Report Rapport

Atomic Energy Control Board

Commission de contrôle de l'énergie atomique

CA8508058

INFO-0143

TOXICITY LEVELS TO HUMANS DURING ACUTE EXPOSURE TO HYDROGEN FLUORIDE

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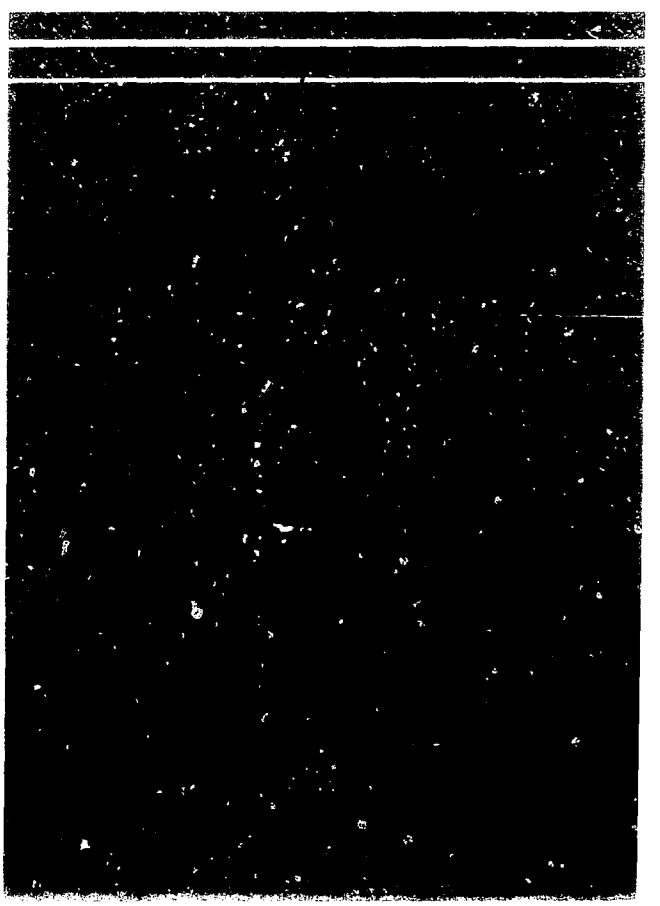

Atomic Energy Control Board
P.O. Box 1046
Ottawa, Canada
K1P 5S9

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A research report prepared for the
Atomic Energy Control Board
Ottawa, Canada

RESEARCH REPORT

November 28, 1984

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ACUTE EXPOSURE TO HYDROGEN FLUORIDE

ABSTRACT

A literature review was conducted of the acute toxicity of hydrogen fluoride (HF) with emphasis on the effects of inhalation of gaseous HF. The data and findings of the relevant references were summarized under four categories: animal studies, controlled human studies, community exposure and industrial exposure. These were critically reviewed and then lethal concentration-time relationships were developed for humans, corresponding to LC_{LO}, LC_{10} and LC_{50} levels. The effects of age, health and other physiological variables on the sensitivity to HF were discussed, as well as antagonistic and synergistic effects with other substances.

RÉSUMÉ

Le présent rapport fait état de l'examen de la documentation relative à la toxicité aiguë du fluorure d'hydrogène (HF) et particulièrement des effets de l'inhalation du HF gazeux. Les données et les conclusions des références pertinentes sont réparties en quatre catégories : études sur les animaux, études contrôlées sur les humains, expositions de la population et expositions industrielles. Les données et les conclusions ont été examinées d'un oeil critique, puis des relations létales de concentration et de temps, correspondant au niveau de la concentration létale la plus basse, au niveau CL_{10} et au niveau CL_{50} ont été mises au point pour les humains. Le rapport touche aussi aux effets de l'âge, de l'état de santé et de certaines autres variables physiologiques sur la sensibilité au HF, ainsi qu'aux effets antagonistes et synergiques avec d'autres substances.

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A. INTRODUCTION

In January 1984, The Atomic Energy Control (AECB) requested a study of the toxicity of hydrogen fluoride (HF). This request was directly related to the AECB's responsibility for regulating the nuclear fuel cycle in Canada, including considerations of health and safety.

The following report documents the study which was subsequently conducted by Monserco Limited, under contract to the AECB. It begins below with a short summary of the general properties of HF and the scope of the present study, including the organization of the report.

Concentration doses in this report are expressed in both milligrams per cubic metre (mg/m^3) and parts per million (ppm). A factor of 1.22 was used to convert mg/m^3 to ppm. The formula used to arrive at this conversion is described in the glossary.

1. Chemical and Physical Properties

Hydrogen fluoride (HF) is a colourless liquid or gas with a sharp irritating odour. It is a liquid at ordinary pressures and temperatures below 19°C, when it is called hydrofluoric acid, and a gas at higher temperatures. HF is monomeric at high temperatures and low partial pressures. At low temperatures, polymers are formed. The degree of polymerization depends on the temperature and partial pressure, but $(HF)_6$ is probably the most common polymeric form. $(HF)_2$ may also exist in small amounts. Further information on the properties of HF is given in Table 1.

2. Uses and Occurence

The gas is used in the production of aluminum fluoride, triolite, uranium hexafluoride, elemental fluorine, aqueous hydrofluoric acid, inorganic fluoride salts, fluorocarbons and in alkylation processes.

The liquid is used in the production of fluorine compounds, cleaning iron and steel castings, etching and frosting glass, the froth floatation of ores, and washing sand free of iron. Small amounts of hydrogen fluoride are found in some commercial cleaning agents. The fluxes used in some welding operations can generate hydrogen fluoride.

3. General Toxicity of Hydrogen Fluoride

The observed symptoms of overexposure to HF are similar to those produced by ammonia or hydrogen chloride. Gaseous HF, being infinitely soluble in water, dissolves in the mucous membranes of the upper respiratory tract producing the following symptoms:

* pulmonary edema (swelling caused by escape of fluid into the air sacs and interstitial tissues of the lung).
* pleural effusion (fluid filling the membranous sac covering the lung and lining of the chest).
* hyperemic action (excess blood flow to an area causing inflammation and congestion).

Death may result from sufficiently high doses. As well, gaseous HF dissolves in the mucous membranes of the eyes, nose and throat and can produce serious injury in this manner.

Liquid HF can cause severe chemical burns of the skin and eyes. It is one of the most corrosive of the inorganic acids and the fluoride ion readily penetrates deep into the skin causing extremely painful ulcers. Systemic poisoning and death can result from such exposure to liquid HF.

4. Scope of Present Study

The primary objective of the present study was to derive dose-response relationships for lethality for human exposure to HF for periods ranging from about 6 seconds (one breath) to two hours. This was to be based on a review of the existing literature and corresponding data. A summary of the health effects on humans and animals was required, and then recommendations for human concentration-time relationships corresponding to LC_{LO}, LC_{10} and LC_{50} levels. The variations in susceptibility due to age, state of health and other factors was also required.

The literature search was conducted using standard reference works on toxicology and a number of computerized bibliographic services. These were: CISDOC, INFODOC, NIOSHTIC, RTECS, TDB and TOXLINE. The search produced over 120 references which were subsequently screened and

reduced to about 60 which were considered to be directly relevant to this study. The earliest reference cited was published in 1909 (Ro 1909) and the most recent was published in 1984 (Sm 1984).

The data and findings of the relevant references were then summarized under four categories: animal studies, controlled human studies, community exposures and industrial exposures. This work is reported in chapter B. The literature was then critically reviewed in an attempt to derive the required dose response relationships (see Chapter C). The limitations of the data were identified and the effects of age, health and other physiological variables were addressed (sections C1 and C2).. Human lethal concentrations for inhalation of HF are discussed in Section C3. Finally, antagonistic and synergistic effects with other substances are identified (section C4).

Chapter D of this report presents the conclusions of the study, in terms of recommended LC_{LO}, LC_{10} and LC_{50} levels, but because of the paucity of the available data on LC_{LO} and LC_{10} values, the authors' recommendations in this area are limited. The concept of an unconsciousness level for HF is briefly discussed.

B. ACUTE TOXICITY

1. Routes of Exposure and Metabolism

Exposure:

Hydrogen fluoride commonly exists in two forms, as a gas or as a liquid when it is called hydrofluoric acid. In the liquid form it may pose an inhalation problem only in solutions more than 50% HF at 19.5°C. At this temperature and concentration HF has a partial pressure of only 1.86 kilopascals (14 mmHg). However, a 70% solution at 27°C has a partial pressure of approximately 20.0 kilopascals (150 mmHg). In this respect HF resembles volatile organics like acetone, chloroform or carbon tetrachloride (Ma 1963). As a dilute liquid, the danger of hydrogen fluoride exposure is probably greatest through skin contact. Hydrofluoric acid displays a rapid and insidious penetrating action when it has contacted the skin of workers. The acid passes easily through pin holes in rubber gloves and may cause delayed agonizing burns of the nail bed. Third degree destruction of tissue can occur from skin contact with 50-70% solution of HF. Pain is felt immediately. Weaker solutions of 25% may take some minutes to be noticed. Burns from solutions of 1-20% may not be noticed for several hours (Ma 1965). Combinations of skin splashing and inhalation have produced severe systemic poisoning and death (Di 1962, Yo 1975, Sch 1978, Bu 1973, Sh 1974).

Exposure to hydrogen fluoride in the gaseous form largely occurs through inhalation. The gas has a marked affinity for water and will combine with mist or water vapour in the air as well as the moisture of the respiratory tract and the eyes. Even at fairly low levels, hydrogen fluoride will combine with moisture on the human skin to produce a smarting sensation (Ma 1934).

There appear to be significant species differences in the consequences of inhalation of hydrogen fluoride. This has most recently been highlighted by studies on the regional deposition of inhaled hydrogen fluoride in rats (Mo 1982). Citing the fact that highly water soluble gases such as ammonia and sulphur dioxide are deposited in the upper respiratory tract with efficiencies of 95% (Da 1963) and at 99.99% (Fr 1969) respectively, the authors suspected that they might find a similar situation with hydrogen fluoride.

In their inhalation study with rats they did indeed observe a deposition efficiency for hydrogen fluoride of greater than 99.9% in the upper respiratory tract for airborne concentrations of up to 71.3 mg/m^3 (87 ppm) (TWA). The authors speculate that this regional deposition in the rat explains the signs of nasal irritation exhibited by rats exposed to HF. In a number of studies (Ro 1963, Di 1971, Wo 1976) mucoid discharge from the external nares, sneezing and/or pawing of the nose have been commonly observed in rats exposed to HF. Work in other laboratories (Ro 1963) noted pathologic damage to the nasal epithelium under conditions of HF exposure but did not mention any pulmonary injury using 4100 mg/m^3 (5000 ppm) and above in the rats exposed to HF during LC_{50} determinations. Morris and Smith (Mo 1982) believe that significant HF deposition in the upper respiratory tract of the rat protects the rat pulmonary tissue. They observed 100% lethality in rats exposed to 156 mg/m^3 (190 ppm) for 6 hours but no lung edema.

It seems unlikely that all mammals possess this protective capacity in the upper respiratory tract. DiPasquale and Davis (Di 1971) reported the 5 minute LC_{50} for mice was 5120 mg/m^3 (6,247 ppm) and Wohlslagel et al (Wo 1976) reported the 60 minute LC_{50} for the mouse was 280 mg/m^3 (342 ppm). These values are approximately one third to one quarter of the comparable values for the rat reported by this group. Morris and Smith (Mo 1982) suggest that the increased sensitivity of the mouse may be due to increased penetration of the inhaled HF to the lungs in this species, but they do not seem to have considered the fact that the difference in species body weight might account for the varying values. A more convincing example of the probable absence of HF nasal scrubbing activity comes from the work of Machle et al (Ma 1934) who noted massive pulmonary edema and haemorrhaging in rabbits and guinea pigs exposed to 1500 mg/m^3 (1833 ppm) HF.

These animal studies concerning regional deposition have considerable significance when considering HF exposure in man. Regional deposition of HF in man has not been investigated. However, human subjects exposed to 26 mg/m^3 (32 ppm) (Ma 1934) experienced irritation of the larger airways. If this represents a direct effect rather than a reflex response, it suggests that the nasal cavity of the human subject is much less efficient than of the rat in scrubbing airborne hydrogen fluoride. This would not be unexpected in the light of the more complex

structure of the nasal cavity of the rat compared to the human (Ba 1977). These relatively recent findings concerning the regional deposition of HF in the rat tend to suggest that the rat might not be an appropriate model upon which to base human inhalation exposure tolerances.

The study by Morris and Smith (Mo 1982) suggested that HF deposited in the upper respiratory tract, where there is a rich vasculature, could be a point of rapid systemic absorption. However, systemic absorption of fluoride after oral administration is also quite rapid (Wa 1954) and it is possible that ingestion of HF contaminated nasal mucosa is also a significant entry route in the systemic absorption of fluoride ion.

Transport:

Regardless of the route of exposure, fluoride ion is readily absorbed into the blood stream and is carried to all organs of the body where it is known to equilibriate very rapidly across biological membrances (Wa 1954). Significant depositions of fluoride occur in calcified tissue such as bone (Wa 1978).

There is growing evidence that the fluoride ion carried in the human blood serum exists in two forms, namely as an inorganic ion F- and in combination with an organic molecule. The latter is a small but apparently significant amount. The nature of the organofluorine molecule is still under investigation (Be 1981, Mo 1983, Ta 1968).

Enzyme Inhibition:

The transformation of a portion of the circulating inorganic fluoride ion to an organic form is not the only metabolic change that is known to occur to circulating inorganic fluoride. Fluoride passing through the soft tissue organs has an adverse effect on many enzymes since it serves as a wide spectrum enzyme inhibitor, even at relatively low concentrations. This is thought to occur because it forms metal-fluoride-phosphate complexes that interfere with the activity of those enzymes which require a metal ion cofactor. In addition, fluoride may interact directly with the enzyme or the substrate. It is a general inhibitor of the energy production system of the cell (oxidative phosphorylation). Despite its obvious importance in enzyme competency there is a paucity of information in the literature concerning the wide spectrum of fluoride morbidity which is undoubtedly related to the

effect of fluoride on many enzymes in numerous organs (Wa 1978). While many of the enzyme activities which are compromised by fluoride ion are known (Bo 1945) the significance of this in terms of human health remains undocumented.

Distribution:

Regardless of what kind of inorganic fluoride is absorbed, fluoride ion is the major form in which fluoride is distributed in the body. Because of its similarity to the chloride molecule it is considered that fluoride distribution is essentially similar to that of chloride but it may be quantitatively different in certain organs.

The distribution of fluoride among the tissues of the body is characteristically simple. An important part goes to the bone for deposition, most of the remainder goes to the kidney for excretion in the urine. No soft tissue stores fluoride (Wa 1958), but the kidney shows a temporary retention. As much as 1% of an intravenous dose may be present per gram of kidney 90 minutes after administration. Fluoride is rapidly removed from the kidney within 24 hours after an intravenous dose and essentially all the fluoride remaining in the body is limited to the skeletal deposit.

Since the thyroid is known to store the related halogen iodine, some studies have been directed to determine if this gland also has the same capacity to store fluoride. At least one of these studies (Wa 1954) has shown that there is no storage of fluoride in the thyroid.

Skeletal Deposition:

Fluoride is a bone seeker. About half of a fluoride dose given to an animal not previously treated will be deposited in the skeleton. The amount of skeletal fluoride and, usually, the concentration of fluoride in the bone increases with increasing fluoride intake when fluoride is supplied regularly. The average human diet probably furnishes between 0.5 and 1.5 milligrams of fluoride daily and bone concentrations of between 41-82 mg/m^3 (50-100 ppm) have been cited as being approximate normal concentrations in skeletal tissue (Ho 1965).

Studies carried out by Neumann (Ne 1957) indicated that bone could reach an equilibrium with a surrounding fluoride solution so that a steady state level of fluoride was achieved in the bone.

Wallace-Durbin (Wa 1954) found that a major part of the ultimate skeletal deposit was removed from the circulation in the first 2 hours following intravenous administration.

Neumann et al (Ne 1950) also showed that fluoride is deposited in bone by a simple exchange reaction with hydroxyl ions. This is thought to occur because the fluoride ion F- is very similar in size to the hydroxyl ion OH- and can therefore substitute for it easily in biochemical reactions.

Fluoride ion is not deposited permanently in the skeleton, it is mobilized slowly with a half-life of something over two years. Largent (La 1960) showed that following a period of measured intake of fluoride the ion could be detected in the urine and feces for some considerable time thereafter. The amounts decreased with time at such a rate that the excretion of the extra fluoride deposit in the skeleton required approximately two years to be removed. Industrial workers in cryolite plants, even after terminating employment, have been shown to excrete more urinary fluoride than unexposed individuals.

Excretion:

The major route for fluoride removal from the body is in the urine. The urine excretion of fluoride is fast. Ericsson (Er 1958) showed that when a normal man ingested a glass of tapwater containing one milligram of fluoride more than 20% of the dose appears in the urine within the first four hours. Smith et al confirmed this finding using 6 young adults drinking water containing 1.5 milligrams (total) of fluoride (Figure 1) (Ho 1965).

From the viewpoint of worker exposure to hydrogen fluoride on a daily basis, it is important to know if monitoring of the urine fluoride is a good indicator of hydrogen fluoride exposure. A number of studies on industrially exposed populations seem to indicate that urine fluoride levels are reasonably accurate indicators of the amount of hydrogen fluoride exposure (Zo 1977, Wh 1980, La 1960) (Table 2).

These findings have been supported by human feeding studies which have correlated fluoride ion intake with urinary fluoride excretion (Figure 2). For man and a number of other species, the relationship appears to be linear and approximately 50% of that fluoride which is absorbed is excreted in the urine.

Fecal excretion of fluoride is highly variable and probably is influenced more by the solubility of the fluoride consumed than by any other single factor. When the fluoride absorbed into the system is from a source of hydrogen fluoride, then it is plausible to assume that ingested mucosa from the nasal passages, which is contaminated with fluoride, will nearly all be absorbed systemically from the gut and very little will be excreted in the feces.

Fluoride can also be excreted in perspiration, but the amounts are probably small, except in extremely hot conditions where excessive sweating may occur. Concentrations reported in perspiration have ranged from 0.16-1.15 mg/m^3 (0.2-1.4 ppm). The percentage of the intake excreted in sweat under high temperature conditions can range from 13 to nearly 50% (Mc 1945).

2. Animal Studies

Inhalation studies involving animals exposed to HF have utilized the rat, mouse, guinea pig, pigeon, rabbit, dog and monkey as test species.

The first reported HF animal inhalation study was performed by Ronzani in 1909 (Ro 1909). Five guinea pigs and 5 rabbits died in 0.5 and 1.5 hours, respectively, while being exposed to HF at airborne levels of 541 mg/m^3 (660 ppm). Five guinea pigs and 5 rabbits exposed to HF at 180 mg/m^3 (220 ppm) died in 1.0 and 3.0 hours respectively. Signs of severe irritation and increasingly difficult breathing were observed from the outset of the experiment. Autopsy revealed ulcerations of the upper respiratory tract and of the cornea of the eyes. At 41 mg/m^3 (50 ppm), 5 guinea pigs died in two hours while 5 rabbits displayed signs of severe physical distress after 3 hours. At 25 mg/m^3 (30 ppm) guinea pigs died after one day, while rabbits exposed to the same levels were in such poor condition after 3 days, the experiment was discontinued. Continuous exposure to 8.2 mg/m^3 (10 ppm) for 5 days was not fatal to either species. The guinea pigs showed laboured breathing and slight eye irritation.

Fifteen rabbits, 21 guinea pigs and 4 pigeons were exposed to 8.2 mg/m^3 (10 ppm) for two 3-hour periods per day over 31 days. During this period, 2 rabbits, 7 guinea pigs and one pigeon died. Autopsies revealed opacity of the corneas with ulcerations, lesions of the nasal mucous membranes, emphysematous lungs, bronchopheumonitis and interstitial pneumonitis. Similar, though less severe findings, were revealed by the autopsy of one of the surviving animals. All surviving animals were severely anemic and had lost up to 23% of their original weight. After immunization against typhus, surviving animals showed a marked decrease in the production of specific antibodies and had reduced resistance to bacterial infection in the lung.

Further experiments using HF levels of 6.1 mg/m^3, 4.1 mg/m^3 and 2.5 mg/m^3 (7.5, 5 and 3 ppm) established 2.5 mg/m^3 (3 ppm) as the no-effect concentration. A 30-day exposure of 16 rabbits, 20 guinea pigs and 3 pigeons to HF at 2.5 mg/m^3 (3 ppm) produced no pathologic changes.

In 1934 Machle *et al* (Ma 1934) studied acute effects in rabbits and guinea pigs exposed to HF at concentrations of 23-8,000 mg/m^3 (29-9,760 ppm) for periods ranging from 41 hours to 5 minutes. For each exposure 3 rabbits and 3

guinea pigs were used. All animals displayed evidence of respiratory tract and eye irritation at all concentrations, although signs were mild and slow to appear in animals exposed to 50 and 24 mg/m^3 (60 and 29 ppm) for 5 to 15 minutes. Slowing of respiratory rate was uniformly observed and was expecially noticeable in rabbits. The frequency of coughs and sneezes increased as the HF level increased. Considerable kidney damage was observed in one rabbit exposed 6 hours per day for a total of 41 hours at 25 mg/m^3 (30 ppm). All animals exposed to levels greater than 500 mg/m^3 (610 ppm) for 15 minutes or more appeared ill and weak. These signs increased in severity as the airborne HF level was increased. Edema of organs and tissues was observed in animals exposed at concentrations of 3,000 mg/m^3 (3,660 ppm) or more for 5-15 minutes. No deaths occurred under the following exposure conditions: 1,000 mg/m^3 (1,220 ppm) for up to 30 minutes, 98 mg/m^3 (120 ppm) for 5 hours and 24 mg/m^3 (29 ppm) for 41 hours. Surviving rabbits returned to normal appearance and activity in a few days to a few weeks, whereas guinea pigs tended towards delayed response and death between the fifth and tenth weeks following exposure. The predominant lesions found in exposed animals were as follows:

* pulmonary haemorrhage, congestion, emphysema and edema with secondary infection in many cases
* hepatic congestion with evidence of parenchymal necrosis and fatty degeneration
* splenic congestion and edema
* myocardial congestion, edema and necrosis
* corneal erosions and ulcerations of nasal turbinates in many animals exposed to higher concentrations

Some of these changes were also common to control groups. The authors were unable to determine to what extent these changes were due to infection, nutritional causes, dietary deficiencies or spontaneous disease processes.

In 1935 Machle and Kitzmiller (Ma 1935) reported the effects of airborne HF on 5 rabbits, 3 guinea pigs and 2 Rhesus monkeys exposed to levels of 15.2 mg/m^3 (18.5 ppm) for 6-8 hours daily except weekends, until a total of 309 hours of exposure had been accumulated. All animals survived 8 months after exposure was concluded, except for 2 guinea pigs. There was no noticeable response following introduction of the animals into the exposure chamber except for occasional coughing by one monkey. All animals exhibited slight lacrimation. No evidence of injury to

the corneas or nasal passages was observed. Exposed rabbits had significantly lower erythrocyte counts than controls. Significant pathologic findings were limited to the lungs, liver and kidneys and were marked in the 2 guinea pigs that died during the study. The following pathologic changes were observed in the 2 guinea pigs that died:

* large pulmonary haemorrhage
* thickening and sloughing off of bronchial epithelium
* congestion, fatty degeneration, necrosis and diffuse periportal fibrosis of the liver
* spotty tubular necrosis of the kidney

The guinea pig that survived showed pulmonary haemorrhages, alveolar exudates and cellular infiltration of the alveola wall with irregular thickening. Considerable lobular degeneration and necrosis were observed in the liver. The lungs of all the rabbits had leukocytic infiltration of the alveolar walls with or without edema or thickening; secondary infection was observed in two animals. Considerable degeneration of fatty tissue was seen in the livers of two rabbits. In all exposed rabbits, extensive renal tubular degeneration and necrosis associated with fibrous tissue replacement were found. The organs of the monkeys, by contrast, showed scarcely any lesions attributable to exposure, with the exception of the kidneys.

In 1949, Stokinger (St 1949) reported the exposure of 29 rats, 20 mice, 20 guinea pigs, 18 rabbits and 4 dogs to airborne HF levels of 25 mg/m^3 (31 ppm) and 7 mg/m^3 (9 ppm) for 6 hours per day, 6 days per week for 5 weeks. A second group of 15 rats, 20 mice, 10 guinea pigs, 10 rabbits and 5 dogs was exposed to 7 mg/m^3 (9 ppm) for the same period. Only at 25 mg/m^3 (31 ppm) did death occur and this was exclusively in rats and mice which had a mortality rate of 100%. All mice died within 17 hours of exposure while rats died throughout the entire exposure period. Twenty-seven of 44 animals examined showed edema and haemorrhages. Four dogs showed degenerative testicular changes and ulceration of the scrotum. In rats, renal cortical degeneration and necrosis were noted in 27 of 30 animals. Only at 25 mg/m^3 (31 ppm) were the above changes found. At 7 mg/m^3 (9 ppm) only one in 5 dogs showed localized haemorrhage of the lungs. Fluoride concentrations in bone of animals exposed to 25 mg/m^3 (31 ppm) for 25 to 95 hours, were found to progressively

increase. There was as much as a 300% increase in the fluoride content of the teeth of rats. Smaller increases were found in the femur.

Rosenholtz et al (Ro 1963), reported on the effects of brief single exposure in animals. Rats in groups of 10 were exposed for single 5, 15, 30 and 60 minute periods to various HF concentrations. The calculated LC_{50} values corresponding to these exposed times for rats were 4,060, 2,200, 1,670, and 1,070 mg/m^3 (4,950, 2,680, 2,040, and 1,310 ppm) respectively. The LC_{50} for guinea pigs exposed for 15 minutes was 3,540 mg/m^3 (4,320 ppm). Respiratory distress and eye and nose irritation were observed in all animals. Pathologic studies, nasal passage necrosis, liver cell congestion and inflammation, renal tubular damage and severe irritation of the skin.

In 1971, Higgins et al (Hi 1971) and DiPasquale and Davis (Di 1971) reported the acute toxicity of short 5 minute exposures to HF. Two groups of 10 rats and 15 mice each were exposed to a series of HF levels to determine the 5 minute LC_{50} values. These were found to be 14,920 mg/m^3 (18,200 ppm) for rats and 5,120 mg/m^3 (6,250 ppm) for mice. Wohlslagel et al (Wo 1976) reported 60 minute LC_{50}'s for rats and mice as 1,143 mg/m^3 (1,395 ppm) and 280 mg/m^3 (342 ppm) respectively.

In summary then, animal studies show that the primary toxic effect of HF is on the respiratory system, with pathologic tissue changes also observed in the kidneys and liver. Table 3 summarizes the relationship between the concentrations of inhaled HF and its effects on animals.

3. Subclinical Exposures (Control Human Studies)

In conjunction with their animal studies, Machle et al exposed two human subjects to low HF levels for brief periods of time (Ma 1934). They found that the two men could tolerate 26 mg/m^3 (32 ppm) for several minutes with some discomfort in the form of mild eye, nose and respiratory irritation. At 49 mg/m^3 (60 ppm) these irritating effects were marked. At 98 mg/m^3 (120 ppm), the highest level that could be tolerated for more than one minute, there was immediate smarting of the skin and eyes and respiratory tract irritation.

Largent (La 1961) performed the most thorough human experimental studies. He exposed 5 subjects, one at a time, to HF levels ranging from 2.12-3.89 mg/m^3 (2.59 ppm-4.75 ppm) for 6 hours per day, 5 days per week for total periods of 10 to 50 days. All subjects showed slight irritation of the exposed skin, eyes and nose. No symptoms or signs of lower respiratory tract irritation were observed at any exposure levels. Thorough medical examinations before and after exposure failed to detect adverse effects of any kind besides minor irritations that quickly disappeared. Table 4 summarizes the results of studies of experimental human exposure to HF.

4. Community Exposures

No documented cases of community exposure to airborne HF leading to adverse health effects were found. The belief that low levels of fluorides prevent dental decay has led to the widespread use of fluoride in drinking water. However, fluoride levels on the order of 1 mg/litre in water and beverages are generally conceded to have a beneficial effect on the rate of occurrence of dental cavities, especially among children.

It is generally recognized that excess intake of fluoride over a long period of time can cause dental fluorosis (mottling of the teeth) and skeletal fluorosis. Epidemiologic studies where water is naturally high in fluoride have shown no adverse effects other than dental mottling except for rare cases. No instances of adverse effects have been reported in controlled studies with fluoridation at the 1 mg/litre level.

5. Industrial Exposure

Mayer and Guelich in 1963 reported three separate accidental deaths due to HF exposure (Ma 1963). Six workers in two separate accidents were splashed with 70% HF acid. In one accident, a metal finisher lifted a 20 gallon steel drum of 70% HF with the help of 3 co-workers. When he removed the bung, HF spewed over all 4 men. Two men jumped into a nearby vat of water and were unharmed. The finisher and the fourth man lay on the ground while other workmen poured water on them. There were no safety showers. The finisher died within two hours of pulmonary edema. His co-worker suffered severe chemical burns but survived.

In another accident (Ma 1963), a 5 pint glass bottle of 70% HF exploded splashing two workmen. They were showered and taken to hospital but died within two hours. The authors estimated that the two men were exposed to breathing zone levels of 8,200-82,000 mg/m^3 (10,000-100,000 ppm). Their estimates were based on the 19.9 kilopascals (150 mmHg) vapor pressure of a 70% HF solution at 80°F and the assumption that the workers' clothing, especially the chest area, became contaminated.

Numerous accounts of death or serious injury due to dermal exposures to HF have been reported, but these are outside the scope of this study.

NIOSH (NI 1978) reports that the only two industrial hygiene studies of HF exposure levels in the manufacturing of HF have been found and that none were found describing exposure levels in the manufacturing of fluorocarbon compounds. The latter processes account for the major portion of HF produced in the U.S. This may be because these processes are completely enclosed and therefore do not produce any workroom exposure but this has not yet been confirmed.

Derryberry *et al* in 1963 (NI 1976) reported the prevalance of osteosclerosis related to fluoride exposure in 74 workers in a fertilizer manufacturing plant. Fluorides in the form of gases and particulates were produced in a range of concentrations throughout the process. Daily average HF exposures for each job were measured. These ranged from 0.5-8.4 mg/m^3 (0.6-10.2 ppm) with 1.8-7.8 mg/m^3 (2.2-9.4 ppm) being associated with increased bone density or with a questionable increase in such density. The average exposure level was 3.4 mg/m^3 (4.12 ppm). Radiologic examination revealed a minimal or questionable

increase in bone density in 17 (23%) of the 74 workers examined. Pulmonary function tests including Forced Vital Capacity (FVC), 1-second Forced Expiratory Volume (FEV-1) and FEV-1/FVC for the total group were roughly 3% of the predicted normal with no significant difference between the chemical workers and the control group.

In 1972 Kaltreider et al (NI 1976) reported the results of roentgenographic examinations and urinary F studies in two aluminum plants. X-ray examinations of 79 potroom workers in one plant revealed increased bone density in 76. Forty-six workmen (58.3%) were categorized as having slight fluorosis; 40 (51%) had "moderate, diffuse structureless" bone appearance and 26 (33%) were categorized as having marked fluorosis. The 8-hour time-weighted average F exposures in the potroom workers ranged from 2.4-5.9 mg/m^3 (2.9-7.3 ppm).

In the second case, roentgenographic examinations revealed no increased bone density in the spines of 231 potroom workers. No airborne F levels were given, although the authors estimated that the airborne F exposure was probably less than in the other plant due to better enclosure of the process.

Elkins (NI 1976) has reported nosebleeds in workers involved in the HF etching process in a plant where airborne HF levels were measured to be 0.4-0.7 mg/m^3 (0.5-0.9 ppm).

Table 5 summarizes the results of these studies.

6. Summary of Human/Animal Health Effects

Comparison of Table 3 (animal data) with Tables 4 and 5 (human data), as far as is possible, given the understandably limited nature of the human data, reveals some general similarities between the animal and human health effects resulting from exposure to airborne HF. These are as follows:

* mild eye and respiratory irritation for short term exposure (less than an hour) to HF levels of 49 mg/m^3 (60 ppm) or less;

* acute pulmonary distress leading to death by pulmonary edema for short term exposures (hours or less) to extremely high HF levels (greater than about 980 mg/m^3 (1,200 ppm)).

Often in toxicity studies there may be a clear relation between sizes or weight and lethal doses. This is not apparent in HF studies and may be an indicator of the species differences in nasal scrubbing capacity.

Further discussion of the health effects on humans is given in the following section of this report.

C. DOSE RESPONSE RELATION - CONCENTRATION TIME PLOTS

1. *Limitations of Data*

Despite the fact that a substantial number of animal studies have been conducted on the inhalation or skin exposure to hydrogen fluoride, there are only five studies that quote LC_{50} values (Di 1971, Wo 1976, Ro 1963, Hi 1971, Am 1971) and two of these reports published the same data (Di 1971, Hi 1971) (i.e. actually, there are only four reports containing different LC_{50} data). There are no studies specifically dealing with LC_{LO} or LC_{10} data.

The studies with animals that were carried out from the early 1900's into the late 1940's (Ro 1909, Ma 1934, Si 1937, St 1949) placed much less emphasis on the exact concentrations which caused specific numbers of deaths under certain conditions. Authors were content to describe their results with terms such as "significant deaths occurred above concentration X", or "no deaths occurred below concentration Y". This rather vague approach to reporting toxicology data probably reflects the absence of clearly defined toxicological concepts of lethal dose at the time of these studies. While these earlier studies can serve as good background information on the toxicology and lethality of hydrogen fluoride, the manner in which this data is reported is usually far too broad and general to be applied in any extrapolation for a possible LC value for man.

Of the four LC_{50} studies which are available, only two graphical points can be plotted for the studies with mice (one LC_{50} value at 5 minutes and another one at 60 minutes). A single LC_{50} value at 15 minutes exists for guinea pigs and a single value at 60 minutes for monkeys. Five points from the four different studies can be plotted for LC_{50} values for rats (Figure 3). The most comprehensive study of LC_{50} data was that conducted by Rosenholtz *et al* (Ro 1963) who obtained LC_{50} values at 5, 15, 30 and 60 minutes. Rosenholtz's 5 minute LC_{50} value of 4,070 mg/m^3 (4,970 ppm) is at considerable variance with that reported by DiPasquale *et al* (Di 1971) or Higgins *et al* (Hi 1971) who obtained values around 14,900 mg/m^3 (18,200 ppm). However, at the other end of the scale, the LC_{50} for 60 minutes reported by Rosenholtz to be 1,070 mg/m^3 (1,310 ppm) compares favourably with that reported by Wohlslagel at 908 mg/m^3 (1,108 ppm).

Since there is little data from either guinea pigs, mice or monkeys to extrapolate possible LC_{50} values for humans, any such derivation would have to come mainly from studies carried out upon the rats. Such an approach has two serious problems:

a. There is a large variation in the 5 minute LC_{50} values reported by DiPasquale and Davis (Di 1971) or Higgins et al (Hi 1971) and those reported by Rosenholtz et al (Ro 1963).

b. Recent studies by Morris and Smith (Mo 1982) suggest that rats may have a highly efficient nasal scrubbing activity for hydrogen fluoride which protects the pulmonary tissue from damage by this gas (see section 2.1). Humans probably do not have this scrubbing capacity and therefore, rats are probably not adequate models from which to project possible human lethal doses. The literature was searched to identify any studies which had compared the human and rat lethal doses, but none was found.

A better method of assessing possible human lethal exposure would be to review the exposure levels that have caused death in industrial or other accidents. Unfortunately, the reports of such case histories are characterized by a total lack of information on the specific airborne levels present at the time of the particular accident. However, a number of blood fluoride plasma levels have been reported in such accident situations and urine fluoride levels have been monitored in individuals exposed to fluoride in industry or in experimental situations. In addition, there have been a number of volunteer exposure studies which have assessed the maximum human tolerance to hydrogen fluoride fumes. Rosenholtz et al (1963) in the conclusion of their report on acute HF exposures in rats, state "human sensory level studies may be more sensitive than animal studies in trying to establish tolerable levels for brief human exposures".

2. Effects of Age, Health and Other Physiological Variables

No reports of animals studies could be found which have assessed the impact of age, sex, state of health, body weight and other physiological variables that might influence the toxicity of hydrogen fluoride. Only with respect to fluoride action on the skeletal system have animal variances been noted to have impact on the

toxicity. Younger animals, not previously exposed to fluoride, are considered to have a higher bone fluoride deposition rate than older animals (Ho 1965).

The human data on this subject are also limited. However, the delineation of human symptoms associated with hydrogen fluoride exposure has been quite extensive. The fact that hydrogen fluoride is highly irritating to the respiratory mucosa indicates that tasks involving hydrogen fluoride should be avoided by those individuals suffering from respiratory disorders such as emphysema or asthma. Similarly, from the well known fluorosis effects of fluoride exposure, it would be prudent for individuals with abnormal bone or joint conditions to be excluded from work with hydrogen fluoride (Gu 1954).

Waldbott and Lee (Wa 1978) reported a series of non-skeletal changes associated with skeletal fluorosis in aluminum workers. These included respiratory and circulatory system disorders (occurring in 97% of retired workers), digestive system disorders (in 52%), gastric ulcer (in 12%), dental changes (74%), and psychiatric disturbances (23%). While it would be tempting to say that individuals predisposed to any of the above disorders should probably avoid exposure to hydrogen fluoride, it has to be recognized that the symptoms described by Waldbott and Lee are not specific for hydrogen fluoride and can have a number of etiologies unrelated to an individual's occupation. However, since fluoride is known as a wide spectrum enzyme inhibitor, individuals with serious diseases should probably avoid any exposure.

3. Lethal Dose Values

There are two lethal dose parameters that are important when considering hydrogen fluoride exposures. For skin contact, lethal dose (usually LD_{50} skin) values would be helpful, while for inhalation, lethal concentration (usually LC_{50}) values would be useful (the LC and LD terms are defined in the glossary at the end of this report).

Toxicity in current acute animal testing systems is usually measured with lethality as the end point.

It is important to understand that these lethal dose (LD) or lethal concentration (LC) parameters are intended as broad indicators of the degree of toxicity of a compound

with respect to a particular species. There may be wide variations in species responses to chemical exposure and this is reflected in differences in LC or LD values.

No LD_{50} (oral) or LD_{50} (skin) assessments have been reported for hydrofluoric acid. As mentioned earlier, four animal inhalation studies have been carried out for hydrogen fluoride and the LC_{50} values that have been obtained for rats, mice, guinea pigs, and monkeys are shown in Figure 3. Other animal data obtained from earlier studies which did not calculate lethal dose values, are summarized in Figure 4. As outlined in section 3.1, there are two confounding factors which make it difficult to extrapolate of the rat data to a possible LC_{50} for man.

4. Extrapolation to Human Lethal Dose Values

The process of extrapolating animal data to derive toxicological parameters for man is fraught with many pitfalls and is an area of considerable scientific controversy (Fr 1969, Ma 1975). A good review of the problems encountered in this kind of extrapolation exercise has been described by Bernard L Oser, under the title "Man is Not a Big Rat", which was delivered at the toxicology forum in Arlington, VA, 1981. This review was later published (Os 1981). A number of models designed to facilitate extrapolation of experimental data from animals to man have been reviewed (Kr 1976, Sm 1984, Ov 1984, Gr 1984, Ra 1981), but they do not necessarily address dose response parameters (Kr 1976) while those that do are usually quite specific for the particular contaminant in question. For example, Smolko et al (Sm 1984), in conducting assessments of health effects following ozone exposure, depend upon a model developed by Miller (Mi 1977) which can theoretically predict the ozone lung dose in animal test species. Such a model is clearly not applicable to other gases, especially not to those such as hydrogen fluoride which have such a high water solubility that significant quantities of the gas may never actually reach lung tissue in some test species, but instead be dissolved in the mucous of the upper respiratory tract. The Miller model, for the extrapolation of ozone exposure from test animals to humans, was the result of a PhD thesis which presumably involved several years of experimentation, specifically with ozone. No such comparable research has been carried out for hydrogen fluoride exposure.

Another model developed for gaseous exposure (Ra 1981) for SO_2, depended heavily upon the availability of specific data concerning pulmonary flow resistance (PFR) and nasal flow resistance (NFR) in humans and test animals. This particular approach has never been published in peer-reviewed scientific journals, and probably would not be excepted as valid by the scientific community. Regardless, derivations, depending on PFR or NFR, cannot be made for HF since such data do not exist, and the relationships cannot be assumed to be the same as that for sulphur dioxide.

It is evident that while a number of models exist for the extrapolation of data from animals to humans, they are frequently substance-specific or else they require data which may not be available for the particular compound in question. It is also worth noting that experimental data which is to be used in the extrapolation of dose response values for man, should have been derived from experimentation which complied with certain guidelines. These guidelines as stated by Weil (We 1972) are as follows:

a. Use, wherever practical or possible, one or more species that biologically handle the material qualitatively and/or quantitatively as similarly as possible to man. For this, metabolism, absorption, excretion, storage and other physiological effects might be considered.

b. Where practical, use several dose levels on the principle that all types of toxicological and pharmacological actions in man and animals are dose related. The only exception to this should be the use of a single, maximum dosage level if the material is relatively non-toxic; this level should be a sufficiently large multiple of that which is attainable by the maximum applicable hazard exposure route, and should not be physiologically impractical.

c. Effects produced at higher dose levels (or within the practical limits discussed in 2) are useful for delineating mechanism of action, but for any material and adverse effect, some dose level exists for man or animal below which this adverse effect will not appear. This biologically insignificant level can and should be set by the use of a proper safety factor and competent scientific judgement.

d. Statistical tests for significance are valid only on the experimental units (e.g. either litters or individuals) that have been mathematically randomized among the dosed and the concurrent control groups. It is to be understood that statistical significance may be of little or no biological importance and, conversely, that important biological trends should be examined further even in the absence of statistical significance.

e. Effects obtained by one route of administration to test animals are not a priori applicable to effects by another route of administration to man. The routes chosen to test animals should, therefore, be the same as those to which man will be exposed. Thus, for example, food additives for man should be tested by a mixture of the material in the diet of animals.

These experimental guidelines are perhaps the most difficult feature to rationalize in the derivation of hydrogen fluoride toxicity values for man from animal studies. This is because recent experimentation (Mo 1982) has indicated that rats have a considerable hydrogen fluoride nasal scrubbing capacity. It is probably true, though it has not been studied, that other rodents also have some degree of nasal scrubbing activity for hydrogen fluoride. Man and primates almost certainly do not have this same capacity for nasal scrubbing of hydrogen fluoride. Given this difference in the biological handling of hydrogen fluoride between rats and man, any extrapolation of the data from rats to man contravenes Weil's (We 1972) number one guideline for animal test experimentation which is to be extrapolated to man.

Recognizing the exceptionally meager background of the hydrogen fluoride data available for extrapolation to humans, the authors have attempted the derivation of lethal dose data from 3 different approaches. The authors caution that the basis for some of these approaches is highly speculative and may not be founded on well established scientific principles.

Approach Number 1: Estimates of LC Values by Other Authors

Deichmann and Gerarde (1969) (Table 6) quoted a figure of 41 mg/m^3 (50 ppm) as a possible fatal human exposure over a 30-60 minute period. Although this figure is quoted in the toxicology databank (TDB) and the registry of toxic effects of chemical substances (RTECS), reference

to the original work of Deichmann and Gerarde is unenlightening as to the origin or derivation of this human lethality figure. One possible origin of the figure comes from an article by Spector (Sp 1956) in which sodium fluoride given orally to guinea pigs has a minimum lethal dose of 250 mg/kg body weight. Hydrogen fluoride given orally to guinea pigs is lethal in doses of 80 mg/kg body weight (Si 1937). Thus, in the guinea pig, hydrogen fluoride by the oral route is three times as toxic as sodium fluoride. Greendyke et al (Gr 1963) suggest that if man exhibits a comparable difference in response, then the oral lethal dose of hydrogen fluoride may be as low as 20-45 mg/kg body weight or 145-3.0 grams in total. Even so, on this empirical basis it would take an average 70 kg man breathing 6 litres of air a minute, a period of almost 4 days to inhale a total of 1400 mg from an atmospheric concentration of 41 mg/m^3 (50 ppm) HF. However, even the limited toxicity data available suggests that morbidity and probably lethality would be evident within minutes or hours of exposure at this level, rather than days. In the interest of erring on the side of safety it is assumed for the purposes of this report that a 30-60 minute exposure to 41 mg/m^3 (50 ppm) may cause lethality.

Figures of 41-205 mg/m^3 (50-250 ppm) hydrogen fluoride, for short exposures, are considered dangerous by Henderson and Haggard (He 1943), but once again, their estimate is unsubstantiated. This suggested lethality range of 41-205 mg/m^3 (50-250 ppm) by two independent groups is probably a fair estimate for inhalation exposures of hydrogen fluoride for 30-60 minutes. Inhalation exposures of this order of magnitude for shorter periods apparently do not result in any acute toxicity responses. This is indicated by the report of Zober (Zo 1977) in a study on occupational exposures in which he observed certain shiftworkers, who were exposed to up to 105 mg/m^3 (128 ppm) (presumably an excursion level) but there was no report of any acute disease consequences of this exposure. Machle et al (Ma 1934) exposed volunteers to up to 100 mg/m^3 (122 ppm) and although the volunteer subjects could only tolerate this level for approximately a minute, there was no severe acute response reported. Waldbott and Lee (Wa 1978) estimated that the patient in their study had been repeatedly exposed, over a number of years, to up to 164 mg/m^3 (200 ppm) for brief periods (presumably minutes) and had suffered common acute symptoms such as shortness of breath or coughing, but had not reported any specific disease condition until many years later when he was diagnosed as a victim of chronic fluorosis.

Conclusion

Although the estimates of the authors for LC_{50} values for hydrogen fluoride in humans are experimentally unsubstantiated, a comparison with the literature on volunteer and occupational exposures tends to support the projection that 41-205 mg/m^3 (50-250 ppm) of hydrogen fluoride would be lethal in human subjects after a 10-30 minute exposure. However, it is probable that these estimates correspond to a lowest lethal dose range, LC_{LO} rather than an LC_{50}.

Approach Number 2: Human Volunteer and Accidental Exposures

Accidental human exposures which have almost resulted in death are of particular interest in assessing the lower range of human lethality. In this respect, the report by Burke et al (Bu 1973) is important. In the first few hours following a 3-5 minute splash and inhalation exposure, the case reported by Burke produced approximately 87 mg of fluoride per litre of urine. This patient barely survived his exposure experience and, to all intents and purposes, his level of exposure could be assumed to be exceptionally close to the lower end of a lethality concentration range for humans. Unfortunately, Burke et al did not quote or estimate the amount of hydrogen fluoride which the patient might have inhaled at the time of his accident.

However, according to Zober (Zo 1977), there is a distinct correlation between atmospheric fluoride concentration and renal excretion. By extrapolation and derivation from a plot of Largent's in Table 2, a urine fluoride (Figure 5) level of 87 mg fluoride per litre could correspond to an equivalent atmospheric concentration of around 27.0 mg/m^3 (33 ppm) (Figure 5). This derivation assumes that Largent's relation between urine fluoride and atmospheric fluoride is linear for all urine concentrations up to 8/ mg F- per litre, though there is no evidence to support this.

It is worthwhile remembering that this derived lower lethality estimate for an inhalation exposure is probably too low. Although only 3.6% of the skin area of Burke's patient was affected by hydrofluoric acid skin burns, this may have contributed significantly to the ensuing systemic poisoning. It would, therefore, be reasonable to assume that 27.0 mg/m^3 (33 ppm) is an underestimate of the inhalation exposure that would produce the symptoms

observed. Unfortunately, there is no way of estimating the amount of fluoride that may have entered through skin absorption.

Table 7 gives the details of urine fluoride levels and their physiological consequences in a variety of studies on hydrogen fluoride exposure. Although in none of these occupational situations was the exact atmospheric exposure quoted, derivations could be made from Table 2 and Figure 5 of Largent (La 1960).

It was thought that similar derivations might be made from accidental exposure instances in which blood serum fluoride found in autopsied patients who had a variety of accidental exposures with hydrogen fluoride. Unfortunately, none of these blood serum levels are correlated with known airborne or skin contact exposure levels during the various accidents. However, from Table 8, it is quite clear that the blood fluoride levels resulting in death in these accidents are exceptionally high. The lowest level of 0.155 mg/100 ml of blood corresponds to levels of almost 2,000 ppm fluoride in the circulation.

Clearly, all these deaths were due to massive overexposures to hydrogen fluoride and are therefore not useful indicators of critical lethal dose ranges for humans.

It is unfortunate, then that we are confined to extrapolating from a single exposure accident in order to estimate the possible lethal exposures in man. Table 6 shows human sensitivity and morbidity data as they have been reported in a number of studies of either volunteers or occupationally exposed individuals.

Conclusion

Lowest lethal dose concentrations (LC_{LO}) of HF for humans in air may be quite low. Around 41 mg/m^3 (50 ppm) for 5 minutes is theoretically sufficient for human lethality.

Approach Number 3: Derivation from Animal Data

For this attempted derivation, a number of angles were considered. These included:

a. a comparison of the urine fluoride levels in animals and in humans;

b. a comparison of blood serum levels in animals and in humans; and

c. a comparison of the symptoms experienced subjectively in humans and subjectively reported by humans in animals as possible basis for the extrapolation of human lethal dose data from animal test systems.

All of these possible approaches were disregarded either because of the non-existence or the inadequacy of the available data.

The authors recognized that what was required in this instance was the application of a very general extrapolation model that would not be either species nor substance specific. A model meeting this criteria was published by Dourson and Stara (Do 1983) and utilizes an interspecies adjustment system based on the difference in body surface areas between experimental animals and man.

Figure 6 is a plot of the experimental animal weight versus an interspecies adjustment factor, calculated as the cubed root of the assumed average human body weight (70 kg) divided by W, the weight of the animal.

$$\sqrt[3]{\frac{70}{W}}$$

These factors account for differences in mg/kg body weight doses due to different body surface areas between experimental animals and man, based on the assumption that different species are equally sensitive to the effects of a toxin on a dose per unit surface area. When this surface area dose is converted to corresponding units of mg/kg body weight, those species with a greater body weight (e.g. humans) appear to be more sensitive to the toxicity of a contaminant than a species of a smaller body weight (e.g. rodents). Dose conversions based on a body surface area are generally thought to more accurately reflect differences among species in several biological parameters when compared to conversions based on mg/kg body weight (Ra 1969).

The factors shown in Figure 6 can be thought of as reductions in experimental animal dose (in mg/kg body weight) needed to estimate a comparable human mg/kg body weight dose. For the purposes of this report, the authors have assumed that the interspecies adjustment for doses in the mg/kg body weight is the same as the interspecies adjustment that would be required for an inhalation exposure. We recognize that this may be an inacccurate

assumption since it does not take account of differences in lung surface area which will affect absorption rate, or differences in pulmonary flow resistance. However, Figure 6 is used in order to determine interspecies adjustment factors and these factors might be similar regardless of the route of administration of the toxin.

From figure 6 we can see that a rat (weight 0.33 kg) given an experimental dose of 100 mg/kg body weight has an interspecies adjustment factor of about 6 (ie. the cubed root of the expression: 70kg/0.33kg). The probable lethal dose for a human is then 100/6 = 17 mg/kg.

According to Dourson and Stara, Figure 6 has a built in tenfold uncertainty factor to account for interspecies variability to the toxicity of the chemical. The adjustment factors derived from Figure 6, presented by these authors, are used in this report to estimate possible LD_{LO}, LD_{10}, and LD_{50} for humans from the four lethal concentration studies reported for hydrogen fluoride in the scientific literature.

Conclusion

LC_{LO}, LC_{10} and LC_{50} values derived by extrapolation from animal data are shown in Table 9. Values obtained for LC_{LO} in the studies of DiPasquale (Di 1971) were so high that they were disregarded in favour of the values obtained by human experience, as outlined in approaches 1 and 2 of our derivations. Similarly, in the LC_{10} (5 min) estimation, only the mouse study was considered and DiPasquale's rat studies were disregarded in our extrapolations. Table 10 summarizes the LC_{50} values obtained by our 3 approaches to derive human HF exposure parameters. Figure 7 shows the plot of human LC_{50} values over a period of one hour.

Using a single point of 41 mg/m^3 (50 ppm) as a possible LC_{LO} (5 min) and a single point of 275 mg/m^3 (336 ppm) as an LC_{10} (5 min) exposure for humans, a purely hypothetical derivation for these parameters is shown in Figure 8. This figure assumes the graphical slope of the LC_{LO} and LC_{10} plots is the same as that for the LC_{50} plot. There is absolutely no evidence to support this assumption.

5. Antagonistic or Synergistic Effects

There have been no reports of exposures to substances that will either antagonize or exaggerate the toxic effects of hydrogen fluoride. There have been a few studies that have investigated the combined effects of exposures to hydrogen fluoride with exposures to other gases in order to determine the possible outcomes of emergency or disaster situations that might expose industrial workers or firefighters to combinations of toxic gases. One such report was that of Higgins et al (Hi 1971) who studied the influence of carbon monoxide exposure in combination with a number of toxic gases, including hydrogen fluoride. The authors concluded that, although there was a greater toxic action due to simultaneous exposure of animals with hydrogen fluoride and carbon monoxide, this double exposure was additive in its effects rather than synergistic. The data of Higgins et al (Hi 1971) was confirmed by DiPasquale and Davis (Di 1971) who did similar studies involving the combination of hydrogen fluoride with carbon monoxide. Their experiments indicated that carbon monoxide concentrations which are not hazardous to life do not enhance the toxicity of hydrogen fluoride. In addition, the times to death for animals from both the singly exposed tests and the carbon monoxide/hydrogen fluoride joint action exposures were comparable. In other words, carbon monoxide did not increase the hazard posed by hydrogen fluoride exposure.

Similar inhalation studies were carried out by Wohlslagel (Wo 1976) with rats exposed to a combination of hydrogen chloride and hydrogen fluoride. The authors concluded that there was no positive or negative interaction of the two compounds to produce a greater or lesser number of deaths than expected.

A Russian study (Aj 1976) combining HF and SO_2 in animal exposures found the toxic effects of the gases were additive but neither one enhanced the toxicity of the other.

Both HF liquid and vapour react violently with bases. The acid will dissolve glass, ceramics, metals containing silica, natural gum rubber and leather. Flammable hydrogen gas can be produced in metal containers. Lead, wax, polyethylene and platinum are not corroded by HF (Hydrofluoric Acid, Canada Safety Council, 1981).

Leleu (Le 1973) reported three chemical interaction hazards associated with hydrofluoric acid. In combination with bismuth acid $HBiO_3$ a 40% solution of hydrofluoric acid will react violently at room temperature, producing fluorinated bismuth compounds and possibly ozone. As well, fluorine gas reacts vigorously with 50% hydrofluoric acid and may burst into flame, and arsenic trioxide becomes incandescent in the presence of hydrofluoric acid.

D. CONCLUSIONS AND RECOMMENDATIONS

Unconciousness Levels

At no time in the literature searching were unconciousness levels mentioned in reference to HF exposure. Asphyxiation from HF has not been reported and this aspect does not appear to be a major concern.

Lethal Concentrations

The derived values for humans are summarized in Table 10. From accidental, occupational and volunteer exposures, it is estimated that the lowest lethal concentration for a five minute period (LC_{LO} 5 min) for human exposure to hydrogen fluoride is in the range of 41-205 mg/m^3 (50-250 ppm). The lethal concentration for 10% of the human population for a five minute period (LC_{10} 5 min) was estimated from a single mouse study only. No other data was available to make this estimation. From this single study the LC_{10} (5 min) for humans exposed to hydrogen fluoride is 275 mg/m^3 (336 ppm). From these single points, speculations were made concerning the LC_{LO} and LC_{10} at other time intervals over a period of one hour (Figure 8). These speculations were based on the assumption that the slope of the graph for LC_{LO} and LC_{10} values would be the same as that obtained for the LC_{50} estimates. There is no evidence to support this assumption.

Only in the LC_{50} studies was there sufficient data to make extrapolations for human exposures for 5, 15, 30 and 60 minutes. These extrapolations were made from a few animal studies involving rats, guinea pigs, monkeys and mice. One of the rat studies (Di 1971) produced LC_{50} values which were of the order of four or five times higher than other animal investigations. These high values were disregarded in subsequent extrapolations to human data since they were inconsistent with the values obtained by other animal studies and the authors of this report would prefer to err on the side of safety in estimating human lethal dose values.

The LC_{50} (5 min) for human exposure to hydrogen fluoride is considered to be in the range 410-679 mg/m^3 (500-828 ppm). The LC_{50} (15 min) is in the range 368-825 mg/m^3 (448-1007 ppm), the LC_{50} (30 min) is 278 mg/m^3 (340 ppm), and the LC_{50} (60 min) is 22-483 mg/m^3 (27-589 ppm). The results are expressed graphically in Figure 7.

It is not uncommon to discover that many high volume, common chemicals used in industry have inadequate toxicity data on which to base safe levels for exposure. The limited data available relevant to HF exposure is a good example. The animal studies on hydrogen fluoride have largely been restricted to investigations using rats and, as pointed out in this report, these may not be good models by which to judge human exposure tolerances.

A feature of HF toxicity, which has only been incidentally addressed in both animal studies and human accident reports, is related to the actual cause of death. There are two possibilities. The first is from systemic fluoride poisoning, and the second is as a result of acid burns upon the tissue. None of the research work cited in this report has established a point at which the concentration of fluoride alone, from HF, absorbed into the systemic circulation, is adequate to cause death. It is possible that the LC_{50} data obtained is a composite of the two effects. However, it seems more likely that at high concentrations of HF, acid damage to pulmonary tissue in the form of acid burns would be the principal cause of death, while at lower concentrations, the build-up in the systemic fluoride is probably the dominant factor in lethality.

In the rat studies of Morris and Smith (1982) 100% mortality was observed after exposure to 190 ppm for 3 hours. Since there was no pulmonary damage evident at these levels, it seems that death in rats probably occurred only from fluoride absorbed from the nasal passages which then causes systemic poisoning. Other animal studies using higher HF exposures and human accident reports nearly always show effects ranging from severe inflammation of the respiratory tree to pulmonary edema (e.g. effects consistent with acid damage to the tissue).

Finally, there is clearly a need for further and more comprehensive animal data with species other than rats. It is preferable that the species be higher up on the evolutionary scale than rats.

Inhalation toxicology studies are rarely carried out with primate monkeys since these are exceptionally difficult to obtain and are often prohibitively expensive. It is more common to use either beagle dogs or mini-swine as test models for the effects of substances on higher mammals.

There is much that remains to be studied regarding the inhalation toxicity of HF. Nasal scrubbing capacities, pulmonary or nasal flow resistance, and the interrelation between acidic burns and fluoride poisoning are all substantial variables that need to be investigated further to assess their impact on HF inhalation toxicity. Only when these parameters have been studied will more scientifically well-founded estimates be available for the human lethal concentrations of this gas.

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GLOSSARY

An LD_{50} (skin) value is that amount of a substance per unit body weight of an animal which will cause death in 50% of the test population when applied on a single occasion to the skin.

An LC_{50} value is that concentration of a substance in air which, when inhaled by test animals, will cause death in 50% of the test population after a specified exposure time. Unless otherwise stated, the quoted values for LC_{50} are for a 4 hour time exposure. Other variants of the LC parameter are the LC_{LO} (sometimes called LC_{min}), the lowest lethal concentration, LC_{10}, the lethal concentration for 10% of the population and LC_{100}, the lethal concentration for all the test animal population.

Conversion between mg/m^3 and ppm is effected by the formula:

$$ppm = \frac{mg/m^3 \times 24.45}{\text{molecular weight}}$$

where 24.45 is the volume in litres occupied by 1 gram molecule of a perfect gas or vapour at 25°C and 760 mmHg.

Fluorosis - chronic fluoride poisoning sometimes accompanied by mottling of the tooth enamel and bone hardening abnormalities (osteosclerosis).

TABLE 1 - PHYSICAL PROPERTIES OF HYDROGEN FLUORIDE

Property	Anhydrous Hydrogen Fluoride		Aqueous Hydrogen Fluoride
	Liquid	Gas	
Colour	Colourless	Colourless	Colourless
Odour	Pungent, irritating	Pungent, irritating	Pungent, irritating
Molecular weight (monomer)	20.01	20.01	20.01
	Note: Hydrogen fluoride is monomeric only at high temperatures and low partial pressures. At lower temperatures polymers, such as (HF)6, and probably (HF)2 are formed.		
Boiling point, 1 atmosphere	19.5°C	--	Varies with concentration
Melting point	-83.37°C	--	"
Specific gravity	1.0 (4°C)	1.27 (34°C, air = 1)	"
Vapour pressure,	42.19 g/sq cm	--	--
70 F (21°C)	4.1 kPa	--	--
100 F (38°C)	86.9 kPa	--	--
Constant boiling mixture (35.35%)	--	--	120°C
Specific volume 1 atm, 21°C	--	1204.8 ml/g	
Solubility in water	---- Miscible in all proportions----		

TABLE 2 - FLUORIDE ELIMINATION IN URINE IN RELATION TO THE INHALATION OF HF BY FIVE HUMAN SUBJECTS (FROM LARGENT 1960)

	Inhalation of HF			F- in urine
Subjects	No of days	Concentration mg/m^3	ppm	Average mg/l
A	15	1.16	1.42	4.49
A	10	2.70	3.30	7.30
B	25	2.12	2.59	9.47
B	16	2.00	2.44	10.58
C	30	2.22	2.71	7.76
C	16	2.44	2.98	7.77
D	25	3.88	4.73	15.88
D	15	3.76	4.59	17.86
E	50	3.45	4.21	9.62
E	20	3.87	4.72	12.10

TABLE 3 - RELATIONSHIP BETWEEN THE CONCENTRATION OF INHALED HYDROGEN FLUORIDE AND ITS EFFECTS ON ANIMALS

Reference	Exposure Concentration (mg/m^3)	(ppm)	Length of Exposure (hrs)	Animal	Effects
Ronzani (1909)	541	660	0.5 - 1	Guinea pigs (5)	Death
	205	250	0.5 - 1	"	"
	541	660	1.5 - 3	Rabbits (5)	"
	205	250	1.5 - 3	"	"
	40	49	2.0	Guinea pigs (5)	"
	40	49	3.0	Rabbits (5)	Physical distress
	25	30	24.0	Guinea pigs	Death
	8	10	120.0	"	Laboured breathing, eye irritation
	8	10	186.0 (6 hrs/day)	Rabbits (15)	Death (2), weight loss and anemia (13)
	8	10	"	Guinea pigs (21)	Death (7), weight loss and anemia (14)
	8	10	"	Doves (4)	Death (1), weight loss and anemia (3)
	2.5	3.0	"	Rabbits (16)	No pathologic changes
	2.5	3.0	"	Guinea pigs (20)	"
	2.5	3.0	"	Doves (3)	"

TABLE 3 - (CONTINUED)

Reference	Exposure Concentration (mg/m^3)	(ppm)	Length of Exposure (hrs)	Animal	Effects
Stokinger (1949)	7	9	180 (6-8 hrs/day)	Rats (15)	Subcutaneous haemorrhages in feet
	7	9	"	Dogs (5)	Haemorrhagic areas in lungs (1)
	25	31	"	Rats (29)	Death
	25	31	"	Mice (18)	"
	25	31	"	Dogs (4)	Degerative testicular changes (4), moderate haemorrhages and edema of lungs (3)
	25	31	"	"	Ulceration of the scrotum
	25	31	"	Rabbits (18)	Slight pulmonary haemorrhage
Rosenholtz et al (1963)	4057	4950	0.08	Rats (10)	Respiratory distress, conjunctival and nasal irritation (10), death (5)
	2197	2680	0.25	"	"
	1672	2040	0.50	"	"
	1074	1310	1.0	"	"
	3541	4320	0.25	Guinea pigs (10)	Death (5)
	14918	18200	0.08	Rats (10)	"
	5123	6250	0.08	Mice (15)	"

* This table is adapted from a similar table in the NIOSH Criteria Document for HF (NI 1976).

TABLE 3 - (CONTINUED)

Reference	Exposure Concentration (mg/m^3)	(ppm)	Length of Exposure (hrs)	Animal	Effects
Machle et et al	49	60	0.08-0.25	Rabbits (3)	Mild eye and respiratory irritation
	49	60	0.08-0.25	Guinea pigs (3)	"
	24	29	0.08-0.25	Rabbits (3)	"
	24	29	0.08-0.25	Guinea pigs (3)	"
	24	29	41.0	Rabbit (1)	Liver and kidney damage
	3000	3660	0.08-0.25	Rabbits (3)	Edema or cloudy swelling of organs and tissues
	3000	3660	0.08-0.25	Guinea pigs (3)	"
Machle and Kitzmiller (1935)	15.2	18.5	309 (6-8) hrs/day)	Rabbits (8)	Leucocytic infiltration of lung (5), fatty degeneration of liver (2), renal tubular degeneration and necrosis
	15.2	18.5	"	Monkey (1)	Renal tissue degeneration and inflammation
	15.2	18.5	"	Guinea pig (1)	Pulmonary haemorrhages alveolar exudates, atelectatic areas, liver degeneration
	15.2	18.5	160 (6-8 hrs/day)	Guinea pig (1)	Death
	15.2	18.5	134 (6-8	"	"

TABLE 4 - HYDROGEN FLUORIDE EXPOSURE - EFFECT DATA - EXPERIMENTAL HUMAN STUDIES

Reference	Exposure Concentration (mg/m^3)	Exposure Concentration (ppm)	Number Exposed	Route of Administration	Effects
Machle et al (1960)	98	120	2	Inhalation of HF for less than 1 minute	Smarting of exposed skin, marked conjunctival and respiratory irritation
	49	60	2	Inhalation of HF for unspecified time	Marked conjunctival and respiratory irritation
	26	32	2	Inhalation of HF for several minutes	Mild eye and nose irritation
Largent (1961)	2.12	2.59 (average)	1	Inhalation of HF 6 hrs/day, 5 days/ week for 15 days	Very slight irritation of eyes and nose, slight cutaneous erythema
	2.77	3.39 (average)	1	Inhalation of HF 6 hrs/day, 5 days/ week for 10 days	"
	2.22	2.72 (average)	1	Inhalation of HF 6 hrs/day, 5 days/ week for 30 days	"
	3.45	4.22 (average)	1	Inhalation of HF 6 hrs/day, 5 days/ weekfor 50 days	"
	3.45	4.75 (average)	1	Inhalation of HF 6 hrs/day, 5 days/ week for 25 days	"

TABLE 5 - HYDROGEN FLUORIDE EXPOSURE - EFFECT DATA - INDUSTRIAL EXPOSURE

Reference	Exposure Concentration mg/m^3 (ppm)	Number Exposed	Route of Administration	Effects
Mayer et al (1963)	8,200- 82,200 (10,000-100,000)	2	Dermal exposure to 70% HF acid on clothing in chest area, resulting in inhalation exposure	Death from pulmonary edema
NIOSH (1976)	2.4-6.0 (2.9-7.3)	46	Inhalation of gaseous and particulate fluorides	Slight blurring of bone structure
	"	4	"	Merging of trabeculae; diffuse stuctureless appearance of bone
	"	26	"	Marble-white opacity of bones of the pelvis, lumbar spine, and ribs; irregular vertebral bodies; calcification of pelvis ligaments; irregular periosteal bone formation. Marked restricted movements of the spine
	3.77 (4.12) (average)	17	"	Increase or questionable increase in bone density
	1.77-7.72 (2.17-9.43) (range)			
	0.40-0.73 (0.50-0.9)	-	Inhalation of HF by etchers and welders	Nosebleeds

TABLE 6 - HUMAN SENSITIVITY AND EXPOSURES TO HF

	Subject	Airborne levels	Effect
Largent 1960	Volunteers	up to 4.1 mg/m^3 (5 ppm)	Redness of the skin 2.8 mg/m^3 (3.39 ppm). Sour taste in mouth).
Deichmann and Gerarde 1969	NQ	41 mg/m^3 (50 ppm) for 30-60 minutes	May be fatal (No indication of origin of this figure)
Zober 1977	Occupational	104.1 mg/m^3 (128 ppm)	Concentration during shift. No acute response mentioned.
Machle et al 1934	Volunteers	up to 100 mg/m^3 (122 ppm)	Tolerated for only 1 minute. Stinging eyes, smarting of skin
Waldbott and Lee 1978	Occupational	41 to 164 mg/m^3 (50 to 200 ppm) (estimated) repeated for brief periods (minutes)	Chronic fluorosis in worker

NQ = Not Quoted

TABLE 7 - CONSEQUENCE OF URINE FLUORIDE LEVELS IN VARIOUS HF STUDY REPORTS

Authors	Atmospheric exposure	Urine level up to mgF-/l	Effect
Lauwerys 1975	NQ	4.0-5.0	'Normal' industrial levels that will not result in fluoride toxicity
Hodge and Smith 1977	NQ	9	Osteosclerosis development a definite possibility
Panchuek 1975	NQ	16.8	Symptoms of fluorosis in approximately 1/2 the workers
DA White 1980	NQ	18	Symptoms of fluorosis in approximately 1/2 the workers
Burke et al 1973	NQ	87	Total systemic F- load at least 404 mg. Patient barely survived

NQ = Not Quoted

TABLE 8 - HUMAN BLOOD SERUM FLUORIDE LEVELS QUOTED IN VARIOUS HF ACCIDENT AUTOPSY REPORTS

	Cases	Blood serum level	Exposure levels
Greendyke and Hodge 1963	A	0.4 mg/100ml	NQ
	B	0.3 mg/100ml	NQ
Gettler and Ellerbrook 1939	A	0.35 mg/100ml	NQ
	B	0.42 mg/100ml	NQ
	C	0.155 mg/100ml	NQ

NQ = Not Quoted

TABLE 9 - THE DERIVATION OF POSSIBLE HUMAN LETHAL HF CONCENTRATION VALUES USING INTERSPECIES ADJUSTMENT FACTORS BASED ON THE DATA OF DOURSON AND STARA (Do 1983)

Parameter	Species	Source	Test value obtained		Interspecies adjustment factor	Projected human values	
			mg/m^3	ppm		mg/m^3	ppm
LC_{LO} (5 min)	Rat	Di 1971	75400	92000	6	12600	15300
	Mouse	Di 1971	14800	18000	12.5	1180	1440
(420 min)	Rat	Tr 1950	260	317	6	43	53
LC_{10} (5 min)	Rat*	Di 1971	10800	13200	6	1800	2200
	Mouse	Di 1971	3440	4200	12.5	275	336
LC_{50} (5 min)	Rat*	Di 1971	14900	18200	6	2486	3033
	Rat	Ro 1963	4070	4970	6	679	828
	Mouse	Di 1971	5120	6250	12.5	410	500
LC_{50} (15 min)	Rat	Ro 1963	2210	2690	6	368	448
	GP	Ro 1963	3550	4330	4.3	825	1000
(30 min)	Rat	Ro 1963	1670	2040	6	278	340
(60 min)	Monkey	AM 1971	1450	1770	3.0	483	590
	Rat	Ro 1963	1070	1310	6	179	218
	Rat	Wo 1976	1150	1400	6	191	233
	Mouse	Wo 1976	280	342	12.5	22	27

* These values for the rat were disregarded in subsequent extrapolation to human - see text.

TABLE 10 - ESTIMATED RANGES FOR HUMAN LC VALUES

Parameter		Concentration Range		Remarks
		mg/m^3	ppm	
LC_{LO}	5 min	41-205	50-250	Estimated from accidental occupational and volunteer exposures
LC_{10}	5 min	275	336	Mouse study only
LC_{50}	5 min	410-679	500-828	One rat study disregarded
LC_{50}	15 min	368-825	448-1007	One rat study disregarded
LC_{50}	30 min	278	340	
LC_{50}	60 min	22-483	27-590	

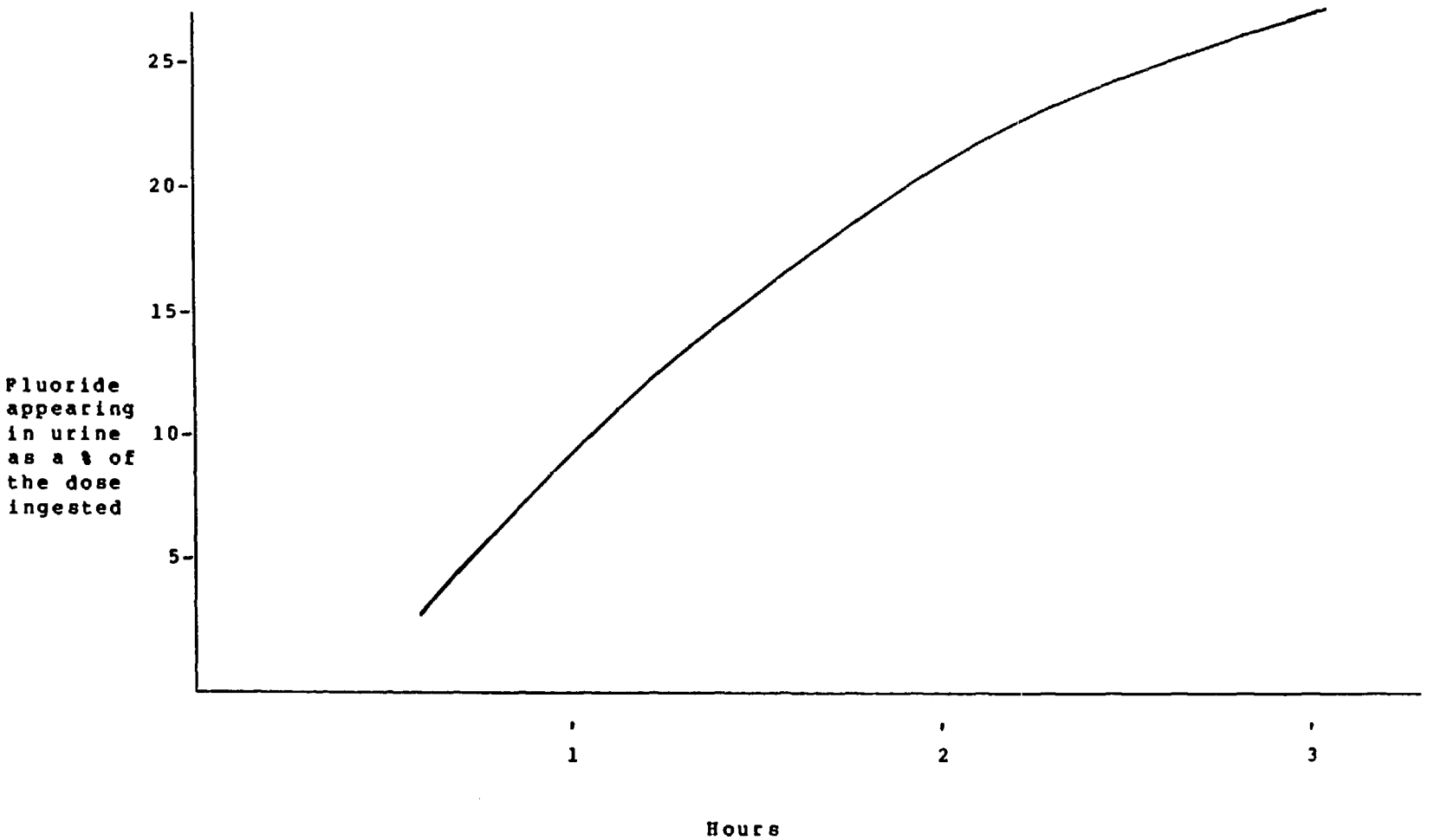


Figure 1 - Urinary excretion of ingested fluoride by six men. Exact points are not shown but the curve represents the best fit of the data. Hodge H.C. Journal of American Dental Association. Vol. 52 (1965), p. 307-313

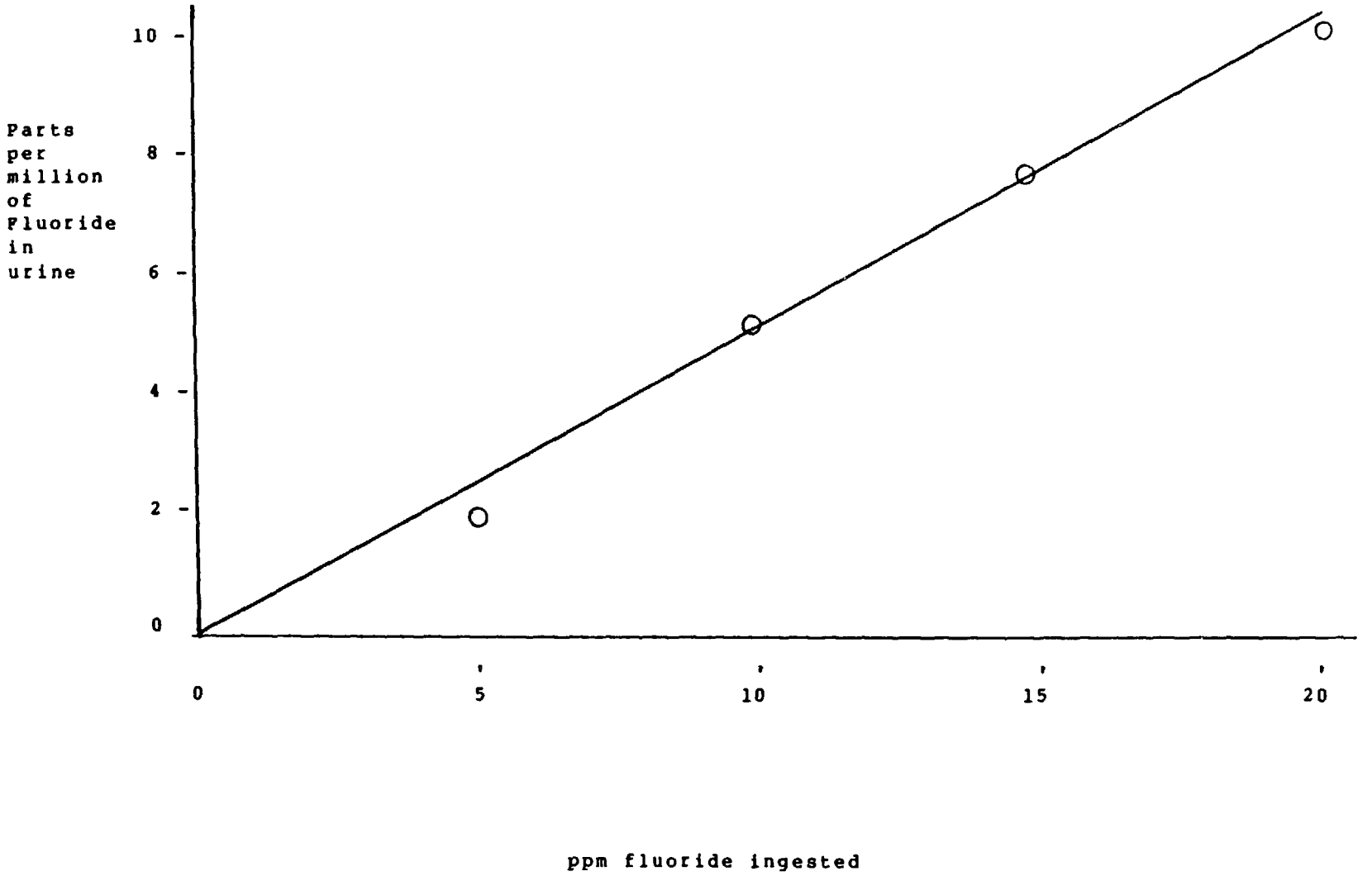


Figure 2 - Relationship between absorption and urinary excretion of fluoride in man (from Machle and Largent 1943. Journal of Industrial Hygiene Toxicology. Vol. 22, p, 112-123)

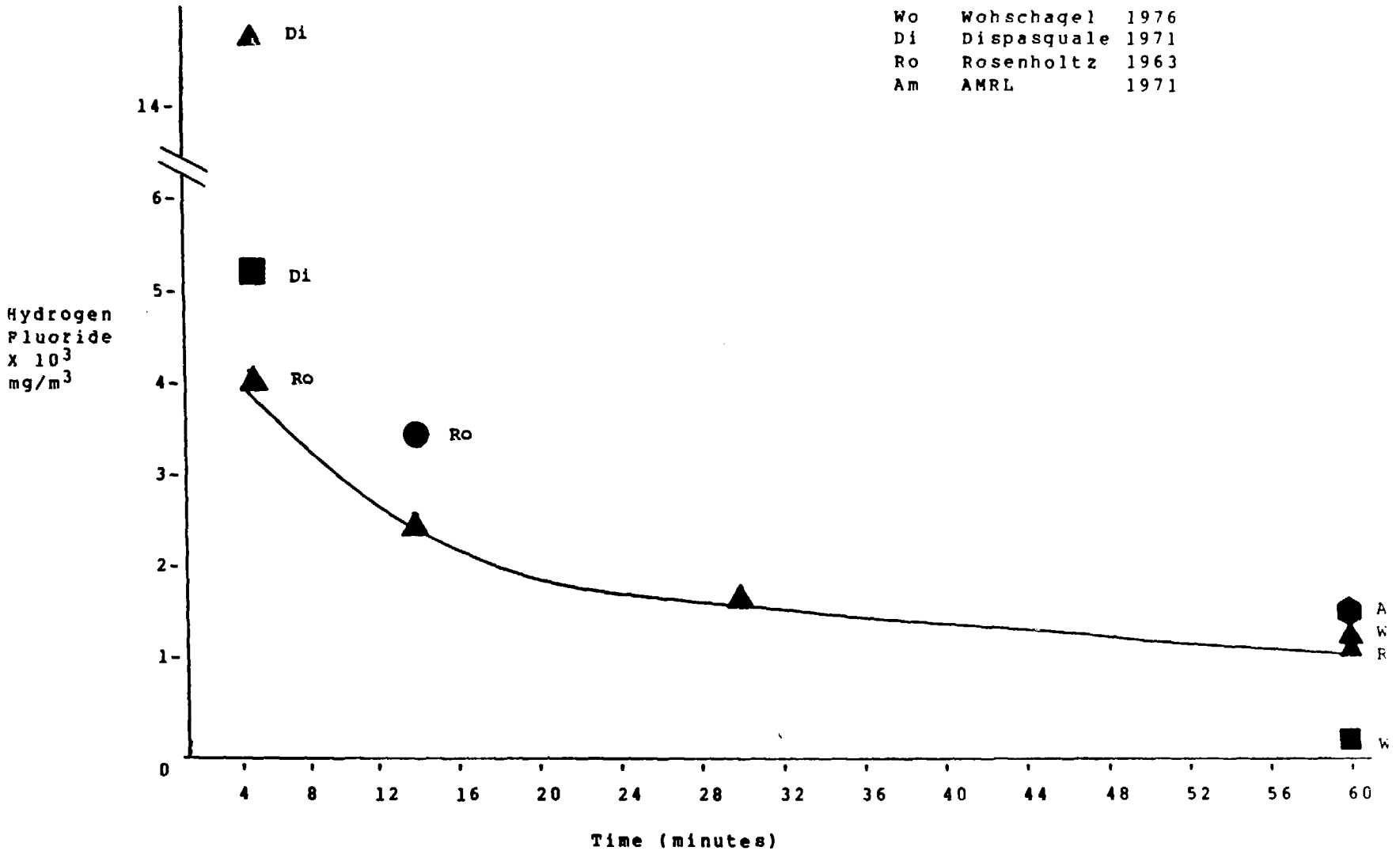
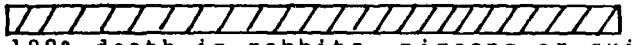


Figure 3. - LC_{50} Hydrogen fluoride levels for rats ▲, guinea pigs ●, mice ■, and monkey ⬢

Figure 4 - HYDROGEN FLUORIDE LETHALITY DATA NOT PRESENTED AS LC_{50} OR LD_{50}

Authors	Exposure Time stated	Concentration Hydrogen Fluoride X 10^3 ppm (0 1 2 3 4 5 6 7)
Ronzani 1909	30 to 90 min	 (4920 mg/m^3) 100% death in rabbits, pigeons or guinea pigs
Ronzani 1909	60 min to 3 days	 (2050 mg/m^3) 100% death in rabbits, pigeons or guinea pigs
Machle et al 1934	All exposure time periods tested	 (1500 mg/m^3) Significant deaths in rabbits and guinea pigs
Machle et al 1934	30 min	 (1000 mg/m^3) No deaths but some lung haemorrhage in rabbits and guinea pigs
Morris & Smith 1982	3 hours	 (156 mg/m^3) 100% death in rats within 3 hours of exposure but no lung edema or injury
Machle et al 1934	5 hours	(100 mg/m^3) Tolerated by rabbits and guinea pigs without injury sufficient to cause death
Ronzani 1909	6-29 days	 (82 mg/m^3) Some deaths in rabbits, pigeons or guinea pigs
Machle 1934	41 hours	(24 mg/m^3) No deaths
Ronzani 1909	28 days	(25 mg/m^3) No deaths
Stokinger 1949	166 hours over 29 days	(25 mg/m^3) 100% mortality in rats and mice but not guinea pigs, rabbits or dogs

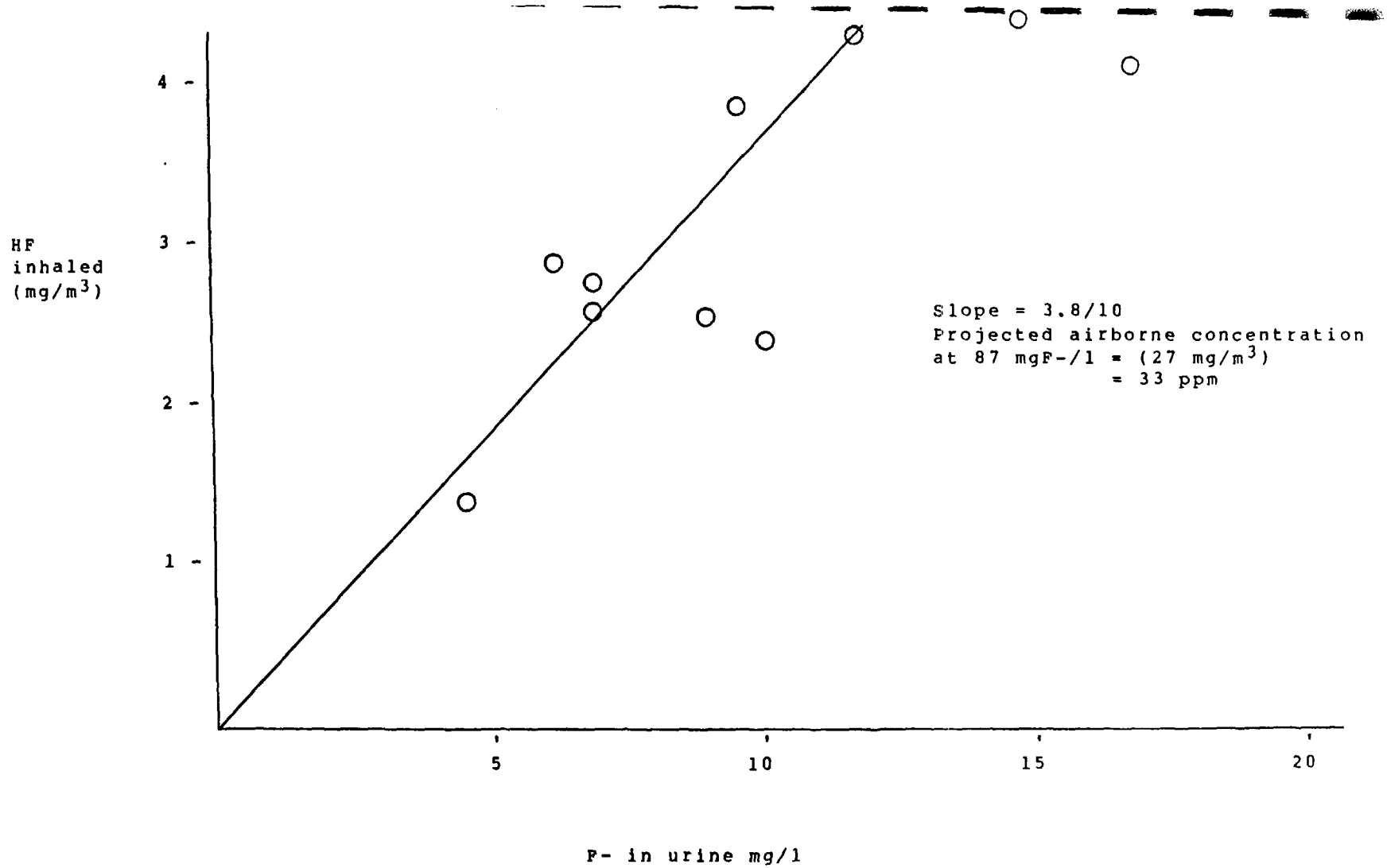


Figure 5 - Plot of Largents (1960) data (Table 2) to obtain possible atmospheric exposure for patient of Burke et al (1973)

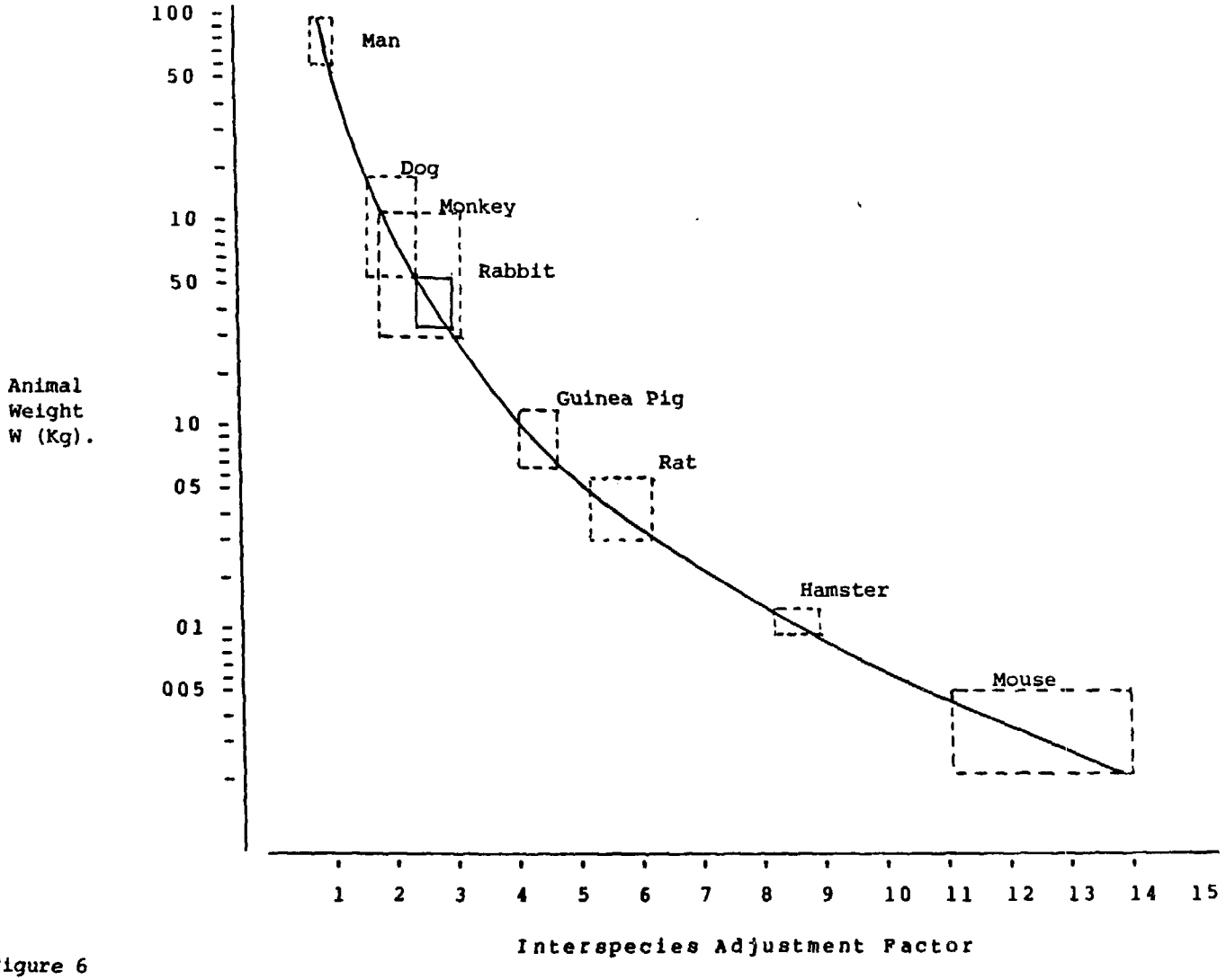


Figure 6

Experimental animal weight (w) vs an interspecies adjustment factor calculated as the cubed root of the ratio between the assumed average human body weight (70kg) and w. Enclosed areas along the function represent general ranges of average body weights of experimental adult animals. Rabbit values are represented by the box with solid lines. (Do 1983)

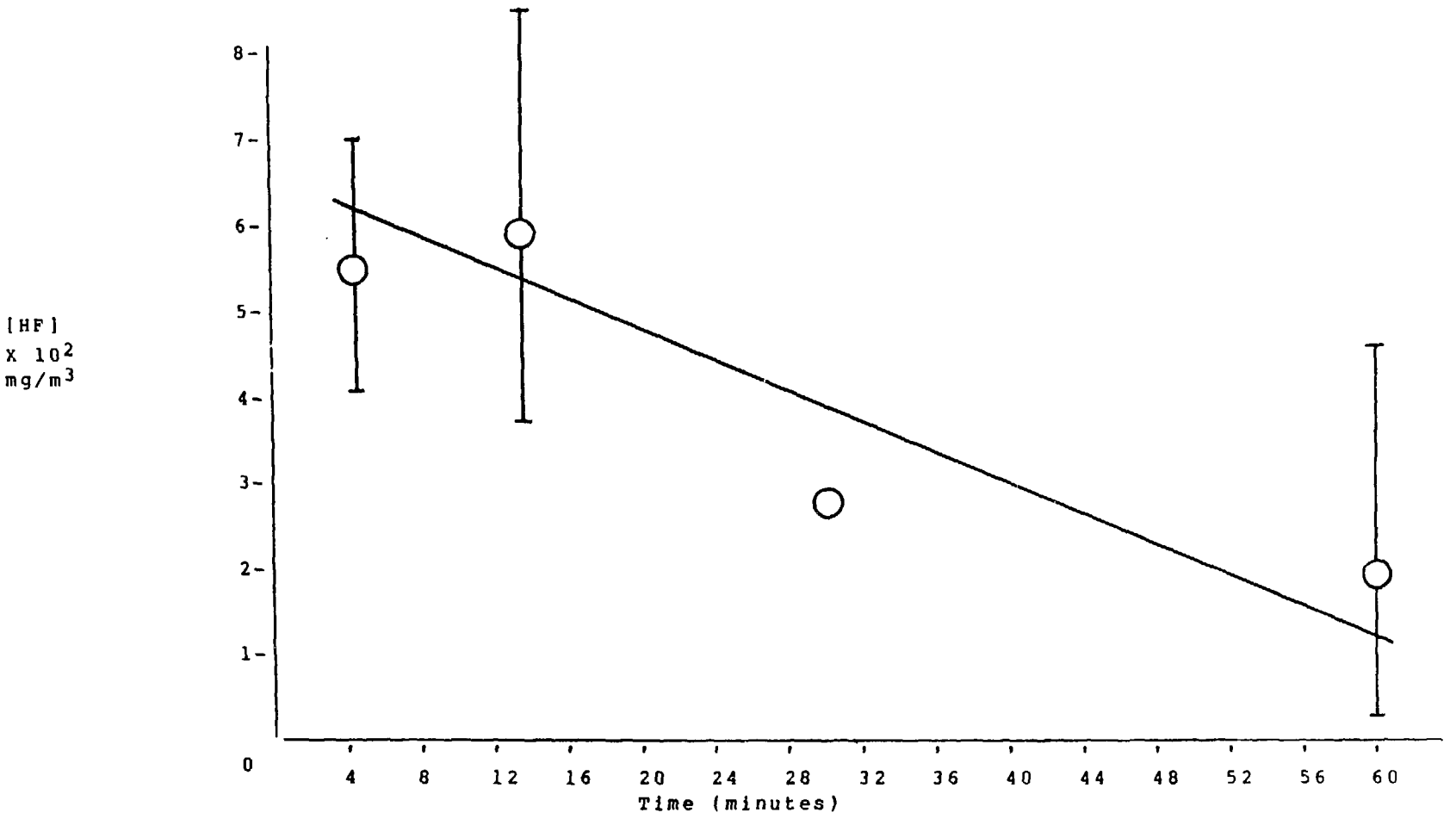


Figure 7 - Estimated HF LC_{50} values for humans over a period of 1 hour. Points plotted are the average of animal extrapolation values. Ranges of the values are shown.

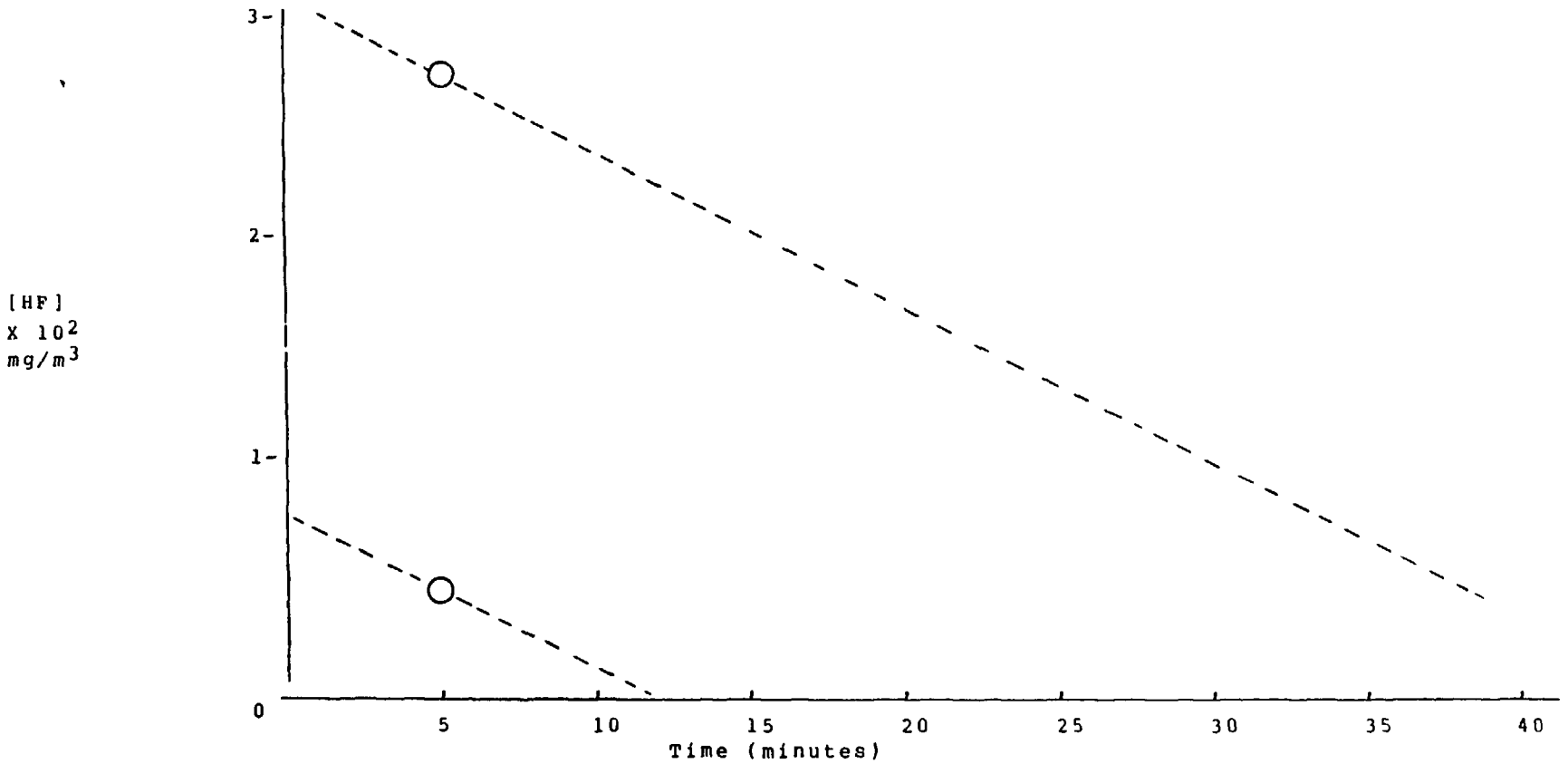


Figure 8 - A hypothetical estimation of HF LC_{LO} and LC_{10} values for humans over a period of 1 hour. Only a single point was available for each parameter. Lines are drawn on the assumption that the slopes are the same as that obtained for the LC_{50} curve (Figure 7).