Corporate Occupational Medicine

3M Center, Building 220-3W-05
St. Paul, MN 55144-1000
651 737 4230 Telephone
651 733 9066 Fax

AR226-0475

3M

7. Serum Perfluorooctanoic Acid and Hepatic Enzymes, Lipoproteins, and Cholesterol: A Study of Occupationally Exposed Men.

This is the published paper (Gilliland and Mandel; Am J Ind Med 1996;29:560-568) from the Gilliland doctoral dissertation (see study # 5) that evaluates the effect of PFOA on hepatic enzymes and lipoproteins. This study of 115 occupationally exposed workers examined the cross-sectional associations between serum PFOA (measured as serum total organic fluorine) and hepatic enzymes, lipoproteins, and cholesterol. There was no significant clinical hepatic toxicity at the PFOA (i.e., total organic fluorine) levels measured in this study. Based on multivariable models, PFOA may exacerbate the effect obesity has on liver transaminase tests and blunt the effect that alcohol has on HDL levels. [Note: In three subsequent time periods, the findings of this study could not be replicated. PFOA, assayed by mass spectrometry methods, did not appear in this production workforce to modulate hepatic responses to either obesity or alcohol consumption. See study #8 below.]

AMERICAN JOURNAL OF INDUSTRIAL MEDICINE 29:560-568 (1996)

Serum Perfluorooctanoic Acid and Hepatic Enzymes, Lipoproteins, and Cholesterol: A Study of Occupationally Exposed Men

Frank D. Gilliland, MD, PhD and Jack S. Mandel, PhD, MPH

Perfluorooctanoic acid (PFOA) produces marked hepatic effects, including hepatomegaly, focal hepatocyte necrosis, hypolipidemia, and alteration of hepatic lipid metabolism in a number of animal species. In rodents, PFOA is a peroxisome proliferator, an inducer of members of the cytochrome P450 superfamily and other enzymes involved in xenobiotic metabolism, an uncoupler of oxidative phosphorylation, and may be a cancer promoter. Although PFOA is the major organofluorine compound found in humans, little information is available concerning human responses to PFOA exposure. This study of 115 occupationally exposed workers examined the cross-sectional associations between PFOA and hepatic enzymes, lipoproteins, and cholesterol. The findings indicate that there is no significant clinical hepatic toxicity at the PFOA levels observed in this study. PFOA may modulate the previously described hepatic responses to obesity and xenobiotics. © 1996 Wiley-Liss, Inc.

KEY WORDS: perfluorooctanoic acid, human, hepatic enzymes, cholesterol, HDL

INTRODUCTION

Perfluorooctanoic acid (PFOA) is a potent synthetic surfactant that is used in a wide variety of industrial processes and products. Organic fluorine has been found in the serum of all human populations studied (Ubel et al., 1980; Taves, 1971; Taves et al., 1976; Guy, 1979, Belisle, 1981). Guy and Taves reported that PFOA was the principal organic fluorine compound in human serum (Taves, 1971; Taves et al., 1976; Guy, 1979). PFOA is found in serum because PFOA has a long biological half-life, allowing accumulation of small doses over time (Ubel et al., 1980). Little is known about the toxic potential of PFOA in humans; however, studies have shown that the liver is an important site of toxicity in animals (Griffith and Long, 1980; Kennedy, 1985; Kennedy et al., 1986; Pastoor et al., 1987; Van Rafelghem et al., 1987; Just et al., 1989).

Animals treated with PFOA rapidly develop hepatomegaly with focal necrosis and show marked hepatic physiologic responses that include hypolipidemia, peroxisome proliferation, induction of xenobiotic metabolic enzymes, increased hepatic tumor incidence, uncoupling of mitochondrial oxidative phosphorylation, and alterations in lipid metabolism (Griffith and Long, 1980; Kennedy, 1985; Kennedy et al., 1986; Pastoor et al., 1987; Van Rafelghem et al., 1987; Just et al., 1989; Takagi et al., 1991, Permadi et al., 1992; Haughom et al., 1992; Sohlenius et al., 1992; Keller et al., 1992; Handler, 1992). Rats treated with PFOA and other peroxisome proliferators (PPs), such as clofibrate, show a 50% reduction of serum cholesterol and changes in the hepatic production and processing of lipoproteins. Haughom et al. (1992) showed that the hypolipidemic response results from downregulation of HMG-CoA reduc-

Division of Environmental and Occupational Health, School of Public Health, University of Minnesota, Minneapolis (F.D.G., J.S.M.).
Department of Internal Medicine, Occupational and Environmental Medicine Section, St. Paul Ramsey Medical Center, St. Paul, Minnesota (F.D.G.).
Address reprint requests to Frank D. Gilliland, University of New Mexico School of Medicine, Epidemiology and Cancer Control Program, 900 Camino de Salud NE, Albuquerque, NM 87131.

Accepted for publication April 25, 1995.

TABLE I. Distribution of Exposed Workers by Total Serum Fluorine Category in 3M Chemolite Plant, Cottage Grove, MN

	Total serum fluorine (ppm)					
	<1	1–3	>3–10	>10–15	>15–26	Total
Age[a]	39.9 (10.2)	39.6 (8.5)	36.0 (7.5)	39.3 (11.1)	41.6 (10.5)	39.2
BMI (kg/m²)[a]	27.6 (5.3)	26.6 (2.6)	26.3 (3.3)	29.4 (3.7)	26.0 (1.4)	26.9
Alcohol use[b]						
<1 oz/day	17 (73.9)	51 (78.5)	9 (56.3)	5 (83.3)	5 (100)	87 (75.6)
1–3 oz/day	2 (8.7)	13 (20.0)	4 (25.0)	1 (16.7)	0 (0)	20 (17.4)
	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Nonresponse	4 (17.4)	1 (1.5)	3 (18.7)	0 (0)	0 (0)	8 (7.0)
Tobacco use[b]						
Smoker	3 (13.0)	16 (24.6)	6 (37.5)	2 (33.3)	1 (20.0)	85 (73.9)
Nonsmoker	19 (82.7)	49 (75.4)	9 (56.2)	4 (66.7)	4 (80.0)	28 (24.4)
Nonresponse	1 (4.3)	0 (0)	1 (6.3)	0 (0)	0 (0)	2 (1.7)
Total	23 (100)	65 (100)	16 (100)	6 (100)	5 (100)	115

BMI, body mass index.
[a]Values are mean (SD).
[b]Values are n (percent).

tase. In addition, PFOA has been associated with hepatocyte necrosis and increased hepatic enzymes, suggesting that irreversible cell damage occurs (Kennedy, 1985; Just et al., 1989). Hepatomegaly and alterations in lipid metabolism appear to be rapidly reversible; however, other hepatic changes are not rapidly reversed (Perkins, 1992; Sohlenius et al., 1992).

Based on findings from the studies of rodents and in vitro experiments, some investigators have suggested that PFOA is likely to present a health risk to humans (Just et al., 1989; Takagi et al., 1991). If the observations in rodent species are relevant to humans exposed to PFOA, it is reasonable to hypothesize that changes in human hepatic enzymes and lipid metabolism are similar to those observed in rodents. Limited data are available to assess the hepatic responses to PFOA in humans. Ubel and coworkers (1980) and Griffith and Long (1980) reported that PFOA-exposed workers showed no clinical evidence of adverse hepatic effects. Furthermore, a retrospective cohort mortality study of exposed workers found no excess mortality from liver cancer or liver disease (Gilliland and Mandel, 1993). To assess whether the changes in cholesterol, lipoproteins, and hepatic enzymes observed in rodents treated with PFOA occur in humans, we studied 115 occupationally exposed employees at a plant that produces PFOA. Production workers with the highest PFOA exposures had serum PFOA levels similar to those in rodents that developed hepatomegaly when treated orally with low doses of PFOA (Ubel et al., 1980). We examined the cross-sectional association between serum PFOA, a validated surrogate measure of total serum fluorine, and cholesterol, lipoproteins, and hepatic enzymes in this group of occupationally exposed men.

TABLE II. Distribution of Age, Alcohol, and Tobacco Use in Participants by Body Mass Index in Study of Workers Exposed to PFOA

	BMI mg/kg²		
	<25	25–30	>30
Total	41 (100%)	57 (100%)	17 (100%)
Tobacco use			
Smoker	11 (26.8%)	15 (26.3%)	2 (11.8%)
Nonsmoker	29 (70.7%)	41 (71.9%)	15 (88.2%)
Nonresponse	1 (2.5%)	1 (1.8%)	0 (0%)
Alcohol use			
<1 oz/day	31 (75.6%)	43 (75.4%)	13 (76.4%)
1–3 oz/day	6 (14.6%)	11 (19.3%)	3 (17.7%)
Nonresponse	4 (9.8%)	3 (5.3%)	1 (5.9%)
Age			
<40 years	31 (75.6%)	8 (49.1%)	6 (35.3%)[a]
≥40 years	10 (24.4%)	29 (50.9%)	11 (64.7%)
Total serum flourine			
Mean ppm (SD)	2.8 (3.7)	4.0 (5.5)	2.1 (3.5)

[a]$p = .005$.
BMI, body mass index.

MATERIALS AND METHODS

Subject Selection

Participants were recruited from current employees at a PFOA production plant that has operated since 1947. The

TABLE III. Serum Cholesterol, Low Density Lipoprotein, and High Density Lipoprotein by Total Serum Fluoride in Study of Workers Exposed to PFOA

Total fluoride	N	Mean	SD	Median	Range	Test*
Cholesterol (mg/dl)						
<1 ppm	23	201	34.7	203	132–268	F = .066
≥1–3	65	211	40.0	212	130–349	p = .62
>3–10	16	206	37.7	198	150–277	
>10–15	6	226	40.0	216	183–298	
>15–26	5	214	27.0	204	184–244	
Total	115	210	38.1	210	130–349	
LDL (mg/dl)						
<1 ppm	23	132	32.4	137	70–196	F = 0.31
≥1–3	65	136	34.5	131	70–264	p = .87
>3–10	16	134	34.5	133.5	83–217	
>10–15	6	124	44.0	139	36–156	
>15–26	5	143	20.8	144	117–171	
Total	115	135	33.8	134	36–264	
HDL (mg/dl)						
<1 ppm	23	45.9	11.7	47	19–67	F = 0.66
≥1–3	65	46.1	10.0	44	30–79	p = .66
>3–10	16	41.8	10.2	40	29–68	
>10–15	6	46.5	6.8	44	40–59	
>15–26	5	45.6	10.2	49	29–54	
Total	115	45.4	10.2	43	19–79	

*Anova.
LDL, low density lipoprotein; HDL, high density lipoprotein.

TABLE IV. Pearson Correlation Coefficients Between Total Serum Fluoride, Age, Body Mass Index, Daily Alcohol Use, Daily Tobacco Consumption, and Lipoproteins

	Total fluoride (ppm)	Age (years)	BMI (kg/m²)	Alcohol (oz/day)	Tobacco (cigs/day)
CHOLESTEROL	.07	.25 p = .008	.19 p = .05	.09	.35 p = .0001
LDL	.02	.13	.06	−.008	.28 p = .00
HDL	−.01	.03	−.13	.18 p = .06	−.09

LDL, low-density lipoprotein; HDL, high-density lipoprotein; BMI, body mass index.

plant produces a number of specialty chemicals in addition to PFOA. Details about the plant have been described previously (Gilliland and Mandel, 1993). All workers employed in PFOA production during the period 1985–1989 were invited to participate in the study. Workers with jobs involving direct contact with PFOA during the 1985–1989 period were considered highly exposed. This group included maintenance and engineering supervisors, as well as production workers. Forty-eight (96%) of 50 exposed workers agreed to participate in the study. In addition, a sample of workers employed in jobs with no apparent PFOA exposure was asked to participate. Those without direct contact with PFOA for at least 5 years were considered to have low exposure. A randomly selected low-exposure group of workers was frequency matched in 5-year age groups to the high-exposure workers. Sixty-five employees from jobs thought to involve no PFOA exposure volunteered for the study. The total number of the presumed unexposed employees invited to participate was not recorded; however, few individuals in this group declined to participate. We estimate that more than 80% of those invited agreed to participate in the study.

TABLE V. Serum Cholesterol by Body Mass Index, Age, Smoking and Drinking Status, 3M Chemolite Plant, Cottage Grove, Minnesota

		Cholesterol (mg/dl)				
	N (%)	Mean	SD	Median	Range	Test*
BMI						
<25	41 (35.7)	195	40.1	186	130–277	F = 5.10
25–30	57 (49.6)	219	36.2	220	146–349	p = .008
>30	17 (14.8)	214	29.3	216	163–268	
Age						
≤30	21 (18.3)	196	37.8	201	130–254	F = 1.60
>30–40	48 (41.7)	2.9	43.8	204	132–349	p = .19
>40–50	27 (23.5)	216	30.2	216	163–263	
>50–60	19 (16.5)	219	29.7	224	164–268	
Alcohol						
<1 oz/d	87 (81.3)	209	38.6	204	135–349	F = .63
1–3 oz/d	20 (18.7)	216	33.5	218	130–277	p = .43
Missing	8	207	45.5	213	132–261	
Tobacco						
Smoker	28 (24.8)	233	41.6	238	167–349	F = 15.63
Nonsmoker	85 (75.2)	203	32.9	203	130–268	p = .0001
Missing	2	198	89.1	198	135–261	
Total	115					

*Anova.
BMI, body mass index.

Total serum fluorine was used as a surrogate variable for PFOA exposure. We assayed total serum fluorine rather than measuring PFOA directly because the assay was less expensive and technically easier to perform on the large number of samples collected in this study. Furthermore, the use of total serum fluorine has been validated as a surrogate marker for PFOA in past biological monitoring in the plant and other plants using PFOA (Ubel et al., 1980). Approximately 90% of total serum fluorine in workers was reported

TABLE VI. Serum Low Density Lipoprotein by Body Mass Index, Age, Smoking, and Drinking Status: 3M Chemolite Plant, Cottage Grove, Minnesota

		LDL(mg/dl)				
	N (%)	Mean	SD	Median	Range	Test[a]
BMI						
<25	41 (35.7)	130	22.8	133	70–217	F = .65
25–30	57 (49.6)	138	34.2	135	36–264	p = .52
>30	17 (14.8)	136	33.0	137	71–196	
Age						
≤30	21 (18.3)	130	29.6	131	75–177	F = .37
>30–40	48 (41.7)	136	36.2	135	70–264	p = .77
>40–50	27 (23.5)	133	34.5	135	36–193	
>50–60	19 (16.5)	140	32.3	137	20–196	
Alcohol						
<1 oz/d	87 (81.3)	135	34.5	133	36–264	F = .01
1–33 oz/d	20 (18.7)	135	31.4	137	78–217	p = .93
Missing	8	134	35.6	141	70–174	
Tobacco						
Smoker	28 (24.8)	152	35.6	146	99–264	F = 9.42
Nonsmoker	85 (75.2)	130	31.3	133	78–217	p = .003
Missing	2	115	55.9	115	70–174	
Total	115					

[a]Anova.
BMI, body mass index; LDL, low density lipoprotein.

TABLE VII. Serum High Density Lipoprotein by Body Mass Index, Age, Smoking, and Drinking Status

		HDL (mg/dl)				
	N (%)	Mean	SD	Median	Range	Test[a]
BMI						
<25	41 (35.7)	46.0	10.7	43	19–68	F = .38
25–30	57 (49.6)	45.6	10.5	44	22–79	p = .69
>30	17 (14.8)	43.6	7.7	43	32–55	
Age						
≤30	21 (18.3)	43.5	14.3	40	19–79	F = .72
>30–40	48 (41.7)	46.7	9.9	46	22–65	p = .55
>40–50	27 (23.5)	46.0	8.3	45	29–61	
>50–60	19 (16.5)	46.6	7.9	43	32–67	
Alcohol						
<1 oz/d	87 (81.3)	44.3	9.2	43	19–65	F = 3.88
1–3 oz/d	20 (18.7)	49.3	13.5	45	29–79	p = .05
Missing	8	48.3	9.3	53	32–55	
Tobacco						
Smoker	28 (24.8)	44.3	8.9	43	29–68	F = .35
Nonsmoker	85 (75.2)	45.6	10.6	43	19–79	p = .56
Missing	2	54.5	21.2	55	53–56	
Total	115					

[a]Anova.
BMI, body mass index; HDL, high density lipoprotein.

to be in the form of PFOA (Venkateswarlu, 1982). Because the vast majority of total serum fluorine in plant employees is in the form of PFOA, total serum fluorine closely reflects serum PFOA in production workers, and its use is unlikely to introduce substantial error into the study.

We expected the group of workers who were selected for the unexposed group based on job history to have total serum fluorine levels similar to the general population. However, we found that this group of workers was not unexposed, having levels 20–50 times higher than levels reported for the general population. We concluded that job history was not an accurate metric for exposure. Because job history performed poorly for exposure assessment, we used measured total serum fluorine to classify individuals in the analyses.

Data Collection

Participants completed a medical history questionnaire, were measured for height and weight, and donated a blood sample by venipuncture for assays of total serum fluorine, rum glutamyl oxaloacetic transaminase (SGOT), serum glutamyl pyruvic transaminase (SGPT), gamma glutamyl transferase (GGT), cholesterol, low-density lipoproteins (LDL), and high-density lipoproteins (HDL). The blood sample for total serum fluorine (TSF) was collected in a fluorine-free 15-ml Vacutainer. Divided aliquots of serum collected for total fluorine assay were frozen at −70°C. After all total fluorine samples had been received, batches of 15 samples were assayed on successive work days. Total serum fluorine, reported as a mean value, was determined using sodium biphenyl extraction and atomic absorption spectroscopy (Venkateswarlu, 1982). Each sample was assayed twice. Each batch included high- and low-quality control samples.

Analysis

Stratified analysis, Anova, Pearson correlation coefficients, and linear multivariate regression were used to evaluate associations between PFOA and the biochemical endpoints. For stratified analyses, Anova procedures were used to assess differences in mean values. Total serum fluorine was divided a priori into five categories—<1 ppm, 1–3 ppm, >3–10 ppm, >10–15 ppm, and >15 ppm—based on the distribution of previous monitoring data. Age, body mass index (BMI), alcohol use, and tobacco use were included in regression models as potential confounders. Number of cigarettes smoked per day was used as a continuous

ABLE VIII. Linear Multivariate Regression Model of Factors Predicting the High Density Lipoprotein in Study of Workers Exposed to PFOA

Variable	β	SE(β)	p value
Intercept	65.00	10.07	.0001
Total fluorine	−1.61	.77	.04
Alcohol[a]			
Low (<1 oz/day)	−9.92	3.51	.006
Nonresponsive (NR)	−6.77	5.73	.24
Low × total fluorine[b]	1.62	.80	.04
NR × total fluorine[b]	2.05	1.63	.21

R^2 = .17.
[a]Reference category is drinkers who consumed 1–3 oz ethanol/day.
[b]Interaction terms between total fluorine and alcohol category.
Adjusted for age, body mass index, smoking, and testosterone.

TABLE IX. Serum Glutamic Oxaloacetic Transaminase, Serum Glutamic Pyruvic Transminase, and Gamma Glutamyl Transferase by Total Serum Fluorine in Study of Workers Exposed to PFOA

Total fluorine	N	Mean	SD	Median	Range	Test[a]
SGOT (IU/dl)						
<1 ppm	23	22.5	4.1	22	13–29	F = 0.41
≥1–3	65	24.1	8.6	23	10–74	p = .80
>3–10	16	25.8	14.5	22.5	17–77	
>10–15	6	25.7	11.3	22.5	17–47	
>15–26	5	22.2	5.1	22	14–27	
SGPT (IU/dl)						
<1	23	47.7	10.7	46	30–69	F = 1.19
≥1–3	65	51.3	30.2	45	4–263	p = .32
>3–10	16	53.0	14.0	50.5	29–40	
>10–15	6	73.2	53.2	52.5	38–177	
>15–26	5	44.6	8.6	42	34–54	
GGT (IU/dl)						
<1 ppm	23	37.2	29.4	27	6–117	F = 0.39
≥1–3	65	32.4	26.7	25	5–174	p = .81
>3–10	16	35.4	35.4	26	10–158	
>10–15	6	38.3	16.7	36.5	19–60	
>15–26	5	22.2	11.5	20	11–37	
Total	115	33.7	27.6	26	5–174	

[a]Anova.
SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; GGT, gamma glutamyl transferase.

TABLE X. Pearson Correlation Coefficients Between Total Serum Fluorine, Age, Body Mass Index, Daily Alcohol Use, Daily Tobacco Consumption, and Hepatic Parameters in Study of Workers Exposed to PFOA

	Total fluorine (ppm)	Age (years)	BMI (kg/m²)	Alcohol (oz/day)	Tobacco (cigs/day)
SGOT	.01	−.10	.09	12	− 11
SGPT	.01	.01	.20	.03	− 11
			p = .02		
GGT	−.04	.12	.27	.15	03
			p = .004		

SGOT, serum glutamic oxaloacetic transaminase; SGPT, serum glutamic pyruvic transaminase; GGT, gamma glutamyl transferase; BMI, body mass index.

TABLE XI. Serum Glutamic Oxaloacetic Transaminase by Body Mass Index, Age, Smoking, and Drinking Status in Study of Workers Exposed to PFOA

	SGOT (IU/dl)					
	N (%)	Mean	SD	Median	Range	Test[a]
BMI						
<25	41 (35.7)	24	12.4	22	13–77	F = .92
25–30	57 (49.6)	23	5.8	23	10–42	p = .40
>30	17 (14.8)	27	8.1	26	17–47	
Age						
≤30	21 (18.3)	25	12.7	23	17–77	F = .78
>30–40	48 (41.7)	24	9.1	23	10–74	p = .51
>40–50	27 (23.5)	22	5.4	23	13–40	
>50–60	19 (16.5)	26	7.8	23	14–47	
Alcohol						
<1 oz/d	87 (81.3)	26	13.5	22	16–77	F = .61
1–3 oz/d	20 (18.7)	24	8.0	23	10–74	p = .44
Missing	8	23	4.3	21	19–31	
Tobacco						
Smoker	28 (24.8)	24	8.4	23	13–77	F = .02
Nonsmoker	85 (75.2)	24	11.0	22	10–42	p = .89
Missing	2	20	3.5	20	17–47	
Total	115					

[a]Anova.
SGOT, serum glutamic oxaloacetic transaminase; BMI, body mass index.

variable if model fit was improved compared with the model using categorical variables. BMI was categorized into three categories, <25 kg/m², 25–30 kg/m², and >30 kg/m². Alcohol use was divided into three categories: <1 k per day, 1–3 drinks per day, and no response to the questionnaire item, and was entered into the models as a set of indicator variables. Significant nonlinear dose-response relationships were evaluated by comparing model fit using residual analysis and by comparing parameter estimates using indicator variables and continuous variables. Interactions between total serum fluorine and the covariates were evaluated based on biologic plausibility. Interaction terms were included in the final model if the parameter estimate had a p value ≤0.05. The two nonrespondents to the smok-

participants only. SGOT and SGPT increased with increasing PFOA. The hypothesis that PFOA may modulate the hepatic effects of obesity is consistent with these changes in enzyme profile. This hypothesis has biologic plausibility because obesity has been associated with elevation of transaminases through fatty infiltration (Ludwig et al., 1980; Hodgson et al., 1989). PFOA may directly or indirectly potentate this effect in susceptible individuals. PFOA alters hepatic lipid metabolism and may block the metabolism of accumulated fatty acids, resulting in an exacerbation of the pathologic process (Haughom et al., 1992).

PFOA may also modulate the effect of alcohol on hepatic metabolism. PFOA is associated with changes in the effect of alcohol consumption on HDL levels, essentially blocking the rise in HDL associated with alcohol consumption. GGT was inversely associated with PFOA in drinkers. Perfluorooctanoic acid may decrease serum GGT by altering cell membrane permeability, by reducing the alcohol-mediated induction of GGT, or by changing alcohol oxidation pathways and reducing the production of such toxic intermediates as acetaldehyde (Bates, 1981; Schuckit and Griffiths, 1982; Orrego et al., 1985; Schuckit and Irwin, 1988). These findings support the hypothesis that PFOA modulates the effects of endogenous and exogenous determinants of hepatic metabolism.

Interpretation of these findings is limited by a number of factors. Only active workers in PFOA production were included in this study. It is unlikely that workers who had significant exposure during the previous 5 years would have been lost to this study because of transfer out of the PFOA production division. Transfer as a result of subclinical changes in such biochemical parameters as SGOT is unlikely. Because of the low turnover rate in plant employees (3% per year) and the inclusion of most current employees with appropriate job histories, selection bias is not a likely explanation for the findings in this study. Given the high participation (>80%), nonresponse bias is likely to be small. Information on smoking and alcohol consumption was collected and used in the analyses; however, measurement error for these variables could allow residual confounding. Because smoking and alcohol consumption are not strong determinants for the endpoints in this study, the magnitude of any residual confounding is likely to be small. The duration of exposure may be an important determinant of PFOA level and effect; however, information on the duration of employment in exposed jobs was not available because plant records did not contain sufficient information to reconstruct exposures. Furthermore, the use of job history resulted in marked misclassification of exposure status, indicating that the use of job duration would be of limited value in determining duration of exposure.

Many of the participants were employed in the production of compounds other than PFOA; however, none of these processes involve substantial exposure to known hepatotoxins. Because PFOA has a long biological half-life in humans, is absorbed easily, and is hepatotoxic in rodents, PFOA production workers have been under medical surveillance for more than 20 years. No adverse clinical outcomes related to PFOA exposure have been observed in these employees.

In summary, PFOA was not associated with the marked hepatic changes in humans that have been observed in rodents. This finding is consistent with the results of a retrospective mortality study that found no increased mortality from liver disease (Gilliland and Mandel, 1993) and with the results from an earlier morbidity study that found no adverse hepatic effects (Ubel et al., 1980). PFOA may modulate the effect of alcohol use and obesity on hepatic lipid and xenobiotic metabolism. Continued epidemiologic surveillance is appropriate in workers exposed to PFOA.

ACKNOWLEDGMENTS

This study was supported in part by NIOSH grant T150H07098-16 and the 3M Medical Department.

REFERENCES

Abdellatif A, Preat V, Vamecq J, Nilsson R, Roberfroid M (1990): Peroxysome proliferation and modulation of rat liver carcinogenesis by 2,3-dichlorophenoxyacetic acid, 2,4,5 trichlororphenoxyacetic acid, perfluorooctanoic acid and nafenopin. Carcinogenesis 11:1899–1902.

Bates H (1981): GGTP and alcoholism: A sober look. Lab Management 19:1–3.

Belisle J (1981): Organic fluoride in human serum: Natural versus industrial sources. Science 212:1509–1510.

Gilliland F, Mandel J (1993): Mortality among employees in a PFOA production plant. J Occup Med. 35:950–954.

Griffith F, Long J (1980): Animal toxicity studies with ammonium perfluorooctanoate. Am Ind Hyg Assoc 41:576–583.

Guy W (1979): Ionic and organic fluorine in blood. In Johansen E, Taves D, Olsen T (eds): Continuing Evaluation of the Use of Fluoride. Boulder, CO: Westview Press.

Haughom B, Spydevold O. (1992): The mechanism underlying the hypolipemic effect of perfluorooctanoic acid (PFOA), perfluorooctane sulphonic acid (PFOSA) and clofibric acid. Biochim Biophys Acta 1128:65–72.

Hodgson M, Van Theil D, Lauschus K, Karpf M (1989): Liver injury tests in harzardous waste workers: The role of obesity. J Occup Med 31:238–242.

Just W, Gorgas K, Hanl F, Heinemann P, Salazar M, Schimassek H (1989): Biochemical effects and zonal heterogeneity of peroxisome proliferation induced by perfluorocarboxylic acids in rat liver. Hepatology 9:570–581.

Keller B, Marsman D, Popp J, Thurman R (1992): Several nongenotoxic carcinogens uncouple mitochondrial oxidative phosphorylation. Biochim Biophys Acta 1102:237–244.

Kennedy G (1985): Dermal toxicity of ammonium perfluorooctanoate. Toxicol Appl Pharmacol 81:348–355.

Kennedy G, Hall G, Brittelli J, Chen H (1986): Inhalation toxicity of ammonium perfluorooctanoate. Food Chem Toxic 24:1325–1329

Ludwig J, Viggiano T, McGill D, Oh B (1980): Nonalcoholic steatohepatitis. Mayo Clin Proc 55:434–438.

Nilsson R, Beije B, Preat V, Erixon K, Rannel C (1991): On the mechanism of the hepatocarcinogenicity of peroxisome proliferators. Chem Biol Interact 78:235–50.

Orrego H, Blake J, Israel Y (1985): Relationship between gamma glutamyl transpeptidase and mean urinary alcohol levels in alcoholics while drinking and in withdrawal. Alcohol Clin Exp Res 9:10–13.

Pastoor T, Lee K, Perri M, Gillies P (1987): Biochemical and morphological studies of ammonium perfluorooctanoate-induced hepatomegaly and peroxisome proliferation. Exp Mol Pathol 47:98–109.

Perkins R (1992): Investigation of ammonium perfluorooctanate effect on hormone levels and peroxysome proliferation in the rat. Toxicologist 12: 38.

Permadi H, Lundgren B, Andersson K, DePierre, J. (1992): Effects of perfluoro fatty acids on xenobiotic-metabolizing enzymes, enzymes which detoxify reactive forms of oxygen and lipid peroxidation in mouse liver. Biochem Pharmacol 44:1183–1191.

Reddy J, Azarnoff D, Hignite C (1980): Hypolipidemic hepatic peroxisome proliferators form a novel class of chenical carcinogens. Nature 283:397–398.

Schuckit M, Griffiths J (1982): Gamma glutamyltransferase values in nonalcoholic drinking men. Am J Psychiatry 139:227–228.

Schuckit M, Irwin M (1988): Diagnosis of alcoholism. Med Clin North Am 72:1133–1153.

Sohlenius K, Andersson K, DePierre J (1992): The effects of perfluorooctanoic acid on hepatic peroxisome proliferation and related parameters show no sex-related differences in mice. Biochem Toxicol. 285 779–783.

Statistical Analysis System (1992). "SAS User's Guide. Version 6." Cary, NC: SAS Institute, Inc.

Takagi A, Sai K, Umemura T, Hasegawa R Kurokawa Y (1991): Short-term exposure to the peroxisome proliferators, perfluorooctanoic acid and perfluorodecanoic acid, causes significant increases of 8-hydroxydeoxyguanosine in liver DNA of rats. Cancer Lett 57:55–60.

Taves D (1971): Comparison of "organic" fluoride in human and nonhuman serums. J Dent Res 50:783.

Taves D, Guy W, Brey W (1976): Organic fluorocarbons in human plasma: Prevalence and characterization. In Filler R (ed): "Biochemistry Involving Carbon-Fluorine Bonds" Washington DC: American Chemical Society, pp 117–134.

Ubel F, Sorenson S, Roach D (1980): Health status of plant workers exposed to fluorochemicals: A preliminary report. Am Ind Hyg Assoc 41: 584–589.

Van Rafelghem M, Mattie D, Bruner R, Andersen M (1987): Patholgoical and hepatic ultrastructural effects of a single dose of perfluoro-n-decanoic acid in the rat, hamster, mouse and guinea pig. Fundam Appl Toxicol 9:522–540.

Venkateswarlu P (1982): Sodium biphenyl method for determination of covalently bound fluorine in organic compounds and biological materials. Anal Chem 54:1132–1137.