NASA RESEARCH GRANT NGR-10-007-012

Semi-Annual Progress Report
November 30, 1965

Fluorine Toxicity Studies at the University of Miami

by M. L. Keplinger, Ph.D.
Research and Teaching Center of Toxicology
University of Miami, Medical School

Summary of Toxicity Studies with Fluorine

Introduction

In order to handle fluorine in our laboratory, special equipment was purchased or built. An exposure chamber of stainless steel was built not only because it had to be inert to fluorine but also because it needed to have features which would allow rapid entrance and egress of the animals for these short-term exposures. Special cylinders containing 6% fluorine in nitrogen were mixed for us by Allied Chemical Co. (to reduce the hazard from handling liquid fluorine in the laboratory). All equipment was checked for safety and efficiency before starting exposures of animals. Any necessary modifications were made and the equipment was ready for use.

Analytical

It was agreed that the air in the chamber would be analyzed for fluorine concentration. This analysis has posed the greatest problem. The concentration of fluorine in the air of the chamber was anticipated to range from 25 to 3000 ppm. Commercially available analytical instruments would not detect directly these concentrations. The concentration of the fluorine in the cylinders also had to be analyzed.

After consideration of many factors such as range of concentration of fluorine, possible formation of some hydrogen fluoride in the chamber, specificity, interference of other oxidizers, time for analytical results, etc., it was decided that gas-liquid chromatography would be feasible and appeared to be the best solution to our analytical problems.

Although gas chromatography appeared to provide a suitable method, other analytical techniques also were investigated as back-up and as a check on the gas chromatography.

It was felt that the concentration of the specially prepared fluorine in the cylinders should be determined first. This was done by passing the fluorine through a mixture of sodium chloride and sodium fluoride. The fluorine reacts to release equimolar quantities of chlorine. The chlorine was then determined by a Volhard titration. This method is satisfactory when the fluorine concentration is high (five or six per cent as in these cylinders), but it was not sufficiently sensitive to detect lower concentrations (in the order of 1000 ppm) such as those in air from the exposure chamber.

The gas chromatograph was designed, built and the materials of construction tested with fluorine. A thermal conductivity detector was used. Although a number of different conditions have been tried and many tests have been run, satisfactory quantitative determination of fluorine in air has not been accomplished with the thermal conductivity detector.

We are currently investigating the direct injection of fluorine into the chromatographic column and through an electron capture detector. With this detector we have been able to resolve fluorine and oxygen at low temperatures provided both are in microgram quantities. It is encouraging that the retention time is short enough to allow results quite rapidly (within two or three minutes). It remains to be determined if the column can be modified to detect fluorine in the presence of oxygen which is at a 10,000 fold greater concentration.

Experiments with the gas chromatograph are being continued.

[redacted]

Wet methods have been used for the measurement of fluorine and fluoride. A wet method was developed for the analysis of fluorine. The air from the chamber is analyzed by simultaneously collecting two samples in impingers, one of which contains dilute sodium hydroxide aqueous solution and the other contains a slightly alkaline solution of potassium iodide. The fluorine is determined by measuring the iodine formed after acidification of the solution in the impinger containing the potassium iodide solution. The total fluoride is determined from the impinger containing the sodium hydroxide solution by measuring the color formed with 4,5-dihydroxy-3-(p-sulfophenylazo)-2,7-napthalenedisulfonic acid trisodium salt.

Animal Exposures

Exposure of animals was started after testing all components of the system for compatability with fluorine and after development of the analytical methods. In fact, a few preliminary exposures were made to check the equipment further before analytical methods were satisfactory.

Several items of interest regarding the concentration in the chamber during exposure of animals have been brought out. The chamber was designed carefully to be as near ideal as possible for the exposure of the numbers per group and size of animals to be exposed. It was found, however, that a concentration of fluorine was very difficult to maintain when ten rats were placed in the chamber. If the fluorine were introduced at a rate which theoretically should have provided a constant concentration, the concentration of fluorine decreased markedly. Even when only one rat was used, the concentration fell.

The loss of fluorine was not due to reaction with the walls of the chamber or the animal cages, because they have been passivated and the concentration could be maintained after introduction of only the cages.

It appeared that the fluorine was lost by conversion to HF due to the water vapor in the expired breath, by absorption in the respiratory tract, by adsorption or absorption to the fur and skin or by all these combined. An attempt was made to compare the loss by reaction with the skin and fur to the loss by all possibilities combined. The loss due to skin and fur was determined by exposing non-breathing (dead) animals. The results indicated that approximately 50% of the loss was due to the skin and fur. Therefore, apparently, the other 50% was lost due to reaction with the expired water vapor and/or with the mucous membranes of the respiratory tract.

In order to maintain a constant concentration of fluorine in the chamber, the fluorine had to be introduced at a concentration higher than theoretically necessary.

Results

As expected, signs of intoxication from high concentrations of fluorine in air were marked irritation of the mucous membranes of the eyes and respiratory tract. The skin of the animals showed very little irritation at the concentrations used.

The LC_{50} (concentration calculated to kill 50% of the animals) was determined for 5, 15, 30 and 60 minutes of exposure in both rats and mice. The LC_{50} for guinea pigs was determined for 15 and 60 minutes of exposure, while the LC_{50} in rabbits was determined after 5 and 30 minutes of exposure. The LC_{50}'s expressed as mg/cuM and as ppm (by volume) for the different species of experimental animals are tabulated as follows:

LC_{50} Values For Animals Exposed To Fluorine

Exposure Time (min.)	Rat Concentration		Mouse Concentration		Guinea Pig Concentration		Rabbit Concentration	
	mg/cuM	ppm	mg/cuM	ppm	mg/cuM	ppm	mg/cuM	ppm
5	1085	700	935	600	---	---	1273	820
15	617	390	545	350	617	390	---	---
30	420	270	350	225	---	---	420	270
60	288	185	234	150	250	160	---	---

As seen in this table there appeared to be very little difference between the LC_{50}'s of the different species.

At lower concentrations there were fewer signs of intoxication. Dyspnea, lethargy, red nose and swollen eyes were observed at concentrations equivalent to 50% of the LC_{50}'s. At concentrations which were 25% of the LC_{50}'s there were only mild signs of intoxication, manifested by slight dyspnea and closed eyes. At lower concentrations there were no gross signs of intoxication.

Complete blood counts on these animals have not shown significant changes, however it is interesting that the clotting time appears to be affected. Although this phenomenon has not been tested (but probably should be) the blood does not seem to clot as rapidly as normal.

Gross Pathology found in animals, which succumbed from exposure or were sacrificed following exposure near the LC_{50}'s, was congestion, hemorrhage and atelectasis in the lungs and some congestion and/or mottling in the liver. Survivors which were sacrificed up to 45 days after such exposures had congestion in the lungs and occasional congestion in the liver. There was some discoloration of the kidneys in animals which were sacrificed 7 to 14 days after exposure. This appeared to be more prevalent in mice than in the other animals.

Gross changes in the lungs have been found after sacrifice of animals which showed no signs of intoxication. The information to date indicates that concentrations of about 10 to 15% of the LC_{50}'s cause little or no gross pathology in the lungs.