sources have also been suggested[3].

In recently published research on exposure to fluorochemicals[20], elevated serum organic fluorine levels were found in chemical employees handling a specific fluorochemical (perfluorooctanoic acid, ammonium salt, $C_7F_{15}CO_2^-NH_4^+$). In addition, that report indicates that this fluorochemical is slowly eliminated from the body. Therefore, it would appear that blood levels of organic fluorine are dependent on the possibility and frequency of exposure to specific fluorochemicals.

It is known that when man[20], rat, or monkey[21] is exposed to the fluoroorganic, perfluorooctanoic acid, ammonium salt, this compound will be found in the blood serum. This is not surprising when one considers the results of a binding study of perfluorooctanoic acid to human serum[6] where it was reported that greater than 99 % of this added organic fluorine was bound to serum constituents. The above cited literature[2,3,7,8,9] would suggest that essentially everyone (>98 %) has both forms of fluorine in their blood and that the reported values are somewhat dependent on the method of analysis. The inorganic value is known to depend on diet

and drinking water while the organic value could be influenced by exposure to certain fluorine containing compounds from both natural and synthetic sources.

While the widespread prevalence of organic fluorine in human plasma was initially suggested to be due to commercial sources, the literature cited by the authors actually shows a decreasing concentration over a period of 15 years though they state that the trend may be due to the analytical methods or the blood samples themselves[2]. As yet, we find no conclusive evidence to indicate that the widespread presence of trace amounts of organic or bound fluorine in human blood is the result of industrial fluorochemicals. Continuing studies will enhance our knowledge and understanding of organic/inorganic fluorine levels in man.

ACKNOWLEDGMENT

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