REPORT

RAPPORT

No 10

Atomic Energy Control Board

Commission de contrôle de l'énergie atomique

Canada

INFO-0583

REPORT

Toxicity Levels to Humans during Acute Exposure to Hydrogen Fluoride — An Update

by

David M. Halton

Prepared for
the Atomic Energy Control Board
under its Regulatory Research
and Support Program
Ottawa, Canada

AECB Project No. 4.142.1

September 1995

Atomic Energy Control Board
Commission de contrôle de l'énergie atomique

Canada

TOXICITY LEVELS TO HUMANS DURING ACUTE EXPOSURE TO HYDROGEN FLUORIDE — AN UPDATE

A report prepared by David M. Halton under contract to the Atomic Energy Control Board.

ABSTRACT

In March 1993, the Atomic Energy Control Board (AECB) commissioned and update of a 1984 review on the acute toxicity of hydrogen fluoride (HF). The study places particular emphasis on the effects of inhalation of gaseous HF and is divided into two main parts: a literature review and a lethal concentration (LC) estimation.

The literature review summarizes data under four categories: animal studies, controlled human studies, community exposure, and industrial exposure. Data in these areas were critically reviewed for their relevance to lethal concentrations at LC_{LO}, LC_{10} and LC_{50} levels that were derived in the 1984 report.

In the last ten years, only one relevant animal study has been published. No new controlled human studies were found but a community exposure incident was reported. There were three new industrial/accidental exposures reported since 1984.

Evaluation of new data does not change the lethal concentration estimates made in the 1984 report, but does indicate the absence of appropriate models to estimate the lethality of irritant and corrosive gasses.

In the last 10 years, much literature on the evaluation of major hazards has been published and suggests that such assessments are of growing political, economic and social importance. Numerous articles have been published on the acute toxicity of HF from skin contact and chronic toxicity from repeated airborne exposure. These publications offer important insights into the nature of HF toxicity. Several avenues of investigative research are suggested.

RÉSUMÉ

En mars 1993, la Commission de contrôle de l'énergie atomique (CCEA) a commandé la mise à jour de l'étude de 1984 sur la toxicité aiguë du fluorure d'hydrogène. L'étude, qui met un accent particulier sur les effets de l'inhalation de fluorure d'hydrogène gazeux, comprend deux grandes parties : un examen de la documentation et une estimation de la concentration létale (CL).

L'examen de la documentation permet de classer les données dans quatre catégories : les études sur des animaux, les études contrôlées sur des humains, l'exposition du public et l'exposition dans l'industrie. Les données concernant ces secteurs ont été examinés avec un oeil critique afin de relever toute pertinence avec les concentrations létales CL_{min}, CL_{10} et CL_{50} indiquées dans le rapport de 1984.

Au cours des dix dernières années, un seul rapport pertinent d'études sur des animaux a été publié. L'examen n'a pas permis de trouver de nouvelles études contrôlées sur des humains, mais indique un cas d'exposition du public. Depuis 1984, il y a eu trois nouveaux cas d'exposition accidentelle dans l'industrie.

L'évaluation des nouvelles données ne modifie pas les estimations de concentration létale mentionnées dans le rapport de 1984, mais fait ressortir l'absence de modèle approprié pour estimer le risque de mortalité dû à des gaz irritants et corrosifs.

L'abondante documentation publiée au cours des dix dernières années sur l'évaluation des principaux risques suggère que de telles évaluations prennent de plus en plus d'importance aux plans politique, économique et social. De nombreux articles font état de la toxicité aiguë du fluorure d'hydrogène lors de contacts cutanés et de la toxicité chronique attribuable à une exposition répétée à la contamination atmosphérique. Ces publications jettent un éclairage important sur la nature de la toxicité du fluorure d'hydrogène. Le rapport propose, en outre, plusieurs nouvelles approches de recherche.

TABLE OF CONTENTS

1.0 INTRODUCTION

As HF is used in bulk at one of the uranium conversion facilities in Canada, there exists a chemical risk to the worker,the public and the environment in the vicinity of that facility.

In March 1993 the Atomic Energy Control Board (AECB) requested an update of an earlier study on the toxicity of hydrogen fluoride (HF) by David M. Halton, published as INFO 0143 (HA 1984). This request is directly related to the AECB's responsibility for regulating the nuclear fuel cycle facilities in Canada, including considerations of health and safety because HF is used in the conversion of uranium, from uranium dioxide (UO_2) to uranium hexafluoride (UF_6).

The following report documents the study which was subsequently conducted by David M. Halton and Associates under contract to the AECB. In each subsection of this report information collected in 1984 is summarized so that new data can be placed in context.

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

1.1 Scope of the Present Study

The primary objective of this study was to update the Info 0143 Report which derived dose response relationships for lethality for human exposure to HF gas.

The scope of the study included an up-to-date review of the literature, use of standard reference works on toxicology, and several computerized data bases, specifically:

- NIOSH (data base of the U. S. National Institute of Occupational Safety and Health)
- RTECS (Registry of Toxic Effects of Chemical Substances),
- HSDB (Hazardous Substances Data Bank of the U.S. National Library of Medicine)
- Toxline

The above databases were used to obtain data for a previous report (HA 1984) Two additional data bases from Europe were searched for this update review namely:

- CIS data base of the International Labour Office in Geneva
- HSE data base of the Health and Safety Executive in the U.K.

The search produced approximately 80 references. These were screened and reduced to about 40 considered to be directly relevant to this study. Some references missed from the 1984 study were also located as well as two overviews published about the same time as Info 0143.

1.2 Chemical and Physical Properties

At ordinary pressures and temperatures lower than 19°C HF is a corrosive, fuming liquid known as hydrofluoric acid. At higher temperatures it is a colourless gas with a sharp irritating odour (AM 1983). HF exists as a monomer at high temperatures and low partial pressures. However it shows complex oligomerization in the vapour phase. This behaviour has been studied but there is controversy about the number and type of oligomeric forms. (RU 1954). There is general agreement that association up to the hexamer and possibly octamer form can occur (SC 1987, MA 1962). An extensive list of information on the properties of HF is given in Table 1. (See Appendix)

1.3 Principle Uses

Despite concerns about the environmental impact of certain fluorocarbon propellants and compounds, it appears that almost 40% of all hydrogen fluoride is used in the production of such materials. A further 30% is used in the production of aluminum, 5% as a gasoline alkylation catalyst, 3% in stainless steel pickling, and the remainder in a variety of applications such as uranium production, the manufacture of fluorine salts, etching of glass and semiconductors and incorporation into commercial cleaning agents.

1.4 Acute Effects of Hydrogen Fluoride

In the last 10 years no new symptoms have been observed in over-exposure to HF gas. The gas is infinitely soluble in water and dissolves in the mucus membranes of the upper respiratory tract producing the following symptoms:

- pulmonary oedema (swelling caused by escape of body fluid into the air sacs and tissues of the lung)
- plural effusion (fluid filling the membranous sac covering the lungs and lining of the chest)
- hyperaemic action (excess blood flow to an area causing inflammation and congestion)

Since 1984 the issue of the impact of skin contact with HF and consequent systemic toxicity has received more prominence.

2.0 ACUTE TOXICITY

2.1 Routes of Exposure and Metabolism

2.1.1 Exposure

A review by the National Institute of Occupational Safety and Health (NI 1976) estimated that in the United States 300,000 workers were potentially exposed to hydrogen fluoride. The American Conference of Government Industrial Hygienists recommends threshold limit values (TLVs) of 2.5 mg/m^3 (3 ppm). This is considered to be a ceiling value not to be exceeded at any time (AC 1993).

For inhalation exposure liquid hydrofluoric acid poses a risk in solutions more than 50% HF at 19.5°C. The partial pressure under these conditions is only 1.86 kPa (14 mmHg). A 70% solution has a partial pressure of 20.0 kPa (150 mmHg).

2.1.2 Transport

Regardless of the route of entry, fluoride ion is absorbed into the blood stream and carried to the organs. About 75% of blood fluoride is present in the plasma and the rest is mainly in or on the red blood cells (CA 1960; HO 1977). The levels of total plasma fluoride reported in literature before 1965 differed by several orders of magnitude from those reported more recently. Differences in analytical methodology may explain these discrepancies. It is now considered that fluoride in human serum exists in both ionic and non-ionic form (TA 1968a; TA 1968b; MO 1983). The non-ionic form has been isolated and is associated with perfluoro-fatty acid derivatives containing six to eight carbon atoms (TA 1968c). Average blood plasma serum levels from several studies are shown in Table 2. (See Appendix)

2.1.3 Enzyme Inhibition

Fluoride is a wide spectrum enzyme inhibitor even in relatively low concentrations. More extensive searching on the topic of enzyme interaction with fluoride reveals that it can have both an activating and an inhibiting effect on different enzyme systems. For example, fluoride is an activator for the enzyme adenyl cyclase (EC4.6.1.1.). Similarly the enzyme alkaline phosphatase (EC3.1.3.1.) activity is also

increased (FA 1983). The biomolecular rationale behind these activity changes is unclear.

Inhibition of enzyme activity seems to be the more common effect of fluoride ion. Inhibition may be caused by indirect complexing with metal cofactors (TA 1970) or it may act directly on the enzyme probably by substituting for hydroxyl groupings (-OH) which are approximately the same molecular size as fluoride ion.

Fluoride ion is a general inhibitor of the energy production system "oxidative phosphorylation".

2.1.4 Distribution

No new data regarding the distribution of inorganic fluoride in the body was found. No soft tissue stores fluoride. The kidney shows temporary retention during excretion but most of the retained fluoride is associated with bone.

2.1.5 Skeletal Deposition

Fluoride is a bone seeker. About half of a dose of fluoride given to an animal will be deposited in the skeleton. A report by the World Health Organization (WO 1984) notes that about 99% of all retained fluoride is found in the skeleton while the rest is in blood and other tissues.

Studies indicated that fluoride deposition in bone occurs through a simple exchange reaction with hydroxyl ions, and subsequent incorporation into the apatite lattice during bone mineralization. The amount of fluoride in bone depends on age, sex, and the extent of exposure.

Fluoride is not deposited permanently in the skeleton but is metabolized slowly with a half life of over two years.

2.1.6 Excretion

Approximately half of all absorbed fluoride is excreted in the urine which is the major route of fluoride removal from the body (WO 1984).

Urine excretion of fluoride is fast and more than 20% of a dose appears in the urine within the first four hours. The amount of fluoride excreted in urine seems to be a reasonably accurate indicator of fluoride exposure (ZO 1977). A recent report indicates that fluoride excretion through hair and nails can also be used as measures of fluoride exposure (CZ 1990).

Renal fluoride excretion involves glomerular filtration followed by pH dependent tubular reabsorption. Reabsorption occurs by non-ionic diffusion of HF and is therefore greater in acidic urine than in alkaline urine (i.e., fluoride removal from the body is greater in alkalosis than acidosis) (SM 1986). It has been noticed that

urine excretion of fluoride is decreased in cases of renal failure or dysfunction and retention in the bone increases accordingly (KO 1984).

Fecal excretion of fluoride depends on the solubility of the fluoride consumed. Small amounts of fluoride can be excreted in perspiration.

3.0 ANIMAL STUDIES

Inhalation studies involving animals exposed to HF have used rats, mice, guinea pigs, pigeons, rabbits, dogs and monkeys. The predominant lesions found in animal studies include:

- pulmonary haemorrhage, congestion, emphysema, and oedema with secondary infection
- hepatic congestion with evidence of cell necrosis and fatty degeneration
- splenic congestion and oedema
- myocardial congestion, oedema and necrosis
- corneal erosion and ulceration of the nasal turbanates

The primary toxic effect of HF is on the respiratory system with tissue changes also observed in the kidneys and liver. Rats appear to have a protective scrubbing activity in the upper respiratory tract and damage is often confined to the anterior nasal passages. Other animals and humans do not have the same effectiveness in HF scrubbing.

A detailed account of animal studies and the results from them have been reviewed elsewhere (HA 1984). At that time only five animal LC_{50} studies existed (Table 3). Since then only one study has examined the acute toxicity of HF on animals (ST 1991) but it did not measure LC_{50}. Instead, the authors investigated the difference between nose breathing and mouth breathing rats in three groups inhaling hydrogen fluoride, hydrogen bromide, or hydrogen chloride. Mouth breathing rats were simulated by inserting tracheal tubes connected to mouth pieces. In each of the three groups rats were exposed to 1300 ppm of HF, HBr, or HCl for 30 minutes. Each of the three groups was divided into nose breathers and mouth breathers. Twenty-four hours after the exposure all animals were killed and histopathologic analysis of their upper and lower respiratory tracts was carried out.

For all three gases, nose breathing groups had tissue injury confined to the nasal region. Damage consisted of epithelial and submucosal necrosis, inflammation of the tissue, exudation and bleeding. No lung or tracheal pathologic evidence was obtained to indicate that HF injury occurred more distally. Moreover the authors indicated that nasal injury was restricted to the more anterior regions of the nasal passages. Thus, even the more posteriorly located olfactory epithelial cells, a cell type reported to be especially sensitive to chemical injury, were spared from the injurious effects of HF. In contrast the mouth breathing rats showed higher post-exposure mortalities with major tissue disruption in the trachea and larger airways of the lungs.

The authors conclude that the injurious response to hydrogen fluoride and other corrosive gases differs markedly according to the route by which they are inhaled; the mouth breathing route has the more life threatening effects. The authors did not look specifically at lethal concentrations of inhaled hydrogen fluoride nor did they report on the number of mortalities within each group.

4.0 COMMUNITY EXPOSURES

4.1 Reported Incidents

No documented cases of community exposure to air-borne HF was found in a previous literature review (HA 1984). However, in the current review a report documenting a release of HF into a community was located. Approximately 3,000 people were evacuated from a Texas community when 24,000 kg of hydrofluoric acid were released from a nearby petrochemical plant. The authors reviewed the emergency room and hospital records of 939 persons who were seen in two area hospitals. The most frequently reported symptoms were eye irritation (40%), burning throat (21%), headache (20%) and shortness of breath (19%). Physical examination of patients revealed normal results for 49% of cases. However, irritation of the eyes, nose, throat, skin and lungs were noted in other examinations.

Ninety-four (10%) of the cases were hospitalized. The authors noted they were unable to find any other reports describing a community exposure to HF. They point out that their report is a unique opportunity to study the immediate health impact

on a community of residents and suggest that initial health problems should be followed up to determine any long term health effects of HF exposure.

The community exposure incident occurred when HF was accidently released from a petrochemical plant located in the southeastern areas of the community. The plant is 0.4 kilometres from residential areas. Most of the HF was ventilated during the first two hours of release into a low-lying plume across the city in a southeast to northwest direction. Samples taken downwind one hour after release contained 10 ppm HF. Minimum traces of HF were found in samples taken two hours after the release. The following day vegetation and exterior surfaces located within 3.2 kilometres northwest of the plant were damaged; foliage was brown, car windows were etched and car paint was streaked.

Symptoms reported most frequently among all cases were eye irritation, throat burning, headache, shortness of breath and throat soreness. Hospitalized cases tended to report more headache, shortness of breath, cough, nausea, vomiting, dizziness and skin burning than did the non-hospitalized cases. In subsequent testing of hospitalized cases 16.3% were mildly hypocalcemic. There was apparently very limited information available from the hospitals on the urine fluoride levels. Only one level was reported and was not considered to be elevated.

The authors report no serious morbidity or death from the community exposure.

4.2 Toxicity Assessments for Major Hazard Locations

Of particular interest during this literature review were the number of publications from Europe describing new techniques, methods and strategies for classifying industrial operations located in, or planned to be located in, residential communities (TU 1989; WI 1986). There also seemed to be considerable data on risk assessments applied during the evaluation of plants designated as potential major hazards.

This type of work appears to originate from two locations namely the Health and Safety Executive in the U.K. and the TNO (Toegepast Natuurwetenschappelijk Onderzoek) Institute in Holland. Such work represents major governmental initiatives to support proactive approaches to hazard recognition in residential communities.

Government support for such initiatives has come in the wake of wide spread injuries and death "off site" caused by catastrophic fires, explosions, or the release of toxic chemicals. Recent examples include the toxic gas release at Bophal, the Liquid Petroleum Gas (LPG) devastation in Mexico City, the incident at Chernobyl, and the explosion which occurred at Flixborough.

In the U.K. the plant hazard problem has been highlighted in various government reports since the late 1960s and since then special controls have been developed. Legislation in various European countries was enacted following the release at Seveso in Northern Italy in 1976 and directives concerning a major industrial hazards are now a part of the European Economic Community (EEC) planning.

From the scientific and technical viewpoint many of the concepts used in Europe to assess community risk and exposure may not be widely known in North America. Canada has taken initiatives in recent years through the formation of the Major Industrial Accidents Council of Canada (MIACC). The council currently has a number of working groups studying aspects such as:

- risk assessment
- qualification and training for emergency responders
- joint municipal and industry emergency preparedness
- accident trend analysis
- buffer zones and land use planning guidelines
- coordination of chemical information systems
- emergency planning for industry
- life cycle management of hazardous substances
- chemical process safety
- legislation
- safety audits
- social and psychological impacts of major industrial accidents

At present no comprehensive overview of scientific assessments and approaches used in the EEC as well as the progress made by MIACC exists.

5.0 INDUSTRIAL AND ACCIDENTAL EXPOSURES

An earlier report (HA 1984) documented several accidental industrial exposures to hydrogen fluoride. These previous reports had inadequate post-mortem data and were equivocal in determining if most deaths were related to fluoride toxicity or corrosive action. In the last 10 years three more reports of death or intoxication due to inhalation of HF were published. These new reports have particularly useful post-mortem findings. Several cases are described by Braun, et al (BR 1984). In one case, after repair work on a pump in a hydrofluoric acid production section, mixed acid (70-80% sulphuric acid and about 10% hydrofluoric) at about 150°C explosively escaped from a leaking flange. Four workers were splashed with the mixed acid and surrounded by fumes. Since the repair work was already finished the workers had taken off their protective clothing and masks. One worker was hit only by a few drops and was able to get out of the way. He was treated for minor acid burns and did not require admission. Another worker died within a few hours of the accident. The hospital report indicates his death was completely unexpected. No post mortem was carried out. The two remaining workers were admitted to hospital. On admission the first worker had superficial burns all over his face, neck and eyes. His throat and upper respiratory tract were also burned by inhalation of the fumes. There were severe acid burns on his lower legs approximating to 8% of his body surface.

Despite aggressive treatment, over the next two weeks the patient deteriorated steadily showing first indications of kidney failure and eventually diffuse haemorraghe of the bronchial tree. Because of increasing respiratory insufficiency death occurred about 4 weeks after the accident.

The second worker admitted to hospital was not splashed with the acid but only inhaled the fumes for a short period. On admission he presented only with a patchy flush on his face, neck, throat and extensor sides of both of his legs. Again treatment of the patient was aggressive. This time the patient survived but even one year after the accident still complained of hoarseness, a recurrent fits of coughing, pain in the naso-pharynx and nose bleeds. Examination revealed fibrous granulating deposits on his vocal chords.

From the post mortem study the authors concluded death was not due to metabolic fluoride poisoning but to consequences of severe acid burns in the respiratory tract after inhaling the mixed acid. This is a key point and very pertinent to the toxicity derivations made in a previous report (HA 84).

A second report by Watson et al (WA 1973) describes the case of a 28 year old male employed in a manufacturing plant using hydrofluoric acid for a glass dissolving process. An explosive fault developed in the apparatus causing the man to be extensively splashed by the acid on the face and in the mouth. Other areas less affected included the head, neck, upper part of the chest, upper arms, forearms and

the feet. Burns in the form of intense skin reddening and large blister formations appeared within a few minutes.

At the time of the accident he had no protective clothing. First aid treatment was speedy but limited to the application of sodium bicarbonate to the burns. The victim rapidly showed signs of shock and marked respiratory distress. He became unconscious and died within 30 minutes.

Post mortem revealed deep skin burns, opacities of the cornea, and intense swelling and congestion in the mucosa of the mouth, larynx and pharynx. The epiglottis was ulcerated. Both lungs were heavy, deeply congested and oedematous. Blood level fluoride was 0.5 mg/100 ml. Again the condition of the respiratory tract and lungs suggested death from the corrosive action of the acid rather than fluoride poisoning.

While not related to industrial exposure a further case of death due to hydrofluoric acid is reported by Chela et al (CH 1989). In this instance the victim was a young woman who was attacked in the street by a person who threw liquid from a container into her face. She reached the casualty department of a hospital where she was noted to have severe chemical burns to the face, lips, nose, right eye, anterior side of the thorax and both arms. Despite emergency treatment the patient's breathing deteriorated and she died from acute respiratory insufficiency three hours after the attack. Post-mortem examination revealed severe chemical burns to the external body surfaces as well as burns of the larynx, trachea and bronchial tree. There was

considerable congestion and intense haemorrhagic oedema in both lungs. Death was attributed to anoxia due to acute respiratory insufficiency caused by severe pulmonary lesions. The report did not record levels of fluoride in body tissues or fluids.

There are numerous reports in the literature of splash exposures to hydrogen fluoride and subsequent treatment of hydrogen fluoride skin burns. These reports are outside the scope of this study but would provide useful documentation and understanding of the mechanism of HF toxicity. In particular a substantial controversy has arisen over the effectiveness of topical treatments for hydrofluoric acid burns (BR 1985). HF burns cannot be treated as ordinary acid burns. Rapid and effective treatment is critical to alleviate excruciating pain and halt potentially lethal systemic toxicity.

6.0 ANTAGONISTIC OR SYNERGISTIC EFFECTS

An earlier report (HA 1984) noted there were no indications of exposures to substances that either antagonize or exaggerate the toxic effects of hydrogen fluoride. No data on this aspect has been published in the last ten years.

7.0 DATA EVALUATION TO DERIVE HUMAN LETHAL CONCENTRATIONS

In the previous report by Halton et al. (HA 1984), three approaches were used for estimating human lethal concentration values for HF. They were as follows:

7.1 Approach No. 1: Estimates by Other Authors

Estimates by other authors for LC_{50} values for hydrogen fluoride in humans are experimentally unsubstantiated (GR 1964; HE 1943; ZO 1977; MA 1934; WA 1978). These various reports tend to support the projection of 41-205 mg/m^3 (50-250 ppm) of hydrogen fluoride as lethal in humans after a 30 to 60 minute exposure. However this level probably corresponds to a lower lethal dose range, LC_{LO}, rather than an LC_{50}. This literature review located three other estimates of lethality ranging from 13.3 mg/m^3 (16.2 ppm) for 10 minute exposure time up to 105,000 mg/m^3 (128,100 ppm) for a 0.5 minute exposure time. Details are given in Table 4. The three additional estimates are given in an article by Just (JU 1984).

The report by Just 1984 was commissioned by the U.S. Department of Energy in an attempt to provide information on the toxicological effect of uranium hexafluoride (UF_6) should it be accidentally released. UF_6 is considered to form uranyl fluoride ($U0_2F_2$) and hydrogen fluoride (HF) when combined with atmospheric moisture. One of the consultants working on the report was a Dr. M. E. Wrenn from the Radiobiology Division, School of Medicine, University of Utah: Dr. Wrenn was asked to produce an estimate of human lethal concentration and submitted figures ranging from 105,000 ppm for 0.5 minutes to 877 ppm for 60 minutes. Unfortunately the work of Dr. Wrenn is not referenced in the work of Just. Neither does the author detail how Wrenn arrived at his derivations. Wrenn's lethality estimates for hydrogen fluoride are shown in Table 4 and based on an estimate that 53,000 mg/m^3 (64,660 ppm) would be lethal for exposure times of between 0.5 and 60 minutes. No rationale

is given for the estimate. These figures are considerably out of line with other estimates of acute lethality levels and should be viewed with some caution, particularly since details of the derivation are not available.

It is interesting to note that the U.S. National Research Council has given a lethal concentration estimate of 13.3 mg/m^3 (16.2 ppm) for 10 minutes and NIOSH/OSHA indicate 13.3 mg/m^3 (16.2 ppm) for 30 minutes as immediately dangerous to life and health (IDLH).

7.2 Approach No. 2: Human Volunteer and Accidental Exposure

No new human volunteer studies have been published in the last 10 years. Unfortunately none of the new case history reports of hydrofluoric acid exposure give details that are helpful in determining the lower levels of lethality. In all cases exposures of those who died seemed substantial. However, the community exposure report published by Wing et al (WI 1991) indicated community exposure levels of 10 ppm HF one hour after escape of the gas. No mortalities were reported.

An estimate in an earlier report (HA 1984) was based on the case described by Burke et al (BU 1973) in which a patient barely survived a 3-5 minute splash and inhalation exposure of hydrofluoric acid. No estimates were made of how much hydrogen fluoride the patient might have inhaled but approximately 87 mg of fluoride per litre were recorded in the urine.

A derivation was made by extrapolating a graph of urine fluoride vs exposure concentration, produced by Largent (LA 1960) and by assuming that urine fluoride shows a direct and linear relationship to fluoride exposure (ZO 1977).

In Burke's patient 87 mg of fluoride per litre were recorded in urine and were considered equivalent to around 27 mg/m^3 (33 ppm) during a 3 to 5 minute exposure.

7.3 Approach No. 3: Derivation from Animal Data

The report by Halton et al (HA 1984) applied a very general extrapolation model originally published by Dourson and Stara (DO 1983) which utilizes an inter-species adjustment system based on the difference in body surface areas between experimental animals and man. The model assumes that different species are equally sensitive to the effects of a toxin on a dose per unit surface area. When the surface area dose is converted to corresponding units of mg/kg body weight, those species with a greater body weight, such as humans, appear to be more sensitive than a species of smaller body weight, such as rodents. Application of the Dourson and Stara model produces a result for a probable lethal dose in humans of 17 mg/kg HF. This deduction has a built in tenfold uncertainty factor.

By a tenuous extrapolation from limited animal data lethal concentration values for LC_{LO}, LC_{10} and LC_{50} are shown in Table 4.

7.4 Impact of New Data on Lethal Concentration Estimates

The report on a community exposure has significant impact on estimated human lethality concentrations by other authors listed in Table 4 Approach No. 1. Hydrogen fluoride was reported present in community air at 10 ppm one hour after its release. No mortalities were recorded and morbidity was restricted to skin, eye and respiratory tract irritation with occasional nausea.

The community exposure report suggests that the estimates by the U.S. National Research Council and the NIOSH/OSHA immediately dangerous to life and health level are conservative.

It also indicates that in the extrapolation from animal data for a 60 minute LC_{50} is conservative at the lower end of a concentration range.

In approach No. 2 the derivation was made from a splash and inhalation reported by Burke et al (BU 1973). The patient barely survived an exposure estimated to be 13.3 ppm for 3-5 minutes. Yet in a whole community not one death was recorded in a 10 ppm exposure for an hour. The difference between the exposure described by Burke and that in the community is that the latter had no instances of skin splash.

The results suggest that the potential lethality of an HF inhalation exposure can be greatly enhanced by simultaneous skin contact.

No new animal lethal concentration data is available to modify or amend approach No. 3 which extrapolated human lethality data from limited animal studies. However, the new accident reports with their more detailed post-mortem studies confirm a dilemma highlighted in the earlier report (HA 1984). To quote from the earlier report:

> *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 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 principle cause of death, while at lower concentrations, the build up of systemic fluoride is probably the dominant factor in lethality.*

The accidental and industrial exposures reported in the last 10 years indicate quite clearly that in high HF exposures death is due to corrosion of respiratory tissue and not from toxicity per se.

This is borne out in a report by Withers and Lees (WI 1986) who discuss the difficulties in assessing lethal concentrations of irritant and corrosive gases. They point out that no known data extrapolation model exists for such gases and indicate that one should be developed which takes into account the corrosive potency of the

gas, of the locus of action in the respiratory tract, the solubility, the respiratory volume and several other parameters.

While such a theoretical model could be developed data availability is likely to restrict its practical application.

8.0 SUMMARY AND SUGGESTIONS FOR FURTHER STUDY

Literature published in the last ten years suggest that HF exposures up to 10 ppm for periods up to an hour cause irritation effects but are neither lethal to human populations nor impair people's ability to take protection actions. However, when people inhale high concentrations of HF death is almost certainly caused by the corrosive action of the gas rather than its toxicity.

No new animal data have been published to merit modification of the original extrapolations from animal LC_{50} data. However, previous derivations of LC_{LO} at 50 ppm for 5 minutes are probably conservative and estimates of LC_{50} values at 50 ppm for 30 minutes are probably very conservative.

The dilemma of noting at what point systemic fluoride poisoning alone (i.e. separate from corrosion effects) would be sufficient to cause death still remains unresolved. New data on the inhalation of HF are unenlightening on this point but indicate that accidental skin splashes can greatly enhance the potential lethality. It is suggested that a further study focussing on skin contact accidents would reveal valuable

information about the levels of fluoride which cause systemic toxicity. A review of this data would also help resolve the controversy surrounding the appropriate treatment of HF skin burns.

Further pertinent information on systemic toxicity could be derived from studies of chronic exposure to hydrogen fluoride. The literature in this area is voluminous since it contains many studies on the fluoridation of water, dental treatments, and tooth cleaning agents.

Finally, the last ten years has seen a sizable growth in the literature on assessments and evaluations of major hazard sites. An overview of approaches and methodologies used in various parts of the world would be eminently useful.

REFERENCES

AC 1993 Threshold limit values for chemical substances and physical agents. American Conference of Governmental Industrial Hygienists, Cincinnati 1992-93.

AM 1983 Amoore, J. E.; Hautala, E. Odour as an aid to chemical safety: Odour thresholds compared with threshold limit values and volatilities for 214 industrial chemicals in air and water dilution. *JAT J Appl Toxicol* (1983) Vol. 3, 272-219.

AN 1981 Anonymous. Hydrofluoric acid dangerous properties of industrial materials report. (1981) Vol. 1, 64-66.

BO 1984 Boublik, T.; Fried, V.; Hala, E. The vapour pressures of pure substances: Selected values of the temperature dependence of the vapour pressures of some pure substances in the normal and low pressure region. *2nd revised edition, Amsterdam, The Netherlands. Elsevier Scientific Publishing Co. Inc.,* 1984 (Physical Sciences Data Series Vol. 17).

BR 1985 Bracken, W. M.; Cuppage, F. et al. Comparative effectiveness of topical treatments for hydro fluoric acid burns. *Journal of Occupational Medicine* (1985) Vol. 27, 733-739.

BR 1984 Braun, J.; Stoss, H.; Zober, A. Intoxication following the inhalation of hydrogen fluoride. *Archives of Toxicology* (1984) Vol. 56, 50-54.

BU 1973 Burke, W.J. et al Systemic fluoride poisoning resulting from a skin burn. *Journal of Occupational Medicine* (1973) Vol. 18, 39-41.

CA 1960 Carlson, C. H.; Armstrong, W. D.; Singer, L. Distribution migration and binding of whole blood fluoride evaluated with radio fluoride. *M. J. Physiol.* (1960) Vol. 199, 187-189.

CH 1989 Chela, A; Reig, R.; Sanz, P.; Huguet, E.; Corbella, J. Death due to hydrofluoric acid. *The American Journal of Forensic Medicine and Pathology* (1989) Vol. 10, 47-48.

CZ 1990 Czarnowski, W.; Krechniak, J. Fluoride in the urine, hair, and nails of phosphate fertilizer workers. British Journal of Industrial Medicine (1990) Vol. 47, 349-351.

DI 1971 Dipasquale, L.D.; Davis, H.F. The acute toxicity of brief exposure to hydrogen fluoride, hydrogen chloride, nitrogen dioxide and hydrogen cyanide singly and in culmination with carbon monoxide *AMRL-TR-71-120* (1971) paper #20, 279-289.

DO 1983 Dourson, M. L.; Stara, J.F. Regulatory history and experimental support of uncertainty (safety) factors. *Regulatory Toxicology and Pharmacology* (1983) Vol. 3, 228-230.

EK 1977 Ekstrand, J. Studies on the pharmacokinetics in man. Stockholm, Karolinska Institute Thesis.

FA 1983 Foley, J. R.; Wergedal, J. E.; Balink, D. J. Fluoride directly stimulates proliferation and alkaline phosphatases activity of bone forming cells. *Science* (1983) Vol. 222, 330-332.

FU 1975 Fuchs, C.; Dorn, D.; Fuchs, C. A.; Henning, H. V.; McIntosh, C.; Scheler, F. Fluoride determination in plasma by ion selective elctrodes: A simplified method for the clinical laboratory. *Clin. Chim. Acta* (1975) Vol. 6, 157-167.

GA 1980 Gall, J.F. Hydrogen Fluoride In: Kirk-Othmer encyclopedia of chemical technology, New York. John Wiley and Sons.

GR 1964 Greendyke, R. M.; Hodge, H.C. Accidental death due to hydrofluoric acid. *Journal of Forensic Sciences* (1964) Vol. 9, 383-390.

HA 1979 Hansen, H.; Leo, I. Substituent constants for correlation analysis in chemistry and biology. New York, NY John Wiley and Sons (1979) 172.

HA 1984 Halton, D.M.; Dranitasaris, P.; Baynes. Toxicity levels to humans during acute exposure to hydrogen fluoride. INFO 0143. Atomic Energy Control Board, Ottawa, Ont. 1984.

HE 1943 Henderson, V. B.; Haggard, H. W. Noxious gases. New York: Reinholdt Publishing Corp. p. 128.

HO 1977 Hosking, D.J.; Chamberlain, M. J. Studies in man with fluoride. *Clin Sci* (1977). Vol. 42, 153-161.

JA 1973 Jardillier, J. C.; Desmet, G. Etude de fluor sérique et des combinaisons par une technique utilisant une électrode spécifique. *Clin. Chim. Acta.* (1973) Vol. 47, 357-360.

JU 1984 Just, R. A. Report on toxicological studies concerning exposures to UF_6 and UF_6 hydrolysis products. The Oakridge Gaseous Diffusion Plant, Oakridge, Tennessee. A report prepared for the U. S. Department of Energy under contract DEAC05-840R21400, 1984.

KO 1984 Kono, K.; Yoshida, Y.; Harada, A. Urinary excretion of fluoride in chronic renal failure and hydrofluoric acid workers. *Collect Med Leg. Toxicol Med* (1984) Vol. 125, 91-99.

LA 1960 Largent, E. J. The metabolism of fluorides in man. *AMA Archives of Industrial Health* (1960) Vol. 21, 318-323.

MA 1970 MacEwan, J.D.; Vernot, E.H. Toxic hazards research unit annual technical report. *AMRL* Ohio 1970.

MA 1962 MacLean, J. N. et al. The self association of hydrogen fluoride vapour. *J En Org Nuclear Chem* (1962) Vol. 24, 1549.

MA 1934 Machle, W.; Thamann, F.; Kitzmiller, K.; Cholak, J. The effects of inhalation of hydrogen fluoride I. The response following exposure to high concentrations. *Journal of Industrial Hygiene* (1934) Vol. 15, 129-145.

MO 1983 Morris, J.B.; Smith, F. A. Identification of two forms of fluorine in tissues of rats inhaling hydrogen fluoride. *Toxicology and Applied Pharmacology*. (1983) Vol. 71, 383-390.

NI 1976 National Institute for Occupational Safety and Health Criteria for Recommended Standard. Occupation exposure to hydrogen fluoride. Washington, DC. U.S. Department of Health, Education and Welfare, Centre for Disease Control. Publication number DHEW/PUB/NIOSH/76-143 (1976).

RO 1963 Rozenholtz, M.J.; Carson, T.B.; Weeks, M.H. et al A toxicopathologic study in animals after brief single exposure to hydrogen fluoride. *Am. J. Ind. Hyg.* (1963) Vol. 23, 253-261.

RU 1954 Rushmere, J. D. The self association of hydrogen fluoride. A short review of the published literature. *SCS-TN-31*, 1954.

SA 1984 Sax, N.I. Dangerous properties of industrial materials. Second edition. New York, NY Van Nostrand Reinhold Company (1984) pp 1427-1428, and 1548-1549, 2430-2431.

SC 1980 Schiffl, H. H.; Binswager, U. Human urinary fluoride excretion as influenced by renal functional impairment. *Nephron* (1980) Vol. 26, 69-72.

SC 1987 Schotte, W. Fog formation of hydrogen fluoride in Air. *Ind Eng Chem Res 1987,* Vol. 26, 300.

SI 1985 Sittig, M. Handbook of toxic and hazardous chemicals and carcinogens. 2nd edition. Parkridge, NJ Noyes Publications (1985) pp 456-459, 408-509, 799.

SM 1986 Smith, G.E. Fluoride, the environment and human health. *Perspectives of Biological Medicine.* (1986) Vol. 28, 560-572.

ST 1991 Stauert, D.M.; Archuleta, D.C.; Behr, M.J.; Lehnert, B. E. Relative acute toxicities of hydrogen fluoride, hydrogen chloride, and hydrogen bromide on nose- and pseudo-mouth-breating rats. *Fundamental and Applied Toxicology* (1991) Vol. 16, 636-655.

ST 1981 Stokinger, H. E. The halogens and the non metals and boron and silicon. In Clayton G.D.; Clayton F.E. eds. Patty's Industrial Hygiene and Toxicology. Vol. 2b, 3rd edition, New York, NY John Wiley and Sons (1981) 2937-2954

TA 1966 Taves, D.R. Normal human serum fluoride concentrations. *Nature* (1966) Vol. 211, 192-193.

TA 1968a Taves, D. R. Evidence that there are two forms of fluoride in human serum. *Nature* (1968) Vol. 217, 1050-1051.

TA 1968b Taves, D. R. Determination of sub-micromolar concentrations of fluoride in biological samples. *Talanta* (1968) Vol. 15, 1015-1023.

TA 1970 Taves, D. R. New approach to the treatment of bone disease with fluoride. *Fed. Proc.* (1970) Vol. 29, 1185-1187.

TA 1968c Taves, D. R. Electrophoretic mobility of serum fluoride. *Nature* (1968) Vol. 220, 582-583.

TU 1989 Turner, R. M.; Fairhurst, S. Assessment of the toxicity of major hazard substances. Health & Safety Executive Specialist inspector report #21. 1989.

WA 1978 Waldbott, G. L.; Lee, J. R. Toxicity to repeated low grade exposure to hydrogen fluoride — case report. *Clinical Toxicology* New York. (1978) Vol. 13, 391-402.

WA 1973 Watson, A. A.; Oliver, J. S.; Thorpe, J. W. Accidental death due to inhalation of hydrofluoric acid. *Medicine Sci. Law.* (1973) Vol. 13, 277-279.

WE 1986 Weiss, G. Editor. Hazardous chemicals data book. Parkridge, NJ Noyes Data Corporation (1980) 473, 511, 515, 82.

WE 1986 Weast, R. C.; Astle, M. J.; Beyer, W. H. editors. CRC handbook of chemistry and physics; ready reference book of chemical and physical data. 67th edition. Boca Raton, FL CRC Press Inc. (1986) pp. B91, B94, B130, D121, D122, D163, and D193.

WI 1991 Wing, J. S.; Sanderson, L. M.; Brender, J. D.; Perrotta, D. M.; Beauchamp, R. A. Acute health effects in a community after release of hydrofluoric acid. *Archives of Environmental Health* (1991) Vol. 46, 155-160.

WI 1986 Withers, R. M. J.; Lees, F. P. The assessment of major hazards: The factors affecting lethal toxicity estimates and the associated uncertainties. Hazards in the process industries: Hazards IX. The Institution of Chemical Engineers Symposium #97 1986, 185-199.

WI 1983 Windholz, M.; Budavari, S.; Blumetti, R. F.; Otterbein, E. S. eds. The Merck Index 10th edition. Rahway, NJ Merck and Co. Inc. (1983) pp 230, 596, 695-696, 1235.

WO 1976 Wohlslagel, R. M. J.; Dipasquale, L.C.; Vernot, E.H. Toxicity of solid rocket motor exhaust: Effects of HCl, HF, and Alumina on rodents. *Journal of Combustion Toxicology* (1976) Vol. 3, 61-69.

WO 1984 World Health Organization. Fluorine and fluorides. Geneva Switzerland WHO (1984) Environmental Health Criteria No. 36.

ZO 1977 Zober, A.; Geldmacher von Mallinckrodt, M.; Schaller, K. H. Renal fluoride excretion as a useful paramter for monitoring hydrofluoric acid exposed persons [International Archives of Occupational and Environmental Health] Berlin (1977) Vol. 40, 13-24.

GLOSSARY

LD_{50} (Lethal Dose 50%) The amount of a susbstance per unit body weight of an animal which will cause death in 50% of the test population when applied on a single occasion.

LC_{50} (Lethal Concentration 50%) Is the concentration of a substance in air which when inhaled by test animals will cause death in 50% of the population after a specified exposure time. Unless otherwise stated the quoted values for LC_{50} are for a four hour exposure time.

LC_{LO} (Lethal Concentration, Lowest) This parameter is sometimes also called the LC Min (minimum) and is the lowest lethal concentration.

LC_{10} (Lethal Concentration, 10) Is the lethal concentration for 10% of a population.

conversion of units Conversion between mg/m3 and ppm is according to the formula:

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

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

APPENDIX

Table 1 Physical and Chemical Properties of Hydrogen Fluoride

Property		Source
Code Numbers	CAS 7664-39-3 RTECS MW 7875000 (solution MW 7890000) UN 1052 (anhydrous), UN 1790 (solution)	SA 1984; SI 1985
Chemical Name	hydrogen fluoride	
Common Synonyms	hydrofluoric acid, hydrofluoric acid gas, hydrofluoric acid, anhydrous, hydrofluoric acid solution, hydrofluoride, fluorhydric acid, antisal 2B, acide fluorhydrique (French): acide fluodrico (Italian): fluoorowodor (Polish): fluorwasserstoff (German): fluorwaterstof (Dutch). RCRA waste number U134, etching acid	MEDLARS II (HSDB, RTECS) (1986), WE 1986, SA 1984, AN 1981
Chemical Formula	HF	
Common Aqueous Concentrations	hydrofluoric acid 40%, 42%, 48% reagent grade hydrofluoric acid, 48-51% grade hydrofluoric acid 52-55% hydrofluoric acid	HA 1979 WE 1980 WE 1980 WE 1980
Formula Weight	20 006	GA 1980
Composition wt %	H 5.038 F 94.96	GA 1980 GA 1980
Molecular Weight	saturated vapor at boiling point 78.24 saturated vapor at 100°C 49.08	GA 1980 GA 1980
Polymerization	exists as an associated molecule up to H_6F_6 at 1 atm and temperatures below 100°C average molecular weight 50-55	ST 1981
Physical State	colorless fuming corrosive liquid or gas	WE 1986
Melting Point	83.1°C	WE 1986
Boiling Point	19.54°C	WE 1986
Refractive Index	gas D_{20}, 1.90	WE 1986

Table 1 Physical and Chemical Properties of Hydrogen Fluoride

Property		Source
Solubility		
cold water	infinite	WE 1986
hot water	very soluble	WE 1986
alcohol	very soluble	WI 1983
ether	slightly soluble	WI 1983
benzene	2.54 (wt % at 5°C)	WI 1983
toluene	1.80 (wt % at 5°C)	WI 1983
m-xylene	1.28 (wt % at 5°C)	WI 1983
tetrain	0.27 (wt % at 5°C)	WI 1983
Many compounds are soluble in HF		WI 1983
Acidity	Anhydrous HF is one of the most acidic substances known	WI 1983
	Harmnet acidity function (H_0) = 10.98	WI 1983
	HF is a weak acid in aqueous solution	
	Ka = 646 x 10^{-4} moles/liter	WI 1983
	K (25°C 0.1-0.01 N) = 3.53 x 10^{-4}	WI 1983
	pK (25°C 0.1-0.01 N) = 3.45	WE 1986
		WE 1986
Vapor Pressure	10 mm Hg at -65.8° C	WE 1986
	40 mm Hg at -45.0° C	WE 1986
	100 mm Hg at -28.2° C	WE 1986
	360 mm Hg (48 025 kPa) at 0.028° C	BO 1984
	394 mm Hg (52 503 kPa) at 2.449° C	BO 1984
	532 mm Hg (70 971 kPa) at 10.006° C	BO 1984
	760 mm Hg (101 325 kPa) at 19.738° C (nbp)	BO 1984
	912 mm Hg (121 650 kPa) at 25.000° C	BO 1984
	1084 mm Hg (144 560 kPa) at 29.954°C	BO 1984
	In general, for HF, log PO = 6.93862 T571 203 (1 + 298 777) where P is the vapor pressure in kPa and + temperature in °C.	BO 1984
	101.325 kPa = 1 atm = 760 mm Hg	

Table 2: Fluoride Blood Serum Levels

F^- ion Serum Level	Comments	Author
13 ug/L	Drinking water was fluoridated - no level given	TA 1966
10.4 ug/L	Drinking water was fluoridated at 0.18 mg/L	FU 1975
9.8 ug/L	Drinking water was fluoridated at 0.06 mg/L	SC 1980
27-99 ug/L	Drinking water was fluoridated at 0.15 mg/L	JA 1973
57-277 ug/L	Drinking water was fluoridated at 3.8 mg/L	JA 1973
Up to 91 ug/L	In fluoride exposed workers	EK 1977

Table 3: LC_{50} Values for Hydrogen Fluoride in Different Species.

Species	Duration of Exposure	LC 50	Reference
Mouse	5 minutes	6,247 ppm	DI 1971
	60 minutes	342 ppm	WO 1976
		501 ppm	MA 1970
Rat	5 minutes	18,200 ppm	DI 1971
		4,970 ppm	RO 1963
	15 minutes	2,690 ppm	RO 1963
	30 minutes	2,040 ppm	RO 1963
	60 minutes	1,276 ppm	MA 1970
		1,310 ppm	RO 1963
		1,395 ppm	WO 1976
Guinea Pig	15 minutes	4,330 ppm	RO 1963
Monkey	60 minutes	1,774 ppm	MA 1970

Table 4: Estimates of HF Lethality Concentrations in Humand by 3 Approaches

Method of Derivation	Source	Human Lethal Concentration Estimate mg/m^3 (ppm)	Exposure Time Minutes	Comments
Approach #1	(DE 1969)	41 (50)	30-60	LC_{50}[1]
Other	(HE 1943)	41-205 (50-250)	30-60	LC_{50}[1]
Authors	(JU 1984)[2]	13.3 (16.2)	10	LC_{50}[1]
	(JU 1984)[3]	13.3 (16.2)	30	LC_{50}[1] IDLH Level
	(JU 1984)[4]	105,000 (128,100) 26,000 (31,720) 10,500 (12,810) 5,250 (6,405) 877 (1,070)	0.5 2 5 10 60	LC_{50}[1]
Approach #2 Industrial Accidents	BU 1973	27 (33)	3-5	extrapolation from urine F^- concentration
Approach #3 Animal Extrapolation	DO 1983 HA 1984	41-205 (50-250) 275 (336) 410 -679 (500-828) 368-825 (448-1007) 278 (340) 22-483 (27-589)	5 5 5 15 30 60	Estimated LC_{LO} Estimated LC_{10} Estimated LC_{50} Estimated LC_{50} Estimated LC_{50} Estimated LC_{50}

---

1 Derivation unavailable.

2 Estimate of the U.S. National Research Council.

3 Estimate of the National Institute of Occupational Safety and Health/Occupational Safety & Health Administration. 13.3 mg/m^3 for 30 minutes is considered as the level Immediately Dangerous to Life or Health (IDLH).

4 Estimate of M. E. Wrenn.