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Assessment of Lipid, Hepatic and Thyroid Function in Relation to an
Occupational Biologic Limit Value for Perfluorooctanoate

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ABSTRACT

Perfluorooctanoic acid [$\text{CF}_3(\text{CF}_2)_6\text{COOH}$] has been used primarily as a surface-active agent in the production of various fluoropolymers, including tetrafluoroethylene. Perfluorooctanoic acid is soluble and readily dissociates to the carboxylate anion, perfluorooctanoate (PFOA) which has been used in industry primarily as the ammonium salt. In 2000 the 3M Company (3M) established a biological limit value (BLV) of 5 $\mu\text{g/ml}$ (parts per million, ppm) for PFOA in the serum of its production workforce. The BLV was considered to represent the best estimate of a level of a chemical substance or its metabolite(s) in a biological fluid that if present, even on a chronic basis, would not be expected to pose, or correlate with, a significant risk of adverse health effects to the worker(s). 3M Cottage Grove (Minnesota) fluorochemical production employees have voluntarily participated in periodic medical surveillance examinations. Surveillance activities include a self-administered questionnaire, hematology, standard clinical chemistry tests and serum PFOA determination. In 2000, 131 male and 17 female employees participated in the fluorochemical medical surveillance program (approximately 70 percent participation). Among the men, serum PFOA concentrations were log normally distributed and ranged from 0.007 to 92.03 ppm with a geometric mean of 0.85 ppm (95% CI 0.64 - 1.22). The 17 female employees' serum PFOA concentrations ranged from 0.04 to 4.73 ppm with a geometric mean of 0.42 ppm (95% CI 0.23 - 0.79). There were no statistically significant ($p < .05$) differences in lipid, hepatic and thyroid hormone test results among male or female employees. There were no statistically significant differences in the percentage of test results that were above or below the reference ranges of the clinical chemistry and thyroid parameters. Higher

serum PFOA concentrations were associated with the specific area where APFO was produced. Employees' serum PFOA concentrations were not correlated ($r = -.02$) with the number of years that they have worked in the Chemical Division at this manufacturing site. These observations firmly support the need to incorporate specific PFOA exposure matrices in epidemiologic assessments of this workforce in order to minimize the probability of exposure misclassification. A limitation of this study was its inability to assess temporal relationships due to its cross-sectional design.

INTRODUCTION

Perfluorooctanoic acid [$\text{CF}_3(\text{CF}_2)_6\text{COOH}$] has been used primarily as a surface-active agent in the production of various fluoropolymers, including tetrafluoroethylene. Perfluorooctanoic acid is soluble and readily dissociates to the carboxylate anion, perfluorooctanoate (PFOA), which has been used in industry primarily as the ammonium salt (APFO). Production may occur by electrochemical fluorination or telomerization. Interest has focused on PFOA and a sulfonate analog, perfluorooctanesulfonate (PFOS), because of their presence in humans (Hansen *et al.* 2001; Olsen *et al.* 2002a; 2002b; 2000c) and the environment (Kannan 2002; Hansen *et al.* 2002), although the properties and toxicology of these two compounds are different.

The potential health hazards of PFOA from experimental studies have been extensively reviewed (U.S. E.P.A., 2002; 2003; Butenhoff *et al.* 2002a). Briefly, PFOA is readily absorbed after oral dosing and is not metabolized (Vanden Heuvel *et al.* 1991). The high rate of absorption of PFOA from inhalation exposure is comparable to oral exposure with dermal absorption less likely (Kennedy *et al.* 1985; 1987; Kennedy *et al.* 1986). There are marked species differences in serum elimination and between sexes in some species. Female rats have the highest rate of elimination with half-lives of hours compared to days in the male rats (Johnson and Ober 1980; Hanhijärvi *et al.* 1982; Vanden Heuval *et al.* 1991). This difference may be due to altered expression of organic anion transporter proteins (Kudo *et al.* 2002). Humans appear to have a much longer serum elimination half-life of several years although the specifics of this assessment are being determined in a current assessment (Burris *et al.* 2002). PFOA activates the peroxisome-proliferator-activated receptor alpha (PPAR- α) (Ikeda 1985) although the

responses that occur in mice and rats may have minimum relevance to primates and humans (Cattley *et al.* 1998). PFOA did not cause adverse effects in mating or fertility in the rat, or malformations in the developing fetus (York 2002). Delays in sexual maturation (both sexes) and an increase in post-weaning mortality (first several days) were observed in the first generation offspring in the highest dose group (30 mg/kg/day). Post-natal developmental effects were not observed in rabbits. Results from sub-chronic repeated oral dose studies of PFOA in mice, rats and monkeys indicate the liver is the primary target organ of toxicity (Griffith and Long 1980; Kennedy 1987; Butenhoff *et al.* 2002b). Liver weight increase in cynomolgus monkeys was not observed in monkeys for which dosing was suspended or in those that were allowed to recover for 90 days (Butenhoff *et al.* 2002b). Altered lipid metabolism occurred in rats (Haughom and Spydevold 1992). Through nongenotoxic mechanisms, an increase in benign adenomas of the testes (Leydig cell), pancreas (acinar cell) and liver in rats was observed at a dietary dose of 300 parts per million (ppm) APFO which approximates 6 mg/kg/day (Biegel *et al.* 2001). An increase in Leydig cell tumors was observed in another lifetime bioassay in rats at 300 ppm but tumors of the liver and pancreas were not observed at 30 or 300 ppm APFO, nor an increase in Leydig cell tumors at 30 ppm (Riker 1983).

In 2000 the 3M Company (3M) established a biological limit value (BLV) of 5µg/ml (ppm) for PFOA in the serum of its workforce engaged in the production of APFO via electrochemical fluorination (Roy *et al.* 2002). The BLV was considered to represent the best estimate of a level of a chemical substance or its metabolite(s) in a biological fluid that if present, even on a chronic basis, would not be expected to pose, or correlate with, a significant adverse health effect to the worker(s). This BLV was based,

in part, on the use of a 10-fold safety factor applied to the mean serum PFOA concentrations associated with liver-to-body weight ratios in the sub-chronic APFO feeding study of cynomolgus monkeys (Butenhoff *et al.* 2002b). These weight changes were not accompanied by any gross or histopathological observations or changes in clinical chemistries.

Serum PFOA concentrations greater than the BLV do not necessarily imply a health risk (Roy *et al.* 2000). If employees' serum PFOA concentrations either meet or exceed the BLV, corrective actions may need to be applied on a case-by-case basis at the direction of medical professionals. This could include temporary removal from the immediate work area. Implementation of the BLV in 2000 at 3M resulted in the work practice evaluations by industrial hygienists for those employees whose serum PFOA concentrations ranged between 5 and 10 ppm. Employees with serum PFOA concentrations at 10 ppm and higher were restricted from potential workplace exposure to APFO until their serum concentrations declined to less than 10 ppm.

The BLV concept is similar to the "Biologische Arbeitstoleranzwerte-Toleranz-Wert" (BAT) (Commission 2002). The BAT is defined as the maximum permissible quantity of a chemical compound, its metabolites, or any deviation from norm of biological parameters induced by these substances in exposed humans. The BAT value is established on the basis of currently available scientific data which indicate that the chemical concentration does not generally affect the health of the employee adversely, even when attained regularly under workplace conditions. BAT values are established for blood and/or urine and take into consideration the effects of the substance

and an appropriate margin of safety based on occupational, medical and toxicological criteria for the prevention of adverse health effects.

The purpose of this study was two-fold: 1) examine whether the BLV level of 5 ppm for PFOA was associated with changes in hepatic, lipid and thyroid function obtained from employee medical surveillance examinations that were conducted at the 3M Cottage Grove (Minnesota) manufacturing facility in 2000; and 2) assess whether these employees' serum PFOA concentrations were associated with specific fluorochemical production areas and the number of years they had worked in the Chemical Division.

METHODS

Description of Facility

APFO was produced by a five-stage process: electrochemical fluorination; isolating and converting the chemical to a salt slurry; converting the slurry to a salt cake; drying the cake; and packaging. The greatest likelihood for exposure occurred in the drying area. All of these APFO-related production activities occurred primarily in one building. Other fluorochemical production occurred at this site, including perfluorooctanesulfonyl-fluoride (POSF, $C_8F_{17}SO_2F$) related materials that were manufactured in a different building than APFO. Also, lower chain perfluorinated materials have been manufactured at this site. Fluorochemical production has historically been referred to as the 'Chemical Division' at this manufacturing facility (Gilliland and Mandel 1993) although this categorization also includes non-fluorochemical production plants. A quality control laboratory is also part of this manufacturing environment. The

remainder of the Cottage Grove manufacturing site belongs to several operations that have been referred to as the 'non-Chemical Division' (Gilliland and Mandel 1993).

Fluorochemical Medical Surveillance Program

3M Cottage Grove fluorochemical production employees have voluntarily participated in periodic medical surveillance examinations (Gilliland and Mandel 1996; Olsen et al. 1998; 2000). Surveillance activities include a self-administered questionnaire, measurement of height, weight and pulmonary function, hematology, standard clinical chemistry tests and serum PFOA determination along with an assessment of serum perfluorooctanesulfonate (PFOS, $C_8F_{17}SO_3^-$). Periodically, non-routine tests are offered to these fluorochemical production employees. These tests have focused on specific toxicological questions and have included assays of reproductive hormones (Olsen et al. 1998) and plasma cholecystokinin (Olsen et al. 2000). In order to assess whether there was evidence of thyroid toxicity in these workers, assays for several thyroid hormones were included in the 2000 fluorochemical medical surveillance program. A brief work history questionnaire was also provided to the participants. Questions involved specific past and present work locations. These questionnaire data were evaluated in context with the measured serum PFOA and PFOS concentrations.

Analysis of Samples

Upon collection and shipment of specimens, Allina Laboratory Services (St. Paul, Minnesota) performed standard hematological and clinical chemistry tests for both manufacturing sites. These included the following hematological tests: hematocrit

(percent), hemoglobin (gm/dl), red blood cells (RBC, $1000/\text{mm}^3$), white blood cells (WBC, $1000/\text{mm}^3$) and platelet count ($1000/\text{mm}^3$); and the following clinical chemistry tests: alkaline phosphatase (IU/L), gamma glutamyl transferase (GGT, IU/L), aspartate aminotransferase (AST, IU/L), alanine aminotransferase (ALT, IU/L), total and direct bilirubin (mg/dl), cholesterol (mg/dl), high density cholesterol (HDL, mg/dl), triglycerides (mg/dl), blood glucose (mg/dl), blood urea nitrogen (BUN, mg/dl) and serum creatinine (mg/dl). Six thyroid tests were conducted by LabCorp (Kansas City, MO): thyroid stimulating hormone (TSH; $\mu\text{IU}/\text{ml}$); serum thyroxine (T4; $\mu\text{g}/\text{dL}$); free thyroxine (free T4; ng/dL); serum triiodothyronine (T3; pg/mL); thyroid hormone binding ratio (THBR, previously referred to as T3 Uptake) and free thyroxine index (FTI). TSH, free T4 and T3 were determined by an immunochemiluminometric assay. T4 and THBR were determined by a cloned enzyme donor immunoassay. FTI was calculated by multiplying T4 and THBR.

The employees' serum samples were extracted and quantitatively analyzed for PFOA and PFOS using high-pressure liquid chromatography electrospray tandem mass spectrometry (Hansen et al. 2001). Serum fluorochemical analyses were determined by Tandem Labs (Salt Lake City, UT). For all employee participants, serum PFOA concentrations were above the lower limit of quantitation (LLOQ). There were nine employees whose serum PFOS concentrations were below the LLOQ [$4.8 \text{ ng}/\text{ml} = 4.8$ parts per billion (ppb)].

Data Analysis

Stratified analyses (e.g., gender), analysis of variance and multivariable regression techniques were used to evaluate associations between PFOA and the biochemical parameters. PFOA serum concentrations were categorized in relation to the BLV: 0 - < 1 ppm; 1 - 4.9 ppm; and ≥ 5 ppm. Besides evaluation of measures of central tendency of the various parameters, percentages of assay values outside their reference ranges were considered in relation to PFOA. Potential confounders included age, body mass index, current cigarette smoking status (yes/no) and number of alcoholic beverages consumed on a daily basis. Analyses of the PFOS concentrations (independent of the BLV for PFOA) in relation to the clinical chemistries were also performed but are not reported due to the lack of associations. The midpoint value between zero and the LLOQ was used for those individuals whose serum PFOS concentrations were <LLOQ.

RESULTS

A total of 131 male and 17 female employees participated in the fluorochemical medical surveillance exams (approximately 70 percent of those eligible). Among the men, serum PFOA concentrations were log normally distributed and ranged from 0.007 to 92.03 ppm (Figure 1). Consequently the median value (0.97 ppm) was comparable to the geometric mean (0.85 ppm, 95% CI 0.64 - 1.22) and not to the arithmetic mean (4.51 ppm, 95% CI 2.42 - 6.61). Twenty (15 percent) of the male employees had serum concentrations greater than the BLV.

Serum PFOS concentrations (Figure 2) had a narrower range (0.02 - 4.79 ppm) than PFOA. The PFOS geometric mean was 0.44 ppm (95% CI 0.35 - 0.55) and similar to its

median value (0.45 ppm). The arithmetic mean for PFOS was 0.85 ppm (95% CI 0.69 - 1.02). There was no association between serum PFOA and PFOS concentrations [Pearson correlation coefficient (r) = .02].

There was a lack of correlation between years worked in the Chemical Division and serum PFOA concentrations measured in 2000 among the 131 male employees (r = -.02, Figure 3). Serum PFOA concentrations, however, were associated with the major production work areas (Table 1). Those employees who had worked only in the PFOA production area had a statistically significant (p < .05) higher mean serum PFOA concentration (18.41 ppm) than the other fluorochemical production areas. These workers also had the highest median serum PFOA concentration (5.20 ppm). Likewise, the employees who had worked only in the PFOS-related production area had a statistically significant greater mean serum PFOS concentration (1.76 ppm) as well as the highest median serum PFOS concentration (1.67 ppm) compared to the other fluorochemical production areas. Employees who had worked in the QC lab, but never indicated on their questionnaire that they had not worked in the PFOA or PFOS-related production areas, had the second highest median serum PFOA concentration (2.62 ppm).

Serum employee PFOA concentrations were stratified (see Table 2) into three groups among the male employees: group 1 (< 1 ppm PFOA, N = 68 employees); group 2 (1 - 4.9 ppm PFOA, N = 43 employees); and group 3: ($\geq$ 5 ppm PFOA, N = 20 employees). Group 3 corresponds to those serum values that exceeded the 3M BLV established in 2000 for PFOA. The median serum PFOA concentrations increased nearly 50 fold between the lowest (0.30 ppm) and highest (13.57 ppm) groups (Table 2). Median serum PFOS concentrations were comparable for the three groups.

There were no statistically significant ($p < .05$) differences in the arithmetic mean lipid and hepatic test results between the three PFOA groups among male employees (Table 3) or with the thyroid hormone assays (Table 4). Furthermore, there were no statistically significant differences in the mean percentage of test results that were above or below the reference ranges of these various clinical chemistry and thyroid parameters.

Nine employees (group 1 = 4, group 2 = 3 and group 3 = 2) indicated on their questionnaire that they were prescribed cholesterol-reducing pharmaceuticals. Because PFOA was associated with hypolipidemia in rats (not primates), inclusion of these employees may have masked a negative association. Exclusion of these nine employees did not alter the lipid findings, as shown in the scatter plots in Figures 4 and 5. In simple linear regression models, neither the slope of the cholesterol ($\text{CHOL} = 210 + 0.13 \cdot \text{PFOA}$) or triglyceride ($\text{TRIG} = 181 + 1.30 \cdot \text{PFOA}$) models were statistically significant ($p = .63$ and $p = .19$, respectively). Figures 6 and 7 are scatter plots between ALT and GGT with serum PFOA concentrations, respectively, among all 131 male employees. The slope of the linear models was not statistically significant ($\text{ALT} = 35 - 0.05 \cdot \text{PFOA}$, $p = .71$; $\text{GGT} = 33 - 0.11 \cdot \text{PFOA}$, $p = .64$). Taking log transformations of the dependent variables in these three models produced similar statistically nonsignificant results.

Figures 8 through 11 are scatter plots of the thyroid hormones by serum PFOA concentrations. Using simple linear regression analyses, the slopes for PFOA in these four models were not statistically significant ($p < .05$) although the negative slope in the T4 model (Figure 10) approached significance ($\text{T4} = 7.93 - 0.02 \cdot \text{PFOA}$, $p = .07$) but there was minimal variation explained ($r^2 = .03$) in the model. Furthermore, all of the lowest T4 values, associated with the highest serum PFOA concentrations displayed in

Figure 10, remained well-within the reference range (4.5 - 12.0 $\mu\text{g/dL}$) of the T4 assay. There were no statistically significant linear associations for TSH (Figure 8: $\text{TSH} = 2.36 + 0.003 \cdot \text{PFOA}$, $p = .78$, $r^2 < .01$), T3 (Figure 9: $\text{T3} = 123 + 0.08 \cdot \text{PFOA}$, $p = .71$, $r^2 < .01$) or free T4 (Figure 11: $\text{T4} = 1.11 - 0.0005 \cdot \text{PFOA}$, $p = .64$, $r^2 = .01$) in relation to serum PFOA concentrations. Again, taking log transformations of the dependent variables in these models produced similar statistically nonsignificant results.

Adjusting for potential confounding factors (age, BMI, cigarette smoker, alcohol drinks) did not result in statistically significant linear associations ($p < .05$) between PFOA and the lipid, hepatic or thyroid hormone assays (data not shown). Hematology and renal clinical chemistry tests were also not associated with PFOA (data not shown). In addition, PFOS and a calculated total organic fluorine value (determined as the percent molecular weight of PFOA and PFOS attributed to organic fluorine) were not associated with the lipid, hepatic and thyroid parameters measured in this study (data not shown).

Besides the self-reported prescribed pharmaceuticals, the employees provided information from a list of medical conditions which focused on thyroid conditions and type II diabetes. There were two self-reported conditions of hypothyroidism: 1 case each in group 1 and group 3. Likewise, there were two self-reported conditions of type II diabetes: 1 case each in group 1 and group 3. None of these self-reported conditions was confirmed via a medical record review.

The 17 female employees' serum PFOA concentrations ranged from 0.04 to 4.73 ppm with a geometric mean concentration of 0.42 ppm (95% CI 0.23 - 0.79). The arithmetic mean serum PFOA concentration was 0.85 ppm (95% CI 0.23 - 1.47). No female employee had a serum PFOA concentration that exceeded the BLV. Their serum

PFOS concentrations ranged from 0.02 to 2.11 ppm with a geometric mean concentration of 0.28 ppm (95% CI 0.15 - 0.52) and an arithmetic mean serum concentration of 0.53 ppm (95% CI 0.20 - 0.87). There were no statistically significant associations between PFOA and clinical chemistries or thyroid test results for the 17 female workers (data not shown). None of the female employees reported thyroid conditions or type II diabetes, or prescribed cholesterol lowering pharmaceuticals.

DISCUSSION

There were no statistically significant differences in lipid, hepatic or thyroid functions in this workforce in relation to the BLV for PFOA. Although the triglyceride concentrations trended higher with serum PFOA concentrations, the response was not statistically significant. A similar positive association between PFOA and triglycerides was reported with analyses of medical surveillance data of 3M's Antwerp (Belgium) and Decatur (Alabama) workforce (Olsen *et al.* 2003a). PPAR- γ , a nuclear receptor expressed mainly in adipose tissue, has been shown to be activated by the antidiabetic thiazolidinendinones, which upregulates glycerol kinase activity stimulating increased hepatic enzymes (Guan *et al.* 2002). Whether this mode of action is plausible for PFOA in humans is questionable as mouse and human PPAR- γ_1 were unresponsive to PFOA when tested at a range of 0.5 to 40 μ M in a cell transfection assay (Maloney and Waxman 1999).

There were no biochemical indications of hepatic injury in the present study at the serum PFOA concentrations measured. These tests included ALT (a hepatic cytosol enzyme used as a measure of increased cell membrane permeability), GGT (a hepatic

microsomal enzyme indicative of enzyme induction) and alkaline phosphatase and bilirubin (measures of cholestasis). These findings support the decision to establish a BLV at 5 ppm serum PFOA that was based on a 10-fold margin of safety in relation to liver-to-body weight changes observed in a sub-chronic APFO primate study where such declines in weight occurred at dosages that were lower than those causing histologic or biochemical indications of hepatic injury (Butenhoff *et al.* 2002b).

Several thyroid hormones were assayed in these workers with no indication of hypothyroidism or hyperthyroidism associated with increased serum PFOA concentrations. A weakly negative, marginally nonstatistically significant association was observed between T4 and serum PFOA. This statistical observation was not considered to represent a biological finding for several reasons. Most importantly, the T4 values associated with the highest serum PFOA concentrations were well within the reference range of the T4 assay. The statistical association explained minimal variation of T4 (less than 3 percent). There was no corresponding negative association between free T4 and PFOA. There was also no indication of a compensatory increase in serum TSH. T3 was unaffected as well.

Toxicologically, Butenhoff *et al.* (2002) reported no clear changes in thyroid hormone homeostasis in relation to PFOA in a six month oral dosing of APFO in male cynomolgus monkeys. Steady-state mean serum concentrations ranged between 77 ± 39 ppm to 158 ± 100 ppm for the three dose groups used in the study. All thyroid hormone values were within normal range and there did not appear to be any relevant histological changes or changes in TSH. Thyroxin values at end of treatment were statistically significantly ($p < .05$) lower in the three dose groups compared to the time-related

control group but not to each dose group's pretreatment values. Three high-dose animals, that were removed from dosing due to evidence of toxicity, had T3 values that trended downward compared to their pretreatment values. There was evidence of a return to pretreatment T3 values upon dose cessation. Butenhoff et al. concluded that these changes were best explained by normal variation or stress and not as a direct effect of APFO on thyroid hormone homeostasis.

Because of the cross-sectional design, a limitation of the present study is its inability to assess temporal relationships. A 6-year longitudinal assessment was conducted of 174 3M employees at its Antwerp and Decatur fluorochemical manufacturing sites (Olsen et al. 2003a). These employees had lower mean PFOA and higher PFOS serum concentrations than the present study population. Adjusting for potential confounding factors, PFOA and a calculated total organic fluorine (determined from the percent molecular weight of PFOA and PFOS attributed to organic fluorine) were reported to be positively associated with cholesterol and triglycerides in a longitudinal analysis. This association was attributed to a subset of 21 Antwerp workers whose serum PFOA concentrations increased from 1.3 to 2.1 ppm in this 6 year time period. Again, this association is opposite the hypolipidemic effects of PFOA observed in rats. Liver function tests were not associated with PFOA in this longitudinal assessment.

Higher serum PFOA concentrations were associated with working in the APFO production area. Employees' serum PFOA concentrations were not correlated with their years worked in the Chemical Division. These two observations firmly support the necessity to incorporate specific APFO exposure matrices in epidemiologic assessments

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of this workforce in order to minimize the probability of exposure misclassification for PFOA. Therefore, the sole use of the exposure metric, months employed in the Chemical Division, in a 50-year follow-up assessment of the mortality experience of employees who have worked at this manufacturing site (Gilliland and Mandel 1993) likely introduced considerably more PFOA exposure misclassification than the methods employed by Alexander (2001) who constructed a specific job-, department- and calendar-year exposure matrix for potential PFOA exposure in an updated mortality analysis of this workforce. As with any epidemiologic assessment, however, some unknown degree of exposure misclassification in the Alexander study likely occurred as well.

Because of the more specific APFO exposure matrix, the Alexander (2001) findings should be considered the definitive study, to date, regarding the mortality experience of this manufacturing workforce in relation to PFOA exposures. Alexander did not observe an excess risk of mortality from cancer (68 deaths, 77.3 expected, Standardized Mortality Ratio = 0.0, 95% CI 0.7 - 1.1) or of any specific type of cancer in relation to employees categorized with a minimum of one year employment in a job with definite or probable exposure to PFOA. Alexander did report a modest and unexpected association with cerebrovascular disease among workers identified with definite exposure to PFOA (5 deaths, 2.3 expected, Standardized Mortality Ratio = 2.6, 95% CI 0.8 - 6.0). The basis for this observation remains to be understood.

The average occupational serum PFOA concentrations of APFO production-related workers in this study are approximately 3 orders of magnitude higher than those reported in the general population [≥ 5 ng/ml (ppb)] (Hansen *et al.*, 2001; Olsen *et al.*,

2002a; 2002b; 2002c; 2003b). Upper bounds of the estimated 95th percentile values approximated 10 ppb in these general population studies and the highest individual value measured approximated 50 ppb. The level of PFOA concentrations determined in the serum and the low rate of serum elimination from the body suggest that the magnitude of exposure in the general population is quite small. The lack of statistically significant associations for lipid, hepatic and thyroid function in relation to serum PFOA concentrations among APFO production workers suggest that the same would be observed in the general population with its much lower serum PFOA concentrations.

Finally, in May, 2000 3M announced its voluntary decision to phase out of the perfluorooctanyl chemistry used to produce certain repellents and surfactant products due to widespread environmental presence of PFOS. This decision included 3M's production of APFO at its Cottage Grove manufacturing site. APFO production continues at other companies in the United States and elsewhere.

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Table 1. Age, Years Worked in Chemical Division, and Serum PFOA and PFOS Concentrations, by Locations Ever Worked in Chemical Division for Male Employees (N=131) Based on Self Reports

	Worked Only in PFOA Production Area (N=21)			Worked Only in PFOS Production Area (N=29)			Worked Only in QC Lab (N=9)			Worked in Both PFOA & PFOS Areas (N=54)			Worked in Other Fluorochemical Areas But Not PFOA, PFOS QC Lab Areas (N=18)		
	Mean (95% C.I.)	Median	Range	Mean (95% C.I.)	Median	Range	Mean (95% C.I.)	Median	Range	Mean (95% C.I.)	Median	Range	Mean (95% C.I.)	Median	Range
Age	39 (35-43)	38	27-59	36 (33-39)	36	26-54	44 (37-52)	41	31-55	45 (42-47)	43	27-67	41 (36-45)	42	24-58
Years Worked in Chemical Division	7.8 (3.6-12.0)	5.0	0.1-33.0	4.6* (2.4-6.7)	3.0	0.2-28.0	14.6 (5.7-23.4)	12.0	3.0-36.0	12.5 (9.8-15.2)	9.5	1.0-40.0	5.5 (1.6-9.5)	3.0	0.1-23.0
PFOA	18.41# (6.71-30.10)	5.20	0.10-92.03	0.46 (0.29-0.63)	0.31	0.02-1.73	3.09 (1.24-4.95)	2.62	0.25-7.93	2.81 (1.68-3.94)	1.45	0.13-17.93	0.67 (0.26-1.07)	0.37	0.01-2.49
PFOS	0.51 (0.24-0.78)	0.31	0.02-2.39	1.76# (1.30-2.21)	1.67	0.13-4.79	0.70 (0.26-1.14)	0.57	0.13-1.83	0.63 (0.43-0.83)	0.36	0.07-4.31	0.55 (0.17-0.93)	0.19	0.02-2.61

* Statistically significant (p<.05) difference compared to QC lab and combined PFOA/PFOS work category

Statistically significant (p<.05) difference compared to other work categories

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Table 2. Age, BMI, Years Worked in Chemical Division and Mean Serum PFOA and PFOS Concentrations by 3 PFOA Categories for Male Employees (N=131)

	Group 1: <1 ppm (N=68)			Group 2: 1-4.9 ppm (N=43)			Group 3: ≥5 ppm (N=20)		
	Mean (95% C.I.)	Median	Range	Mean (95% C.I.)	Median	Range	Mean (95% C.I.)	Median	Range
Age	39 ² (37-41)	39	24-61	46 ^{1,3} (44-49)	45	27-67	39 ² (35-43)	40	28-54
BMI	29.8 ¹ (28.6-30.9)	29.2	19.7-40.1	30.1 (28.4-31.8)	29.5	23.5-52.1	29.7 (28.1-31.4)	30.8	22.0-36.0
Years Worked Chemical Division	6.9 (4.7-9.0)	3.0	0.1-37.0	12.5 ¹ (9.6-15.5)	10.5	0.1-40.0	10.1 (5.9-14.3)	5.5	2.0-33.0
PFOA	0.36 ^{2,3} (0.29-0.43)	0.30	0.01-0.99	2.26 ^{1,3} (1.96-2.57)	1.99	1.10-4.96	23.48 ^{1,2} (12.48-34.48)	13.57	5.20-92.03
PFOS	0.84 (0.60-1.09)	0.32	0.02-4.79	0.83 (0.57-1.09)	0.49	0.02-4.21	0.95 (0.47-1.43)	0.53	0.14-4.31

^{1, 2, 3} Statistically significantly different than mean of group 1, 2, or 3.

Table 3. Mean Lipid and Hepatic Function Test Results by Three Serum PFOA Categories for Male Employees (N=131)

	<1 ppm (N=68)				1-4.9 ppm (N=43)				≥5 ppm (N=20)			
	Mean (95% C.I.)	% Above Reference Range	% Below Reference Range	Mean (95% C.I.)	% Above Reference Range	% Below Reference Range	Mean (95% C.I.)	% Above Reference Range	% Above Reference Range	Mean (95% C.I.)	% Above Reference Range	% Below Reference Range
Cholesterol	210 (201-219)	54	0	207 (196-218)	56	0	218 (196-240)	70	0			
HDL	47 (44-50)	3	18	46 (43-49)	0	16	43 (38-48)	0	15			
Triglycerides	175 (148-203)	29	2	186 (141-232)	33	0	226 (144-309)	40	5			
Glucose	100 (93-107)	16	NA	102 (98-106)	19	NA	97 (90-103)	15	NA			
Alk Phos	65 (62-69)	0	NA	67 (62-73)	0	NA	62 (54-70)	0	NA			
ALT	37 (32-42)	22	NA	31 (26-36)	9	NA	36 (31-42)	15	NA			
AST	27 (25-29)	6	NA	25 (22-28)	5	NA	24 (21-26)	0	NA			
GGT	37 (26-47)	16	NA	28 (22-34)	12	NA	29 (22-35)	5	NA			
T. Bilirubin	0.9 (0.8-1.0)	2	NA	0.8 (0.7-0.9)	0	NA	0.9 (0.7-1.0)	0	NA			

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Table 4. Mean Thyroid Function Test Results by Three Serum PFOA Categories for Male Employees (N=131)

	<1 ppm (N=68)				1-4.9 ppm (N=43)				≥5 ppm (N=20)			
	Mean (95% C.I.)	% Above Reference Range	% Below Reference Range	Mean (95% C.I.)	% Above Reference Range	% Below Reference Range	Mean (95% C.I.)	% Above Reference Range	% Below Reference Range	Mean (95% C.I.)	% Above Reference Range	% Below Reference Range
TSH	2.3 (2.0-2.6)	3	0	2.5 (2.0-3.1)	7	0	2.3 (1.8-2.7)	0	5			
T3	123 (117-129)	2	0	124 (116-133)	2	0	124 (103-145)	5	0			
T4	8.0 (7.7-8.3)	0	0	7.8 (7.5-8.1)	0	0	7.5 (7.1-7.9)	0	0			
Free T4	1.11 (1.08-1.15)	2	0	1.10 (1.07-1.14)	0	0	1.08 (1.02-1.14)	0	0			
THBR	29.4 (28.7-30.0)	0	0	29.5 (28.7-30.3)	0	0	29.3 (28.2-30.4)	0	0			
FTI	2.27 (2.18-2.37)	0	2	2.26 (2.17-2.35)	0	0	2.15 (2.04-2.26)	0	0			

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Figure 1. Ascending Distribution of Serum PFOA Concentrations for Male Employee Participants (N = 131), 3M Cottage Grove, 2000

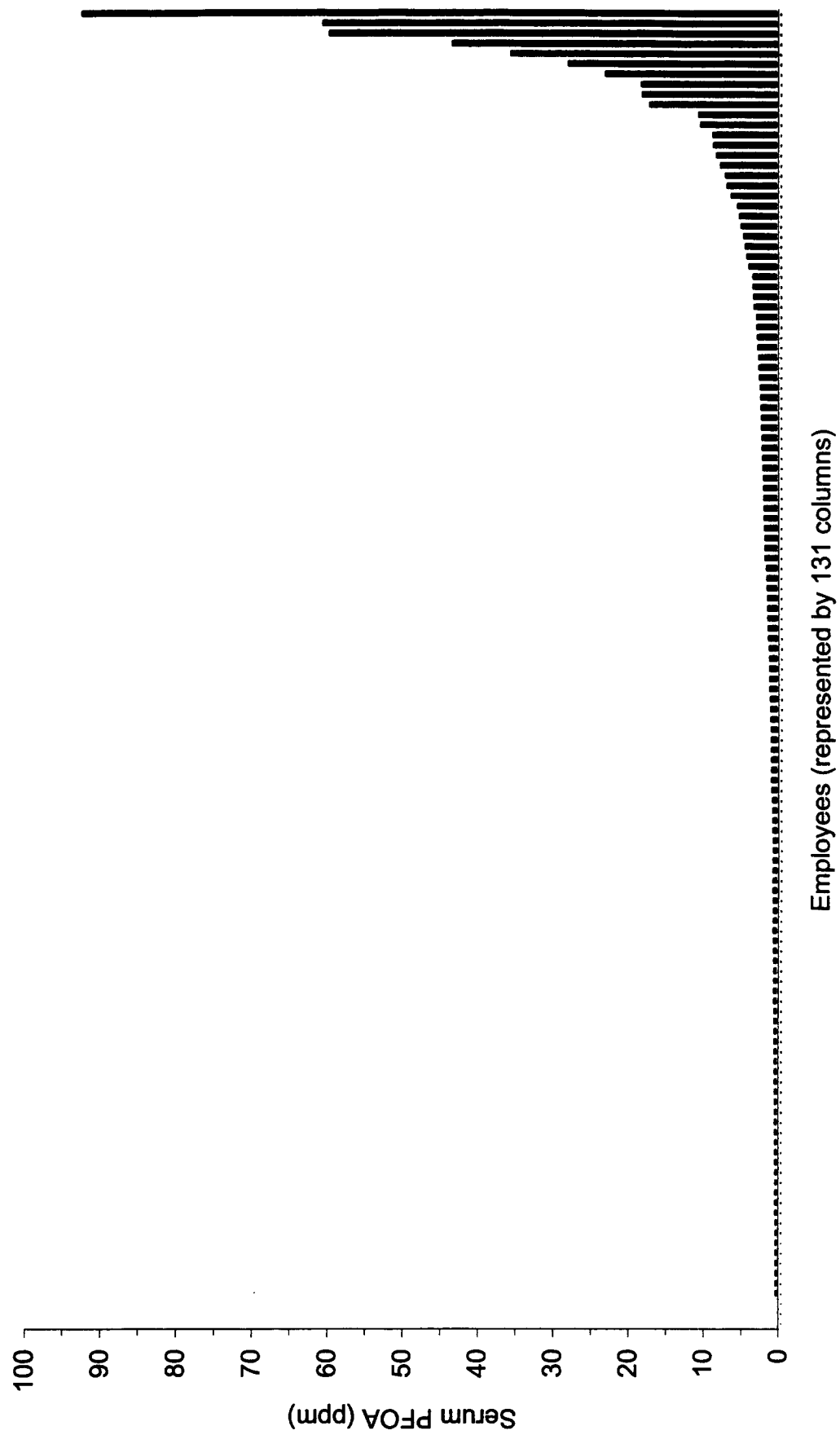


Figure 2. Paired Serum PFOS Concentration Distribution (ppm) Corresponding to the Male Employee (N = 131) PFOA Serum Concentration Distribution Presented in Figure 1

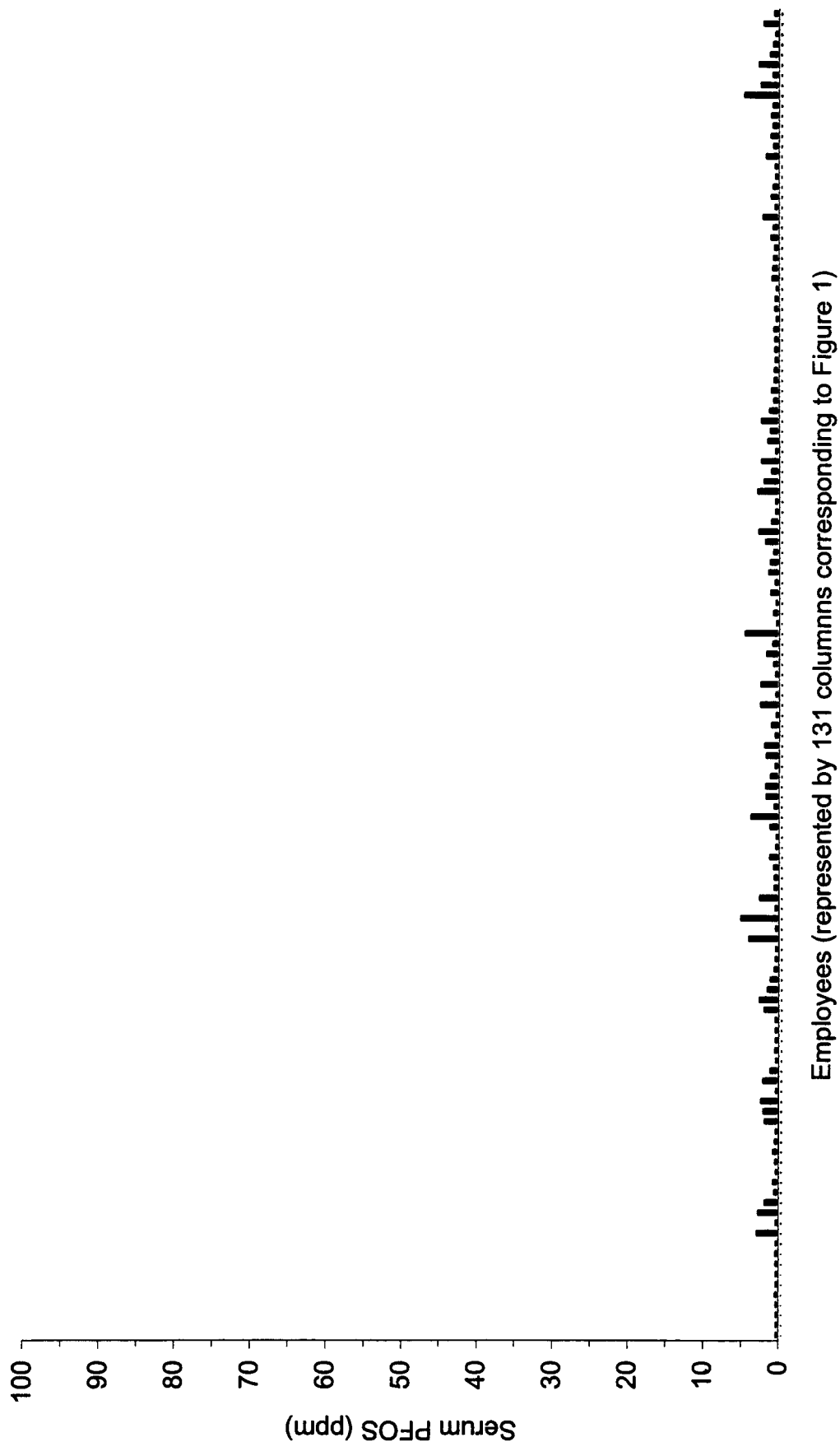
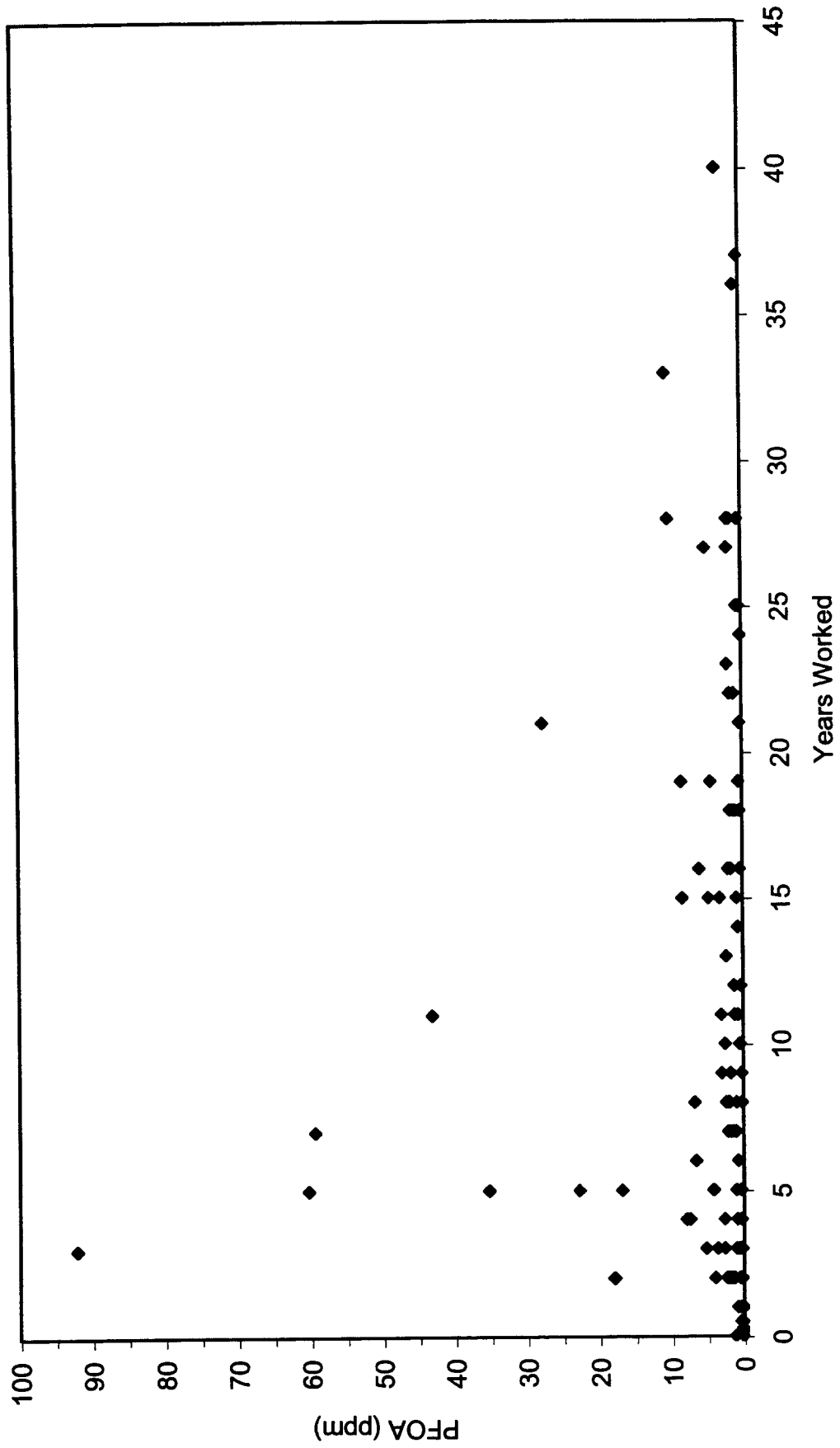


Figure 3. Serum PFOA Concentrations by Years Worked in Chemical Division
for Male Employees (N = 131)



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Figure 4. Serum Cholesterol Levels (mg/dl) by Serum PFOA Concentrations (ppm) Among Male Employees (N = 122) Not Prescribed Cholesterol Lowering Pharmaceuticals

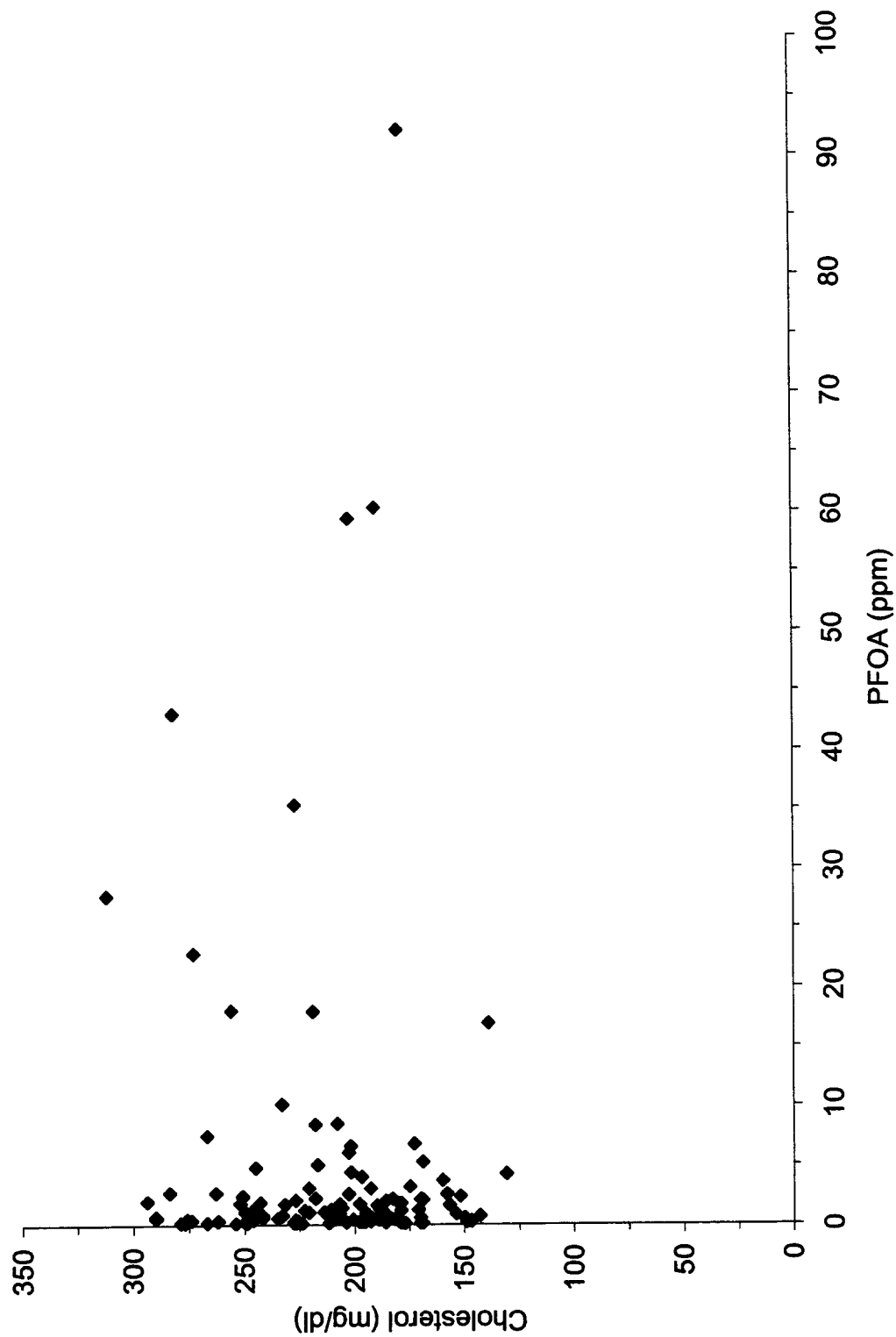


Figure 5. Serum Triglyceride Levels (mg/dl) by Serum PFOA Concentrations (ppm) Among Male Employees (N = 122) Not Taking Cholesterol Lowering Pharmaceuticals

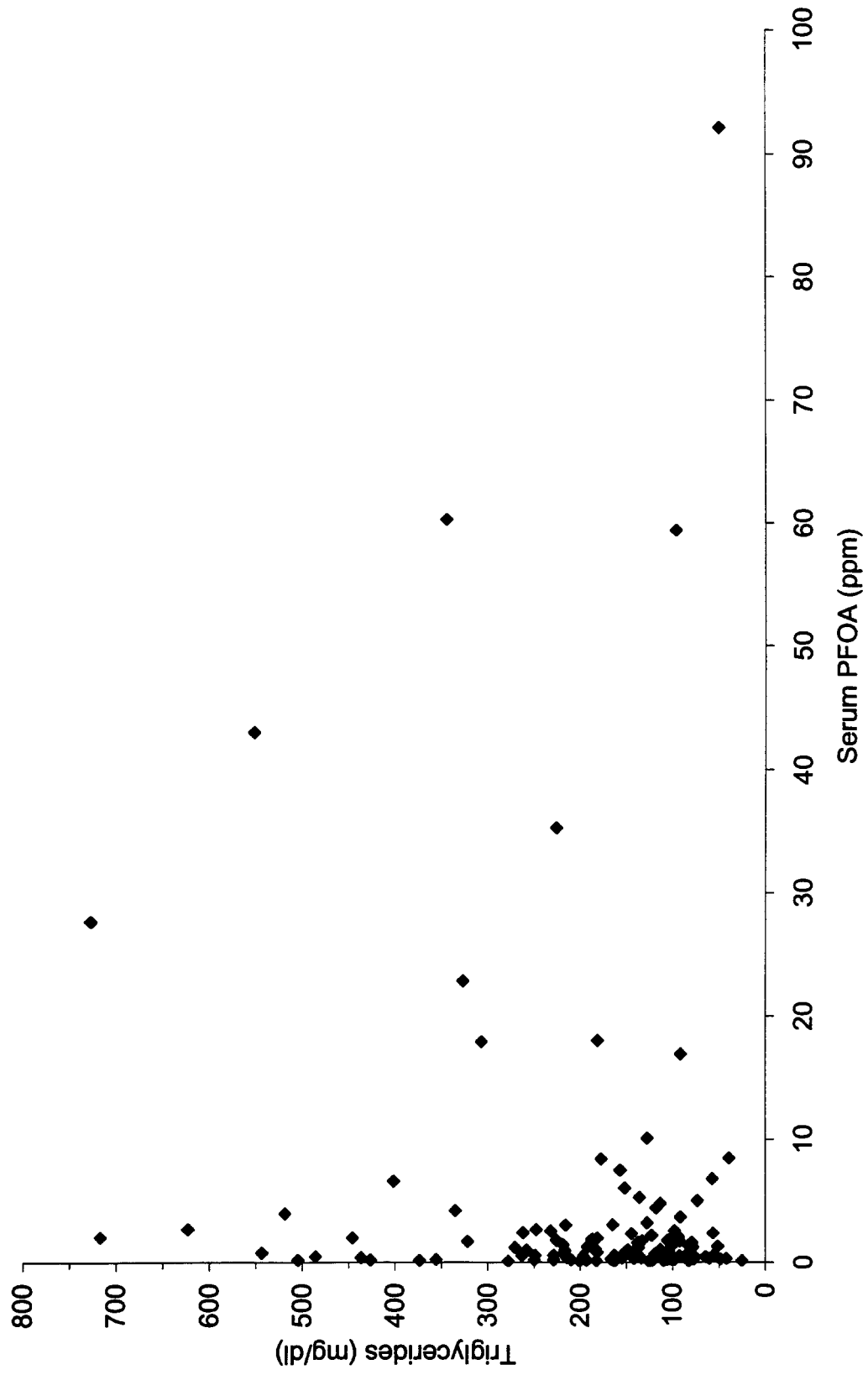


Figure 6. Serum ALT (IU/L) by Serum PFOA Concentrations (ppm)
Among 131 Male Employees

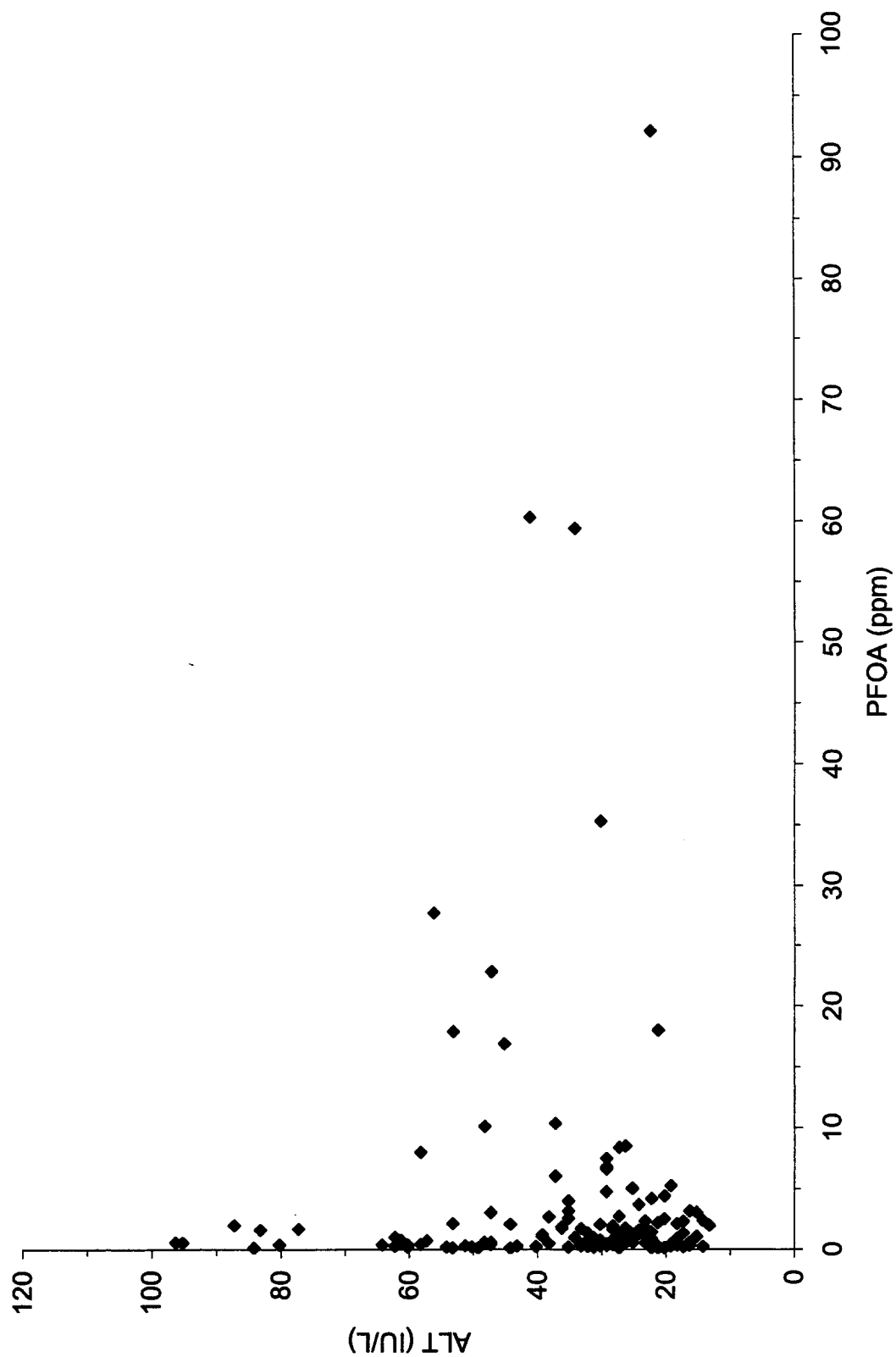


Figure 7. Serum GGT (IU/L) by Serum PFOA Concentrations(ppm)
Among 131 Male Employees

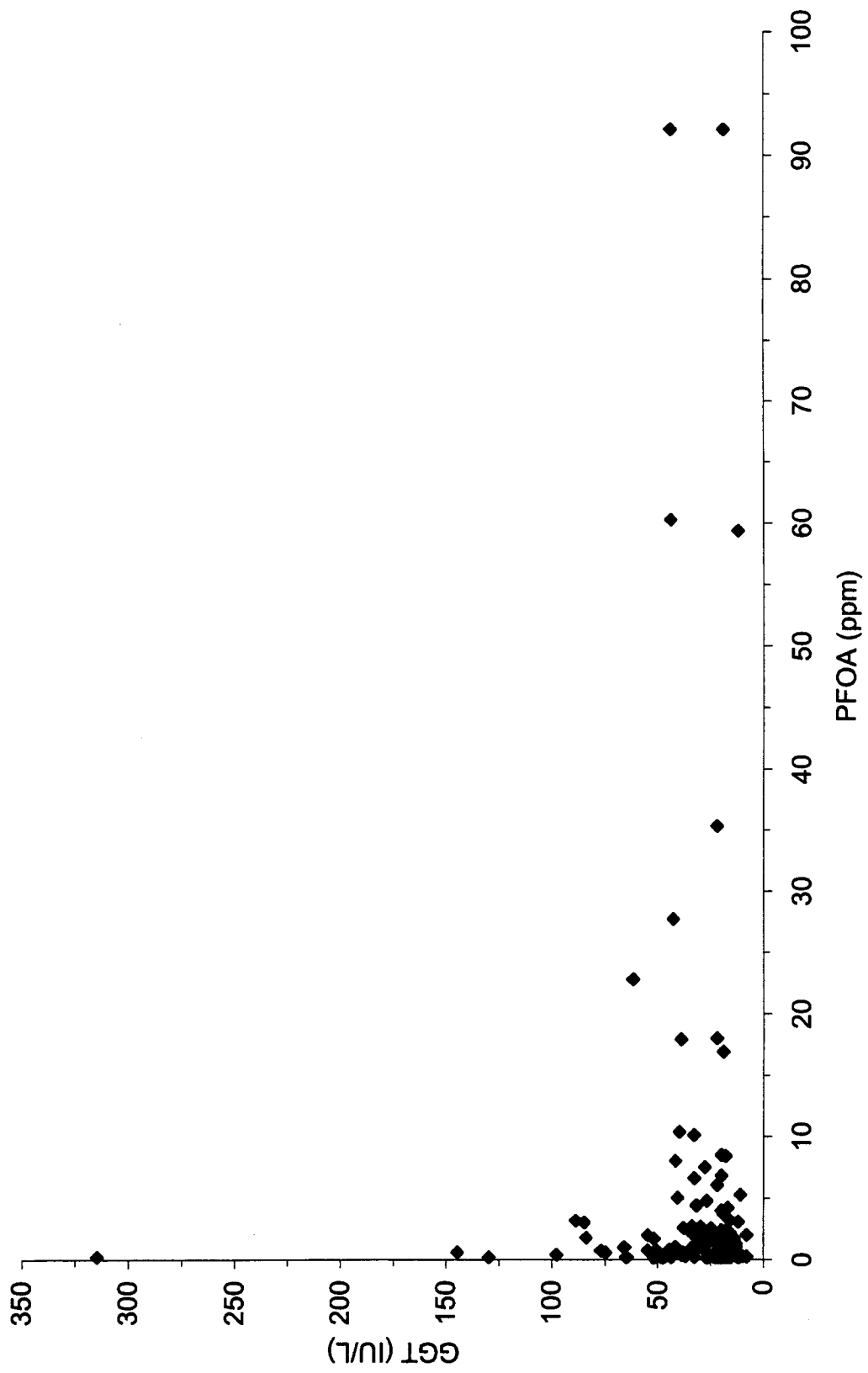


Figure 8. Serum TSH Levels by Serum PFOA Concentrations
Among Male Employees (N = 130)

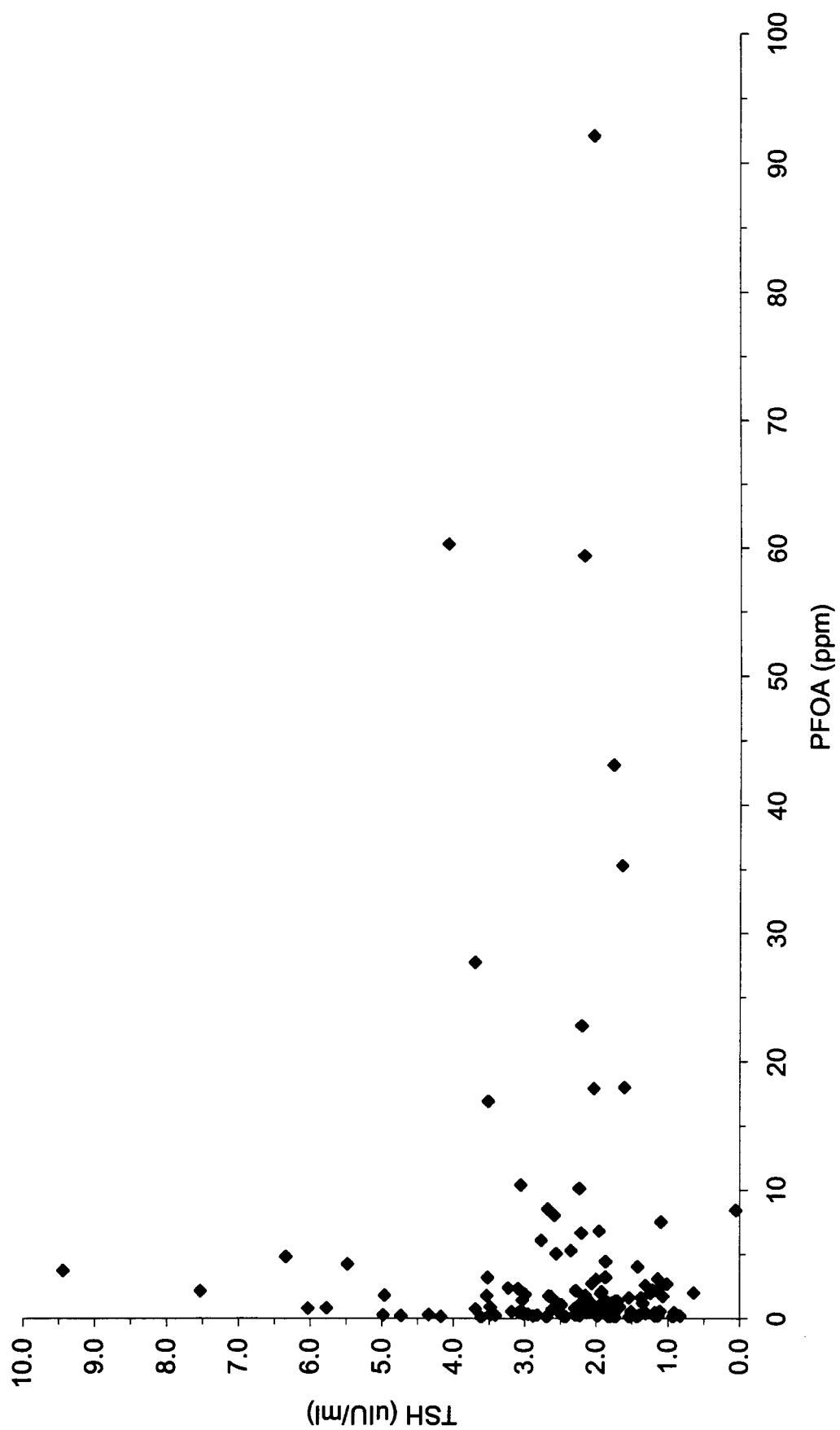


Figure 9. Serum T3 Levels by Serum PFOA Concentrations
Among Male Employees (N = 130)

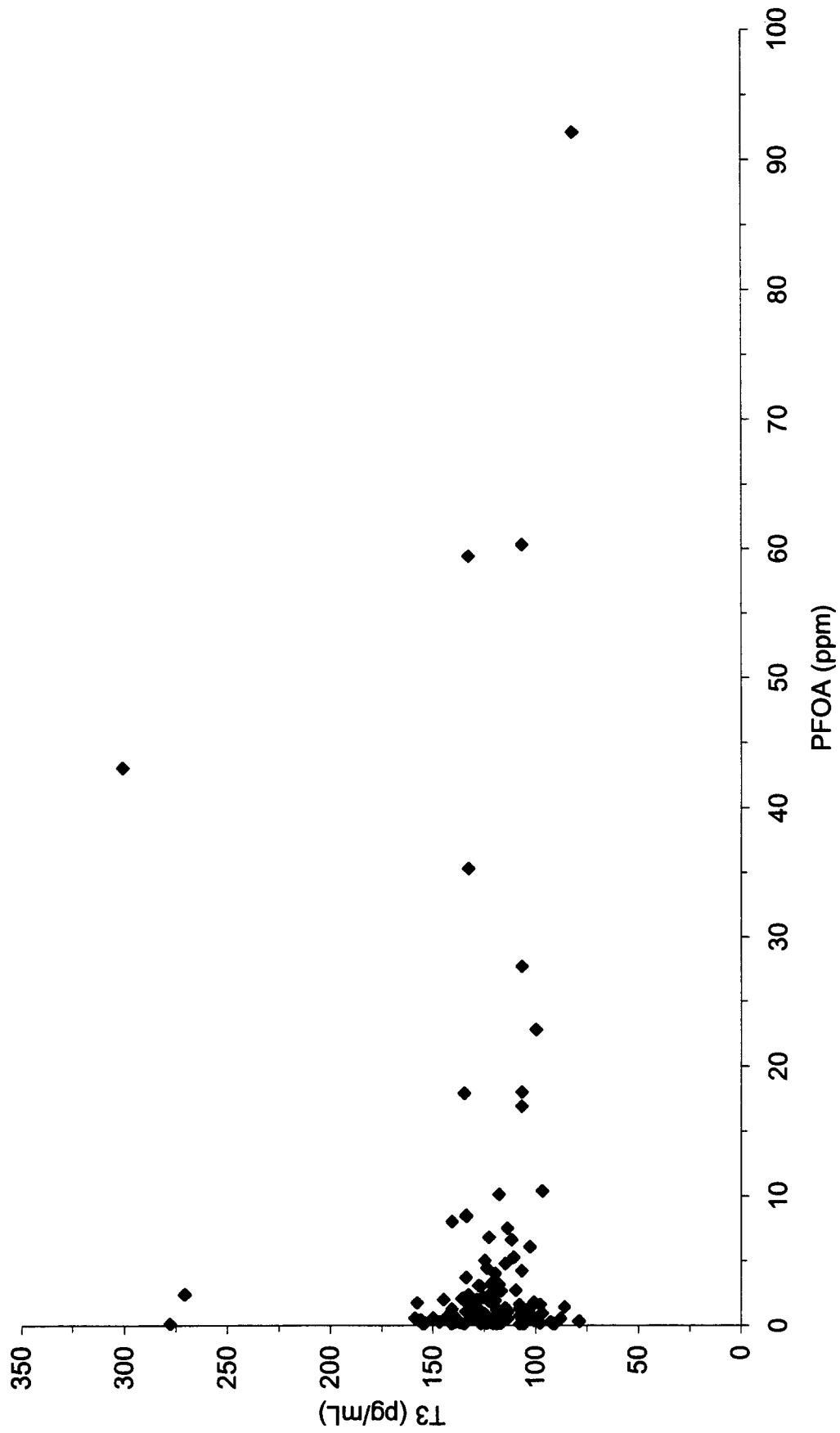


Figure 10. Serum T4 Levels by Serum PFOA Concentrations
Among Male Employees (N = 130)

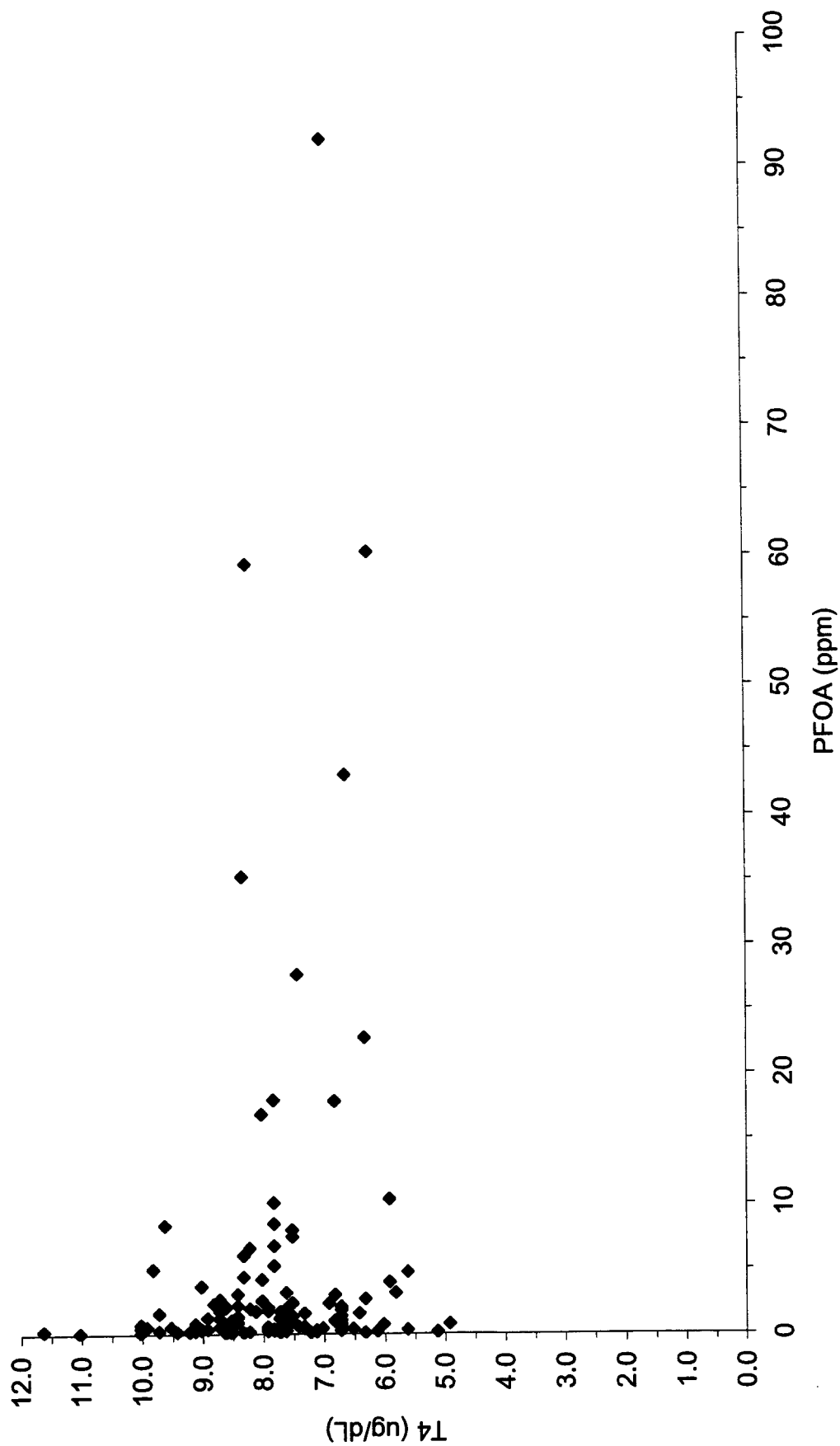
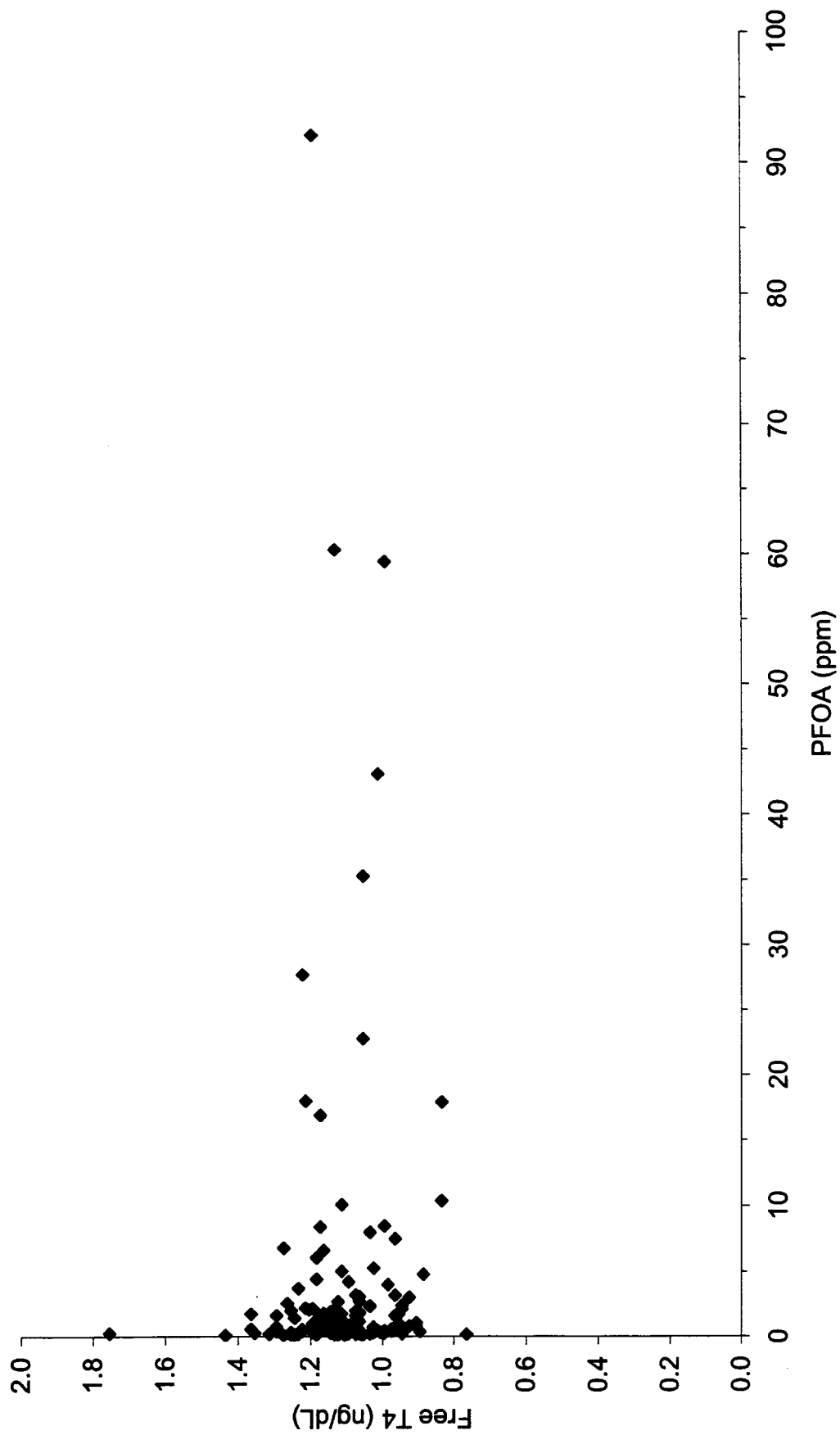


Figure 11. Serum Free T4 Levels by Serum PFOA Concentrations
Among Male Employees (N = 130)



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