Environmental Health Criteria 21

CHLORINE AND HYDROGEN CHLORIDE

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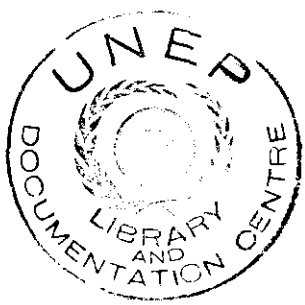

World Health Organization
Geneva, 1982

The International Programme on Chemical Safety (IPCS) is a joint venture of the United Nations Environment Programme, the International Labour Organisation, and the World Health Organization. The main objective of the IPCS is to carry out and disseminate evaluations of the environment. Supporting activities include the development of epidemiological, experimental laboratory, and risk assessment methods that could produce internationally comparable results, and the development of manpower in the field of toxicology. Other relevant activities carried out by the IPCS include the development of know-how for coping with chemical accidents, coordination of laboratory testing and epidemiological studies, and promotion of research on the mechanisms of the biological action of chemicals.

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NOTE TO READERS OF THE CRITERIA DOCUMENTS

While every effort has been made to present information in the criteria documents as accurately as possible without unduly delaying their publication, mistakes might have occurred and are likely to occur in the future. In the interest of all users of the environmental health criteria documents, readers are kindly requested to communicate any errors found to the Division of Environmental Health, World Health Organization, Geneva, Switzerland, in order that they may be included in corrigenda which will appear in subsequent volumes.

In addition, experts in any particular field dealt with in the criteria documents are kindly requested to make available to the WHO Secretariat any important published information that may have inadvertently been omitted and which may change the evaluation of health risks from exposure to the environmental agent under examination, so that the information may be considered in the event of updating and re-evaluation of the conclusions contained in the criteria documents.

WHO TASK GROUP MEETING ON ENVIRONMENTAL HEALTH CRITERIA FOR CHLORINE AND HYDROGEN CHLORIDE

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ENVIRONMENTAL HEALTH CRITERIA FOR CHLORINE AND HYDROGEN CHLORIDE

Further to the recommendations of the Stockholm United Nations Conference on the Human Environment in 1972, and in response to a number of World Health Assembly resolutions (WHA23.60, WHA24.47, WHA25.58, WHA26.68) and the recommendation of the Governing Council of the United Nations Environment Programme (UNEP/GC/10, 3 July 1973), a programme on the integrated assessment of the health effects of environmental pollution was initiated in 1973. The programme, known as the WHO Environmental Health Criteria Programme, has been implemented with the support of the Environment Fund of the United Nations Environment Programme. In 1980, the Environmental Health Criteria Programme was incorporated into the International Programme on Chemical Safety. The result of the Environmental Health Criteria Programme is a series of criteria documents.

A WHO Task Group on Environmental Health Criteria for Chlorine and Hydrogen Chloride met in Geneva from 22 to 26 February 1982. Dr M. Mercier, Manager, International Programme on Chemical Safety, opened the meeting on behalf of the Director-General. The Task Group reviewed and revised the second draft of the criteria document and made an evaluation of the health risks from exposure to chlorine and hydrogen chloride.

The first and second drafts of the criteria document were prepared by Dr R.R. Cook, Dr R.J. Kociba, and Dr R.R. Langer of Dow Chemical USA. The comments on which the second draft was based were received from the national focal points for the WHO Environmental Health Criteria Programme in Australia, Bulgaria, Canada, Czechoslovakia, Federal Republic of Germany, Finland, Greece, India, Italy, Japan, Norway, Poland, Thailand, the United Kingdom, the USA, and the USSR, and from the United Nations Environment Programme, the International Labour Organisation, the International Agency for Research on Cancer, the International Union of Pure and Applied Chemistry, and the European Council of Chemical Manufacturers' Federations.

The collaboration of these national institutions, international organizations, and WHO collaborating centres is gratefully acknowledged. Without their assistance, this document would not have been completed. The Secretariat wishes, in particular, to thank Dr R.R. Cook for his help in the final scientific editing of the document.

This document is based primarily on original publications listed in the reference section.

Details of the WHO Environmental Health Criteria Programme, including definitions of some of the terms used in the documents, may be found in the general introduction to the Environmental Health Criteria Programme, published together with the environmental health criteria document on mercury (Environmental Health Criteria I - Mercury, Geneva, World Health Organization, 1976) and now available as a reprint.

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1. SUMMARY AND RECOMMENDATIONS FOR FURTHER STUDIES

1.1 Summary

1.1.1 Sampling and analytical methods

A variety of methods are available for collecting and concentrating airborne chlorine and hydrogen chloride, using either liquid or solid absorbents. Analysis is carried out using colorimetric and potentiometric methods. Various modifications of these techniques have resulted in the development of direct reading instruments. However, most of these monitoring methods are cumbersome and non-specific. The choice of analytical procedure depends on the atmosphere to be sampled, the analytical tools available, and the sensitivity and accuracy needed.

1.1.2 Sources and pathways of exposure

The major sources of exposure to chlorine and hydrogen chloride that are of significance for human health are found in industry. Both chlorine and hydrogen chloride are corrosive to most construction materials, as well as tissue, and closed process systems are used to contain the compounds. Exposure mainly occurs as a result of plant malfunction or through accidental releases.

Though gaseous chloride species have been detected in the atmosphere, specific identification has not been possible. Chlorides are natural constituents of fossil fuels, and organochlorides have been added to premium grades of gasoline, but this use has decreased in recent years.

While the main use of chlorine is in the production of chlorinated hydrocarbon solvents and intermediates for polyvinyl chloride and polyglycols, large quantities are also used in the bleaching of pulp and paper. Another application of chlorine is in the disinfection of water.

Hydrogen chloride (HCl) is a by-product of hydrocarbon chlorination and dehydrochlorinations. Much of the hydrogen chloride produced is consumed by the chemical industry. Large quantities are also used in the pickling of steel. Acidification of oil wells with hydrogen chloride, to increase the flow, is rapidly increasing. Smaller amounts are used for adjusting the pH in the treatment of water.

Occupational exposure to both chlorine and hydrogen chloride has long been regulated by consensus guides and by governmental standards. Since both materials are gases at normal temperature and pressure, exposure of workers is usually limited to inhalation.

1.1.3 Experimental animal studies on the effects of chlorine

Under physiological conditions (pH 7.4, 37 °C), chlorine reacts with water to produce hypochlorous acid. There is evidence to suggest that chlorine and chlorides produce oxygen radicals. Elemental chlorine, hypochlorous acid, hydrogen chloride, and oxygen are all thought to contribute to the biological activity. Apparently, hypochlorous acid can penetrate the cell wall, disrupting its integrity and permeability, and by reacting with sulfhydryl (SH) groups in cysteine, can inhibit various enzymes. Since chlorine can be distributed throughout the entire respiratory tract, these effects follow a similar distribution.

From data selected to represent the overall single and repeated inhalation toxic effects of chlorine in animals (Table 1), it can be seen that a single exposure for 30-60 min to concentrations in the range of 368-2900 mg/m³ (127-1000 ppm) caused death in various species of animals. A single exposure of several hours to a chlorine concentration of 29-87 mg/m³ (10-30 ppm) induced definite adverse effects, including high mortality rates, in rodent species tested. Repeated exposure to chlorine concentrations of 2.9-26 mg/m³ (1-9 ppm), for a period of several weeks to months, induced dose-related pulmonary and other adverse effects. A level of 2 mg/m³ (0.7 ppm) was reported to be a "no-observed-adverse-effect" level, for rabbits and guinea-pigs, repeatedly exposed to chlorine through inhalation.

In studies designed to evaluate the effects of chlorine exposure on resistance to disease, repeated exposure to 261 mg/m³ (90 ppm) for 3 h/day, during a 20-day period, had a greater effect on rats with spontaneous pulmonary disease (SPD) than on those that were specific pathogen-free(SPF). A higher mortality rate and a greater incidence of pulmonary tract abnormalities were noted among the SPD rats. At lower levels, guinea-pigs, exposed to chlorine at 5.0 mg/m³ (1.7 ppm) for 5 h/day, over 47 days, before or after injection with a virulent strain of human tuberculosis, showed decreased average survival rates compared with unexposed, injected animals.

Table 1. Summary of selected experimental animal studies on the single and repeated inhalation of chlorine

Species	Chlorine concentration (mg/m^3)(ppm)	Exposure time	Effects	Reference
rat	2900 (1000)	53 min (LT_{50})	50% mortality	Weedon et al. (1940)
mouse	2900 (1000)	28 min (LT_{50})	50% mortality	Weedon et al. (1940)
dog	2220-2610 (800-900)	30 min	3-50% mortality (3-day observation)	Underhill (1920) & NAS/NRC (1976)
mouse 3 strains	1100-2580 (378.4-887.5)	10 min	10-100% mortality (10-day observation)	Silver et al. (1942)
rat	850 (293)	60 min	50% mortality	Vernot et al. (1977)
cat, rabbit, guinea-pig	870 (300)	60 min	asphyxia	Flury & Zernik (1931)
mouse	368 (127)	30 min	50% mortality (4-day observation)	Schlagbauer & Henschler (1967)
cat, rabbit, guinea-pig	87 (30)	few h	pulmonary inflamation and haemorrhage	Flury & Zernik (1931)
mouse	64 (22)	3 h	100% mortality within 2 days	Schlagbauer & Henschler (1967)
mouse	29 (10)	3-6 h	80-90% mortality after 4 days	Schlagbauer & Henschler (1967)

Table 1 (contd).

Species	Chlorine concentration (mg/m^3)(ppm)	Exposure time	Effects	Reference
rat	26 (9)	6h/day 5 days/ week for 6 weeks	some mortality; pulmonary, hepatic, and renal effects	Barrow et al. (1979a)
mouse	14.5 (5.0)	8h/day for 3 days	loss of body weight; pulmonary effects	Schlagbauer & Henschler (1967)
rat	8.7 (3.0)	6h/day, 5 days/ week for 6 weeks	pulmonary and other effects	Barrow et al. (1979b)
mouse	7.3 (2.5)	8h/day for 3 days	loss of body weight	Schlagbauer & Henschler (1967)
rabbit, guinea-pig	4.9 (1.7)	hours at a time for numerous days	deterioration in nutritional condition, etc.	Flury & Zernik (1931)
rabbit	1.7-4.4 (0.58-1.51)	5h/day, every other day for 1-9 months	loss of body weight; pulmonary effects (possibly due to concurrent infectious processes)	Skljanskaja & Rappoport (1935)
rat	2.9 (1.0)	6h/day, 5 days/ week for 6 weeks	loss of body weight; pulmonary effects	Barrow et al. (1979a)
rabbit	2.0 (0.77)	hours at a time for numerous days	no adverse effects noted	Flury & Zernik (1931)

No adverse effects were observed in pregnant rabbits or their offspring following exposure of the rabbits, through inhalation, to chlorine concentrations of 1.7-4.4 mg/m³ (0.6-1.5 ppm). Furthermore, adverse effects were not seen in 7 generations of rats given highly chlorinated water (100 mg/litre daily) throughout the entire life span.

Chlorine does not appear to be teratogenic, mutagenic, carcinogenic, or cocarcinogenic in animals. In a series of studies on mice, chlorine solution, applied before, after, or during treatment of the shaved skin with repeated applications of benzpyrene, reduced the carcinogenic effects of the benzpyrene.

1.1.4 Experimental animal studies on the effects of hydrogen chloride

A summary of the animal toxicity data related to single exposures to hydrogen chloride vapour is given in Table 2. No immediate deaths occurred among rabbits and guinea-pigs exposed for 5 min to a concentration of 5500 mg/m³ (3685 ppm), but 100% mortality was noted in the same animal species exposed to a concentration of 1000 mg/m³ (670 ppm) for 6 h. In other studies, exposures insufficient to cause immediate death were associated with delayed mortality, secondary to nasal and pulmonary infections. Presumably, disruption of normal protective mechanisms allowed bacteria to invade the damaged tissues. In support of this, focal superficial ulceration of the respiratory epithelium at its junction with the squamous epithelium of the external nares was reported in mice, 24 h after a single 10-min exposure to 25-30mg/m³ (17 ppm).

Based on the respiratory irritation reaction in mice exposed to air levels of hydrogen chloride of 59.6-1405 mg/m³ (40-886 ppm), for 10 min, it has been projected that human exposure levels should not exceed 4.5-46.2 mg/m³ (3-31 ppm).

Few repeated exposure studies have been conducted in animals. Exposure of rabbits and guinea-pigs to a level of hydrogen chloride in air of 100 mg/m³ (67 ppm) for 6 h/day, for 5 days did not result in any deaths. Exposure of the same animal species and one monkey to a level of 50.0 mg/m³ (33 ppm) for 6 h/day, 5 days/week, for 4 weeks was not associated with any adverse effects, according to necropsy, several months later. Slight respiratory difficulties and eye and nasal irritation were observed in rabbits, guinea-pigs, and pigeons exposed to 149 mg/m³ (100 ppm), for 6 h/day for 5 days.

Table 2. Summary of selected toxicity data from studies on the single exposure of animals to hydrogen chloride

Species	HCL concentrations mg/m (ppm)	Exposure time	Effects	Reference
rat	60 938 (40 898)	5 min	50% mortality	Darmer et al. (1972, 1974)
mouse	20 487 (13 750) (LC_{50})	5 min	50% mortality	Darmer et al. (1972, 1974)
rat	7004 (4701) (LC_{50})	30 min	50% mortality	Darmer et al. (1972, 1974)
mouse	3940 (2644)	30 min	50% mortality	Darmer et al. (1972, 1974)
rabbit, guinea-pig	6400 (4288)	30 min	100% mortality	Machle et al. (1942)
rabbit, guinea-pig	5500 (3685)	5 min	No deaths	Machle et al. (1942)
rabbit, guinea-pig	1000 (670)	360 min	100% mortality	Machle et al. (1942)
rabbit, guinea-pig	5066 (3400) 2012 (1350)	90 min 75 min	Death in 2-6 days severe respiratory irritation	Flury & Zernik (1931) Flury & Zernik (1931)
cat, rabbit	149-209 (100-140)	up to 360 min	Only slight irritation	Flury & Zernik (1931)
mouse	460 (309)	10 min	50% decrease in respiratory rate	Barrow et al. (1977)
mouse	195-417 (131-280)	10 min	Diffuse ulceration of nasal respiratory epithelium	Lucia et al. (1977)
mouse	25.3 (17)	10 min	Focal superficial ulceration of localized area of respiratory epithelium	Lucia et al. (1977)

It has not been possible to assess the carcinogenic potential of hydrogen chloride, because of lack of adequate studies.

1.1.5 Controlled, clinical, and epidemiological studies on the effects of chlorine

Controlled human studies have generally been conducted at much lower levels of chlorine exposure than those administered to animals. Instead of mortality and gross or histological abnormalities, studies on human subjects have been aimed at the determination of threshold levels for odour perception, irritation, and changes in reflex neurological activity, and to the evaluation of short-term exposure effects on pulmonary

Table 3. Chlorine concentrations associated with odour perception and irritation

Chlorine concentrations mg/m (ppm)	Subjective reaction	Reference
11.6 (4.0)	intolerable	Matt (1889)
5.8-8.7 (2.0-3.0)	annoying	Matt (1889)
2.9 (1.0)	burdensome	Beck (1959)
2.9-5.8 (1.0-2.0)	odour perception and irritation	Matt (1889)
0.9 (0.3)	odour perception	Leonardas et al. (1969)
0.8-1.3 (0.28-0.45)	odour perception and irritation	Tahirov (1957)
0.75 (0.26)	odour perception	Stjažkin (1964)
0.7 (0.24)	odour perception	Stjažkin (1963)
0.3 (0.10) (1952)	odour perception	Ugrymova-Sapožnikova
0.23 (0.08)	odour perception	Dixon & Ikels (1977)
0.12 (0.04)	odour perception	Beck (1959)
0.06-0.15 (0.02-0.05)	odour perception and irritation	Rupp & Henschler (1967)

functions. Table 3 is a summary of the reported threshold levels for chlorine in relation to olfaction and various subjective levels of irritation. Values for the former ranged from 0.06 mg/m^3 (0.02 ppm) to 5.8 mg/m^3 (2 ppm). While biological variability and adaptation are responsible for some of the differences observed, definition as to what constitutes a threshold response is probably the cause of many of these differences. For example, in one study, the lowest level at which all participants provided a response consistent with the response at higher concentrations was considered the threshold; whereas, in another study, the level used was that at which the most sensitive subject reported some kind of response.

Similar ranges were found for the irritation threshold level, 0.06-5.8 mg/m^3 (0.02-2 ppm). At and above 2.9-5.8 mg/m^3 (1-2 ppm), irritation became a problem and, above 11.6 mg/m^3 (4 ppm), it became intolerable.

Optical chronaxie, visual adaptometry, and other behavioural tests have generally demonstrated effects only at, or above the threshold for odour perception.

At low concentrations, the acute effects of chlorine exposure are confined to the perception of a pungent odour and mild irritation of the eyes and upper respiratory tract. These resolve shortly after exposure stops. Subjective reaction is variable and adaptation has been reported with a resultant loss or diminution in the sensations of smell and irritation. For a few hypersensitive individuals, exposure to low levels of chlorine has reportedly precipitated asthma attacks.

As concentrations increase, symptoms become more severe and involve more distal portions of the respiratory tract. In addition to immediate irritation and associated paroxysmal cough, victims manifest anxiety. At higher levels, there is dyspnoea, cyanosis, vomiting, headache, and a heightening of anxiety, especially in those prone to "neurosis". Expiratory volumes become diminished and pulmonary oedema can develop. Generally, with palliative treatment, the patient recovers within 2 days to 2 weeks. In more severe cases, complications such as pneumonia, either infectious or aspiration, should be anticipated.

Short-term, high-level exposures have apparently aggravated pre-existing heart disease, producing electrocardiographic changes in a middle-aged male, and congestive heart failure among several elderly persons. Both conditions resolved.

Most research workers have concluded that even the victims of severe gassing have minimal or no long-term sequelae; however, a few workers have suggested that there are indications of respiratory tract impairment, olfactory deficiency, and neurosis.

Fatalities following chlorine exposure have been few, even under wartime conditions. However, at sufficiently high concentrations, the chemical can cause shock, coma, respiratory arrest, and death. Those exposed during physical exertion appear especially vulnerable.

The effects of long-term exposures to chlorine have been investigated, mainly in workers exposed to time-weighted average levels of less than 1.28 mg/m^3 (0.44 ppm), but with a few exceptions exposed to average levels of up to 4.2 mg/m^3 (1.44 ppm). Any effects that occurred appeared to be limited to minor modifications of pulmonary function.

Unusual patterns in general mortality have not been reported, nor has chlorine been shown to induce mutagenic, carcinogenic, or teratogenic effects in human beings.

1.1.6 Controlled, clinical, and epidemiological studies on the effects of hydrogen chloride

As with chlorine, controlled studies related to hydrogen chloride have been aimed at the determination of threshold levels for odour perception and reflex neurological changes. Odour thresholds have been reported to be as low as 0.1 mg/m^3 (0.07 ppm) and as high as 462 mg/m^3 (308 ppm) depending on the method used. Other possible reasons for this marked discrepancy are not clear.

Threshold levels for the various tests of reflex neurological activity were the same or higher than threshold levels reported, for odour perception.

The major effects of hydrogen chloride are those of local irritation. It is generally believed that exposure to hydrogen chloride does not result in effects on organs some distance from the portal of entry.

The chemical is highly soluble in moisture. At low levels, acute effects are limited to odour perception and upper respiratory tract irritation. Higher concentrations can cause conjunctival irritation, superficial corneal damage, and transitory epidermal inflammation. The last of these conditions has been reported to occur, when the chemical dissolves on perspiration-soaked clothing.

Short-term exposures have been reported to induce transitory obstruction in the respiratory tract, which diminishes with repeated exposure, suggesting adaption. Acclimatized workers can work undisturbed with a hydrogen chloride level of 15 mg/m^3 (10 ppm), but long-term exposure can affect the teeth, resulting in erosion of the inciso-labial surfaces.

No mutagenic, teratogenic, or carcinogenic effects, related to exposure to hydrogen chloride, have been reported in human beings.

1.1.7 Evaluation of health risks

On the evidence available, the Task Group concluded that, apart from accidental releases, the general population was not exposed to any significant health risks from either chlorine or hydrogen chloride.

The Task Group also proposed that ambient levels of chlorine should be kept below about 0.1 mg/m^3 (0.034 ppm) to protect the general population from sensory irritation and significant reduction in ventilatory capacity. A warning was added that this value must be used cautiously, because of the inherent limitations of the underlying data.

Because of the limited data available, the Task Group was unable to establish a comparable figure for hydrogen chloride.

1.2 Recommendations for Further Studies

1.2.1 Monitoring

Short- and long-term sampling methods for chloride species are both cumbersome and non-specific, and the limited understanding of atmospheric chemistry is an additional analytical problem.

Further studies are needed to develop simple methods for the determination of the source and the identity of the different chloride species found in the ambient air, in the presence of interfering substances. Studies are also needed to determine the role and fate of gaseous chlorine in the total atmospheric chemistry, and the secondary reactions of hydrogen chloride.

1.2.2 Human exposure

Additional surveys of worker exposure to both chlorine and hydrogen chloride under the various conditions of use, are needed.

When analytical methods have been developed that make it possible to identify and quantify the gaseous chloride

species, collection of general population exposure data may be warranted.

1.2.3 Experimental animal studies

The mechanisms of action of chlorine on the cell should be studied. Furthermore, the highest priority should be given to animal studies directed towards the emergency management of high-level exposures. Levels simulating accidental releases to which the general population may be inadvertantly exposed should be studied.

1.2.4 Controlled, clinical, and epidemiological studies

Adaptation in human subjects deserves further study in relation to both chlorine and hydrogen chloride.

With few exceptions, the epidemiological studies reported to date have been cross-sectional. Longitudinal studies of human populations, exposed to adequately documented concentrations of either chlorine or hydrogen chloride, should focus on pulmonary functions, olfaction, respiratory disease, or mortality, and should give due consideration to race, smoking habits, other environmental exposures, and to the therapy used at the time of accidental high exposure.

1.2.5 The significance of biological effects

Further research is needed to determine the long-range biological significance of transient or non-symptomatic shifts in pulmonary functions associated with exposure to either chlorine or hydrogen chloride.

2. PROPERTIES AND ANALYTICAL METHODS

2.1 Physical and Chemical Properties of Chlorine and Hydrogen Chloride

Under normal conditions of temperature and pressure, both chlorine and hydrogen chloride are gases. Chlorine is greenish in colour and pure hydrogen chloride is colourless. Both gases have a pungent odour with irritating properties. Chlorine reacts with most organic compounds and many inorganic compounds. Some physical characteristics of chlorine and hydrogen chloride are listed in Table 4.

Table 4. Some physical characteristics of chlorine and hydrogen chloride[a]

Variable	Chlorine	Hydrogen chloride
Relative molecular mass	70.906	36.46
Boiling point at 1 atm	-34.6 °C	-84.9
Freezing point at 1 atm	-100.98 °C	-114.8 °C
Vapour pressure at 0 °C	3.6065 atm	25.807 atm
Density at 0 °C, 1 atm	3.214	1.187
Water solubility at 0 °C, 1 atm	14.6g/litre	823 g/litre
Conversion factors at 25 °C, 1 atm	1 ppm = 2.90 mg/m³	1 ppm = 1.49 mg/m³
	1 mg/m³ = 0.344 ppm	1 mg/m³ = 0.670 ppm

[a] From: Weast (1974).

2.2 Sampling and Analytical Methods

2.2.1 Chlorine

The choice of collection medium and sampling technique depends on the analytical procedure to be used, which in turn depends on the environment to be monitored, the analytical instrumentation available, and the sensitivity and accuracy needed.

In the o-tolidine method (Wallach & McQuary, 1948), the collection medium is a dilute caustic soda solution. The chlorine content of the solution is determined by adding an o-tolidine solution and measuring the resulting yellow colour on a spectrophotometer. According to Johnson & Overby (1969), limitations of the method are the fading of the yellow colour and its sensitivity to pH. Interference by iron (III), manganese (III), manganese (IV) and nitrite was eliminated by these authors by the introduction of a stabilized neutral o-tolidine reagent.

An improved method in which an aqueous sulfamic acid or p-toluene-sulfonamide absorption medium was used, eliminated the colour fading problem and improved trapping efficiency (Takeuchi et al., 1974).

In another method, methyl orange indicator dye is used to absorb the chlorine (APHA, 1977b). The methyl orange is bleached and the colour change read on a spectrophotometer. Limitations of the analytical procedure include poor precision and accuracy at low concentrations, and the instability of the colour. The presence of other oxidizing agents in the air may cause interference. However, Krivorutchko (1953) suggested analytical conditions under which nitrogen dioxide, sulfur dioxide, and ozone, at low concentrations, would not interfere with this method.

In the iodide method, air is drawn through 20% potassium iodide solution at pH 7, and the yellow colour that develops is measured spectrophotometrically. The chlorine concentration is determined from a standard curve (Elkins, 1959). This method has been tested, improved, and modified (Noweir & Pfitzer, 1972). The liberated iodine may also react with N, N'-dimethyl-p-phenylenediamine dihydrochloride (or sulfate), the colour that develops being measured spectrophotometrically (Poležaev, 1955).

Chlorine can be adsorbed on activated carbon, desorbed with an alcoholic solution of potassium hydroxide, and the chloride ion determined potentiometrically (Peterson et al., 1979) or spectrophotometrically after treatment with arseneous oxide (Noweir & Pritzer, 1972). Adsorption on carbon is favoured by a low air flow rate, high relative humidity, and a large carbon bed.

The method has been used successfully at air levels as low as 0.29 mg/m^3 (0.1 ppm). Both accuracy and precision have been difficult to reproduce and validation under different field conditions is not easy using this method. Another limitation is the difficulty of preparing spiked samples under field conditions, for quality assurance.

Instrumental methods have mainly included gas chromatography, UV spectrophotometry, colourimetry, amperometry, mass-spectrometry, catalyic combination, the use of direct

reading detector tubes (American Conference of Governmental Industrial Hygienists, 1978). Bethea & Meada (1969) listed 15 gas chromatographic methods for the determination of chlorine. Mass spectrometry and catalytic combustion procedures, can be used for the determination of single halide compounds but complications arise with mixtures. Generally, all of the direct reading instruments require calibration, especially at low ambient air levels.

A new monitoring dosimeter is available, with a reported sensitivity at the 0.29 mg/m^3 (0.1 ppm) level, which is independent of temperature between 0-55 °C and relative humidity between 0-97%, has a response time of less than 0.5 min, and is suitable for either personal or area monitoring (Hardy et al., 1979). Longer sampling periods increase the sensitivity to 0.038 mg/m^3 (0.013 ppm) over an 8-h sampling period. The device contains 10 ml of a fluorescein-bromide solution buffered to a pH of 7. The chloride oxidizes the bromide to bromine, which reacts with the fluorescein to form eosin. The amount of eosin formed is determined spectrophotometrically.

Though the o-tolidine method is the most sensitive spectrophotometric procedure for determining trace amounts of chlorine, o-tolidine is a suspected carcinogen (IARC, 1972). Thus the methyl orange method, which is not affected by iron (III) or compounds containing available chlorine, such as chloramine, and yet has 70% of the sensitivity of o-tolidine has been proposed as the method of choice (NIOSH, 1976). This procedure is designed to cover the range of 5-10 mg of free chlorine/10 ml of sampling solution. For a 30-litre air sample, this corresponds to approximately 0.145-2.9 mg/m^3 (0.05-1.0 ppm) in air. The method has an accuracy of ±5%. Reagent stability is good and the preparation time, short. Samples remain stable for 24 h. Equipment and apparatus needed are uncomplicated, sampling and analysis are straightforward, and the results are easily interpreted.

2.2.2 Hydrogen chloride

In monitoring for hydrogen chloride, the solution sampling techniques are similar to those used for chlorine. Analytical measurements have been based on the neutralization of a weak caustic solution that can be readily titrated or measured potentiometrically. Other acidic ions such as NO_3^- or SO_4^{--} will cause interference.

Ion specific electrodes have been developed, but these react to all chloride ions and to determine the amount of airborne hydrogen chloride requires a combination of analytical methods.

Air levels of total chlorides can also be determined colorimetrically (APHA, 1977a). This method is applicable to long-term sampling and has a sensitivity of 5.8 mg/m^3 (2 ppm).

3. SOURCES OF CHLORINE AND HYDROGEN CHLORIDE IN THE ENVIRONMENT

3.1 Natural Sources of Chlorine and Hydrogen Chloride

Though there are no known natural sources of gaseous chlorine, it exists in nature in measurable concentrations (Duce, 1969). There have been suggestions that ultraviolet radiation from the sun may react with airborne sodium chloride aerosols found over the oceans to form free chlorine aerosols (Cauer, 1935). Volcanoes have also been postulated as sources of gaseous chlorine, but Valach (1967) reported that the gas was hydrogen chloride rather than free chlorine. Katz (1968) suggested that nitrosyl chloride, which may be formed from nitrogen dioxide and chlorides, may decompose to form free chlorine and nitrous oxide (NO).

Volcanoes are a source of atmospheric hydrogen chloride, and their contribution has been reported to vary widely (Eriksson, 1960; Valach, 1967). Chemical reactions in the atmosphere may also contribute to the airborne hydrogen chloride, but since the other reactive components are generally from man-made sources, the hydrogen chloride formed should not be considered to have originated from a natural source.

3.2 Man-made Sources of Chlorine and Hydrogen Chloride

3.2.1 Chlorine manufacture

Briefly, the major man-made source of chlorine is the electrolysis of chloride salts. Sodium chloride is the most common salt used but calcium, magnesium, and potassium salts have been used in special processes. The diaphragm cell process is the most widely used process, but production from mercury cells continues. The diaphragm process produces gaseous chlorine (Cl_2) at the anode, hydrogen (H_2) at the cathode, and dilute caustic soda (NaOH). In the mercury cell, the cathode mercury forms an amalgam with the sodium metal, which is separated and reacts with water to form sodium hydroxide and hydrogen. In both processes, the dilute chlorine stream is dried, refrigerated, and compressed to a liquid or used in a gaseous form (NAS/NRC, 1976).

There are several sources of chlorine emission in the electrolytic processes. Though the electrolytic cells are

operated under a slight vacuum, the pressure may rise too high during a breakdown in operating conditions, and chlorine may be released into the atmosphere. Small quantities may be released into the air during process sampling and through leaks that may develop in cell bonding materials. As with all mechanical equipment, leaks may also occur in the valves, pump seals, and compressor shafts. Cylinders and tank cars are potential sources of emission during loading and unloading, but, with modern engineering procedures, there is normally little or no release into the atmosphere. Shipping containers, cylinders, and tank cars have been designed for the safe transport of liquid chlorine. In modern, computer-operated plants, breakdowns are infrequent and chlorine releases few. However, there have been occasional massive releases, with concomitant human exposure, in the water purification and cellulose industries (Baader, 1952).

3.2.2 Hydrogen chloride manufacture

Hydrogen chloride is a by-product of hydrocarbon chlorination processes. It is also formed as a by-product in the numerous dehydrohalogenation processes used to make unsaturated compounds from the parent chlorinated hydrocarbon. Limited quantities of high purity hydrogen chloride are made by reacting chlorine with hydrogen. Smaller amounts are formed by reacting sodium chloride with sulfuric acid. The hydrogen chloride produced by these various processes may be recycled into the process, piped to an adjacent process, absorbed in water, or purified, compressed, and packaged as anhydrous hydrogen chloride. Potential emissions occur during process sampling, from leaking valves, flanges, pumps, and reactor and compressor seals. Because it is highly corrosive to both human tissue and metals, such leaks are generally repaired rapidly. As in the case of chlorine, cylinders and tank cars have been designed for the safe transport of anhydrous hydrogen chloride. Aqueous scrubbers are used to control hydrogen chloride emissions from vent stacks and other sources (NAS/NRC, 1976).

3.2.3 Combustion of fuels

Fossil fuels contain chlorides (Bergman & Sanik, 1957; Smith, 1962; Stahl, 1969a). In addition to those occurring naturally, small amounts of organic chlorides have been

blended with premium grades of gasoline to improve engine performance. Irrespective of the source of the chlorides, combustion of these fuels produces hydrogen chloride.

3.2.4 Waste disposal

Chlorides are ubiquitous in nature and the burning of natural products contributes to the chloride concentrations in the ambient air. The gaseous product emitted is primarily hydrogen chloride and not chlorine. Most of the incinerated solid waste products are cellulosic and contain 0.03-0.06% chloride (Bethga & Troeng, 1959). There has been increasing production of chlorinated plastics, since World War II, and polyvinyl chloride is the major product. The products of combustion will vary with the conditions of burning (Warner et al., 1971) but hydrogen chloride is the principal gaseous chloride released. With open-pit burning, all of the emitted hydrogen chloride enters the atmosphere, while emissions from municipal incinerators depend on the technology and control methods used.

3.2.5 Transportation

As mentioned earlier, chlorides are a natural constituent of fossil fuels (Smith, 1962) and chlorinated compounds are also added to premium gasolines as lead scavengers (Ethyl Corporation, 1963). The use of these premium fuels is rapidly decreasing and this will be a minor source of hydrogen chloride emissions in the future.

Since chlorine is shipped by both road and rail, accidents during transport are of concern (Römcke & Evenson, 1940; Chassis et al., 1947). However, railcars have been specifically designed for the transport of chlorine, to minimise emissions during accidents.

No accidental major releases of hydrogen chloride during transportation have been reported. Furthermore, hydrogen chloride has a high affinity for water, and solutions of hydrochloric acid do not present the same degree of hazard as chlorine, when spilled.

3.3 Industrial Consumption of Chlorine and Hydrogen Chloride

3.3.1 Chlorine

3.3.1.1 Chemical industry

The industrial consumption of chlorine is a good indicator of the economy of the chemical industry. In recent years, the growth rate has been reduced, because of the general economic recession and a reduction in the use of several chlorinated hydrocarbons, such as the chlorinated methanes and insecticides. Whereas the annual growth rate in the past has been about 6.5%, the predicted rate is 4.5% (Hanson, 1978). There will probably be an increase in the developing countries, since chlorine and caustic are basic chemicals. About 25 million tonnes of chlorine are consumed on a global basis. Most of the chlorine is used by the producers for the manufacture of chemicals such as 1,2- dichlorethane (ethylene dichloride), chloroethylene (vinyl chloride), chlorinated ethane solvents, and 2-chloro-1-propanol-methyloxirane (propylene chlorohydrin-propylene oxide) (Anon, 1980).

3.3.1.2 Pulp and paper industry

The pulp and paper industry is the second major user of chlorine and the amount used equals that used in the production of chlorinated ethane solvents (Hanson, 1978). The primary use of chlorine is for bleaching the pulp to produce white paper and this process consumes about 10% of the global production.

3.3.1.3 Water and waste treatment

The use of chlorine for disinfecting drinking-water supplies has been significant in the reduction of enteric disease (Orihuela et al., 1979). Only a small fraction of the chlorine produced is used for this purpose (Hanson, 1978). This use may decrease in future years, if the application of other strong oxidizing agents such as ozone, hydrogen peroxide, or ultraviolet light proves feasible (WHO, 1977).

3.3.2 Hydrogen chloride

The consumption of hydrochloric acid parallels that of chlorine. The oxychlorination process for producing vinyl chloride and other chlorinated hydrocarbons consumes large volumes of anhydrous hydrogen chloride and allows for balancing the chlorine-hydrogen chloride supply. A decrease in steel production, because of the economic recession, has resulted in a reduction in the amount of hydrochloric acid used for pickling, though this use had grown rapidly during the last decade. A small, but increasing, use of hydrochloric acid is in the acidification of oil wells, to increase the flow of oil through limestone rock structures.

4. ENVIRONMENTAL TRANSFORMATIONS, LEVELS, AND EXPOSURES

4.1 Exposure of the General Population

4.1.1 Air

There is a lack of data regarding ambient air levels of either chlorine or hydrogen chloride. Most studies refer to gaseous chlorides, but do not differentiate between chlorine, hydrogen chloride, or other possible chloride ions. Mean ambient air levels between 1 and 3.7 mg/m^3 (0.344 and 1.27 ppm) have been reported (NAS/NRC, 1976). Chlorine is a very reactive molecule and its stability, and consequently its presence, in the atmosphere is questioned (Zafiriou, 1974). Various atmospheric reactions involving sodium choride aerosols appear to be the major source of the gaseous chlorides. These have been reviewed by Duce (1969). Indeed, there are not any data, which indicate that the general population is being exposed to measurable quantities of chlorine. Gaseous chlorides have been detected in the atmosphere, but the presence of gaseous hydrogen chloride has not been established.

4.1.2 Water

Chlorine is widely used to purify drinking water and is being increasingly used as a disinfectant of sewage effluent (Bierman, 1978). In both cases, chlorine is added in controlled amounts at the final stages of processing. A public health concern is that this type of disinfection may produce chlorinated by-products. The potential health effects of these compounds have been considered (WHO, 1977; Jolley et al., 1978).

Chlorine, or the easier to handle hypochlorite, is used in many swimming pools to control both fungus and bacterial growth. Though the level of either chemical should be controlled, there are occasions when an odour is detectable. Pool operators generally check the chlorine concentration in water, but do not determine the level in air.

Chlorine has limited use in the wool-shrink process. This process has only recently been developed and modern control technology is generally used.

Hydrogen chloride, as hydrochloric acid, may be added to water supplies or swimming pools to adjust pH and to prevent

carbonate (scale) formation. Since the acid is usually well controlled and is neutralized, such use does not present an exposure hazard for the general public.

4.2 Occupational Exposure

4.2.1 Chemical industry

4.2.1.1 Chlorine

The occupational exposure limits for chlorine in the air of work places vary in different countries from 1 to 3 mg/m³ (0.344 to 1.032 ppm), as time-weighted averages, and from 1 to 8.7 mg/m³ (0.344 to 2.99 ppm) as short-term exposure limits (ILO, 1980). Because of its mode of use and excellent warning properties, there have been few in-plant surveys and published reports of over-exposure are sparse. Industrial hygiene studies, during production, indicate that workers are exposed to chlorine levels of less than 2.9 mg/m³ (1 ppm) (Patil et al., 1970; Pendergrass, 1974) during normal operations. Respirators are generally only used to prevent worker exposure during breakdowns or maintenance work, when emissions are likely.

Chlorine is transported either by pipeline or in cylinders. The liquid is generally revapourized before addition to a chemical process. Many years of engineering experience have reduced the potential for worker exposure in these operations to a minimum; however, occasional equipment failure does occur. Exposure is minimized through training and the use of respirators and other protective clothing. Data concerning exposure in the work place are even more sparse for plants where chlorine is used in various processes, than for the primary production plants.

4.2.1.2 Hydrogen chloride

Hydrogen chloride is produced chiefly as a co-product in hydrocarbon chlorination and dehydrochlorination processes. These are closed system processes and, under normal operating conditions, there is little likelihood of workers being exposed. Process sampling, maintenance, and breakdowns may result in limited short-term exposure.

Exposure limits have been developed for occupational exposure to hydrogen chloride as well as chlorine. Recent exposure data are sparse.

4.2.2 Pulp and paper industry

Chlorine is used in the pulp and paper industry to bleach the finished pulp, before producing the sheet paper. A limited number of exposure reports indicate the occurrence of chlorine levels of up to 44 mg/m^3 (15 ppm) (McCord, 1926). Chlorine dioxide may be present in the ambient air (Ferris et al., 1967).

Hydrochloric acid may be used to adjust the pH in these plants. Exposure is limited by the design of the machinery.

4.2.3 Water and waste treatment

During these operations, the chlorine is continuously fed from cylinders into the circulating water. The major potential for exposure occurs during the changing of the feed supply. The valve system used prevents the release of chlorine under normal operating conditions. Worker exposure has occurred during valve failures.

The addition of hydrochloric acid to adjust the pH, is carried out under conditions designed to minimize worker exposure.

4.2.4 Miscellaneous

Both chlorine and hydrogen chloride are used in several small industries. Chlorine is generally used as a germicide or as a bleaching agent. Hydrochloric acid is used in some processes to adjust the acidity (pH). There are no published exposure data concerning these operations.

5. EFFECTS OF CHLORINE AND HYDROGEN CHLORIDE ON SOME ELEMENTARY FORMS OF LIFE AND ON EXPERIMENTAL ANIMALS

5.1 Chlorine

5.1.1 Effects of chlorine on bacteria, viruses, and other elementary forms of life

Certain bacteria and viruses in water are killed by exposure to chlorine at concentrations of less that 1 mg/litre (1 ppm) for 1 min or less (Clarke et al., 1956). However, other bacteria, fungi, and protozoa are only killed by much higher concentrations or by longer contact (Clarke et al., 1956; NAS/NRC, 1976). Butterfield (1948) compared the bactericidal efficiency of free and combined available chlorine. The time required for a 100% kill was 100 times longer for residual combined than for free chlorine, when the same amounts were used. Patton et al. (1972) demonstrated that aqueous solutions of hypochlorous acid can react with cytosine, and Knox et al. (1948) demonstrated that hypochlorous acid inhibits the action of enzymes, essential for energy production within bacteria.

5.1.2 Effects of chlorine on experimental animals

Considerable differences in the results of studies on animals exposed to chlorine may be due to variations in gas generation and in the determination of the chlorine concentration in the air, or the mode and duration of exposure, the health status and species of animals as well as other factors. It is also important to keep in mind that the various experimental studies concerned with the exposure of animals to chlorine have been conducted over a time span of more than 50 years, during which time equipment may have changed and knowledge increased.

An example of the variables that must be considered, when interpreting animal toxicity data on chlorine, is the study by Barrow & Dodd (1979), who documented the formation of chloramines from the reaction of chlorine with ammonia evolving from animal urine and faeces. The outcome of some animal studies concerned with chlorine, especially long-term studies, may be affected by a number of such factors.

5.1.2.1 Qualitative toxicological and related effects

Results of animal studies concur with the observations on human subjects over-exposed to chlorine, namely that chlorine is a primary irritant of both the upper respiratory passages and the deeper structures of the lung. Sudden death without pulmonary lesions may occur, and Schultz (1919a) described 3 types of chlorine toxicity: (a) acute toxicity unaccompanied by gross pathological effects, with acute or delayed death; (b) acute toxicity accompanied by pulmonary oedema; and (c) chronic low-level toxicity, due to exposure to low concentrations of chlorine.

Other studies by Schultz (1919b) showed that inhalation of chlorine by anaesthetized dogs and cats caused temporary cardiac arrest; this was prevented by cutting the vagal nerves prior to the inhalation of chlorine. Similarly, inhalation of chlorine at 580-2900 mg/m^3 by anaesthetized rabbits caused a reduction in the respiratory excursion of the lungs (Gunn, 1920). The acute effects caused by exposure to high concentrations of chlorine have been well documented in the studies on dogs, reported by Underhill (1920). The dogs inhaled chlorine concentrations in air of 145-5800 mg/m^3 (50-2000 ppm) for 30 min. Dogs inhaling concentrations of chlorine at the higher end of the range exhibited an immediate respiratory arrest and bronchoconstriction. At the end of a 30-min exposure, there was a gradual increase in the respiratory rate from 20/min to about 35/min during the first hour following exposure; this gradually subsided to about 25/min, 17 h after the exposure. The pulse rate declined initially, but increased to double the normal rate, 10 h after exposure. These clinical, respiratory, and cardiovascular changes correspond to the development of pulmonary oedema, which was noted in the dogs that died as a result of a 30-min exposure to chlorine. Clinically, the dogs initially exhibited general excitement, indicated by restlessness, barking, urination, and defecation. Irritation of the eyes, sneezing, copious salivation, retching, and vomiting also occurred. As the pulmonary oedema developed, there was laboured respiration with frothing at the mouth. The respiratory distress increased, until death occurred from apparent asphyxiation. Pathological examination of these dogs (Winternitz et al., 1920a) indicated that exposure to chlorine induced necrosis of the epithelium lining the respiratory tract. The destruction of the epithelium of the trachea and bronchi removed the protective mechanism of the upper respiratory tract. This allowed pathogenic bacteria from the oral cavity to gain access to the lung, as early as 30 min after exposure. Pneumonia developed as a result of the bacterial infection and

persisted in surviving dogs. Chronic bronchitis, obliterative or organizing bronchiolitis, and fibrosis were seen in dogs dying or killed as late as 6 months after exposure to chlorine (Winternitz et al., 1920a). Similarly, in the studies of Silver et al. (1942) in which mice were exposed to various concentrations of chlorine 1100-2580 mg/m³ (378.4-887.5 ppm) for 10 min, most deaths were attributed to pulmonary oedema, with fewer deaths related to secondary pneumonia. In studies on acid-base balance, Hjort & Taylor (1919) reported acidosis in dogs exposed to chlorine concentrations of 2320-2610 mg/m³ (80-90 ppm) for 30 min.

Barbour & Williams (1919), who demonstrated that excised rings of bronchi, pulmonary arteries, and pulmonary veins contracted vigorously in the presence of large amounts of chlorine (600 mg/litre of Lock's solution), suggested that this might play a role in the occurrence of pulmonary congestion and oedema resulting from chlorine exposure. An *in vitro* method for the quantitative study of the effects of irritant gases on ciliary activity was developed by Cralley (1942), who noted cessation of ciliary activity in the excised rabbit trachea with exposure to a chlorine level of about 87 mg/m³ (30 ppm) for 5 min or to 52-58 mg/m³ (18-20 ppm) for 10 min.

Studies on the sensory irritation reaction in mice exposed to chlorine and hydrogen chloride were reported by Barrow et al. (1977). Mice were exposed for 10 min to concentrations of chlorine varying from 20 to 111 mg/m³ (7.0 to 38.4 ppm), and the percentage decrease in respiratory rate was used as a reflection of sensory irritation of the upper respiratory tract. Exposure to a chlorine concentration of 27 mg/m³ (9.30 ppm) caused a 50% decrease in the respiratory rate of the mice (RD_{50}).[a]

Barrow & Smith (1975) studied the effects on lung function in rabbits given a single, 30-min exposure to a chlorine concentration of 145, 290, or 580 mg/m³ (50, 100, or 200 ppm). Respiratory volumes, flow rates, pressure measurements, and pulmonary compliance were used for evaluating lung function, prior to exposure, and 30 min, 3, 14, and 60 days after exposure. Respiratory flow rates decreased initially after exposure to concentrations of 580 or 290 mg/m³ (200 or 100 ppm) but returned to normal within 60 days of exposure. Rabbits exposed to 145 mg/m³ (50 ppm) did not exhibit any significant change in respiratory flow rates. A decrease in pulmonary compliance was noted initially in rabbits exposed to

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[a] RD_{50} = Concentration expected to elicit a 50% decrease in respiratory rate.

chlorine levels of 145, 290, or 580 mg/m³ (50, 100, or 200 ppm). During the post-exposure phase, pulmonary compliance returned to normal in rabbits exposed to 145 mg/m³ (50 ppm), but there was a subsequent compensatory increase in pulmonary compliance in rabbits exposed to a chlorine concentration of 290 or 580 mg/m³ (100 or 200 ppm).

Pathological examination of the lungs of rabbits exposed to chlorine concentrations of 580 or 290 mg/m³ (200 or 100 ppm) revealed initial haemorrhage and oedema, followed by chronic inflammation, which receded during the post-exposure phase. The lungs of rabbits exposed to 145 mg/m³ (50 ppm) did not show the pathological changes attributed to the higher exposures of 290 or 580 mg/m³ (100 or 200 ppm).

5.1.2.2 Quantitative effects of short-term exposure

Over 100 dogs were exposed for 30 min to various concentrations of chlorine. The "minimum acute lethal toxicity" values (3-day observation period) ranged between 2320-2610 mg/m³ (800-900 ppm). In Table 5, it should be noted that, though no immediate deaths occurred in the group exposed to 145-725 mg/m³ (50-250 ppm) for 30 min, some delayed deaths occurred in dogs after the initial 3-day observation period (Underhill, 1920).

Weedon et al. (1940) used rats, mice, and houseflies in studies designed to determine the lethal time for 50% mortality (LT_{50}) resulting from exposure to chlorine. They reported LT_{50} values of 28 and 53 min for mice and rats, respectively, when exposed to a chlorine concentration of 2900 mg/m³ (1000 ppm), and 410 min for both species, when exposed to a level of 725 mg/m³ (250 ppm). At an exposure concentration of 183 mg/m³ (63 ppm), the LT_{50} was not reached during the 16-h period of exposure. However, it is likely that some animals received lethal doses of chlorine prior to the time of actual death, as deaths occurred after, as well as during, exposure. Autopsy examination of rats and mice indicated the primary lesions to be pulmonary oedema and haemorrhage.

LT_{50} values for male mice that had undergone a single exposure to a chlorine concentration of 841 or 493 mg/m³ (290 or 170 ppm) were 11 and 55 min, respectively (Bitron & Aharonson, 1978). This study confirmed the importance of delayed death in chlorine toxicity studies, with some deaths occurring up to 30 days after exposure. Exposure of mice to chlorine at 841 mg/m³ (290 ppm) for 25 ± 6 min (mean ± SD) resulted in about 100% mortality over 30 days. About 80%

Table 5. Acute toxicity of chlorine for dogs[a]

Chlorine (mg/m³) concentration (ppm)	145-725 (50-250)	1160-1450 (400-500)	1450-1740 (500-600)	1740-2030 (600-700)	2030-2320 (700-800)	2320-2610 (800-900)	2610-5800 (900-2000)
			Number of deaths				
1st day	0	0	0	4	3	12	10
2nd day	0	1	1	5	4	6	3
3rd day	0	0	1	0	2	2	0
total deaths in first 3 days	0	1	2	9	9	20	13
delayed deaths	1	4	2	5	2	1	0
recoveries	8	12	6	7	7	2	1
total number exposed	9	17	10	21	18	23	14

[a] Adapted from: Underhill (1920).

mortality was recorded in mice exposed to 841 mg/m³ (290 ppm) for 15 ± 2 min. Whereas exposure to 841 mg/m³ (290 ppm) for 9 ± 1 min caused almost 40% mortality, limiting the exposure to 6 min allowed all the mice to survive. Exposure of mice to a chlorine concentration of 493 mg/m³ (170 ppm) for 120 ± 40 or 52 ± 13 min caused almost 80% and 50% mortality, respectively. When exposure at 493 mg/m³ (170 ppm) was limited to 28 ± 8 min, there were no immediate deaths, but about 10% delayed mortality occurred over the 30-day observation period.

Schlagbauer & Henschler (1967) determined a lethal concentration for 50% mortality (LC_{50}) for chlorine of 368 mg/m³ (95% confidence limits, 307-441) (127 ppm, 106-152 ppm), for mice exposed for 30 min and observed for 4 days. Exposure to a chlorine concentration of 29 mg/m³ (10 ppm) for 3 h killed 8/10 mice, within 4 days (Table 6). Pathological examination of these mice revealed pulmonary oedema plus necrosis and inflammation of the respiratory epithelium.

Table 6. Mortality rates and body weights of mice after single or repeated exposure to chlorine[a]

Chlorine mg/m³ (ppm)	Duration of exposure	Mortality after 2 days	4 days
64 (22)	3 h	10/10	10/10
29 (10)	6 h	9/10	9/10
	3 h	7/10	8/10
Chlorine mg/m³ (ppm)	**Duration of exposure**	**Minimum body weight in %**	
14.5 (5)	8 h/day for 3 days	87.5	
7.3 (2.5)	8 h/day for 3 days	93.1	

[a] Adapted from: Schlagbauer & Henschler (1967).

In 2 studies, Silver & McGrath (1942) exposed mice to various concentrations of chlorine for 10 min, and found median lethal concentrations of 1520 and 1728 mg/m³ (523 and 594 ppm), based on a 10-day observation period. In a subsequent study on CR-1 male mice (Silver et al., 1942), the

median lethal concentration based on a 10-min exposure and a 10-day observation period was 1960 mg/m³ (674 ppm).

Studies in which guinea-pigs were exposed for 15-30 min to chlorine vapour, obtained by reacting hydrochloric acid and potassium chloride, were described by Faure et al. (1970). The authors did not give any data on mortality. However, they described pulmonary oedema and haemorrhages which they claimed were similar to those described in previous published reports.

In studies on male mice observed for 10 days after a single 10-min exposure to chlorine, Geiling & McLean (1941) reported a median lethal concentration of 1820 mg/m³ (626 ppm) for a 10-min exposure. A recent report by Vernot et al. (1977) reported a 1-h LC_{50} of 850 mg/m³ (293 ppm) for rats.

In a publication in 1931, Flury & Zernik summarized much of the early toxicity data on chlorine. Acute toxicity data indicated that for cats, rabbits, and guinea-pigs, exposure to 870 mg/m³ (300 ppm) caused asphyxiation after 1 h, exposure to 87 mg/m³ (30 ppm) caused injury after only a few hours, exposure to 29 mg/m³ (10 ppm) caused inflammation of the respiratory mucosa, and exposure to 8.7 mg/m³ (3.0 ppm) caused distinct irritation. The authors cited a report describing the death of horses within 35-40 min of inhaling a concentration of 2900 mg/m³ (1000 ppm).

5.1.2.3 Effects of repeated exposure to chlorine

(a) Death and other toxic effects

Underhill (1920) conducted studies in which dogs that had survived a single initial exposure to chlorine were exposed for a second time. The more susceptible animals were killed by the first exposure in proportion to the concentration, but the survivors had a good chance of recovery, when exposed a second time to the same concentration. However, when the level of the second exposure was higher, a proportionate increase in percentage mortality occurred. Thus, Underhill concluded that any apparent, beneficial effect of previous exposure to high concentrations was mainly the result of the elimination of the weaker or more susceptible individuals. He also concluded that there were no indications of increased susceptibility with repeated exposure to chlorine. However, it must be borne in mind that this study was conducted in dogs of undefined background, and was limited to only 2 exposures to chlorine.

In a report by Schlagbauer & Henschler (1967), mice exposed to chlorine concentrations of 14.5 and 7.3 mg/m³ (5.0 and 2.5 ppm) for 8 h/day for 3 consecutive days showed a loss in body weight, and microscopic examination of the lungs

of mice exposed to 14.5 mg/m³ (5 ppm) yielded findings similar to these following lethal or near lethal short-term exposures. Unfortunately, Schlagbauer & Henschler did not state whether the lungs of mice exposed to a chlorine concentration of 7.3 mg/m³ (2.5 ppm) had been examined for possible microscopic changes. A study in which rabbits and guinea-pigs inhaling chlorine at approximately 4.9 mg/m³ (1.7 ppm) for "hours at a time" for "numerous" days showed "deterioration of the nutritional condition and blood changes, as well as in reduced resistance to infectious diseases" was reported by Flury & Zernik (1931). Under similar conditions, exposure to a concentration of approximately 2.0 mg/m³ (0.7 ppm) was not harmful.

Skljanskaja & Rappoport (1935) conducted a long-term toxicity study on rabbits. The duration of exposure ranged from 1 to 9 months, during which time the rabbits were exposed to chlorine concentrations of approximately 1.7-4.4 mg/m³ (0.58-1.51 ppm) for 5 h/day, every other day. The authors reported that most of the exposed rabbits showed significant weight loss, with nasal irritation, sneezing, and laboured respiration. Pathological findings in the respiratory tract of the rabbits included catarrhal inflammation of the upper respiratory tract, suppurative bronchitis, suppurative pneumonia, pleuritis, emphysema, atelectasis, and metaplasia of the bronchial epithelium. The exposed rabbits also had granulomas in the brain (and other organs) and necrotic caseation in the liver. It was assumed by the authors that all changes were the result of a generalized toxic action of chlorine, but they acknowledged that they could not provide strict proof of this, because there was an accompanying infectious disease problem. Though these infectious diseases were not identified, it is highly probable that Skljanskaja & Rappoport were describing pathological lesions of several infectious diseases, common to rabbits. The lesions described for the respiratory tract of the rabbits are compatible with Pasteurella infection, and the granulomas and related lesions of the brain, liver, and other organs are compatible with Encephalitozoonosis. As there was only one control rabbit, and the conditions under which it was maintained were not defined in the report, it is impossible to ascertain the role that long-term exposure to this low level of chlorine may have played in initiating, promoting, or exacerbating the infectious diseases of the test rabbits.

No adverse effects were reported in mice maintained on drinking-water containing free chlorine concentrations of 0.2 g or 0.1 g/litre (200 or 100 ppm) for 33 or 50 days, respectively. However, only limited variables were monitored in this study (Blabaum & Nichols, 1958).

Most of the early studies on chlorine toxicity were limited in scope. However, a recent study has been conducted concerned with the full extent of the mammalian reaction to chlorine. In this inhalation study by Barrow et al. (1979a), rats were exposed to chlorine concentrations of 0, 2.9, 8.7, or 26 mg/m^3 (0, 1, 3, or 9 ppm) for 6 h/day, 5 days/week, for 6 weeks. Some mortality occurred in female rats exposed to 26 mg/m^3 (9 ppm) and smaller gains in body weight were noted in females exposed to 2.9, 8.7, or 26 mg/m^3 (1, 3, or 9 ppm) and in males exposed to 8.7 or 26 mg/m^3 (3 or 9 ppm). Clinical signs of ocular and upper respiratory tract irritation, such as lachrymation, hyperaemia of the conjunctiva, and nasal discharge occurred in rats exposed to 8.7 or 26 mg/m^3 (3 or 9 ppm); rats exposed to 2.9 mg/m^3 (1 ppm) showed occasional slight indications of irritation. All groups of rats, exposed to chlorine concentrations of 2.9, 8.7, or 26 mg/m^3 (1, 3, or 9 ppm), had urinary staining of the perineal fur, and the urinary specific gravity was elevated in females at all 3 exposure levels and in males at levels of 8.7 and 26 mg/m^3 (3 and 9 ppm).

Pathological examination of the rats exposed to a chlorine level of 26 mg/m^3 (9 ppm) revealed inflammation of the upper and lower respiratory tract. Focal to multifocal mucopurulent inflammation of the nasal turbinates and necrotic erosions of the mucosal epithelium were observed. Inflammation and epithelial hyperplasia in the trachea and bronchiolar areas and epithelial hyperplasia and hypertrophy of the respiratory bronchioles and alveolar ducts accompanied by inflammation were also observed. The alveolar sacs contained increased numbers of alveolar macrophages and secretory material. Focal necrosis, hypertrophy, and hyperplasia of the alveolar epithelial cells adjacent to the alveolar ducts was found together with areas of atelectasis and interstitial inflammation in the lungs.

In the upper respiratory tract of rats exposed to 8.7 or 2.9 mg/m^3 (3 or 1 ppm), the lesions were limited to a focal mucopurulent inflammation of the nasal turbinates and submucosal inflammation of the tracheal epithelium. Lung changes in rats exposed to chlorine levels of 8.7 or 2.9 mg/m^3 (3 or 1 ppm) included a slight to moderate inflammatory reaction around the respiratory bronchioles and alveolar ducts, increased numbers of alveolar macrophages within the alveoli, and isolated areas of atelectasis.

Pathological examination also revealed slight degenerative changes in the renal tubules of kidneys of rats exposed to a chlorine concentration of 26 mg/m^3 (9 ppm), and this was accompanied by elevations in blood urea nitrogen. Slight,

Table 7. Major toxic effects observed in rats exposed to chlorine for 6 h/day, for 5 days/week, for 6 weeks[a]

Chlorine concentration mg/m³ (ppm)	Observations		
	Clinical evaluation	Clinical pathology	Morphological pathology
26 (9)	Ocular and upper respiratory tract irritation; mortality in 3/10 females; decreased body weight gain; urinary staining of perineum	Elevation in segmented neutrophils and haematocrit; elevation in urine specific gravity; elevation in serum enzymes and urea nitrogen	General toxicity, indicated by decreased size of carcass, emaciation and decreased adipose reserves; inflammatory, necrotic, and hyperplastic reaction of respiratory tract; minor renal tubular and hepatocellular cytoplasmic changes
8.7 (3)	Ocular and upper respiratory tract irritation; urinary staining of perineum; decreased body weight gain	Elevation in urine specific gravity	Less severe general toxicity and inflammatory reaction in respiratory tract; minor hepatocellular cytoplasmic changes
2.9 (1)	Slight irritation of nasal mucosa; urinary staining of perineum; slight decrease in body weight gain in females	Elevation in urine specific gravity of females	Less severe inflammatory reaction in respiratory tract

[a] Adapted from: Barrow et al. (1979a).

degenerative changes in the hepatocytes of the livers of rats exposed to levels of 26 or 8.7 mg/m³ (9 or 3 ppm) were accompanied by elevations in various serum enzymes, such as alkaline phosphatase (EC 3.1.3.1), gamma-glutamyl transpeptidase (EC 2.3.2.2), and glutamic pyruvic transaminase (EC 2.6.1.2) (Table 7).

The authors state that the results of these investigations, as well as those of previous studies on the toxicity of chlorine based on repeated exposure, may have been affected by the presence of chloramines formed by the reaction of chlorine with ammonia evolving from excreta.

(b) Resistance to diseases

Elmes & Bell (1963) conducted studies on rats with spontaneous pulmonary disease (SPD). Exposure of these rats to chlorine at approximately 46.4 mg/m³ (16 ppm), for 1 h/day, for 4 weeks or 116 mg/m³ (40 ppm), for 2 h/day, for 5 weeks induced inflammatory changes in the trachea and bronchi, resulting in bronchitis, and death. In a subsequent study (Bell & Elmes, 1965), specific pathogen-free (SPF) rats and rats with SPD were exposed to chlorine concentrations of approximately 261 mg/m³ (90 ppm) for 3 h/day for 20 days or 302 mg/m³ (104 ppm) for 3 h/day, for 6 days. Mortality was higher in the SPD rats than in the SPF rats, the inflammation reaction in the lungs of the rats with SPD was greater and there was a higher incidence of emphysema and pneumonia.

Long-term exposure to chlorine accelerated the evolution of tuberculosis in guinea-pigs injected with a virulent strain of human tuberculosis (Arloing et al., 1940). Guinea-pigs were exposed to a chlorine level of 5 mg/m³ (1.69 ppm) for 5 h/day, for 47 days, prior to or after the injection. The average survival rate was lower in guinea-pigs exposed to chlorine before injection with tuberculosis than in either guinea-pigs exposed after injection, or in control animals, which were injected but not exposed to chlorine.

5.1.2.4 Multigeneration and reproductive studies

Druckrey (1968) conducted a multigeneration toxicity study on rats exposed to chlorine in the drinking-water. Highly chlorinated water, containing free chlorine at a level of 100 mg/litre, was given daily, as drinking-water, over the entire life span of rats in 7 consecutive generations. The chlorine was well tolerated, and there were no adverse effects on fertility, life span, growth pattern, haematology, or

histology. The incidence of malignant tumours was the same in experimental and control groups of rats.

A normal course of pregnancy and parturition was reported by Skljanskaja & Rappoport (1935) in 6 rabbits exposed to chlorine concentrations of 1.7-4.4 mg/m³ (0.58-1.51 ppm), with the delivery of healthy, well-developed offspring. They also reported the occurrence of macerated fetuses in the abdomen of 2 rabbits exposed to chlorine, but this observation is difficult to attribute to chlorine exposure, in view of the spontaneous disease complications that occurred and the other deficiencies of the study, reviewed in section 5.1.2.3.

5.1.2.5 Carcinogenicity

The potential cocarcinogenicity of chlorine was studied by Pfeiffer (1978). A benzpyrene solution was applied to the shaved skin of NMRI mice twice weekly for 10 weeks, with a total dose per animal of 750 µg or 1500 µg benzpyrene applied during this time. Some groups were also treated with a 1% solution of sodium hypochlorite (NaOCl), applied either before, during, or after the benzpyrene treatment. After 128 weeks of observation, it appeared that pre-treatment with the chlorine solution retarded tumour development and markedly reduced total tumour rates in the groups given either 750 or 1500 µg of benzpyrene. Treatment with the chlorine solution after application of benzpyrene also retarded tumour development in the group given 750 µg of benzpyrene. The number of carcinomas was reduced by about 40% by the chlorine solution applications, independent of the method of treatment or the dose of benzpyrene. Thus, under the conditions of the study, the chlorine solution decreased the carcinogenic reaction to benzpyrene.

In the multigeneration toxicity study conducted by Druckrey (1968) and described in section 5.1.2.4, the incidence of malignant tumours in rats maintained on drinking-water containing free chlorine at a level of 100 mg/litre was the same as in the control rats.

5.1.2.6 Mechanisms of action

An early and popular theory on the action of chlorine was based on oxidation potential. According to this theory (NAS/NRC, 1973), chlorine reacts with hydrogen from the water of moist tissue, causing tissue damage. However, the role that

"activated" oxygen may play was questioned by Hayaishi (1969); Barrow et al. (1977) also cast doubt on the historic hypothesis proposed for the biological activity of chlorine. According to these authors, biological conditions of pH 7.4 and 37 °C are not conducive to the formation of elemental oxygen, and it is most probable that chlorine would react with water to give hydrogen chloride and hypochlorous acid. The same authors published data indicating that hypochlorous acid is biologically more active than hydrogen chloride. In contrast, a series of more recent studies clearly indicates that chlorine and chlorides have a significant role in the genesis of free oxygen radicals (Ciba Symposium, 1979).

Chlorine persists as an element only at a very low pH (less than 2), and at the higher pH found in living tissue it is rapidly converted into hypochlorous acid. In this form, apparently, it can penetrate the cell and form N-chloroderivatives that damage cellular integrity (Patton et al., 1972). According to microbial test systems, chlorine can also disrupt cell wall permeability, which possibly explains its ability to cause oedema and acute tissue injury. Hypochlorous acid has been shown to react with sulfhydryl groups in cysteine (Pereira et al., 1973) and to inhibit various enzymes, including the aldolase enzyme essential for glucose oxidation in Escherichia coli (Knox et al., 1948).

5.2 Hydrogen Chloride

5.2.1 Effects on experimental animals

5.2.1.1 Single exposure toxicity studies

Flury & Zernik (1931) summarized the earlier animal toxicity data on hydrogen chloride and stressed the occurrence of irritation and corrosion of all mucous membranes that came into contact with the gas. The early acute toxicity data for different animal species, indicated that exposure to a hydrogen chloride concentration of 447 mg/m³ (300 ppm) for 6 h caused slight respiratory and ocular irritation. Exposure to higher concentrations induced more serious effects, with death following a 90-min exposure to 5066 mg/m³ (3400 ppm). Single exposures to concentrations of less than 298 mg/m³ (200 ppm) were tolerated with only slight, or without any after-effects (Table 8).

Table 8. Effects of a single exposure to hydrogen chloride[a]

Animal species	HCl mg/m³ (ppm)	Duration of exposure	Effects
cat rabbit	149-209 (100-140)	up to 6 h	Only slight reaction (nasal irritation, salivation); no adverse effects
rabbit guinea-pig	447 (300)	6 h	Slight corneal erosion; respiratory irritation
rabbit guinea-pig	2012 (1350)	90 min	Severe irritation, shortness of breath
rabbit guinea-pig	5066 (3400)	90 min	Death in 2-6 days

[a] Adapted from: Flury & Zernik (1931).

Flury & Zernik also stated that, in general, guinea-pigs were more sensitive to hydrogen chloride than cats and rabbits. They reported that raising the temperature to 38 °C enhanced the inhalation effect by causing an acceleration in the breathing rate of the animals. Autopsy examination of animals dying from acute hydrogen chloride toxicity revealed pulmonary oedema and hyperaemia, and occasionally haematemesis.

More recently, Darmer et al. (1972, 1974) conducted single-exposure, acute-toxicity studies in rats and mice with both hydrogen chloride gas and hydrogen chloride aerosol, and reported that the adverse reactions to exposure to hydrogen chloride gas or the aerosol were essentially identical. Hydrogen chloride was extremely irritating to the eyes, mucous membranes, and exposed areas of the skin, such as the scrotum. Corneal erosion and cloudiness occurred in both species, and pathological examination of animals that died during or shortly following exposure showed that the respiratory tract was the primary target for the hydrogen chloride. Alveolar emphysema, atelectasis, and oedema of the lungs were observed; there was also severe injury to the epithelial lining of the nasotracheal passages. Necropsy examination of the animals surviving for 14 days after exposure revealed residual injury in the respiratory tract. The death patterns observed were similar for both the gas and the aerosol, with delayed deaths in both cases. Single exposure LC_{50} values and minimum lethal concentrations for hydrogen chloride gas and aerosol

from the studies in rats and mice, reported initially by Darmer et al. (1972), and subsequently in more detail by Darmer et al. (1974) are summarized in Table 9.

Table 9. Single exposure LC_{50} and minimal lethal concentrations of hydrogen chloride gas or aerosol for rats and mice[a]

Species	Duration of exposure (min)	LC_{50} mg/m³ (ppm)	Minimal lethal concentration mg/m³ (ppm)	No. of deaths observed
gas				
rat	5	60 938 (40 989)	48 060 (32 255)	1/10
mouse	5	20 487 (13 750)	4768 (3200)[b]	1/10
rat	30	7004 (4701)	3990 (2678)	1/10
mouse	30	3940 (2644)	1690 (1134)	2/15
aerosol				
rat	5	45 000 (31 008)	28 775 (19 312)	1/10
mouse	5	16 500 (11 238)	13 496 (9058)[b]	3/10
rat	30	8300 (5666)	4336 (2910)[b]	1/10
mouse	30	3200 (2142)	1794 (1204)[b]	2/10

[a] Adapted from: Darmer et al. (1972) and Darmer et al. (1974).
[b] Lowest concentration tested in study; actual minimal lethal concentration may be lower.

Machle et al. (1942) exposed rabbits and guinea-pigs to various concentrations of hydrogen chloride gas (Table 10). The highest concentration that failed to cause any deaths was 5500 mg/m³ (3685 ppm), but the exposure time was only 5 min. With longer exposure periods or higher concentrations, the guinea-pigs were apparently affected more acutely than rabbits, many guinea-pigs dying due to acute respiratory damage. However, the rabbits died later as a result of nasal and pulmonary infections. High concentrations of hydrogen chloride induced necrosis of the epithelium of the trachea, bronchi, and alveoli, accompanied by pulmonary oedema, atelectasis, and emphysema.

Table 10. Toxicity to animals of single or repeated exposure to hydrogen chloride gas[a]

Animal	HCl conc. mg/m³ (ppm)	Exposure time	Observations
rabbit and guinea-pig	6400 (4288)	30 min	100% deaths
rabbit and guinea-pig	5500 (3685)	5 min	No deaths; transient weight loss
rabbit and guinea-pig	1000 (670)	6 h/day for 5 days	100% deaths
rabbit and guinea-pig	100 (67)	6 h/day for 5 days	No deaths; transient weight loss
rabbit, guinea-pig & 1 monkey	50 (34)	6 h/day, 5 days/week for 4 weeks	No adverse effects, when killed several months later

[a] Adapted from: Machle et al. (1942).

The pulmonary vessels had oedema of the intima and media, with resultant pulmonary thrombosis, infarcts, venous stasis, and haemorrhage. In animals that survived for a few hours or days, there was a severe inflammatory reaction in the respiratory tract. The reaction included: exudative bronchial inflammation, scattered and confluent lobular pneumonia and frequent bronchopulmonary abscesses. Variable lesions were found in some animals up to 18 months after exposure.

In addition to the lesions of the respiratory tract, the authors reported inflammatory lesions in the arteries and veins of various organs. There were emboli and thrombotic lesions associated with infarctions in the heart, liver, kidney, and spleen. High concentrations of hydrogen chloride also caused hepatic oedema congestion, necrosis, haemorrhage, and fatty metamorphosis. In animals surviving the initial exposure, the authors reported hepatic cirrhotic sclerosis and regeneration, plus renal and myocardial lesions of questionable significance.

As Machle et al. (1942) did not provide photomicrographs of reported lesions in the non-respiratory organs, and damage was not observed in the non-respiratory organs of rats or mice in more recent LC_{50} studies using hydrogen chloride gas and aerosol (Darmer et al., 1972, 1974), it would appear prudent to consider such lesions as questionable, and requiring further study.

Respiratory irritation in mice exposed to hydrogen chloride gas was studied by Barrow et al. (1977). Mice were exposed for 10 min to concentrations ranging from 59.6 to 1405 mg/m^3 (40 to 943 ppm), and dose-response curves were plotted, using the percentage decrease in respiratory rate for each exposure as the reaction reflecting sensory irritation of the upper respiratory tract. The results showed chlorine gas to be 33 times more irritating than hydrogen chloride gas, based on RD_{50} values of 27 mg/m^3 (9.3 ppm) for chlorine and 460 mg/m^3 (309 ppm) for hydrogen chloride. The authors applied a 10-100 fold safety margin on the results of this study and projected that an appropriate threshold limit value range for human exposure to hydrogen chloride gas would be from 4.5 to 46.2 mg/m^3 (3 to 31 ppm). However, the authors pointed out that other factors, besides sensory irritation, must also be considered when selecting exposure limits for man.

Barrow et al. (1979b) conducted a study to assess the role of hydrogen chloride gas in explaining the overall toxicity of the thermal decomposition products of polyvinyl chloride. Mice were exposed to hydrogen chloride concentrations ranging from approximately 29.8 to 29 800 mg/m^3 (20 to 20 000 ppm) with deaths occurring above 12 367 mg/m^3 (8300 ppm). Histopathological changes noted in mice, killed 24 h after the exposure, revealed that the target organs included the upper respiratory tract and the eyes, with secondary changes and passive congestion in the lungs, intestine, liver, and kidneys.

The histopathological effects in the upper respiratory tracts of mice that had been given a single 10-min exposure to hydrogen chloride, 24 h previously, were described by Lucia et al. (1977). Single exposure to the lowest concentration of hydrogen chloride gas tested, 25.3 mg/m^3 (17 ppm), caused minimal superficial ulcerations only in the respiratory epithelium at its junction with the squamous epithelium of the external nares. As the exposure was increased to 195.2-417 mg/m^3 (131-280 ppm) the adjacent respiratory epithelium underwent mucosal ulceration in a contiguous fashion; and, at 737.6 mg/m^3 (493 ppm), the squamous epithelium of the external nares was also affected. At concentrations of hydrogen chloride gas of 2940 mg/m^3 (1973 ppm) or more, portions of the squamous, respiratory, and olfactory epithelium of the upper respiratory tract were all affected, with mucosal damage, followed by damage to the underlying supportive tissues.

Cralley (1942) conducted studies of the effects of irritating chemicals on the mucociliary activity of excised rabbit trachea, and reported that there was a cessation of mucociliary activity after exposure to hydrogen chloride gas at a concentration of 89.4 mg/m^3 (60 ppm) for 5 min or at 44.7 mg/m^3 (30 ppm) for 10 min.

5.2.1.2 Dermal toxicity studies

In a dermal toxicity study, Vernot et al. (1977) reported a corrosive skin response in rabbits after a 4-h application of 0.5 ml of a solution of hydrogen chloride in water at 170g/litre. A similar application using a solution of hydrogen chloride in water of 150 g/litre was not corrosive to the skin, under the test conditions.

5.2.1.3 Intrabronchial insufflation of hydrochloric acid

In a number of reports, the use of intrabronchial insufflation of hydrogen chloride solutions has been cited but because of their limited relevance, such reports have not been reviewed in this document (Winternitz et al., 1920b; Wamberg & Zeskov, 1966; Greenfield et al., 1969).

5.2.1.4 Repeated exposure to hydrogen chloride

There is a paucity of data on the animal toxicity of repeated exposures to hydrogen chloride gas. Table 11 is a summary of the limited data available. Machle et al. (1942) reported that rabbits and guinea-pigs were exposed to hydrogen chloride gas at 100 mg/m^3 (67 ppm) for 6 h/day for 5 days, with no deaths. Rabbits, guinea-pigs, and 1 monkey exposed to a concentration of 50.0 mg/m^3 (33.5 ppm) for 6 h/day, 5 days/week for 4 weeks, did not show any adverse effects when killed several months later. Based on their results, these authors stated that the upper limit of safety for man for exposure to hydrogen chloride gas must be about 45 mg/m^3 (30 ppm), and suggested that even this concentration of might be harmful, if daily exposures were continued over periods longer than 1 month.

Flury & Zernik (1931) cited a study in which rabbits, guinea-pigs, and pigeons were exposed to a hydrogen chloride gas concentration of 149 mg/m^3 (100 ppm) for 6 h/day for 5 days. These animals exhibited slight respiratory difficulties and eye and nasal irritation, and slightly decreased haemoglobin levels.

Table 11. Summary of toxicity data after repeated exposure of animals to hydrogen chloride

Species	HCl concentration mg/m³	(ppm)	Exposure time	Effects	Reference
rabbit, guinea-pig	100	(67)	6 h/day for 5 days	No deaths	Machle et al. (1942)
rabbit, guinea-pig, monkey	50	(33.5)	6 h/day, 5 days/week for 4 weeks	No toxic effects when killed several months later	Machle et al. (1942)
rabbit, guinea-pig, pigeon	149	(100)	6 h/day for 5 days	Eye and nasal irritation; slight respiratory difficulty; slight decrease in haemoglobin	Flury & Zernik (1931)

5.2.1.5 Carcinogenicity

Suntzeff et al. (1940) conducted a study in which mice were given subcutaneous injections of 0.25 cc of a hydrogen chloride solution buffered to pH 5 with 1.02% acid potassium phthalate. The subcutaneous injections, repeated 6 times weekly for 10.5-16 months, induced local sarcomas at the site of injection in 4 out of the 8 mice. In view of the well-known potential of a wide range of materials to induce a local sarcoma at the site of subcutaneous injection, this study cannot be used to assess the oncogenic potential of hydrogen chloride.

5.2.1.6 Mechanisms of action

The biological activity of hydrogen chloride is associated with its high solubility in water i.e., 23 moles/litre at 0 °C (Elkins, 1959). The classical reaction of hydrogen chloride with water is: $HCl + H_2O = H_3O^+Cl^-$. The hydrogen chloride in water dissociates almost completely, with the hydrogen ion captured by the water molecules to form the hydronium ion. The hydronium ion becomes a donor of a proton (Bell, 1941) that possesses catalytic properties and thus is capable of reacting with organic molecules. This may explain the ability of hydrogen chloride to induce cellular injury and necrosis. Green (1950) studied the reaction of anydrous hydrogen chloride with collagen, and postulated a rapid reaction between hydrogen chloride and the basic amino-acid residues, and a much slower reaction with the aliphatic hydroxyl groups of the side chains of collagen.

Oedema is probably the most characteristic initial manifestation of hydrogen chloride toxicity, proceeding to additonal inflammation, degeneration, and necrosis of the tissues in contact with the material (NAS/NRC, 1976). Experimental studies on animals exposed to hydrogen chloride gas or aerosol have revealed injury to: the cornea and conjunctiva in mice and rats (Darmer et al., 1972); and the skin and surface mucosa, and the lower respiratory tract in rabbits and guinea-pigs (Machle, 1942). The muscosal lining of the upper respiratory tract is especially prone to injury, including necrotic erosions, during inhalation of hydrogen chloride vapour or aerosol. Following inhalation, death of the experimental animals has typically been attributed to respiratory injury, including pulmonary oedema, emphysema, and atelectasis.

6. EFFECTS IN MAN - CONTROLLED, CLINICAL, AND EPIDEMIOLOGICAL STUDIES

6.1 Chlorine

A Swedish chemist, K.W. Scheele, first described chlorine in 1774, and over the next century it became a commercial product (Kramer, 1967; de Nora & Gallone, 1968). During this period, a few scientists explored the chemical's biological properties, but it was not until the spring of 1915 that the irritant characteristics of chlorine generally became known to the public. At the beginning of the second battle of Ypres, at 17.30 h on 22 April 1915, warfare gassing was initiated using chlorine (Gilchrist & Matz, 1933). It was not ideal for this application and was soon replaced by other materials, but the acute results of these initial gassings were so dramatic that the general public still considers chlorine a poisonous war gas.

Because of its physical and chemical characteristics, chlorine is a bulk commercial chemical. Large quantities are used in the chemical and plastics industries, in pulp and paper production, and in water and sewage treatment plants, and the clinical and epidemiological studies of chlorine are mainly associated with these uses. In addition to the acute exposures experienced by troops during the First World War, there have been a few catastrophic accidental exposures of both industrial and general populations. Studies on the effects of long-term, low-level exposure to chlorine have been confined to occupational situations.

6.1.1 Controlled human studies

6.1.1.1 Odour perception and irritation

A variety of factors can affect the determination of the odour threshold level under laboratory conditions including the mode of presentation, the presence of extraneous odorants, the degree of subject training, definition of reaction, analysis of the data, and the chemical purity of the odorant.

The wide spread of these variables is apparent in Table 12, in which the information available on the subject of odour perception and irritation levels is summarized.

Table 12. Summary of controlled human studies on odour perception and irritation threshold levels for chlorine

Odour threshold mg/m³ (ppm)	Threshold of irritation mg/m³ (ppm)	Intolerable mg/m³ (ppm)	Number of subjects	Comment	Reference
3.8 (1.3)	3.8 (1.3) 8.7 (2.3)	11.6 (4)	2 1	Method of chlorine generation crude	Matt (1889)
0.3 (0.09)				Experimental method not described	Gyrgorova-Spižnikova (1952)
0.8-1.3 (0.24-0.39)			11 (238 tests)	Methods of selection of participant not discussed	Tahirov (1957)
0.13 (0.044) - Two subjects noticed odour as chlorine 0.26 (0.09) - all subjects noticed odour 0.29 (0.1) recognized as chlorine	0.13 (0.044) (1 subject of 10)	2.9 (1.0)	10	Perception of odour lost between 1 and 24 min; at 1 ppm some complaints of metallic taste and constriction of breathing	Beck (1959)
0.9 (0.3) - (most sensitive subject after 31 min) 1.3 (0.46) (least sensitive subject after 48 min)	0.9 (0.3) (3 subjects)	4.1 (1.4)	4	Throat and conjunctival irritation at 4.1 (1.4); some evidence of adaptation	

Table 12 (contd).

Odour threshold mg/m³ (ppm)	Threshold of irritation mg/m³ (ppm)	Intolerable mg/m³ (ppm)	Number of subjects	Comment	Reference
0.7 (0.24)			12 (aged 17-28)		Styažkin (1963)
0.75 (0.26)					Styažkin (1964)
0.06-0.15 (0.02-0.5) 50% of subjects reacted 0.15 (0.5) all subjects	0.06-0.15 (0.02-0.5) very mild		8-20 per study	Healthy chemistry students as subjects; some adaptation of odour threshold; difficulty in monitoring stability of exposure level	Rupp & Henschler (1967)
0.9 (0.314) (all subjects identify chlorine)			4	Trained analytical odour specialists used as subjects	Leonardas et al. (1969)
0.23 (0.08) perceived by 50% of subjects, at least 50% of the time			11	Double blind experiment	Dixon & Ikels (1977)

6.1.1.2 Reflex neurological changes

Much of the research involving chlorine has been related to effects on tissues with which it comes into direct contact, such as the olfactory nerve end organ and the mucous membranes of the eye and respiratory tract. A series of studies has been conducted on indirect effects including reflex changes in neurological activity. It has been argued that such adaptational reactions should be avoided (Rjazanov, 1965).

(a) Optical chronaxie

Chronaxie is the minimum time required to just excite a tissue with a current twice the rheobasic strength. In optical chronaxie testing, an electrical stimulus results in a sensation of light. Excitation of the cerebral cortex in one region (e.g., olfactory), can produce inhibition in another region (e.g., visual) (Rjazanov, 1965). Thus, the inhalation of a chemical such as chlorine may induce a simultaneous shift in the baseline optical chronaxie. Tahirov (1957) reported prolongation of optical chronaxie in 3 subjects exposed to a chlorine concentration of 1.5 mg/m^3 (0.52 ppm), but did not observe an appreciable effect at chlorine concentrations ranging from 0.6 to 1.0 mg/m^3 (0.21 to 0.34 ppm) (odour perception threshold: 0.8 mg/m^3). Approximately 2-2.5 min after cessation of exposure to the higher chlorine levels, the optical chronaxie returned to baseline levels.

(b) Visual adaptometry

Reaction to a visual stimulus can be defined in terms of threshold luminosity and speed of adaptation in darkness. Such reactions can be modified by exposure to some chemical substances, e.g., furfural and sulfur dioxide, which induce changes in light sensitivity at concentrations well below their respective odour thresholds (Rjazanov, 1965). This does not seem to be the case with chlorine (Tahirov, 1957). In a series of 75 tests on 3 subjects, a chlorine concentration of 1.5 mg/m^3 (0.52 ppm) elicited heightened light sensitivity, but exposure to a concentration of 0.8 mg/m^3 (0.28 ppm) did not induce any effects. Changes in sensitivity to light became evident only at, or above the odour perception threshold level.

(c) Other tests

A number of other test techniques (respiration frequency or rhythm, visual motor reaction, electrocortical conditioned reflexes, plethysmographic evaluation of peripheral blood

vessels) have been applied to evaluate the influence of chlorine on human reflexes. In general, no effects on these measurements have been noted on exposure to chlorine levels below the odour perception threshold (Tahirov, 1957).

6.1.1.3 Respiratory diseases

As early as 1816, Wallace suggested that chlorine might have medical applications; and in 1833, Bourgeois was reported to have used it successfully in the treatment of tuberculosis (Gilchrist, 1924). During the latter part of the nineteenth century and the first decades of the twentieth century, there were sporadic reports of the therapeutic effects of chlorine. Baskerville (1919) was of the opinion that small amounts of chlorine decreased the incidence of respiratory disease among workers. Vedder & Sawyer (1924) reported that chlorine inhalations were used in 1915 in Germany, to clear meningococcus and diphtheria carriers, and in 1918 in the USA as a treatment for influenza. They conducted a series of studies based on clinical observations that workers at a war gas production plant did not suffer from influenza during the great epidemic. They found that cultures of a variety of bacterial agents were effectively destroyed by exposure to chlorine at concentrations of 21 mg/m^3 of air (0.021 mg/litre, 7.2 ppm), a level they considered well within the limit of safety for human exposure. The bactericidal action was reported to be greater in vivo. A 1-h exposure to 20 mg/m^3 of air (6.9 ppm) effectively sterilized the tonsillar, postnasal, and pharyngeal surfaces of one subject, and a level of 15 mg/m^3 (0.015 mg/litre, 5.2 ppm) cured or produced clinical improvement in 95% of a series of 931 patients suffering from a variety of respiratory tract infections. In a follow-up series of 93 patients with coryza, acute bronchitis, chronic bronchitis, or influenza, 100% were reportedly cured or improved.

The therapeutic effects of chlorine were further discussed by Gilchrist (1924). During World War I, medical officers assigned to the front lines observed an apparent immunity to influenza in their troops. They attributed this lack of susceptibility to the disease to chlorine exposure and therefore used chlorine to treat respiratory diseases. Following these observations and the work of Vedder & Sawyer, Gilchrist constructed an inhalation chamber and treated some 900 patients with chlorine. Those with infectious diseases tended to show improvement; those with asthma or hay fever did not. He was of the opinion that 1-h exposures to levels

sufficient to produce mild irritation of the throat and eyes were the most efficacious.

While the results of these controlled therapeutic inhalations appear dramatic, the studies of both Vedder & Sawyer and Gilchrist were conducted without unexposed comparison groups. In Gilchrist's study, no attempt was made to document disease at the onset or to evaluate its evolution medically. The patients came with their own diagnosis and reported the outcome.

Though these studies reflect an interesting and historical hypothesis for the medical application of chlorine, experience has not provided justification for its practical use in this context.

6.1.2 Clinical studies

The classic treatise of Flury & Zernik (1931) remains an excellent review of studies on chlorine. They noted that chlorine affects the upper and lower respiratory tracts, either via the formation of hydrochloric acid or, according to Henderson & Haggard, by direct oxidation. Flury & Zernik reported the findings of Henderson & Haggard that high concentrations of chlorine irritate the skin, producing burning, stinging, inflammation, achrodermatosis, shrivelling, development of nodules, and blistering.

6.1.2.1 Immediate effects and sequelae of short-term exposures

Meakins & Priestley (1919) reviewed the medical records of 700 soldiers of the 1st Canadian Division, who had been gassed with chlorine during the attacks of 1915. While the authors' main interest was to evaluate the after-effects of the chlorine gas poisoning some 4 years later, they noted that the immediate effects were of both a physical and mental character.

Of all the troops exposed during the attacks, about one third returned to duty after a minimum amount of first aid. The remainder (478) were evacuated. Among 146 treated only at base hospitals, 6 died (presumably of the gassing) and 140 returned to duty. The other 332 were sent to the United Kingdom. In this group, the symptoms while in hospital were noted in 192 (57.8%) men. Bronchitis, pneumonia, or asthma was diagnosed in 69 (20.8%); 3 men died of acute pneumonia; and 2 died suddenly (possibly due to cardiovascular or cerebrovascular effects).

The physical condition, 4 years after exposure to chlorine, of 188 cases invalided out to Canada is shown in Table 13. The syndrome "irritable heart" remained the most prevalent condition in 78 (41.5%) cases. Unfortunately, this syndrome is not described in detail and it is difficult to equate it with any currently diagnosed conditions. The small number of cases that exhibited signs of bronchitis was most striking, with only 18 (9.6%) cases, 4 years after exposure. Furthermore, there appeared to be little correlation between the pulmonary signs shortly after exposure and those many years later.

Table 13. Physical condition, four years after wartime exposure to chlorine: most severe cases[a]

Condition	Number
no appreciable disease	54
irritable heart	78
neuroses	18
bronchitis, etc.	18
asthma	8
unable to trace	14
total	188

[a] Adapted from: Meakins & Priestley (1919).

With exposures of sufficient magnitude to induce marked dyspnoea and pulmonary oedema, death usually occurred within 24 h. Those surviving 48 h tended to recover, but exhibited weakness for several weeks.

Gilchrist & Matz (1933) carried out an extensive evaluation of the residual effects of warfare gases including chlorine. Using US War Department statistics, they determined that there had been 70 752 casualties as a result of gassing. Less than 3% of these were related to chlorine. They described the acute symptoms and signs as varying from irritation of the upper respiratory passages with cough and a sense of suffocation, to syncope, respiratory arrest, and death.

Residual effects of chlorine were evaluated by studying 838 of the total 1843 ex-members of the American Expeditionary Forces, who had been victims of chlorine gassing. Review of the records, 8-10 years after exposure, indicated that 28 had died, 16 due to trauma other than chlorine gassing, and 12 from disease. The causes of the 4 deaths that the authors attributed to the after-effects of chlorine gassing, were: broncho-pneumonia, lobar pneumonia, purulent pleurisy, and tubercular meningitis. A number of the men were also given disability discharges for the following conditions: pulmonary tuberculosis, bronchitis, pleurisy, neurocirculatory asthenia, tachycardia, dyspnoea, nephritis, laryngitis, valvular heart disease, keratitis, and conjunctivitis.

In a more detailed clinical follow-up of 96 of this subgroup of 838, 9 showed definite after-effects attributed to chlorine gassing, 7 had disabilities questionably related to gassing, and the remaining 80 had disabilities unassociated with the exposure. Pulmonary tuberculosis was the most common clinical picture in the 9 positive cases. A total of 5 had the disease, 3 with co-existing emphysema and 2 without. Bronchitis was the predominant condition in another 3 of the positive cases, and chronic adhesive pleurisy in the remaining case. In their preface, the authors emphasized that the great majority of the gas casualties made a complete recovery.

In his review of the data, Gerchik (1939) noted that a concentration of chlorine gas of 29 mg/m^3 (10 ppm) can be subjectively determined, 58 mg/m^3 (20 ppm) produces slight symptoms, and 2900 mg/m^3 (1000 ppm) causes death within 5 min. He broke the clinical picture into 2 phases. In the first, which he labelled the "asphyxiating phase" and thought lasted up to 36 h after exposure, the symptoms and signs included a burning sensation in the throat, coughing, dyspnoea, aphonia, bradycardia, pulsus tardus, cyanosis, and a subnormal temperature. He attributed death, when it occurred, to pulmonary oedema. In the second or "post-asphyxiating phase", he felt there was a subsiding of the pulmonary oedema but a development of serious bronchitis. In addition, the symptom complex included headaches, nausea, vomiting, weakness, and diarrhoea. If death occurred within 48 h, the lungs were reportedly grossly swollen and purplish-red. There was mixed atelectasis and emphysematous patches with sticky membranous exudate on the trachea and bronchial mucosa. He reiterated the possible relationship between chlorine exposure and pulmonary tuberculosis.

Römcke & Evensen (1940) described a massive chlorine release that took place in Mjondalen, Norway, as a result of a tank-car leak. Approximately 7-8 tonnes of chlorine gas formed a cloud over part of Mjondalen and down the valley to Drammen, 10 kilometres away. A total of 85 people, whose ages ranged

from 6 months to 82 years, were hospitalized with respiratory problems. The acute symptoms and signs included cough, dyspnoea, expectoration, physical changes in the lungs, fever, and vomiting. Only 6 had pulmonary oedema, but 3 of these died, 2 immediately, and 1 after 5 days in hospital. Autopsy on the last subject disclosed a confluent broncho-pneumonia in both lungs. The authors noted that the severest symptoms of pulmonary oedema developed most rapidly in patients who had been exposed during physical exertion.

In a follow-up to the accident in Mjondalen reported by Römcke & Evensen (1940), Hoveid (1966) described the chronic effects of short-term chlorine exposure. He felt that the after-effects were few and trivial, the most frequent complaint being dyspnoea. While there was not a control population, the author noted some dose response and therefore concluded that the reported difficulties may have been true consequences of the accident. On reconstructing the accident, Hoveid was of the opinion that all of the hospitalized casualties were exposed to a gas concentration of 87 mg/m^3 (30 ppm), and many to levels of 174 mg/m^3 (60 ppm), or more.

In an onboard submarine accident, 47 crew members were exposed to the gas (Tatarelli, 1946). Most of them smelled the chemical and some were thought to have been exposed to a concentration of chlorine equal to or higher than 100 mg/m^3 (34 ppm) for about a quarter of an hour. The 26 most serious cases underwent frequent medical examinations during the 2 months following the accident. In addition to the usual acute respiratory symptoms, 4 were found to have a palpable and painful liver, a condition that persisted during the entire course of surveillance. In another 4 cases, the hepatomegaly was of a transitory nature. Whilst the author attributed this condition to absorption of chlorine, 2 additional crew members, who had not been poisoned by the gas, also exhibited this clinical abnormality.

Exposure to chlorine from a leaking cylinder containing 40 kg of liquid chlorine resulted in 418 casualties in Brooklyn, New York, USA (Chasis et al., 1947). Most of these people were exposed when the chlorine gas flowed down into an adjacent subway. Though the authors were unable to determine the actual concentrations in the subway, they reported that the chlorine was perceived by witnesses as a cloud. There were no deaths among the casualties, but 208 required hospitalization. Chasis et al. described in detail the clinical features of a subgroup of 33 of the patients.

The immediate symptoms consisted of choking, nausea, vomiting, anxiety, and syncope. In milder cases, there was some burning of the eyes and nose. In the more severely affected, more marked respiratory distress was evident

including substernal pain, burning and constriction, and a choking sensation. These problems subsided in most patients within the 3-5 days following exposure. Cough, present in every patient as an immediate symptom, was controlled easily with medication during the first few days. It then increased in frequency and severity, becoming productive of thick, tenacious, mucopurulent sputum. Within 2 weeks, the cough disappeared.

Physical examination some hours after exposure revealed acutely ill patients in moderate to marked respiratory distress. Cyanosis was frequent, but conjunctival infection was rare. The respiration rate had increased and breathing was laboured. This was accompanied by suppression of the breath sounds and by the presence of dry and moist rales. The heart rate and body temperature was elevated. Though the respiratory distress tended to resolve quickly, suppression of breath sounds and dry rales, throughout both lung fields, tended to disappear more slowly. Moist rales, confined primarily to the bases posteriorly, increased during this period and persisted into the second week. Sputum production began between the second and sixth day. It was yellow-green, tenacious, and occasionally tinged with blood. Microscopic examination demonstrated moderate numbers of polymorphonuclear leukocytes and large numbers of epithelial cells in which degenerative changes were marked, the cytoplasm having a foamy appearance. Bacterial flora was mixed. The white blood count showed a slight increase.

In the majority of patients, X-rays of the lungs were reported to be unremarkable: however, serial X-rays showed some subtle changes; unequal aeration, pulmonary oedema followed by basilar pneumonia, and hilar pneumonia. Arterial oxygen saturation was measured in 8 patients 7-8 h after exposure. Compared with a normal of 96 (± 1.8)%, 6 patients showed abnormal values of 91.2, 90.5, 88.1, 84.6, 82.3, and 81.8%, respectively. Serial electrocardiograms in 12 patients either did not reveal any significant abnormality or showed changes indicative of pre-existing heart disease. Some 48 h after exposure, respirograms were made for 8 patients. The vital capacity and the (1 min) maximal breathing capacity were markedly reduced. Tracheobronchitis was diagnosed in all 33 patients, pulmonary oedema in 23, and pneumonia in 14. Predominance of abnormal physical signs at the bases of the lungs together with the roentgen records indicated that the pulmonary lesion induced by chlorine was predominantly basilar. The authors were not sure whether this was owing to ventilatory or circulatory factors. Among the 33, 14 had pre-existing disease. It was postulated that these individuals were either predisposed to a more severe form of intoxication

or, because of their infirmities, were unable to get away from the danger area as rapidly and, thus, suffered a longer period of exposure. The episode did not have any demonstrable effect on 2 pregnancies.

The authors were able to follow up 29 of the 33 patients. Over a 16-month period, none showed evidence that exposure to chlorine had resulted in permanent pulmonary disease. The most marked sequelae were anxiety reactions with phobias occurring in 16 of the 29 patients. One patient died 6 months later, following an appendectomy. Postmortem examination revealed a pulmonary embolus, but otherwise the lungs and bronchi were normal.

Jones (1952) summarized 16 years of clinical experience with 820 cases of chlorine gassing. The author did not see any evidence of pulmonary oedema or pneumonia, even among the most severe cases. Follow-up did not reveal any clinical or radiological evidence of permanent damage to the respiratory tract. Review of death certificates and sickness absenteeism did not show any excessive tendency towards the development of chronic bronchitis or emphysema.

In the Walsum disaster, which occurred in 1952, 17 tonnes of liquid chlorine were released, when a storage tank at a cellulose mill exploded (Baader, 1952). As a result, 240 persons were poisoned, 50 of them seriously and 8 fatally. The author noted symptoms related to respiratory tract irritation, headaches, and diarrhoea, the last of which, he felt, was probably neurogenic. Autopsies on 3 of the fatal cases showed "cerebrae purple" localized in the white matter of the brain and cerebellum, and diverse pictures of pulmonary abnormalities.

Approximately 100 persons were treated for various degrees of exposure to chlorine following the derailment and rupture of a railroad tank car (Joyner & Durel, 1962). The 24 000 litres (6000 gallons) of liquid chlorine produced a cloud that spread over 2400 ha. A chlorine concentration in air of 29 mg/m^3 (10 ppm) was found at the fringe of the contaminated area, and a level of 1160 mg/m^3 (400 ppm), 68 metres from the wreck. At least 10 casualties developed pulmonary oedema and an 11-month old infant, who had been in a house some 45 metres from the tank car, died. Frantic over the infant's choking and gasping, the father carried him out into the thicker clouds of gas. A 21-month-old sibling, who remained in the house, survived. Some victims were noted to have minor first degree burns, principally of the face. The authors reported that these burns resulted from vapour exposure and not from splashes. Chest X-rays made on the hospitalized patients, 3 to 4 days after exposure, revealed fine miliary mottling distributed bilaterally and symmetrically throughout

both lung fields. There were no indications of localized pneumonitis and the findings had cleared 12 days after exposure.

In a detailed investigation of the same accident (Segaloff, 1961), the strong psychological reactions of the victims were emphasized. A degree of mass hysteria seems to have been evident, and it was most prominent among those with "slight tendencies towards neurosis". In addition to the respiratory complaints, noted by Joyner & Durel, Segaloff related that one physician reported several cases of congestive heart failure among elderly victims. All responded to treatment.

A group of 12 subjects from this episode was assessed for up to 7 years after the exposure to chlorine gas (Weill et al., 1969). These subjects were among the most severely affected in the accident. They included the parents and 3 of the siblings of the single fatal case. The authors concluded that their data were consistent with the clinical view that significant permanent lung damage does not result from short-term exposure to chlorine.

On the basis of their clinical experience as occupational physicians in the chemical industry, Gay (1963), Flake (1964), and Kramer (1967) outlined the effects of short-term chlorine exposures. At lower concentrations, the effects are confined to the perception of a pungent odour and a mild irritation of the eyes and upper respiratory tract. These symptoms resolve shortly after cessation of exposure. Slightly higher levels produce immediate severe irritation of the mucous membranes of the nose, throat, and eyes, a paroxysmal cough, and anxiety. With oxygen and a sedative cough syrup, the patient becomes asymptomatic within a few hours. At still higher levels of short-term chlorine exposure, the patient develops a severe productive cough, difficulty in breathing, and cyanosis. Vomiting and anxiety are often marked. While forced expiratory volumes tend to be reduced, and rales may be heard on auscultation, X-rays of the lungs are usually negative. With palliative treatment, the patient tends to recover within a few days. Because of the irritant qualities of chlorine, most people tend to remove themselves voluntarily from significant exposures. However, a person who has been trapped in an area with a high air concentration of chlorine gas constitutes a medical emergency. Shock, coma, and respiratory arrest may be present. Pulmonary oedema may develop and complications, such as pneumonia either of infectious or aspiration origin, should be anticipated.

In the spring of 1961, 156 longshoremen were exposed to chlorine, when the main valve of a cylinder was snapped off during unloading. Kowitz et al. (1967) examined 11 of the more

seriously affected at four different times after exposure: 30-60 days, 6 months, 14 months, and 2 years. They also studied 59 of the men 19-35 months after the accident. Among those examined repeatedly, all symptoms had cleared within 1-3 weeks with the exception of exertional dyspnoea, easy tiredness, and cough; however, pulmonary function testing at 4-6 weeks revealed findings compatible with a picture of acute alveo-capillary injury. Abnormalities were also noted at 6 months, but were less severe. In later examinations, lung volumes continued to improve. The authors interpreted their findings as indicative of persistent lung damage with trends towards recovery. Among the 59 patients studied 19-35 months later, the authors noted decreased lung capacity, increased elastic work of breathing, and decreased diffusing capacity. These findings were considered to be the result of exposure to chlorine.

While these studies were exhaustive, certain limitations should be taken into account when interpreting the results. There were no pre-exposure base-line values. Furthermore, Kowitz et al. (1967) relied on volunteers, thereby introducing a possible selection bias, and no control populations were used in either of the investigations. Instead, the authors applied clinical standards as reference points. For example, predicted vital capacity was derived from the nomogram of Kory et al. (1961). This nomogram, in turn, was developed from a study of hospital workers, patients, medical students, and resident and full-time physicians, and did not produce separate formulae according to race and smoking habits (Damon, 1966).

Dixon & Drew (1968) published a clinical case report of a 49-year old man who, without respiratory protection, remained in a chlorine gas cloud for 30 min. The man died of pulmonary oedema, 3 h after exposure.

In another series of case reports, Beach et al. (1969) discussed 7 persons who were exposed to chlorine in separate accidents. Respiratory symptoms lasted 2-8 days; and chest X-rays, while initially abnormal, cleared within 1-10 weeks. All the patients recovered completely.

Uragoda (1970) reported the case of a 37-year-old man, exposed to chlorine during the course of employment at a water purification plant. In addition to the familiar respiratory complaints, the man had ventricular extrasystoles. While reluctant to attribute the arrhythmia to chlorine, the author noted a change in its pattern and frequency over a 1-month period and postulated that the gas might have aggravated a pre-existing condition.

In a review of the records of 99 people acutely exposed to chlorine (87 cases) or phosgene (12 gases), Faure et al. (1970) came to the following conclusions: that the toxic

effects of chlorine gas occur exclusively in the respiratory system, that poisoning is relatively benign, that few exposures result in fatalities; and, that sequelae are infrequent.

Sessa et al. (1970), disagreed to some extent. Based on observations of 12 people, they concluded that the clinical signs of chlorine exposure were confined mainly to the upper airways (pharynx, larynx, trachea, and large bronchi). Furthermore, chlorine inhalation, especially if repeated, and even if associated with minor signs of damage that were transitory and well tolerated, could produce persistent functional damage, adversely affecting the working capacity of those exposed. These authors felt that the effects could continue to evolve after cessation of exposure.

Thirty-five residents of Cleveland, Ohio, were affected when a liquid chlorine storage tank at a water filtration plant developed a leak. Adelson & Kaufman (1971) reported on the 2 deaths that occurred, a husband and wife in their late twenties. The man was alert and without serious respiratory distress until about 10 h after exposure, when he developed acute hypertension and tachypnoea. He died 15 h later. The woman demonstrated dyspnoea and cyanosis from the outset. After a brief amelioration in her condition, she became comatose and died 76 h after exposure. At autopsy, both had severe pulmonary oedema, pneumonia, hyaline membrane formation, multiple pulmonary thrombosis, and ulcerative tracheobronchitis. In addition, the woman had glomerular capillary thrombosis and multiple focal and confluent brain haemorrhages.

The clinical course of 18 other adults who were victims of the same accident was studied by Kaufman & Burkons (1971). All were examined within 7 days of exposure and 1, 2, and 4 months later. A subgroup of 12 of the victims was also studied again, 12-14 months after exposure. All developed acute obstructive airway disease. The symptoms and signs in those who lived in the neighbourhood of the filtration plant were transitory. In contrast, 4 of the 5 workers at the plant showed persistent obstructive airway defects and mild hypoxaemia.

In an article by Chester et al. (1977), it was suggested that the chronic effects of chlorine exposure may be the results of both the initial exposure and the subsequent therapy. Two sisters were exposed to toxic quantities of chlorine gas in the same room at their home during the industrial accident described by Kaufman & Burkons (1971). One patient was treated as an in-patient with oxygen therapy and adrenocortical steroids; the second received brief oxygen therapy in the emergency room and was discharged. Though both patients were presumably exposed to equivalent sublethal

concentrations of chlorine, the first sister was essentially normal at the end of 2 years, the second had demonstrable abnormalities in gas exchange after 55 months.

In another clinical report, Leube & Kreiter (1971) described the clinical pictures of 90 persons who had undergone short-term, high-level exposure to chlorine. In addition to the usual respiratory problems, several had mild electrocardiographic abnormalities. The sedimentation rate was not elevated, but most showed marked leukocytosis (maximum 26 500 per mm^3), and 40% had elevated levels of glutamate-pyruvate-transaminase. There were also a few persons with low grade increases in glutamic-oxaloacetic transaminase (EC 2.6.1.1), but all determinations for lactate-dehydrogenase (EC 1.1.1.27) activity were judged normal. The leukocytosis apparently resolved rapidly and the enzyme profile was postulated to be a result of temporary toxic injury to the liver.

Colardyn et al. (1976) reported the results of a 3-month follow-up of 14 people, who had been involved in an industrial accident. The initial obstructive airway pattern, as seen in pulmonary function tests, resolved rapidly after 5 days and disappeared after 20.

Most short-term, high-level exposures are associated with industrial accidents. However, a number of authors have also reported accidental and, in at least one case, probably intentional, inhalation of fumes from common household cleaning agents (Malone & Warin, 1945; Faigel, 1964; Jones, 1972; Murphy et al., 1976). Murphy et al. (1976) described a case in which a woman was exposed in the home, when she mixed several cleansing agents together in an attempt to unclog a kitchen drain. On reviewing the chemicals, the authors postulated a mixed exposure to chlorine, nitrogen dioxide, and phosgene. The woman exhibited grossly reduced flow rates, hyperinflation, and was diagnosed as having diffuse airway obstruction, probably associated with bronchiolitis obliterans. After 4 months treatment with prednisone, total forced vital capacity (FVC) increased from 2.59 litres to 2.95 litres.

Hicks (1977) discussed briefly the drying effects on the skin and hair of chlorinated water. Swimmers have reported a bleaching effect of chlorine on their hair, some have developed "green hair", and many a chemical conjunctivitis. There have also been occasional reports of asthma precipitated by exposure to chlorinated water (Watson & Kibler, 1933; Sheldon & Lovell, 1949).

6.1.3 Effects of long-term (industrial) exposure - epidemiological studies

In their review of harmful gases, Flury & Zernik (1931) suggested that long-term exposure to chlorine contributed to premature aging, bronchial afflictions, pulmonary haemorrhages, and tuberculosis.

The degree of olfactory deficiency associated with long-term exposure to chlorine was studied by Laciak & Sipa (1958). Among 17 workers, abnormal olfaction was found in 100%, with the most severe aberrations among those with long employment and a past history of chemical intoxication (Table 14 and 15).

Table 14. Olfactory deficiency by years of employment among workers exposed to chlorine[a]

Years of employment	Degree of olfactory deficiency				
	none	slight	moderate	severe	total
0-1	0	2	1	1	4
2-5	0	1	1	11	13
total	1	3	2	12	17

[a] Adapted from: Laciak & Sipa (1958).

Table 15. History of acute attacks by degree of olfactory deficiency among workers exposed to chlorine[a]

History of acute attacks	Degree of olfactory deficiency				
	none	slight	moderate	severe	total
yes	0	0	0	11	11
no	0	3	2	1	6

[a] Adapted from: Laciak & Sipa (1958).

While this was a cross-sectional study and, thus, the temporal relationship between chlorine exposure and olfactory

deficiency could not be determined, the authors implied that chlorine exposure - possibly short-term to high levels - decreased the olfactory sense. This, in turn, allowed the workers to be exposed more often and more severely.

A group of 271 men employed in Berlin, New Hampshire, USA were studied by Ferris et al. (1967). Of these, 147 worked in a pulp mill and were potentially exposed to chlorine, sulfur dioxide, chlorine dioxide, and/or hydrogen sulfide. The remaining 124 worked in a paper mill without these concurrent exposures. Among those working in the pulp mill, there were 2 sub-groups, one exposed mainly to sulfur dioxide, the other to chlorine (mean concentration 7.38 mg/m^3 in the first and traces in two follow-up surveys) or chloride dioxide. Respiratory function among men working with chlorine was lower than that of men associated with sulfur dioxide, but the difference was not statistically significant. When both mills were compared, the prevalence of respiratory disease was equivalent, but the prevalence was lower for the total mill population in comparison with the control local male population. The authors noted that a selection process may have been operative in the mills.

Krause et al. (1968) and Chester et al. (1969) reporting on the prevalence of chronic obstructive pulmonary disease in chlorine gas workers, indicated that patterns of short-term, high-level exposure combined with occasional long-term, low-level exposure in contrast to only long-term, low-level exposures, may be associated with decreased maximum mid-expiratory flow. Furthermore, the combined effects of smoking and chlorine seemed to be worse than those of either agent alone.

In studies by Capodoglio et al. (1969), 52 workers in a mercury-cell chlorine production unit, with a mean duration of employment of 10 years were examined. Environmental levels of chlorine at the time of the study were reported to be less than 1.1 mg/m^3 (0.37 ppm) (mean: 0.86 mg/m^3). However, all the employees had also experienced previous short-term, high-level exposure. As controls, the authors selected 27 unexposed employees from the same plant. Apart from a lower carbon monoxide diffusion capacity, which the authors attributed to cigarette smoking, respiratory function and prevalence of chronic lung diseases were not statistically significantly different between the two groups.

Among a total population of 600 diaphragm cell workers from 25 plants manufacturing chlorine in North America, Patil et al. (1970) were able to obtain time-weighted exposure data and medical information on 332. The duration of chlorine-exposure was about 11 years; many workers also had undergone concurrent exposure to mercury. The chlorine exposure ranged from < 0.03 mg/m^3 (0.01 ppm) to 4.12 mg/m^3 (1.42 ppm) (mean 0.44 ± 0.84 mg/m^3) with 78.6% of this study group being exposed to between 0.03 mg/m^3 (0.01 ppm) and 1.28

mg/m^3 (0.44 ppm). The control group, consisting of workers from many of the same plants, who were not considered to be routinely exposed to chlorine, numbered 382. Symptoms such as nervousness, frequent colds, chest pains, shyness, tooth decay, and anxiety were complained of by diaphragm cell workers more often than by controls ($P<0.05$), while the reverse held for the symptoms of palpitation and insomnia, and for objective signs such as abnormalities of teeth and gums, abnormal reflexes, objective tremors, and abnormal chest X-rays. Pulmonary function tests revealed normal values in the vast majority of both exposed and control workers. The prevalence of abnormal findings was not higher in the exposed group than in the controls. In the absence of a dose-response relationship, the authors could not attribute any of the findings to chlorine exposure. From the point of view of dose-response, they were only able to find inverse correlation with haematocrit. An increase in tooth decay on history was not corrobarated by examination.

By the nature of the study and the data presented, the hypothesis suggesting that olfactory deficiency is caused by chlorine exposure may not necessarily be correct and therefore requires further investigation.

It should be noted that in the absence of unexposed controls, another hypothesis is also possible, namely that those with pre-existing olfactory deficiencies may be more susceptible to subsequent accidental over-exposure through being unable to detect the warning properties (odour) of the chemical.

Ferris et al. (1979) conducted a 10-year follow-up study on the group of New Hampshire pulp and paper mill workers described earlier (Ferris et al., 1967), studying the mortality experience of all 271 and the morbidity patterns in the available subgroup of 200. Overall, among the 71 workers identified in the 1963 cohort as being exposed to chlorine, 9 deaths were observed with 9.06 expected, giving a standardized mortality ratio of 99. While absolute numbers were small in the various specific cause-of-death categories, the authors concluded that the mortality pattern was consistent with that seen for the USA as a whole.

Health questionnaire results and various physiological measurements were available for 48 of the original 1963 chlorine cohort. Among the actively employed chlorine workers (n=27), forced vital capacity (FVC) and one second forced expiratory volume ($FEV_{1.0}$) were above expected, whereas among the retired (n=21), these were lower. The 1963 pulmonary functions of the 9 who had died prior to the 1979 studies were below the comparable figures for either employed or retired. The authors alluded to the possibility of effects due to earlier exposure to high levels of chlorine.

6.1.4 Teratogenicity, mutagenicity, and carcinogenicity

Skljanskaja et al. (1935) reported the outcome of 15 pregnancies among female workers at a chlorine plant in the years 1932-33. Of these, 13 births were normal and 2 were premature. In one of these 2 cases, a 6 1/2-month-old female fetus was stillborn; induced abortion was suspected. In the other, the 4 1/2-month-old fetus was macerated and no definitive cause was established. No mention was made of possible congenital malformations. The authors concluded that pregnancy, delivery, pueperium, and lactation were not affected.

In a series of *in vitro* experiments on a human lymphocyte culture system, Mickey & Holden (1971) reported that chlorine concentrations 2-20 times those normally found in drinking water induced chromatid and chromosome breaks, translocations, dicentric chromosomes, and gaps. They doubted that chlorine was absorbed from drinking water, but suggested that *in vivo* studies were needed.

Ferris et al. (1979) determined that unusual patterns of cancer mortality were not evident from a mortality study of 71 chlorine workers. This finding is in agreement with the conclusions in other reviews (NIOSH, 1976; NAS, 1976).

6.2 Hydrogen Chloride

6.2.1 Controlled human studies

6.2.1.1 Odour perception threshold levels

A wide variety of results has been reported in the literature concerning the odour perception threshold level for hydrogen chloride. Much of this variation may depend on the duration of exposure and the training of the observers. As with chlorine, the threshold figure will depend on whether the level is set when only one or all subjects detect the odour (Table 16).

In the process of recording their subjective reactions to hydrogen chloride exposure in the field and correlating these with the results of concurrent environmental measurements, trained industrial hygienists reported no reaction at 0.09-2.68 mg/m^3 (0.06-1.8 ppm), minimum reaction at 0.10-3.23 mg/m^3 (0.07-2.17 ppm), obvious perception at 2.83-12.8 mg/m^3 (1.9-8.6 ppm), and strong reaction at 8.3-32.9 mg/m^3 (5.6-22.1 ppm) (NAS/NRC, 1976).

Table 15. Odour perception threshold levels for hydrogen chloride

Odour threshold mg/m³ (ppm)	No. of subjects	Comments	Reference
28.3 (19) (perceived by 1 subject) 135.6 (91) (perceived by 50% of subjects) 459 (308) perceived by 2 subjects)	23	Unaffected by smoking habits	Rinehart & Jacobson (1955)
0.1 (0.07) (3 subjects) 0.2 (0.13) (9 subjects) 0.3 (0.20) (1 subject)	13 (336 tests)		Elfimova (1959)
0.15-0.20 (0.10-0.13)	not stated		Stjažkin (1963, 1964)
0.39 (0.20)	not stated		Melahina (1966)
14.5 (10) (all 4 subjects recognized the odour as hydrogen chloride)	4	Trained odour panel used	Leonardas et al. (1969)
0.1 (0.07) (in presence of chlorine at 0.3 (0.10)) 0.13 (0.09) (in presence of chlorine at 0.2 (0.07))	22 (404 tests)		Stjažkin (1963, 1964)

6.2.1.2 Reflex neurological changes

In addition to determining odour threshold levels, Elfimova (1959) conducted tests to evaluate the effects of hydrochloric acid aerosols on optical chronaxie, blood vessel tone, dark adaptation, and respiration. The results varied. Inhalation of the aerosol in concentrations of 0.6-1.5 mg/m³ (0.40-1.01 ppm) shifted the value for optical chronaxie, but those of 0.2-0.4 mg/m³ (0.13-0.27 ppm) did not induce any appreciable effect. The threshold level for this test was determined statistically to be 0.6 mg/m³ (0.40 ppm), a value higher than the odour threshold reported by this author.

Changes in blood vessel tone were also observed at levels above the values related to odour threshold. Only at, or above 0.5 mg/m³ (0.34 ppm) did inhalation of hydrochloric acid aerosols effect changes in vascular reactions. In contrast, the threshold levels for dark adaptation and respiration effects were similar to that for odour perception, i.e., 0.2 mg/m³ (0.13 ppm) and 0.1-0.2 mg/m³ (0.07-0.13 ppm), respectively.

In a subsequent article (Elfimova, 1964), more detailed descriptions of the tests were presented. While the figures relating to the threshold levels for optical chronaxie, dark adaptation, plethysmographic, and pneumographic shifts were comparable to those previously reported, the author emphasized the effects on dark adaptation of exposure to the then acceptable hydrogen chloride concentration of 10 mg/m³ (6.7 ppm), suggesting that this value was too high.

Melehina (1966) also investigated the reflex effect of hydrochloric acid on eye sensitivity to light. Using volunteers, 17, 27, and 32 years of age, the author obtained results consistent with those of Elfimova. The threshold levels for both odour and light adaptation were the same. In Melehina's tests, the value was 0.4 mg/m³ (0.27 ppm).

6.2.1.3 Effects of hydrogen chloride in combination with chlorine

(a) Odour perception and irritation

The threshold levels of odour perception for a combination of chlorine and hydrogen chloride were determined by Stjažkin (1963, 1964). In a series of 404 tests on 22 volunteers, using the methods previously described, the following threshold odour perception concentrations of chemicals simultaneously present in the air were observed; chlorine at 0.3 mg/m³ (0.10 ppm) with hydrogen chloride at 0.1 mg/m³ (0.07 ppm) and chlorine at 0.2 mg/m³ (0.07 ppm) with hydrogen chloride at 0.13 mg/m³ (0.09 ppm).

(b) Reflex neurological changes

Stjažkin (1963, 1964) noted that combinations of chlorine at 0.3 mg/m³ (0.10 ppm) with hydrogen chloride at 0.2 mg/m³ (0.13 ppm) or chlorine at 0.2 mg/m³ (0.07 ppm) with hydrogen chloride at 0.3 mg/m³ (0.20 ppm) were effective in altering threshold levels in optical chronaxie. However, the simultaneous presence of chlorine and hydrogen chloride gas at concentrations of 0.1 mg/m³ and 0.05 mg/m³ (0.03 and 0.034 ppm), respectively, did not have any effect on dark adaptation.

6.2.2 Short-term exposures

Hydrogen chloride, a strong irritant, dissolves rapidly in water, manifesting its effect in the presence of moisture. Small quantities are reportedly more easily detected by taste than by smell; and eyes, skin, nose, mouth, pharynx, larynx, and trachea are the primary targets (Flury & Zernik, 1931). Short-term exposures may cause conjunctival irritation, superficial corneal damage, and transitory epidermal inflammation, but effects on the upper respiratory tract are predominant. According to Flury & Zernick (1931), 52 mg/m^3 (approximately 35 ppm), a level below the threshold for taste or eye irritation, can induce sneezing, laryngitis, chest pain, hoarseness, and a feeling of suffocation. Exposure to hydrogen chloride can also cause ulceration of the nasal septum. The authors suggested that tolerance can be acquired, with some individuals capable of enduring short-term exposures of up to 998-1863 mg/m^3 (670-1250 ppm). According to these authors, long-term exposures induced brown spots and the erosion of the crowns of teeth, especially the incisors.

Perspiration-soaked clothing can absorb the chemical, producing an acid solution against the skin, with consequent irritation and possible burns (MCA, 1970). Nagao et al. (1972) reported the results of skin biopsies taken from 7 volunteers, 15-180 min after application of 1 N hydrochloric acid, but apparently this was a study conducted to establish a baseline picture of histopathology.

A report of 3 cases of hydrochloric acid poisoning, 2 fatal and 1 non-fatal, was published by Jacobziner & Raybin (1962). In all 3 cases, the material was ingested. In the authors' opinion, in acute poisoning, the concentration of the solution is more important than the volume in relation to symptomatology and outcome. They offered the following symptom complex for chronic poisoning: laryngitis, bronchitis, coryza, and conjunctivitis.

6.2.3 Long-term exposure

Toyama et al. (1962) discussed their studies on hydrochloric acid aerosol inhalation and associated changes in maximum expiratory flow rate. Using 2 exposed groups, "habituated" workers (n = 13) and previously unexposed controls (n = 10), and evaluating pulmonary function measurements before and after treatment with bronchodilators, the authors concluded that inhalation of hydrochloric acid

aerosols caused a transitory constriction of the respiratory tract. Following prolonged exposure, this reaction became dulled.

Ten Bruggen Cate (1968) studied dental erosion in 555 workers, 352 of whom were exposed to combinations of acids that included hydrochloric acid. He concluded that the erosion affected the incisors, the teeth most exposed to the atmosphere, and became more prevalent as the acid level increased. The earliest sign of abnormality was etching of the inciso-labial surfaces progressing to actual loss of enamel and, in some cases, production of an open bite. The erosion typically had rounded margins and was confined to the anterior teeth, differentiating it from other types of dental destruction. The author postulated that acid-eroded enamel was also more easily attrited; this accelerated the loss of tooth structure among the exposed workers. In contrast, the acid environments did not influence dental caries or calculus deposition.

According to Stahl (1969a), there are no known chronic or acute systemic effects of hydrochloric acid; it produces only local effects on the membranes of the eyes and upper respiratory tract. No damage occurs with exposure to a concentration of 7.0 mg/m^3 (4.7 ppm), but irritation of the mucous membrane can result at 15 mg/m^3 (10.0 ppm). Acclimatized workers can work undisturbed at the second concentration. Above this level, irritation increases and work becomes intolerable at 75-150 mg/m^3 (50.3-100.5 ppm).

6.2.4 Teratogenicity, mutagenicity, and carcinogenicity

Teratogenic, mutagenic, or carcinogenic effects have not been reported in man in relation to hydrogen chloride exposure. It has been suggested that hydrogen chloride and formaldehyde can react in the atmosphere to form bis-chloromethylether, a carcinogen, but the reaction occurs at levels of chloride and formaldehyde between 745 and 4470 mg/m^3 (500-3000 ppm) (NIOSH, 1976). At the levels at which mixtures of these two chemicals are encountered in the industrial environment, bis-chloromethylether has been found to be non-detectable in the low parts per trillion range (Tou & Kallos, 1976).

7. EVALUATION OF HEALTH RISKS TO MAN FROM EXPOSURE TO CHLORINE AND HYDROGEN CHLORIDE

Neither chlorine nor hydrogen chloride from natural sources is found at significant background levels. Some groups of workers undergo long-term, low-level exposures and they, as well as small numbers of the general population, are occasionally exposed to higher levels, as a result of industrial or transportation accidents.

7.1 Exposure Levels

There is little evidence that the general public is exposed routinely to measurable quantities of gaseous chlorine and/or hydrogen chloride. Even the hydrogen chloride produced during the combustion of fossil fuels or the incineration of solid waste apparently lasts too short a time in the unreacted state to pose a significant health risk.

Though both chemicals are commonly added to municipal drinking water to control pathogenic organisms or to adjust pH, they do not pose any appreciable exposure potential for those who consume the water. Additional chlorination is used in swimming pools, sometimes to the extent of producing an obvious odour, presumably at air concentrations between 0.06 mg/m^3 (0.02 ppm) and 5.8 mg/m^3 (2 ppm), the possible presence of chloramines being perhaps a complicating factor in this estimate.

At present, exposures of workers during the manufacture and use of chlorine usually fall below 2.9 mg/m^3 (1 ppm), but occasional excursions up to 44 mg/m^3 (15 ppm) have been recorded in the past. In addition, higher concentrations have been reached during plant malfunctions. Members of the general population have occasionally been exposed to high concentrations of chlorine after massive accidental releases, mechanical rupture of transportation vessels, or malfunction of water or waste treatment facilities.

Hydrogen chloride levels during routine occupational exposures are usually controlled at time-weighted averages of 7 mg/m^3 (5 ppm) or less. Accidental exposures to higher levels have occasionally been reported in industry, but not in the general population.

7.2 Experimental Animal Studies

Chlorine, presumably due to direct action of the chemical at the site of contact, manifests its major effects on the pulmonary tissues. Short-term exposure to 370-2900 mg/m³ (127-1000 ppm) caused death in several animal species; levels as low as 29-87 mg/m³ (10-30 ppm) have been associated with definite signs of toxicity in rodents. Dose-related effects have also been noted in rats with repeated exposures of 2.9-26 mg/m³ (1-9 ppm). In rabbits and guinea-pigs, 2 mg/m³ (0.7 ppm) is the reported no-observed-adverse-effect level.

Hydrogen chloride has a strong affinity for water; consequently, the ocular conjunctiva and mucous membranes of the upper respiratory tract are predominant targets. Short-term exposures (5 min) to 5500 mg/m³ (3685 ppm) were found not to be lethal for rabbits and guinea-pigs; however, 100% mortality was reported at 1000 mg/m³ (670 ppm), when the duration of exposure was extended to 6 h. Some effects have been noted in mice following single, 10-min exposures to 25.3 mg/m³ (17 ppm). The Task Group did not find any reports of long-term exposure studies.

7.3 Controlled Studies in Man

Human studies with chlorine have focused on the subjective perception of odour and irritation, objective measurements of reflex neurological activity and pulmonary function, and clinical observations of respiratory infection. Threshold levels for both odour perception and irritation have been reported in the range of 0.06-5.8 mg/m³ (0.02-2 ppm); however, the odour perception threshold, under laboratory conditions, is likely to be about 0.3 mg/m³ (0.1 ppm). Sensory irritation, i.e., conjunctival and upper respiratory discomfort, is obvious at 2.9 mg/m³ (1.0 ppm), and intolerable at 11.6 mg/m³ (4.0 ppm). Generally, changes in chronaxie, visual adaptation, and related activity have been observed at, or above, the threshold level for odour perception; the significance of these effects for human health is not clear.

Studies with hydrogen chloride have been more limited. Odour perception threshold levels, measured under laboratory conditions, have been reported over a wide range: 0.1-459 mg/m³ (0.07-308 ppm). While there have been occasional reports of acquired tolerance, it is difficult to believe that this phenomenon could account for the range in odour

perception threshold levels found in the literature. It was the Task Group's opinion, that most people in the general population would probably perceive hydrogen chloride near the lower end of the range. Exposure to hydrogen chloride is probably uncomfortable at 45 mg/m^3 (30 ppm) and extremely uncomfortable at 450 mg/m^3 (300 ppm), even for brief periods, for those without acquired tolerance.

7.4 Field Studies in Man

Chlorine is a highly reactive compound that is used in large quantities by the chemical and plastics industries, pulp and paper producers, and water and sewage treatment facilities. While manufactured, transported, stored, and used predominantly in closed systems, inadvertent exposures of the general and industrial populations have occurred.

Subjective complaints of odour, and irritation of the eyes and upper respiratory tract, under field conditions, are associated with short-term, low-level exposures to chlorine. At higher levels, the irritation becomes more pronounced and the lower respiratory tract may become affected. There may be paroxysms of cough, dyspnoea, and anxiety. At still higher levels, probably above 87-116 mg/m^3 (30-40 ppm), the dyspnoea and anxiety become more pronounced, and vomiting, cyanosis, and pulmonary oedema are observed. In addition, those involved in some form of exertion seem to be at greater risk at the higher exposures, presumably because of increased ventilatory exchange. Symptomatic treatment is usually effective and long-term sequelae are uncommon.

From three cross-sectional surveys of workers exposed respectively to mean chlorine levels of: (a) 0.86 mg/m^3 (0.298 ppm); (b) 0.44 mg/m^3 TWA (0.15 ppm) (78.6% being exposed to 0.03-1.28 mg/m^3); and (c) 21.5 mg/m^3 (7.4 ppm) at early stages of exposure but only traces at later stages, it does not appear that long-term exposure to the chemical induces any increased or unusual illness.

Apparently, because of its mode of use and excellent warning properties, fewer episodes of overdosing have been reported for hydrogen chloride than for chlorine. Short-term exposures to hydrogen chloride levels exceeding 52 mg/m^3 (35 ppm) have resulted in conjunctival irritation, superficial corneal damage, and transitory epidermal inflammation; however, effects on the respiratory tract, especially the upper respiratory tract, predominate. No studies concerning the long-term effects of short-term, high-level exposures have been reported.

Long-term exposure to hydrogen chloride (presumably above 45 mg/m³ (30 ppm)) reportedly erodes the teeth, especially the incisors. Although some evidence of acquired sensory tolerance in long-term exposures has been reported, the Task Group recognised the need for further observation.

7.5 Evaluation of Health Risks

Since the health risks associated with occupational exposures to these two chemicals will be considered by a future WHO Task Group, this Task Group focused on the health risks to the general population.

It is the opinion of the Task Group that, with the present analytical techniques, it is difficult to distinguish between chlorine and other chloride species and impossible to distinguish between man-made and natural contributions at the ambient levels to which the general population may be exposed.

On the evidence available, the Task Group believes that exposure of the general population to either chlorine or hydrogen chloride, other than during accidental releases, is minimal and almost unmeasurable. On the basis of the limited information available from industrial survey data, and from the observations of controlled exposure studies, it is most unlikely that the general population is exposed routinely to any significant health risks from either of these two chemicals.

There are not sufficient epidemiological data related to community exposure to serve as a basis for reliable environmental quality guides for chlorine or hydrogen chloride. Therefore, in an endeavour to develop some guidelines for the protection of the health of the general population, the Task Group had also to rely on limited data from controlled human and experimental animal studies. The Group considered sensory irritation and objective changes in pulmonary function to be likely critical effects.

From the available data, the Task Group concluded that, if irritation is the critical effect from which the general population is to be protected, ambient levels of chlorine should be kept below 0.1 mg/m³ (0.034 ppm). The Task Group believes that this may also protect the general population from any significant reduction in ventilatory capacity. The Task Group warns that this value must be used cautiously, because of the inherent limitations of the underlying data.

In view of the limited data available, the Task Group was unable to establish a comparable figure for hydrogen chloride.

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