

FLUOROCHEMICALS IN HUMAN BLOOD

Introduction

The presence of two specific fluorochemicals, perfluorooctane sulfonate (PFOS), and to a lesser extent, perfluorooctanoate (PFOA), is described in human blood. The presence of an organic form of fluorine in human blood was observed 30 years ago. PFOA has been suspected of being a significant component of this fraction, but we find little current evidence to support this view. Evidence is presented below that PFOS is a more significant constituent of the organic fluorine found in blood. Based on the PFOS contribution to organic fluorine and the measurement of PFOS in historical samples, PFOS levels in blood samples from the United States do not appear to have changed significantly in the last three decades.

Historical Finding of the Organic Form of Fluorine in Blood

The presence of an organic form of fluorine in human serum has been recognized for 30 years. Taves (1968a) described two forms of fluorine in serum, one that was exchangeable with radioactive fluorine-18 and one that was not. Venkateswarlu et. al. (1971) also described two forms, ionic and nonionic. Taves (1968b) showed that the nonexchangeable fluorine was bound to albumin. This finding, along with results of extraction and precipitation and the need for ashing to release this form of fluorine, led to the conclusion that the nonexchangeable or nonionic fluorine was "organic", i.e. covalently bound to carbon (Taves et. al., 1976).

Considerable research has been done on measuring the level of organic fluorine in human blood serum. Table 1 presents the study author, level measured, population and method. The variety of methods used for determination of fluorine does suggest that some caution be used in interpreting results. All reported levels were in the low tens of part per billion levels, only one exceeding 50 ppb. The average of reported values from United States sources was 33.5 ppb.

The nature of the organic fluorine molecule or molecules is of interest. Taves et. al. (1976), using NMR spectroscopy, tentatively identified a component of the organic fluorine as perfluorooctanoic acid (PFOA). This is an eight carbon perfluorinated carboxylic acid ($C_7F_{15}CO_3^-$). There was some variation in the observed spectra from sample PFOA, however, leading Taves et. al. (1976) to suggest that branching, or the presence of a sulfonate, was possible.

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

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Production and Medical Monitoring of PFOA AND PFOS

3M has produced PFOA (the ammonium salt) by electrochemical fluorination since the early 1950's. It is a surfactant used in Teflon production. The company began monitoring employees involved in PFOA production in 1976, by measuring serum levels of organic fluorine (OF) and performing medical assessments. Employee monitoring was expanded significantly in 1981 following the development of a more rapid test for organic fluorine. Serum levels of OF in these employees were measured in the parts per million level with annual averages less than 10 ppm. Medical monitoring has shown no consistent clinical finding that relates to OF level, or to PFOA level, when this specific measurement was done beginning in 1993 (Ubel et. al., 1980; Gilliland, 1992; Gilliland and Mandel, 1995, Olsen et. al., 1998a). A retrospective cohort mortality study, conducted by University of Minnesota School of Public Health investigators, was first reported for this location in 1980 (Ubel et. al., 1980) with the most recent vital status update through 1990 (Gilliland and Mandel, 1993). No statistically significant increases for any specific cause of death were found in the original study or the most recent update.

3M manufactures other products which contain chemical compounds, either as intentional components or residual impurities, that have as a parent molecule perfluorooctane sulfonyl fluoride ($C_8F_{17}SO_2F$). These compounds may be expected to transform metabolically, to an undetermined degree, to perfluorooctane sulfonate (PFOS, $C_8F_{17}SO_3^-$). Potassium perfluorooctane sulfonate ($C_8F_{17}SO_2K^+$) is, itself, a surfactant used as a wetting and foaming agent in industrial and commercial processes. Perfluorooctane sulfonyl fluoride-based materials have been produced since the early 1950's, also by electrochemical fluorination. Since 1980 this has occurred at primarily one location in the United States (Decatur, Alabama). This site consists of a fluorochemical plant and a film plant which are physically separate entities. Chemical plant employees have been offered a medical monitoring program that includes standard medical testing as well as measurement of serum levels of OF. Among employees with six or more measurements, OF levels averaged 2.9 to 6.5 ppm from 1981 to 1992 (Figure 1). Because of the introduction of high performance liquid chromatography mass spectrometry mass spectrometry, serum PFOS, and not OF, was measured in 1994 and 1997 (see also Figure 1). No clinical or subclinical findings relating to OF, and later, beginning in 1994, to PFOS specifically, have been reported (Roach, 1982; Olsen et. al., 1998b). A retrospective cohort mortality study (1961-1991), conducted by epidemiologists at the University of Minnesota School of Public Health, reported no statistically significant increases for any specific cause of death among the 1,957 male and female employees at the chemical and/or film plants (Mandel and Johnson, 1995). Outside the United States, 3M manufactures PFOS at its Antwerp, Belgium plant. PFOS levels have been measured in Antwerp employees in 1995

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(mean = 1.8 ppm, range 0.0 - 9.9 ppm) and in 1997 (mean 1.5 ppm, range 0.1 - 4.8) ppm. Medical monitoring of these employees has also shown no significant hematological, clinical chemistry or hormonal abnormalities associated with these serum PFOS levels (Olsen et al. 1998b).

Development of Specific Tests for PFOA and PFOS

As noted above, methods to test specifically for PFOA and PFOS were developed in the mid-1990's by Johnson et. al. at the 3M Environmental Laboratory (Johnson et al., 1996). These tests replaced the nonspecific OF measurement previously used. The technique has been improved over time, so that detection limits and quantitation limits are now (April, 1998) in the 1 to 2 part per billion range.

We have been interested in determining how widespread this finding may be and also have wanted to evaluate it in the historical context of the previously reported organic fluorine values in the general population. We have subsequently tested multiple serum samples as presented in Table 2. Additional detail of these findings is also summarized below.

Non-Occupationally Exposed 3M Employees

A total of 31 3M employees were tested for PFOS in serum. All were corporate staff or division managers. None had worked in fluorochemical production or in fluorochemical research and development. There were from 5 females and 26 males. Employees ranged in age from 37 to 62 years. All employees had measurable PFOS in their blood serum (mean = 47 ppb; range = 28 to 96 ppb). Age was significantly associated with increased serum PFOS and it accounted for 24% of the variance in PFOS levels. There was no gender-related difference if age was considered. Only four employees had PFOA measured above the detection limit of 10 ppb. The average of these four PFOA measurements was 12.5 ppb. Thirteen employees were re-tested eight weeks later to check for reliability of the analytical method. The findings suggested reliability ($R^2 = .94$) in the range of detection (Figure 2).

Commercial Pooled Serum Samples

Commercially available pooled sera samples (6) were tested. No information is available about the donor pool, such as age, sex or geographical location. Samples from Intergen came from donor pools consisting of approximately 500 individuals. Three Intergen pools measured 43, 44 and 44 ppb of PFOS. Sigma pools were from an unknown number of donors. The pools from which the

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samples were drawn were 50 liters, suggesting a minimum of 100 donors, but more likely twice that number per pool. The three Sigma pools were 26, 28 and 45 ppb of PFOS.

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Blood Bank Pooled Sera

In February and March, 1998, 21 blood banks from various geographic areas across the continental United States and Alaska donated 3 to 6 pooled samples that had from 5 to 10 donors per pool. Altogether there were 63 total pools, representing 315 to 630 individual donors. The range found in the pooled serum was 9 to 56 ppb of PFOS (Figure 3). The location means ranged from 14 ppb in Santa Barbara, California to 52 ppb in Greenville, South Carolina (Figure 4). PFOA levels were detected in 20 of the samples but quantifiable in only 2 samples (12 and 22 ppb).

Historical Samples

Nine sets of historical samples have been analyzed for PFOS and preliminary results have been reported for PFOA. These are presented chronologically.

Korean War era U.S. military recruits, 1948 to 1951. Ten pooled samples consisting of ten individual samples each were measured. All were below 1 ppb, the limits of detection..

Swedish samples, 1957. Ten individual samples ranged from below limit of detection to 4.1 ppb. Two were below detection limit (1 ppb). The mean was 1.98 ppb.

Michigan Breast Cancer Study, 1969 - 1971. Five individual samples ranged from 11.8 to 59.4 ppb. The mean was 33.4 ppb.

Swedish samples, 1971. Ten individual samples ranged from below detection limit (1 ppb) to 2.8 ppb. Three were below detection limit. The mean was 1.13 ppb.

MRFIT pooled calibration samples, 1976. Six pooled calibration samples ranged from 13.7 to 55.5 ppb. The number of donors per pool is unknown. The mean was 30.9 ppb.

MRFIT pooled calibration samples, 1980. Three pooled calibration samples ranged from 13.8 to 40.5 ppb. The number of donors per pool is unknown. The mean is 25.5 ppb.

China samples, 1984. Six individual samples from Linxian province in rural China were all below limits of detection or quantitation. The samples were from an NCI study on nutrition and cancer prevention.

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MRFIT individual samples, 1985. Three individual samples from participants in the MRFIT study were below limits of quantitation (5 ppb), 43.3 and 43.9. Assuming the LOQ for the low sample, the mean was 30.7.

China samples, 1994. Six individual samples from Shandong province in rural China were all below limits of detection or quantitation. The samples were from an NCI study on nutrition and cancer prevention.

At the present time, preliminary results of the above samples suggest that PFOA is either not detected, or detected but not quantifiable. There were only two samples where PFOA was quantifiable. This was in 2 of the U.S. geographical samples from blood banks (at 12 and 22 ppb).

Relationship of Organic Fluorine to PFOS and PFOA

Fluorine is 65% of the molecular weight of PFOS and 69% of the molecular weight of PFOA. The contribution of a PFOS value to organic fluorine, in ppb, will therefore be $[0.65 \times (\text{PFOS value in ppb})]$. Similarly, the contribution from PFOA will be $[0.69 \times (\text{PFOA value in ppb})]$.

The blood bank samples from across the U.S. probably provide the best representation of current PFOS blood values, because of the number of individual donors and the geographical dispersion of the findings. The mean value is 28.6 ppb PFOS, or a contribution of 18.6 ppb to organic fluorine.

Comment

Organic fluorine has been noted in human serum since the late 1960's. We have now identified PFOS as a part of this organic fluorine fraction. When looking at the data overall, the serum levels, recognizing difficulties with sampling, do not appear to have changed significantly in the last 25 to 30 years.

PFOS related materials were not produced commercially prior to 1948, and only in small quantities for several years thereafter. It is not surprising that samples from 1948 to 1951 show undetectable levels. There was clearly an increase 20 years later; however no further upward trend is observed. It should be noted that it is uncertain whether body burden is adequately reflected by serum levels. Information on distribution and kinetics is needed to shed further light.

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PFOA may have been misidentified as a major component of organic fluorine in 1976. Neither historic nor current samples confirm this as a major fraction, except in occupationally exposed employees.

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Table 1. Literature Review - Total Organic Fluorine Levels

YEAR	AUTHOR	OF (ppb)	n	METHOD	COMMENT
1959	Singer				TF = 120
1972	Guy	30	65	ash	
1975	Venkateswarlu	36	2	O bomb	mid range
1976	Guy, Taves	25	106	ash	
1978	Belisle	20	9	O bomb	
1979	Singer	45	264	ash	
1980	Paez	85	pooled	ash	Argentina
1980	Ubel	45	4	mod O bomb	mid range
1981	Belisle	11	8	O bomb	China
1989	Yamamoto	32	11	LOPA	Japan

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Table 2.
Summary of Mean and Range of PFOS (ppb) Levels in Current and Historical Human Populations,
All Data Analyzed in February - April, 1998

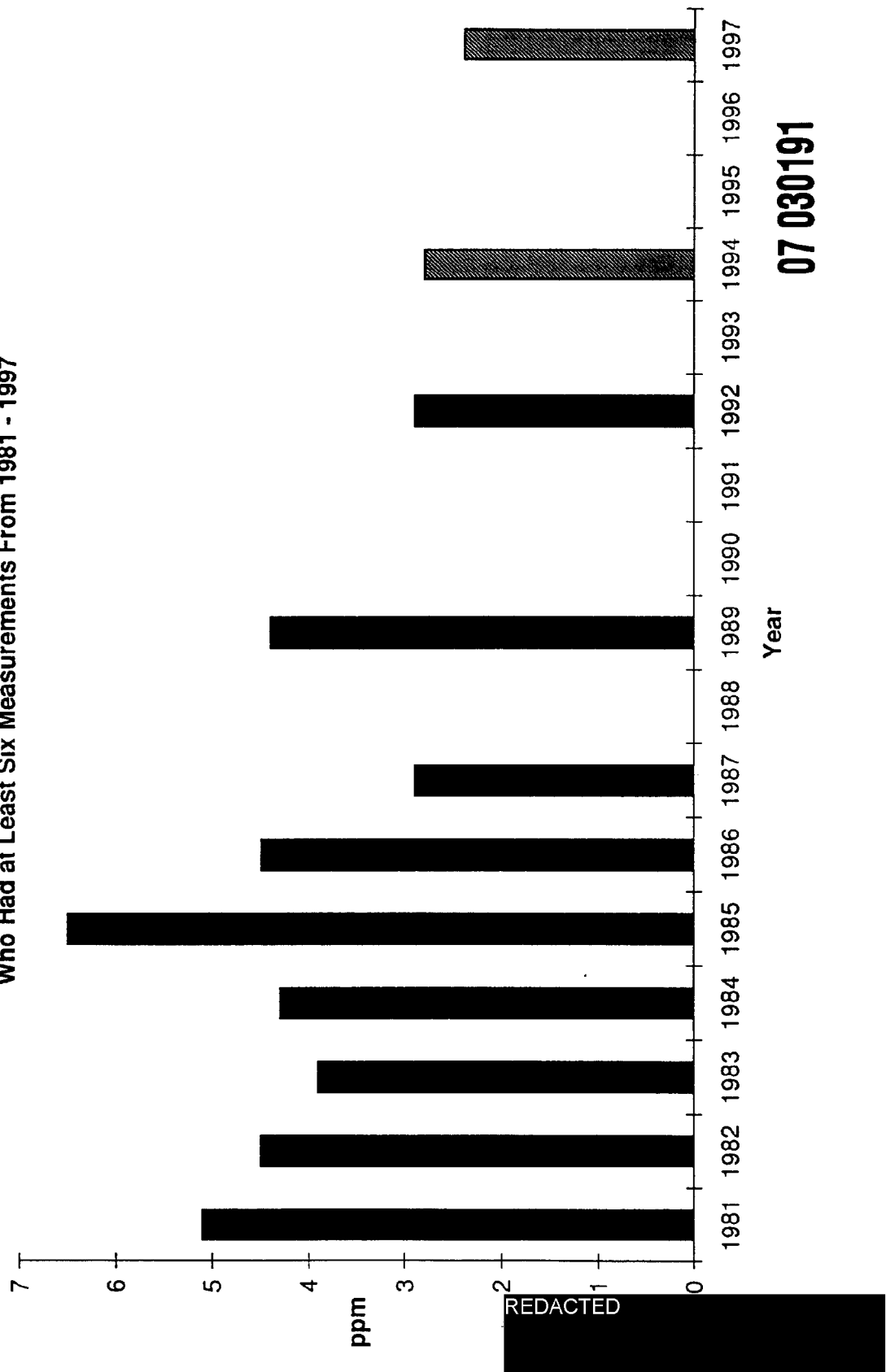
Populations	Description of Sample	Mean* (ppb)	Range* (ppb)
A. Current Populations (blood collected in 1998)			
1. Non-occupationally exposed 3M employees	31 individuals	47	28-96
2. Commercial pooled serum samples InterGen Laboratory	3 samples each with ≥ 100 donors	44	43-44
Sigma Laboratory	3 samples each with ≥ 100 donors	33	26-45
3. Pooled serum from 21 separate U.S. blood banks (see Figure 1 for more detail)	3 to 6 pooled samples per location with 5 to 10 donors per sample	29	9 - 56
B. Historical Samples (chronological order)			
1. Korean War era U.S. military recruits, 1948 to 1951	10 pooled samples with 10 donors per sample	N.D.**	N.D.
2. Swedish samples, 1957	10 individual samples	2	N.D. - 2
3. Michigan Breast Cancer Study, 1969-1971	5 individual samples	33	N.D. - 59
4. Swedish samples, 1971	10 individual samples	1	N.D. - 1
5. MRFIT pooled calibration samples, 1976	6 pooled samples with unknown number of donors per sample	31	14 - 56
6. MRFIT pooled calibration samples, 1980	3 pooled samples with unknown number of donors per sample	23	14 - 41
7. China samples (Linxian, rural province), 1984	6 individual samples	N.D.	N.D.
8. MRFIT individual samples, 1985	3 individual samples	31	N.D. - 44
9. China samples (Shandong, rural province), 1994	6 individual samples	N.D.	N.D.

Rounded to nearest ppb
Not detected

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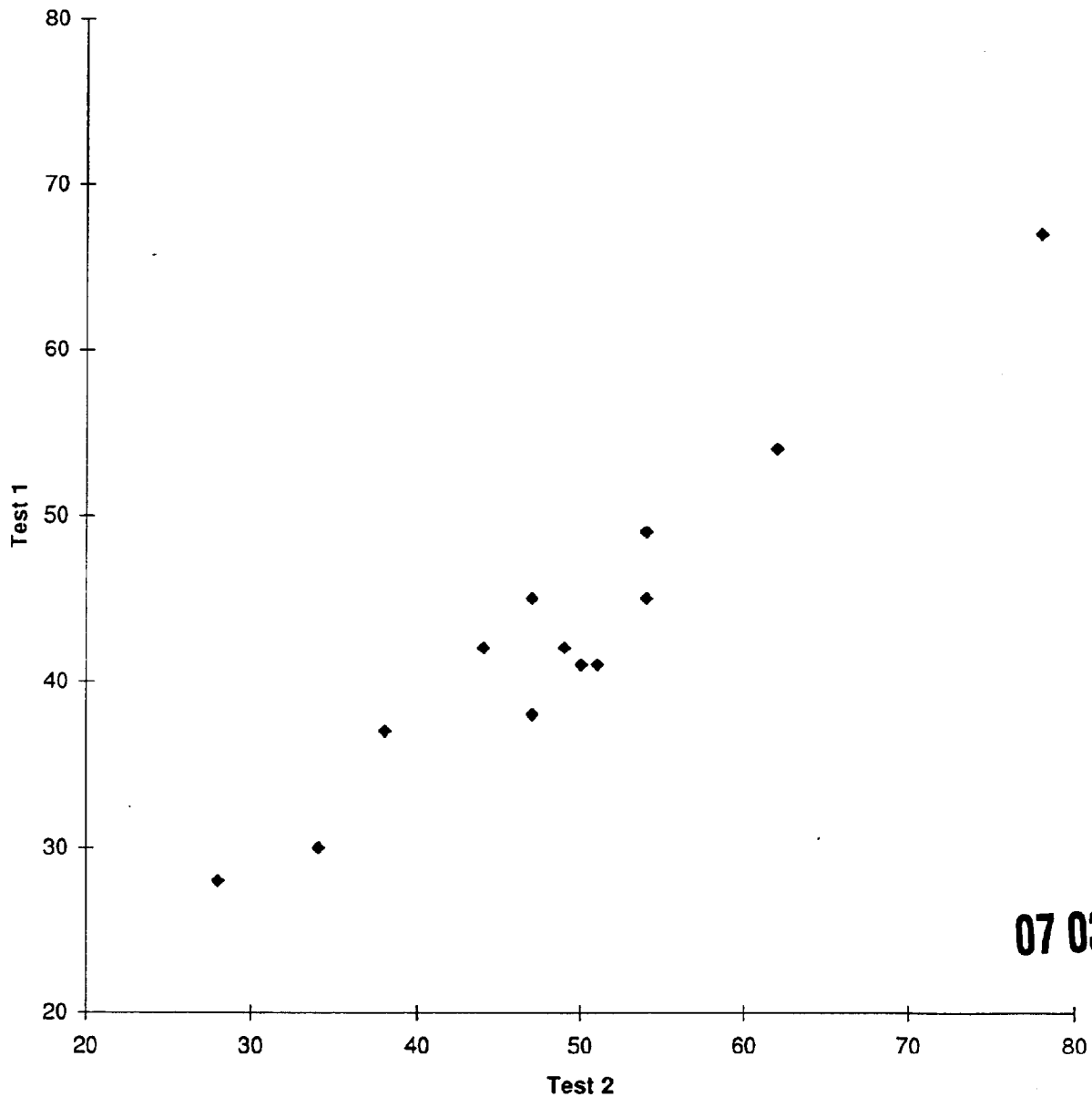
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Figure 1.
Mean Levels (ppm) of Total Serum Organic Fluorine (solid black bars)
or Perfluorooctane Sulfonate (striped bars) in Decatur Employees
Who Had at Least Six Measurements From 1981 - 1997



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Figure 2
Reliability Test of PFOS (ppb) Levels in 13 3M Employees (Test 1 =
February, 1998; Test 2 = April, 1998)

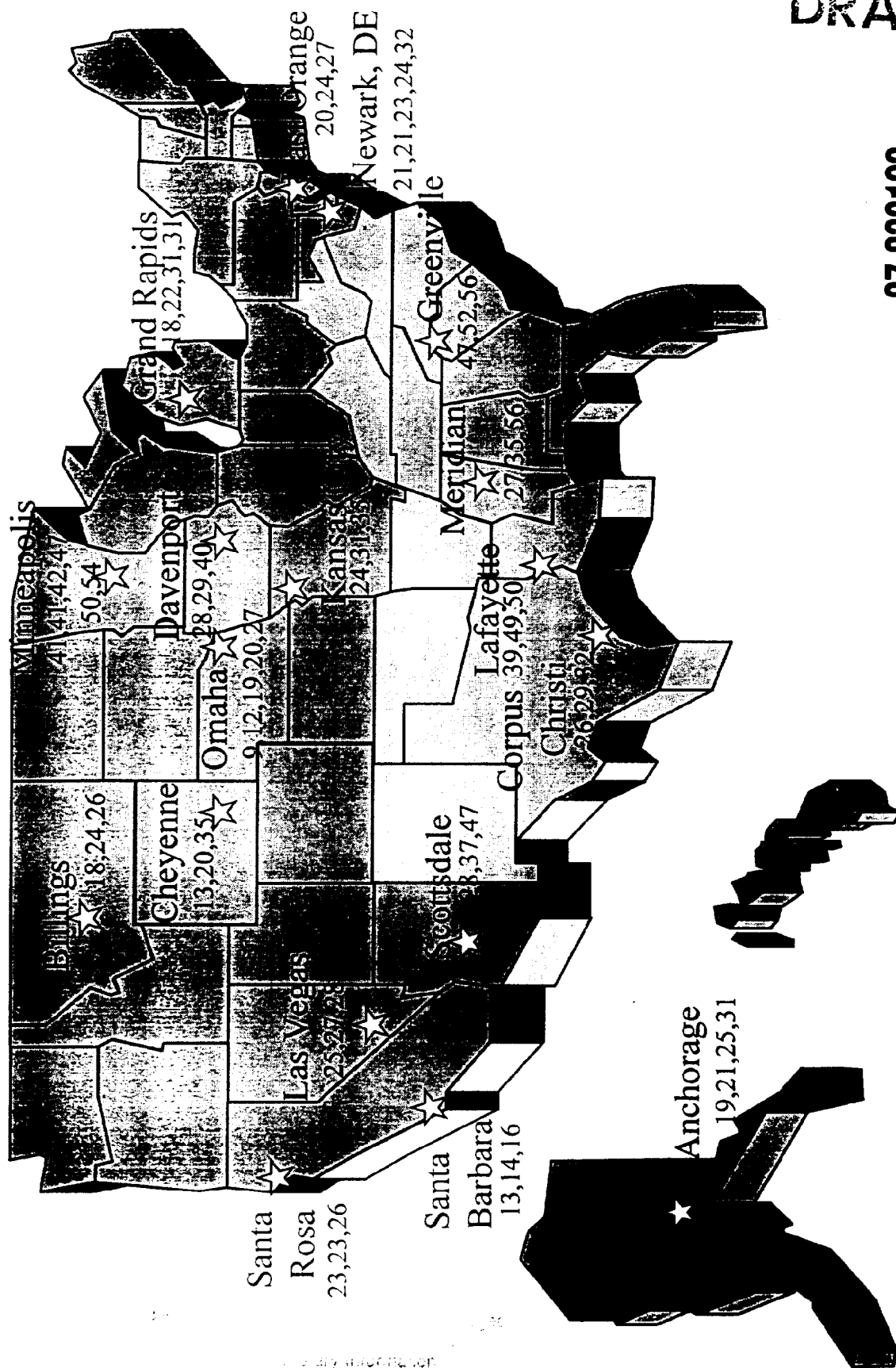


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Figure 3

Determination of PFOS (ppb) Levels from 18 Blood Banks

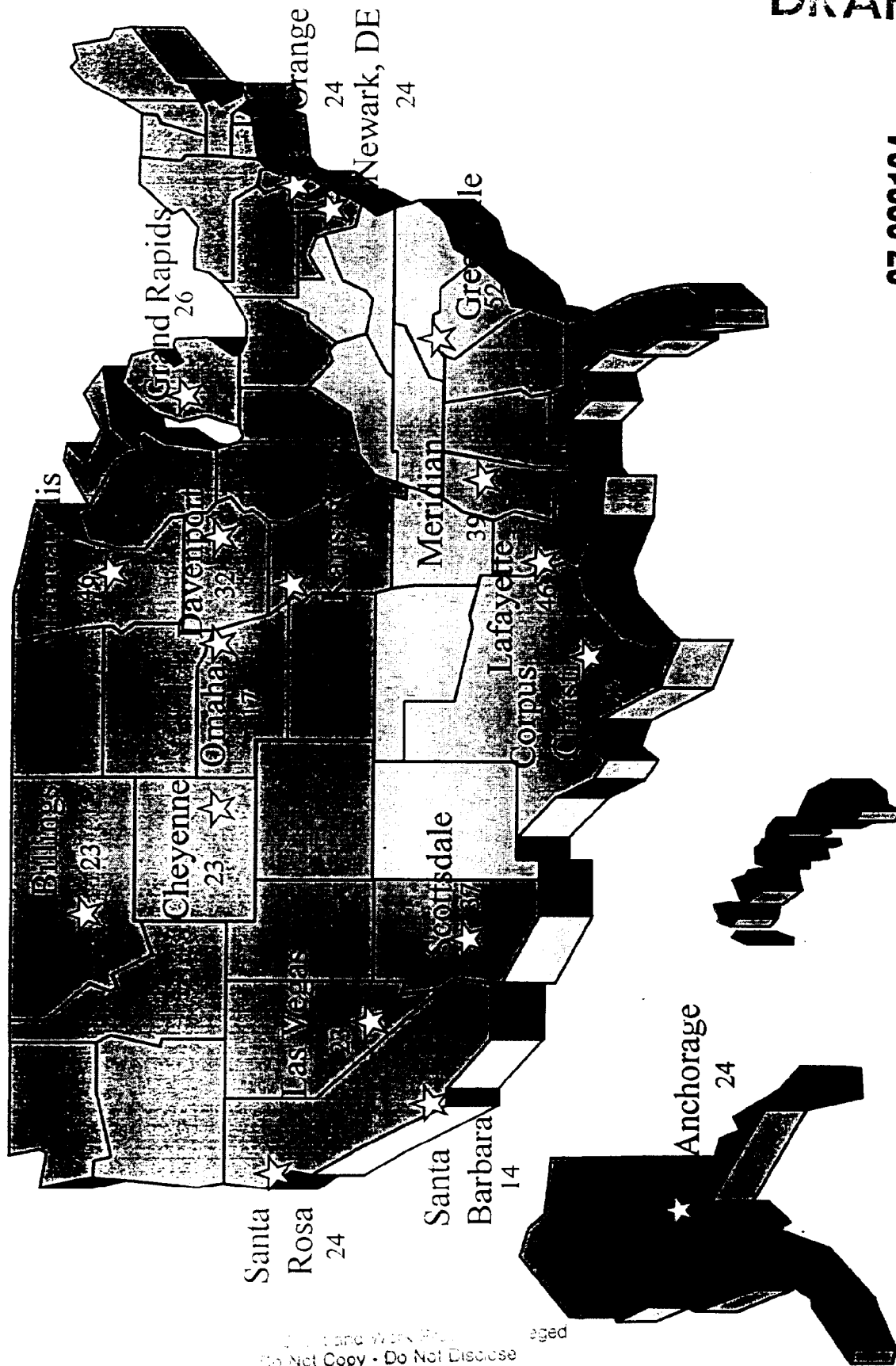


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Figure 4

Average PFOS (ppb) Levels from Samples of 18 Blood Banks



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