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1. Health Status of Plant Workers Exposed to Fluorochemicals - a Preliminary Report

This published paper by Ubel et al (Am Ind Hyg Assoc J 1980;41:384-389) provides an overview of fluorochemical industrial hygiene, medical surveillance and epidemiology research data collected in the late 1970's at the Chemolite (Cottage Grove, Minnesota) facility. The authors concluded that total organic fluorine was found in the blood of workers exposed to industrial fluorochemicals. Medical examination of exposed workers and a brief summary of the initial retrospective epidemiologic mortality study (see study # 2) of the plant employees indicated that there were no ill health effects attributable to fluorochemical exposure.

Higher than normal levels of organic fluorine were found in the blood of workers exposed to fluorochemicals in an industrial environment. No ill health effects attributable to exposure to fluorochemicals were found among these workers. The ambient air in the process operation areas in the plant was found to contain measurable amounts of organic fluorine. Through certain modifications in the process steps and improvements in engineering controls, a substantial reduction in the airborne fluorochemical levels within the plant was achieved.

Health status of plant workers exposed to fluorochemicals - a preliminary report

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Introduction

This report provides interim results of an ongoing program which evaluates the health status of a group of production workers exposed to fluorochemicals.

It was recognized as early as 1856 that normal human, animal and avian blood contains small amounts of fluorine.[1] It was recently reported that human blood contains two forms of fluorine, *"exchangeable"* and *"nonexchangeable"*.[2] This finding was corroborated by another study which described *"ionic"* and *"nonionic"* fluorine fractions in the blood.[3] Essentially, in either study one form can be regarded as inorganic fluoride and the other covalently bound organic fluorine.

Very little organic fluorine was found in the blood sera of several species of animals, when the samples were processed by an open ashing procedure.[4] However, when the samples were analyzed following confined combustion in an oxygen bomb, the concentrations of organic fluorine found in some bovine sera were comparable to those found in human sera.[3] No clear cut relationship between the two forms of fluorine in a given sample could be demonstrated.[3,4]

The precise nature of the organic fluorine fraction in the blood is still speculative and could be very complex, containing more than one organic fluorine compound and from more than one source, including the diet. Organic fluorine compounds such as fluoroacetate and fluorocitrate have been identified in lettuce, forage crops, soybean and tea, when the growing plants or single cell cultures of plants were exposed to high levels of inorganic fluoride.[7-12] Perfluorooctanoic acid ($C_7F_{15}CO_2H$) or a similar compound of industrial origin was believed to be present in a plasma fluorine fraction isolated from a large pool of human plasma samples.[6]

Since some 3M plant workers are exposed to industrial fluorochemicals, we considered it important to (a) determine the fluorochemical levels in the blood of the plant workers, (b) monitor the fluorochemical levels in the ambient air in the fluorochemical plants, (c) minimize worker exposure to fluorochemicals, (d) conduct special medical examination of selected workers and (e) institute a retrospective epidemiological investigation in order to evaluate the overall impact of exposure of fluorochemicals on the health of workers. In addition, we have also undertaken toxicological and metabolic studies in experimental animals.

We believe that it is now appropriate to report in a preliminary way on blood organic fluorine levels and the health status of a group of chemical production workers at one chemical plant which produces ammonium perfluorooctanoate. As the program progresses and as other investigations are completed, it is expected that more detailed papers and more definitive conclusions will be forthcoming.

methods and investigations

a. Fluorine determination in blood serum: The concentration of organic fluorine in blood was determined by subtracting the inorganic fluoride concentration from total fluorine concentration. The latter was determined by gas chromatography,[13] following combustion of the sample by a modified oxygen bomb technique.[3] Perfluorooctanoic acid was also determined by gas chromatography following its extraction from serum and conversion to its methyl ester using diazomethane.[14]

b. Fluorine measurement in air samples: Air samples were obtained by using midget impingers containing spectrograde methanol through which the air was drawn with a portable battery-operated sampling pump. Particulate sampling was done using Nuclepore ® 0.8 μm pore sized filters in 37 mm plastic cassettes. Samples so collected were analyzed for perfluorooctanoate ion by the method described above.[14]

c. Health evaluation: Evaluation of the health of the employees was based on a careful study of the clinical history, a review of the multiple laboratory tests and a physical examination by a physician (Table I). Subsequent annual screenings included the same questionnaire on clinical history and the laboratory tests, while examination by the physician were conducted on employees selected on

TABLE I
Medical Examination

1. Clinical history and physical examination
2. Height, weight, blood pressure
3. Electrocardiogram
4. Chest examination, forced vital capacity, forced expiratory volume per second.
5. Vision
6. Audiograms
7. Complete blood count: Hemoglobin, RBC, WBC, Differential count, Cell indices
8. Urine analysis
9. Blood chemistry:

Glucose	Total protein	Alkaline phosphatase
Urea	Albumin	Lactate dehydrogenase (SLDH)
Cholesterol	Globulin	Glutamic-oxaloacetate transaminase (SGOT)
Uric acid	A/G ratio	Glutamic-pyruvate transaminase (SGPT)
Calcium	Bilirubin	Gamma-glutamyl transferase (SGGT)
Phosphorus		

the basis of test results. Routine clinical laboratory determinations were carried out according to standard procedures by an outside contract laboratory.

d. Epidemiological investigations: These investigations were structured after the principles of relative survival and proportional mortality analysis described recently.[13] The overall analysis essentially converges on a comparison of the observed to expected death rates specific for cause, age, time, sex and race.

e. Other supportive studies: *In vitro* mutagenicity test (Ames) and animal toxicity studies related to ammonium perfluorooctanoate were conducted by contract laboratories under 3M sponsorship. The studies included acute oral toxicity, primary skin irritation, eye irritation, one hour inhalation effects, two 28-day oral toxicity studies in rats and mice and 90-day oral toxicity studies in rats and monkeys.

results and discussion

a. Fluorine levels in blood serum: The first series of workers was chosen on the basis of their estimated degree of exposure to fluorochemicals: Group A, 3M controls, who are never directly exposed to fluorochemicals; Group B, laboratory personnel who routinely handle fluorochemicals on a laboratory scale during their research and development work and Group C, selected employees in a chemical plant where fluorochemicals have been produced over approximately 30 years and where the potential for the exposure to fluorochemicals is the greatest.

The results of fluorine analysis of serum samples are presented as ranges of values obtained and the number of samples involved per group (Table II).

The inorganic fluoride levels in the case of all groups are within generally reported normal ranges.

The levels of organic fluorine in blood serum in Group A, 3M controls (0.01 to 0.08 ppm) are similar to those reported in the literature for normal human plasma/serum (0.01 to 0.13 ppm).[12,14-16,18] The concentrations of organic fluorine in Group B, laboratory personnel (0.04 to 2.0 ppm) are somewhat higher than those of Group A and the concentrations of organic fluorine in Group C, plant

TABLE II
Levels of Inorganic Fluoride and Organic Fluorine in Blood Sera of Selected Groups of Employees

Group	Number of Samples Analyzed	Inorganic Fluoride ppm	Organic Fluorine ppm
Normal human sera (reported in published literature).		0.01 - 0.17	0.01 - 0.13
A. 3M Controls.	4	0.04 - 0.08	0.01 - 0.08
B. Laboratory personnel, over 20 years exposure.	8	0.01 - 0.07	0.04 - 2.00
C. Chemical Plant workers.	49	0.01 - 0.09	1.00 - 71.00

TABLE III
Levels of Organic Fluorine in Blood Serum and Urine of a Worker Removed from Exposure to Fluorochemicals

Duration of No Exposure to Fluorochemicals	Organic Fluorine in Blood Serum, ppm	Perfluorooctanoate Excreted in Urine, µg/24 hrs.
1 week	66	387
2 weeks	71	218
2 months	68	128
3 months	55	175
5 months	59	160
8 months	45*	220
11 months	47	110
14 months	44	80
18 months	39	-

*80% of the organic fluorine was perfluorooctanoate ion.

workers, (1.0-71.0 ppm), are higher than those in the other groups.

The highest levels were found in workers with the longest work history in fluorochemical production. The majority of the values have remained at about the same level during monitoring over a two and one-half year period.

Throughout the years of service, these plant employees were in situations with a potential for multiple chemical exposures. There was considerable mobility of workers within the chemical plant itself, as well as transfer to and from other non-fluorochemical production areas on the same site. These circumstances make it difficult to define precisely the duration of exposure of the subject to fluorochemicals.

One group of 15 employees had a range of 1.0-10.5 ppm organic fluorine in serum when their serum samples were analyzed before changing to a job involving packaging the dry fluorochemical powder. In seven months, 11 of the employees had an increase in serum organic fluorine concentration to a range of 2.2 to 18.1 ppm. These levels were approximately the same or somewhat lower when their sera were again analyzed three months later.

The majority of serum samples were analyzed solely for organic fluorine and inorganic fluoride. When a method became available, a selected number of serum samples from the workers engaged in the production of ammonium perfluorooctanoate were analyzed for perfluorooctanoic acid. About 90% of the organic fluorine in these serum samples was composed of the perfluorooctanoate anion.

In the case of one worker, the organic fluorine in blood, which was about 40 ppm over a one year period, suddenly rose to 70 ppm for no apparent reason. The worker was then moved to a plant location free of fluorochemical exposure and his blood and urine samples were periodically analyzed for organic fluorine and perfluorooctanoate over several months. The results presented in Table III indicate a gradual but slow return of the serum organic fluorine levels toward the earlier level. Eighty percent of organic fluorine in the 8th month serum sample was found to be perfluorooctanoate ion. These blood and urine values suggest that some fluorochemicals are very slowly eliminated in humans.

b. Fluorine levels in air samples: There has been an industrial hygiene program at the plant for a number of years. When it was recognized that organic fluorine could be found in the employees' blood, the level of industrial hygiene activity was increased.

Air sampling was conducted at points throughout the various process steps. The samples were collected in the operator's breathing zone (OBZ samples) or in work areas while the particular step was in progress (area samples). The latter was considered representative of an operator's exposure while in the area. Many of the samples were collected during charging and draining steps when exposure levels were likely to be highest.

Table IV shows the four main stages and the process steps in the production of ammonium perfluorooctanoate, the concentrations of perfluorooctanoic acid or its ammonium salt in area samples and in OBZ samples and the time span of sample collections. Stage I involves preparation and isolation of perfluorooctanoic acid and its conversion to an ammonium salt slurry, Stage II involves conversion of the salt slurry to a salt cake, Stage III involves drying the cake and Stage IV involves further processing and final packaging of the ammonium salt.

Phase A in Table IV refers to the circumstances as they existed when the present studies were initiated. During Phases B and C, new measures were introduced in Stages II III, and IV to minimize the levels of exposure t fluorochemicals. No changes were made in Stage I.

Phase A: The concentrations of fluorochemicals in are samples and OBZ samples in Stage I were 0.03 to 0.5 mg/m and the concentrations in OBZ samples in Stage II were 0.(to 1.04 mg/m^3.

However, the fluorochemical levels in OBZ samples we relatively higher, 3.90 mg/m^3, during drying in the ov (Stage III) and 3.27 mg/m^3, during further processing a packaging (Stage IV). These operations entailed a l enclosed procedure with more opportunity for exposi than in the previous stages.

Phase B: Because of the higher levels, attention v focused on minimizing the exposures in Stages III and By making appropriate modifications such as (a) replac

TABLE IV

Concentrations of Perfluorooctanoic Acid and Its Ammonium Salt in Air During Various Stages of Production

Stage and Process Steps in Production	Phase A			Phase B			Phase C		
	Sample	Time Mins.	Conc. mg/m³	Sample	Time Mins.	Conc. mg/m³	Sample	Time Mins.	Conc. mg/m³
I (a)	A (PL)	13	0.51						
(b)	A	75	0.05	A	40	0.01			
	A	21	<0.07	A	37	0.02			
	A	60	<0.05	A	55	0.68			
	A	48	<0.07	A	55	0.03			
	A	30	<0.05	A	18	0.14			
	A	60	<0.03	A	27	0.04			
	A	average:	0.05	A	average:	0.05*			
	OBZ	12	0.34	OBZ	6	<0.01			
	OBZ	5	0.50	OBZ	5	0.25			
	OBZ	5	0.17						
		average:	0.34		average:	0.13			
(c)	A	30	0.04						
	A	23	0.05						
	A	48	0.07						
		average:	0.05						
				OBZ	26	0.16			
				OBZ	25	0.03			
					average:	0.10			
II (a)				A	90	1.10	A	60	0.06
				A	325	1.50	A	60	0.05
(b)	OBZ	30	<0.03	OBZ	30	<0.03			
	OBZ	20	0.21						
(c)	OBZ	28	1.04	OBZ	21	0.40			
(d)				OBZ	20	0.18			
III	OBZ	59	3.90	OBZ	11	0.42	P	11	0.20
IV				OBZ	250	2.12			
				OBZ	340	1.18			
				OBZ	129	2.30			
				OBZ	212	0.30			
				OBZ	120	0.07			
				OBZ	223	2.56			
				OBZ	65	7.60			
				OBZ	198	0.04			
				OBZ	370	0.33			
				OBZ	180	0.95	OBZ	48	0.30
				OBZ	123	0.40	OBZ	49	0.57
				OBZ	45	0.08	OBZ	30	0.54
	OBZ	285	3.27		average:	1.49		average:	0.47

A - Area Sample

PL - Peak Level

* - excluding the 55 min. value of 0.68 mg/m³

OBZ - Operators breathing zone sample

the tray drying in the oven with closed system drying, from which point the salt could be passed through a grinder, directly into the packaging drums and (b) improving the local exhaust system, the fluorochemical levels in Stages III and IV were reduced from 3.9 and 3.27 mg/m³ in Phase A to 0.42 and 1.49 mg/m³ in Phase B, respectively.

Phase C: In Stage II, Phases A and B, two successive filtration steps were involved. Under Phase C, the first

filtration step was replaced by a more rapid filtration process, which was also amenable to a better local exhaust system. As a result, it was possible to shorten the exposure time during the first filtration from 6-8 hours to 1-2 hours and also to reduce the level of fluorochemicals in the area samples from 1.1-1.5 to 0.05-0.06 mg/m^3.

Further, in Stage IV, Phase C, grinding was eliminated resulting in a lower mean concentration, 0.47 mg/m^3 in the OBZ air samples compared to mean concentrations of 3.27 and 1.49 mg/m^3 in Phases A and B, respectively. The period of exposure during Stage IV was also reduced from 6-8 hours in Phases A and B to 1-2 hours in Phase C.

Careful examination of the data in Table IV reveals sporadic high values relative to other values in the same set of samples (Phase B, Stage I, 0.68 mg/m^3, 55 min. area sample; Phase B, Stage IV, 7.60 mg/m^3, 65 min. OBZ sample). However, the overall results do show a decrease in levels of exposure to fluorochemicals as a result of the process modifications described.

In addition to exposure by inhalation, exposure by dermal absorption has been considered and measures have been taken to reduce this type of exposure.

Additional modification and process changes are under continual review. The objectives of these changes are better containment of fluorochemicals and reduced reliance on personal protective devices. Until complete control of the fluorochemical dust is achieved, the personal protection program consisting of a dust respirator (3M Brand No. 9900), daily clean overalls and rubber gloves will continue to be enforced.

c. Health evaluation: Beginning in late 1976, special health screening examinations were offered on a voluntary basis to employees in the chemical plant. About 300 employees have been examined yearly over the three year period. Approximately 90% of the plant workers participated in the program each year, although only 50% of the employees took part for three consecutive years. The examination results were given to the employees and, at their request, were sent to a physician of their choice.

No health problems related to exposure to fluorochemicals were encountered among those examined.

In any large scale clinical laboratory testing program such as the present one, difficulties invariably arise in assessing the weight to be placed on those laboratory test results which show minor excursions from the normal values. This is especially true in the absence of clinical evidence of any health impairment as is the case now. All deviations from the normal values in the laboratory test results were critically scrutinized during our clinical assessment, and were also evaluated statistically when possible. Occasional variations from the normal in isolated liver enzyme tests were encountered. Detailed histories were again reviewed with the employees about medication, alcohol consumption and other personal habits. The most frequently encountered liver enzyme exceeding the normal range was the serum gamma-glutamyl-transferase (SGGT) included for the first time in our liver function profile. With its exquisite sensitivity to alcohol consumption,[19-20] the SGGT was the most difficult to evaluate. In a few instances, through episodes unrelated to plant work, the elevated SGGT levels were traceable to alcohol consumption. A consultant hepatologist who examined the subjects concurred with our conclusion that these minor deviations from the normal in the liver function tests were most likely unrelated to plant work and are compatible with the individuals' predisposition toward alcohol. Further a review of the results of laboratory tests performed on other plant workers and on a large number of management personnel shows the same general degree of variations from the normal values as in the case of fluorochemical production area employees. During the course of this three year monitoring program there has been a general decline in the number of individuals with "abnormal" laboratory findings. This is possibly attributable to the implementation of a concerted program of medical concern and personal health care counselling and to improved personal habits of the employees.

No relationship was observed between the few test result deviations (from normal) and the blood levels of organic fluorine.

As was mentioned earlier, we have not detected any disease pattern attributable or related to fluorochemical exposure. Furthermore a review of absenteeism and illness patterns in these employees does not suggest any work related problems.

d. Epidemiological studies: A retrospective cohort mortality study of employees at this plant site, covering a period of the past 30 years (1948-78), was conducted by an independent group under 3M sponsorship. The main objective was to determine (a) whether the mortality experience of employees at the plant was significantly different from that expected in a population group of the same demographic composition and (b) whether the mortality experience of the chemical workers of the plant was significantly different from that expected.

Records of 4218 employees at the plant site were screened and a comprehensive mortality study was carried out on the 3688 employees who had worked at the plant for at least six months.

In this group, a total of 180 deaths were identified (159 males and 21 females) and death certificates for 177 of these cases were traced. All efforts to locate the remaining 3 death certificates were unsuccessful. The number of deaths among females was too few to permit statistical evaluation. Results of mortality analyses for the males indicated no disagreement between the observed mortality and that expected. This was true of all the various causes of death and also of various specific causes of death due to cancer. In addition, mortality analyses for the chemical workers at the plant revealed no disagreements between observed and expected mortality for any cause of death.

e. Other supportive studies (details in a separate publication): Ammonium perfluorooctanoate was examined for mutagenic activity in microbial assays employing Salmonella typhimurium strains TA-98, TA-100, TA-1535, TA-1537 and TA-1538 and Saccharomyces

cerevisiae strain D4. The compounds were tested by two laboratories with and without liver microsomal enzyme preparations from Aroclor®-induced rats. Ammonium perfluorooctanoate was not mutagenic under the test conditions.

The toxic effects of ammonium perfluorooctanoate (LD_{50}: 540 mg/kg, rat) were fairly consistent in rodents. The liver was the target organ. An apparent sex related difference in toxicity was also evident. The males developed hepatotoxic effects at lower treatment levels than the females and at comparable treatment levels the males had more pronounced histopathologic effects than the females. Serum and liver concentrations of organic fluorine were appreciably greater in males than in females. These findings have been corroborated in our laboratories by metabolism experiments in rats involving the use of C^{14}-labelled ammonium perfluorooctanoate.

In the rhesus monkey, the major site of toxicity appeared to be the reticuloendothelial system. The sex related difference in the concentrations of organic fluorine in serum and liver noted in the rodent studies was not evident in the primate study.

Such species and sex differences in the toxicity of ammonium perfluorooctanoate make extrapolation of results of these studies to the human difficult.

conclusions

Organic fluorine was found in the blood of workers exposed to industrial fluorochemicals. The levels of organic fluorine in blood appear to be related to the degree and duration of exposure. Although it is assumed that high organic fluorine levels in the blood are a result of high concentration of airborne fluorochemicals, the contribution from dermal absorption may also be significant.

Limited data from the study of one individual who was removed from exposure to industrial fluorochemicals suggest that some fluorochemicals are very slowly eliminated from the body.

Medical examination of exposed workers and a retrospective epidemiologic mortality study of the plant employees indicate that there are no ill health effects attributable to fluorochemical exposure.

In vitro mutagenicity testing has shown that perfluorooctanoic acid is nonmutagenic.

Certain species and sex-related differences were found in animal toxicity studies, which make extrapolation of results of such studies to the human difficult. This observation emphasizes the importance of the information on humans, such as that presented in this paper.

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