III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Phosgene is a colorless gas at normal temperatures and pressure. When liquified under pressure or refrigeration, it is a colorless-to-light yellow liquid. [1] In low concentrations, its odor has been variously described as resembling that of musty hay [2] or green corn. [3] Phosgene is easily manufactured by passing chlorine and excess carbon monoxide over activated carbon. [3] Shortages of chlorine and attendant high prices have somewhat restricted the manufacture of phosgene in recent years. [4] Some phosgene can also be produced by the decomposition of chlorinated hydrocarbons by heat or by ultraviolet radiation. [5,6,7,8,9] Relevant properties of phosgene are presented in Table XIII-1. [1,2,10,11,12]

Phosgene was first used as a chemical warfare agent during World War I. Its use in industry is a relatively recent development. [3] Accordingly, much of the literature on phosgene is concerned with its military applications. Phosgene production in the United States in 1957, the first year the US Tariff Commission started reporting phosgene output, was only 5 million pounds. [3] In 1967, production reached 350 million pounds, [3] in 1971, 530 million pounds, [13] while in 1972, it had increased to 657 million pounds. [14] In contrast to these figures, sales in 1971 were only 11,215,000 pounds [13] and 11,678,000 pounds in 1972. [14] The apparent discrepancy between production and sales is due to the fact that the major portion of the phosgene manufactured is for "captive" use (use by the phosgene manufacturer), while the relatively small remainder is sold. [3] In 1974, phosgene was being produced in 18 plants

and capacity was on the increase. [4] It has been estimated that demand will be 1,630 million pounds in 1978. [4]

The relatively recent revitalization of the phosgene industry and the rapidly increasing demand are due largely to the use of phosgene in the synthesis of isocyanates, which are starting materials for polyurethane resins. Production of isocyanates accounted for about 75% of all phosgene produced in 1967. [3] In 1974, the uses of phosgene were distributed as follows: production of toluene diisocyanate, 62%; other polymeric isocyanates, 23%; polycarbonates, 6%; pesticides, carbonates, and "specialties," 9%. [4]

Some occupations with potential exposure to phosgene are listed in Table XIII-2. [15] NIOSH estimates that 10,000 workers have potential occupational exposure to phosgene during its manufacture and use.

Historical Reports

Berghoff [16] reported his observations of 2,000 cases of exposure to war gases during World War I. These included chlorine, mustard gas, and phosgene. The main complaint expressed by those exposed to phosgene was a weakness which developed as early as 2 hours or as late as 3 days after exposure. This weakness lasted for weeks or months. The author also noted that emphysematous patients had a more protracted convalescence than those classified as bronchitic.

Effects on Humans

Wells et al [17] published a detailed report on effects of barely detectable concentrations of phosgene on humans. Fifty-six military personnel, without upper respiratory problems, were exposed to increasing concentrations of phosgene until all the subjects could detect phosgene by odor. The authors reported that 50% of "technically trained" (without further clarification) observers detected phosgene at a concentration of 6.1 mg/cu m (1.5 ppm). Thirty-nine percent detected it at a concentration of 4.7 mg/cu m (1.2 ppm). None detected it below a concentration of 1.5 mg/cu m (0.4 ppm). The authors exposed the subjects to phosgene in increasing concentrations until they detected an odor. No effort was made to distinguish phosgene from other odors. No effects other than odor detection were reported.

Leonardos et al [18] studied phosgene odor thresholds using a panel of 4 members. The odor threshold was defined as the first concentration at which all 4 members recognized the odor. They distinguished this from the "detection threshold" which they felt was neither reliable nor reproducible. They determined a "hay-like" odor threshold for phosgene of 1.0 ppm.

Thiess and Goldmann [19] described their experience with 109 cases of accidental phosgene inhalation, including one fatality, in one industrial plant. The patients reported that they were exposed to only 1 or 2 whiffs of phosgene each, but some exposures were probably more severe. No further quantitation was described by the authors. Of these cases, 70 had insignificant clinical problems, hence were not studied in detail by the industrial physician. No details were given concerning these so-called

insignificant complaints. Of 31 cases in which X-ray studies were performed after exposure, 5 showed pulmonary abnormalities upon radiological examination. Only 3 of these showed the characteristic picture of pulmonary edema. The authors reported that the patients followed the "typical symptoms and course of phosgene poisoning: after an almost unnoticed inhalation,...a certain symptom-free latent period of 2 to 8 hours follows, and then the typical pulmonary edema (occurs)...." These three cases were described in detail.

A 19-year-old chemical laboratory assistant was accidentally sprayed with an unknown volume of liquid phosgene. The gas mask he was wearing was not leakproof, hence phosgene penetrated the mask. The mask and upper clothing were removed immediately. No first aid was administered. Upon admission to the hospital a little more than half an hour after exposure, the patient was observed to be in respiratory distress. Chest films showed infiltration of the lungs and pulmonary edema. Therapy consisted of phlebotomy, digitalization, intravenous fluids, and antibiotics. Three weeks of hospitalization were required before the patient could return home. No sequelae were described.

A 20-year-old chemical laboratory assistant was sprayed in the face with chlorobenzene saturated with phosgene under pressure. It was estimated that one mole of gaseous phosgene was released during the accident. First aid consisted only of washing the face and hair in water. Five hours after exposure, the patient felt a slight pressure on his chest. Eight hours after exposure, he became dyspneic and expectorated bloody sputum. He was admitted to the hospital one hour later. Chest films showed pulmonary edema. Thirteen days of hospitalization, which included

treatment with corticosteroids, digitalis, and oxygen, were required to resolve his pulmonary problems.

The fatal accident involved a 55-year-old mason who was presumed to have been exposed to phosgene released by chipping of brick which had possibly adsorbed phosgene. In this case, phosgene was a byproduct in the production of aluminum chloride. An analysis of the apparatus the patient worked on revealed that 2.5 liters of interstitial air volume in the brick at 360-400 C was available for absorbing the phosgene. The amount of dust inhaled by the patient is unknown. He was exposed for 30 minutes and first complained of dyspnea about 2 hours after completing the job. No first aid was given. Five hours after exposure, he was admitted to the hospital in severe respiratory distress. Chest films showed pulmonary edema. Despite phlebotomy and treatment with digitalis and diuretics, the patient died of acute right heart failure about 14 hours after his initial exposure.

Two cases of phosgene exposure were reported by Gerritsen and Buschmann. [6] They were due to accidental formation of phosgene from chlorinated hydrocarbons. Both cases involved the use of chemical paint removers in poorly ventilated areas heated by portable kerosene stoves. The first case involved a 52-year-old man who was exposed for an unknown period. He noted respiratory irritation soon after beginning work but persisted working for several hours. Chest symptoms occurred thereafter and the patient, upon examination, exhibited signs of pulmonary congestion. Approximately 5 hours later, the patient went into frank pulmonary edema and died within a few hours. Autopsy showed extensive degenerative changes in the epithelium of the trachea, bronchi, and bronchioli, together with hemorrhagic edematous focal pneumonia.

The second case [6] involved a 38-year-old woman, in her 7th month of pregnancy, who was exposed in a similar manner for 3 hours in the afternoon. That evening hemoptysis occurred. The next morning, symptoms worsened and she was hospitalized. A chest film upon admission showed pulmonary edema. After 8 days' hospitalization, she was released even though her chest film did not yet show a complete return to normal. After 2 months, she gave birth to a healthy child. This is the only case found which reported phosgene exposure during pregnancy.

In attempting to reproduce the circumstances of exposure of the above 2 cases, [6] it was found that methylene chloride was rapidly decomposed with phosgene being the main decomposition product when methylene chloride was exposed to heat in a poorly ventilated area. The authors stated that this was in contrast to the results reported by Little [20] when methylene chloride was decomposed by hot surfaces and low amounts of phosgene were produced in comparison with hydrogen chloride and chlorine.

Another case of possible phosgene poisoning resulting in death was reported by Spolyar et al. [5] The case involved a chlorinated solvent degreaser which was inadvertently filled with trichloroethylene instead of perchloroethylene. The operator of the degreaser was found dead 3 1/2 hours after exposure began and 1 hour after he reported that fumes were escaping from the apparatus. Autopsy showed pulmonary edema consistent with exposure to phosgene. It was assumed that the trichloroethylene vaporized and passed through the firebox of a nearby space heater, with decomposition of the trichloroethylene and the production of phosgene. Cause of death was consistent with phosgene exposure but it was suggested that trichloroethylene might have contributed to the circulatory collapse.

An attempt was made to reproduce the environmental situation. [5] Sampling of the breathing zone of the operator revealed a phosgene concentration of 15 ppm. The analytical method was altered to correct for interferences by trichloroethylene at 3,300 ppm in air, the estimated trichloroethylene concentration at the time of exposure. During the test simulation, trichloroethylene levels exceeded 10,000 ppm after 1 hour and 20 minutes of degreaser operation.

Glass et al [21] reported a case of poisoning attributed to phosgene following the welding of a metal which was damp with trichloroethylene used for cleaning purposes. After 4 1/2 hours' exposure, the worker noted respiratory symptoms and felt unwell. He returned home, but the next morning he was dyspneic. Chest films taken 24 hours after exposure and 90 days later showed the diaphragm below the eleventh rib posteriorly with limited excursion and clear lung fields. Pulmonary function tests, including spirometry, carbon monoxide uptake, and arterial blood gases, abnormal at first, improved over a 3-month period following exposure. The authors' impression was that the patient suffered from chronic bronchitis which was exacerbated by phosgene. Unfortunately, no studies of phosgene in the air were conducted in the workplace under conditions simulating that of the original exposure.

Derrick and Johnson [22] reported a case of presumed phosgene exposure due to the breakdown of trichloroethylene by cigarette smoking. The patient had worked as a drycleaner for 3 months. Studies indicated that the average concentration of trichloroethylene in the room was 488 ppm. The authors indicated that this level would be exceeded when clothing was removed from the cleaning machine. The patient was known to smoke 40

cigarettes/day. He frequently smoked in the cleaning room. He left work at 4:00 p.m., and about 90 minutes later he collapsed and died. An autopsy showed pulmonary edema. Phosgene was believed to have been generated by the decomposition of trichloroethylene in contact with the hot tip of a burning cigarette. This theory is contradicted by the work of Little [20] who measured phosgene in the effluent gas of cigarettes and did not detect any in atmospheres containing trichloroethylene, chloroform, carbon tetrachloride, perchloroethylene, or even small amounts of phosgene.

Everett and Overholt [23] reported a case of phosgene poisoning but gave no details of exposure other than "massive exposure to phosgene." Initial symptoms were burning of the eyes and coughing. These cleared after a few minutes, but dyspnea occurred in 3 hours. X-ray studies showed pulmonary edema which resolved over 7 days of hospitalization and treatment which included antibiotics, corticosteroids, and oxygen. The patient remained well during the ensuing 2 years.

The Bureau of Engineering Safety, Department of Labor and Industry, State of New Jersey, [24] reported one fatality among 6 employees exposed to phosgene at unknown concentrations in separate accidents over a 2-year period. The exposures occurred in a plant conducting "phosgenation" where measurements of air concentrations were normally reported to be below 0.1 ppm. Subsequently, all phosgene operations were stopped because of inadequate engineering controls.

Delepine [25] described 2 cases of fatal phosgene poisoning. The first man had his clothing saturated with phosgene and was treated almost immediately. He appeared well but experienced symptoms 6 hours after exposure. Treatment (details not given) was temporarily helpful, but the

patient died 11 hours later. The second man was exposed as a result of the explosion of a phosgene cylinder. Death occurred 22 hours after exposure. At autopsy, both cases showed evidence of severe irritation of the respiratory tract with almost complete shedding of the laryngeal, tracheal, and bronchial epithelium.

English [8] reported a case of poisoning attributed to phosgene in a 67-year-old male with several years' history of chronic bronchitis and a quiescent duodenal ulcer. After an 8-hour exposure in a room heated by a stove burning paraffin in which paint-strippers containing chlorinated hydrocarbons had been used, the worker experienced dyspnea. The next morning, his symptoms increased and he was hospitalized. Chest X-rays showed diffuse bronchiolitis. Despite treatment, dyspnea persisted for 4 days in the hospital. He was discharged after 6 weeks. English stated that phosgene dissolved in saliva irritated the alimentary mucosa and, hence, was responsible for reactivation of a duodenal ulcer in this patient. He cited no authorities for this statement or clinical or experimental evidence to support it. No other references to the effects of phosgene on gastrointestinal mucosa were found other than Cherkes' [26] statement that stasis and venous hyperemia occur in the gastrointestinal tract as a result of pulmonary edema.

Seidelin [7] reported a case of probable phosgene inhalation leading to pulmonary edema in a 16-year-old woman. This occurred after she had used a carbon tetrachloride fire extinguisher in an enclosed space. Inhalation of smoke and fumes resulted in immediate coughing. Six hours later, she developed respiratory symptoms and subsequently was admitted to the hospital with pulmonary edema. Complications ensued including

mediastinal emphysema and bilateral pneumothoraces. Oxygen therapy resulted in considerable clinical improvement in 8 days, but she was unable to leave the hospital until 13 days after exposure.

Stavrakis [27] described 7 cases of phosgene exposure. The first was a worker who developed dyspnea, cough, and chest pain 4 hours after exposure, which were severe enough to bring him to a hospital emergency room. Treatment with hexamethylenetetramine was given immediately, followed by standard therapy consisting of steroids, oxygen, and antibiotics. He was discharged in good health after 5 days. The other 6 workers were exposed when a pipe ruptured and released phosgene. The extent of exposure was not described. One heavily exposed worker was treated immediately with hexamethylenetetramine. He remained asymptomatic until his discharge 24 hours later. Another worker, similarly exposed, waited until symptoms occurred before seeking treatment. He died despite treatment with hexamethylenetetramine. Four others, who were treated in the symptomatic stage, required hospitalization for various periods until recovery occurred.

In 1946, Galdston et al [28] reported studies of 6 cases of acute exposure to phosgene with residual effects up to 19 months after the last known acute exposure. Evaluation of each patient included physical examinations, chest X-rays, pulmonary function tests, and a psychiatric summary. These cases shared a common background of brief single exposures to phosgene at unknown concentrations which usually led to delayed pulmonary edema. One of the cases is interesting in that exposure occurred at a hood which contained an ampule of only 40 ml phosgene. All were treated at Johns Hopkins Hospital and released, some returning to a normal

work routine. However, follow-up examinations revealed that all had lingering complaints, and although physical examinations and chest X-rays up to 19 months later were generally normal, pulmonary function tests always revealed some abnormalities consistent with beginning pulmonary emphysema. The authors felt that psychological factors contributed to the lingering symptomatology. Their findings are summarized in Table III-1.

Cherkes, [26] in an extensive review of the literature concerning the clinical course of acute phosgene exposure, noted that most fatalities occur during the first 24-48 hours. He reported that most patients dying within the first 72 hours died of pulmonary edema or cardiac problems. Those dying later usually succumbed as a result of complications, such as infection (usually pulmonary), thrombosis, or embolism. He gave no source for these statements other than "according to the data of various authors." The clinical course following phosgene exposure reported by Cherkes is generally in agreement with other reports following human and animal exposure. [5,6,21,25,27,29,30,31]

Ardran [32] pointed out that many victims of phosgene poisoning showed radiological evidence of increased lung volumes. His experiments with dogs [33] indicated that animals that failed to develop an increase in lung volume after phosgene exposure also failed to develop pulmonary edema. This test had been used by him clinically. [32] He reported that, if an expiratory lung film shows evidence of an increase in volume after exposure to phosgene, then pulmonary edema may be expected. He stated that he had looked for this sign in humans exposed to lung irritants and that never, in 20 years, had he found pulmonary edema to develop in the absence of antecedent increased lung volume. There has been no independent

TABLE III-1

SUMMARY OF CLINICAL OBSERVATIONS AND DATA ON STUDIES PERFORMED AFTER ACUTE EXPOSURES

Case Number*	1	2	3	4	5	6
Age	38	39	30	48	43	49
Months after accident**	14	6	6	3	5	5
Months worked with phosgene	6	12	18	24	2	1
Chronic symptoms	A	N	N	A	A	A
Physical signs						
Acute	A	A	A	A	N	N
Chronic	N	N	N	B	N	N
Roentgenogram of chest	N	N	N	N	N	N
Volume						
(Vital capacity + % residual air) = Total capacity	N	N	N	A	N	N
	B	N	N	B	N	N
Intrapulmonary mixing of gases	N	N	B	A	N	B
Pulmonary emptying	N	N	N	A	N	B
Resting pattern of breathing						
High rate	N	A	A	A	A	A
Low tidal air	N	N	A	B	A	A
High min. volume	N	A	A	A	A	A
Low oxygen extraction	B	A	A	B	A	A
Exercise pattern of breathing						
High rate	N	B	B	B	A	A
Low tidal air	B	N	B	B	N	A
Low oxygen extraction	N	N	N	B	A	A
Arterial blood						
At rest	N	A	N	N	A	N
After exercise	N	A	N	N	N	-
After oxygen administration	-	N	-	N	A	-
Breath holding	N	N	N	A	A	N
Voluntary breathing capacity	N	A	A	N	A	N
Postural tests	N	N	N	N	N	N
Cardiac output	N	A	N	N	-	N

A = Definitely abnormal B = Borderline abnormal
N = Normal - = Not done

* Listed in order of severity of exposure.
** Applies to all special studies except arterial blood and alveolar air oxygen and carbon dioxide tensions and cardiac output which were performed 4-8 months later. Symptoms, physical and X-ray findings were unchanged on reexamination of all available patients (except No. 5) 4-8 months later.

From reference 28

confirmation of his interesting findings, and he gave no pulmonary function test data on his patients.

Steel [34] described 2 cases of exposure to phosgene at low concentrations (figures for duration or concentration not stated). Both patients developed delirium, fever, tachycardia, tachypnea, and a painful cough. The more exposed patient developed pulmonary edema; the other showed only acute bronchitis. Steel noted that both patients developed amnesia about their exposure. He stated that he regarded neither fever nor amnesia as characteristic of exposure to phosgene.

One of the few publications relating to workers with multiple exposures to phosgene at low concentrations over prolonged periods is that of Galdston et al. [35] Their observations are summarized in Table III-2. The study involved the pulmonary function, cardiovascular and psychiatric status of 5 workers who had repeated exposures to small amounts of phosgene during the course of 18-42 months. In none of the cases was notation made of odor detection by the patients during exposure, prior to the development of more serious symptoms. The first patient, age 32, had a noncontributory past history except for conjunctivitis and laryngitis after working with mustard gas during 2 time periods. Several exposures to phosgene caused a feeling of chest constriction, dizziness, headaches, blurred vision, and mental confusion. The same year, he experienced severe irritation of the throat from inhaling chlorine. He worked with phosgene for another 4 months and noted chest tightness, dyspnea on exertion, and muscular twitching he ascribed to recent minor exposures to phosgene. The findings of his physical examination and chest roentgenogram were normal; however, pulmonary function studies showed a decrease in vital capacity, impaired

intrapulmonary gas mixing and other changes consistent with pulmonary emphysema.

The second patient, [35] age 50, also had a noncontributory past history prior to working with phosgene. He had had numerous minor exposures to phosgene which were usually followed by a sense of constriction in the throat, dyspnea, cough, nausea, and vomiting. After working with phosgene, he had a productive cough which occasionally tasted of phosgene. Findings from his physical examination were normal, but his chest roentgenogram and pulmonary function studies were consistent with pulmonary emphysema.

The third patient, [35] age 24, had had a history of asthma since childhood. He had several minor exposures to chlorine before working with phosgene. On 6 occasions, he inhaled enough phosgene to induce coughing, choking sensations, nausea and vomiting, headache, and sweating, which disappeared the day following exposure. Physical examination demonstrated only thoracic kyphosis and bilateral basilar rales. Roentgenograms and pulmonary function studies were consistent with pulmonary emphysema.

The fourth patient, [35] age 31, had chronic tonsillitis, otitis, and adenoiditis apparently prior to his phosgene exposure. He also had minor symptomatic episodes of exposure to chlorine and mustard gas. After about 6-9 months of exposure to phosgene, physical examination showed a perforated right eardrum and bilateral basilar rales. Roentgenograms of the lungs showed what was described as an old obliteration of the left costophrenic angle. Pulmonary function studies were consistent with pulmonary emphysema.

The fifth patient, [35] age 26, had worked with both phosgene and chlorine during separate periods. He had a few minor exposures to phosgene which resulted in conjunctival irritation, dyspnea, and headache. Physical examination and roentgenographic studies were normal. Pulmonary function studies showed only a reduction in voluntary breathing capacity. The authors concluded that "emphysema of the lungs may develop after chronic exposure to phosgene."

This study is an important one in that it deals directly with the problem of repeated minor exposures to phosgene. Unfortunately, Galdston et al [35] did not comment on how these patients were selected or on any quantitation of the phosgene exposures. This paper also did not consider continuous exposures at a low level of phosgene during a full workday and workweek over an extended period. It is, however, the only paper available with clinical and laboratory data collected on humans with repeated exposures to phosgene. (see Table III-2)

TABLE III-2

SUMMARY OF CLINICAL OBSERVATIONS AND DATA ON STUDIES PERFORMED AFTER CHRONIC EXPOSURES

Case Number*	1	2	3	4	5
Age	32	50	24	31	26
Months worked with phosgene	42	36	30	16	30
Chronic symptoms	A	A	A	A	A
Physical signs					
Acute	N	N	N	N	N
Chronic	N	B	A	N	N
Roentgenogram of chest	N	A	A	N	N
Volume					
(Vital capacity + % residual air) =	A	N	B	N	N
Total capacity	A	B	A	B	N
Intrapulmonary mixing of gases	A	A	A	A	N
Pulmonary emptying	N	B	A	A	N
Resting pattern of breathing					
High rate	N	A	A	A	N
Low tidal air	N	A	A	B	N
High min. volume	N	A	A	A	N
Low oxygen extraction	N	N	B	A	N
Exercise pattern of breathing					
High rate	N	B	B	B	N
Low tidal air	N	B	B	B	N
Low oxygen extraction	N	N	A	A	N
Arterial blood gases**					
At rest	N	A	N	N	-
After exercise	N	N	A	A	-
After oxygen administration	N	-	-	-	-
Breath holding	N	A	-	N	N
Voluntary breathing capacity	N	A	A	N	A
Postural tests	N	-	-	-	-
Cardiac output	N	A	N	N	-

A = Definitely abnormal
B = Borderline abnormal
N = Normal
- = Not done

* Listed in order studied

** Arterial blood oxygen, alveolar air oxygen and carbon dioxide tension studies at rest and after exercise were performed 4-8 months after all other studies were completed. Symptoms, physical and roentgenographic findings were unchanged on reexamination of all available patients (all but one) at that time.

From reference 35

Epidemiologic Studies

Levina et al [36] described the working environment in the monuron, 3-(p-chlorophenyl)-1,1-dimethylurea, industry. Phosgene is involved in its synthesis and was found to be contaminating 90 workers' production areas at a concentration of 1.0-2.0 mg/cu m (0.25-0.5 ppm) over a 6-month period under investigation. According to Smelyanskiy and Ulanova, [37] the permissible level for the USSR was 0.5 mg/cu m (0.125 ppm). Other contaminants included chlorobenzene, dimethylamine, and parachlorophenylisocyanate. Levina et al [36] reported no pulmonary problems in these workers, but did not describe searching for them.

Levina and Kurando [38] reported their studies of a plant manufacturing a weed killer (isopropylphenylcarbamate) using phosgene, isopropyl alcohol, aniline, and caustic soda as raw materials. Although a closed process was used, phosgene was found in 30% of all air samples, most frequently at a concentration of 0.5 mg/cu m (0.125 ppm). A total of 89 workers were studied for evidence of hematological abnormalities. Methemoglobinemia and anemia were detected which were attributed to the weed killer and aniline. No mention was made of pulmonary problems.

At a plant where phosgene is manufactured, the medical records of all exposed workers (326) were compared with those of 6,288 nonexposed workers. (AF Myers, written communication, November 1974) Pulmonary function, lung problems, and deaths related to lung problems were tabulated for both groups. The data were taken to indicate that there were no chronic lung problems related to working in these phosgene operations. By using the age distribution of employees and pensioners and comparing their deaths from lung problems with those expected from a similar age group (described as

taken from National Statistics) not exposed to phosgene, no increase in lung-related deaths was noted in the phosgene-industry workers. The details of pulmonary function testing were not provided. The results of a limited program of air sampling conducted during a 2-month period were provided. Fifteen personal air samples collected for 20-minute periods and analyzed using the NBP method used by AF Myers (written communication, November 1975) and described in Chapter IV of this document showed concentrations ranging from nondetected to 0.08 mg/cu m with an average concentration of 0.012 mg/cu m. From a total of 56 fixed-position samples collected for 2-hour or 20-minute periods, 51 samples showed concentrations ranging from nondetected to 0.52 mg/cu m (ND-0.13 ppm). The remaining 5 samples showed "off-scale" measurements (greater than 0.55 mg/cu m) reportedly due to leaks.

Animal Toxicity

Clay and Rossing [39] exposed 25 mongrel dogs to phosgene at a concentration between 24 and 40 ppm for 30-minute periods at a rate of 1-3 exposures/week. Those exposed once or twice showed acute bronchiolitis and peribronchiolitis involving terminal and respiratory bronchioles. The trachea and bronchi were visually unaffected and the proximal bronchioles were seldom damaged. Those exposed 4-10 times had chronic bronchiolitis of the proximal and intermediate portions of the respiratory bronchioles. The animals exposed 30-40 times showed changes which were described as resembling those of early emphysema.

Box and Cullumbine [40] studied the problem of an apparent reduction in susceptibility to phosgene intoxication by prior exposure. They exposed

rats for 10 minutes to phosgene at concentrations of 80 mg/cu m (20 ppm). Five days later, the preexposed animals and an equal number of control animals were exposed to phosgene at lethal concentrations (230-440 mg/cu m, 55-110 ppm) for 10 minutes. The mortality rate for controls was 74%, while for pregassed animals it was only 33%. They attributed this finding to rapid and shallow breathing caused by pulmonary damage in the first exposure.

Rinehart and Hatch, [41] using low concentrations of phosgene (0.5-4 ppm for 5-480 minutes) on rats, attempted to work out the validity of the concentration-time product (Ct) in ppm-minutes as a measure of dose of sublethal exposures to phosgene. On the basis of the responses (expressed in terms of impaired pulmonary gas exchange capacity as measured by the decreased rates of uptake of carbon monoxide and ether) of 118 Wistar rats, the authors concluded that the Ct was a suitable way to express the magnitude of the dose, and that low-level exposure to phosgene with a Ct equal to or less than 100 ppm-minutes caused increased resistance to breathing and poorer distribution of air within the lungs. Above a Ct of 100 ppm-minutes, decrease in diffusion capacity became more important. They attributed this to differences in the major site of action, ie, the respiratory bronchioles in the first case, and the alveoli in the second. The authors noted that above a Ct of 30 ppm-minutes gas exchange capacity decreased directly with the logarithmic increase in Ct. Rinehart and Hatch [41] noted no significant effect of phosgene on the test animals' pulmonary performance when subjected to exposures less than a Ct of 30 ppm-minutes. The animals' exposures were varied to cover a Ct product range of 12-360 ppm-minutes.

Gross et al [42] studied the effect of low concentrations (0.5-4 ppm for 5-480 minutes) on rats. They found that they could produce a chronic pneumonitis which was reversible but left detectable lesions for up to 3 months. They felt they could explain this by the fact that low dosages of phosgene merely irritated the pulmonary alveolar epithelium, resulting in proliferation. The more severe exposures of phosgene usually reported in the literature destroyed the surface epithelium and attacked the underlying alveolar capillaries, thus resulting in pulmonary edema. The authors noted that the severity of the chronic pneumonitis correlated well with the Ct value of the phosgene exposure and seemed to be largely independent of the concentration of the gas in the same bracket of Ct values. Animals in the study by Gross et al [42] were subjected to Ct products ranging from 13 to 360 ppm-minutes. In the 18 rats exposed to phosgene with Ct products equal to 30 ppm-minutes or less, 5 (28%) showed no abnormalities on pathologic examination; 11 (61%) showed slight chronic pneumonitis; and 2 (11%) showed moderate chronic pneumonitis.

Wirth [43] studied the effect of low concentrations of phosgene upon cats. He reported that, if the concentration was expressed as mg/cu m, the lethal concentration x the survival time in minutes was approximately 1,000. At low concentrations (5-7 mg/cu m, 1-2 ppm), the constant was as high as 3,000. This shows that the lethal Ct product is considerably higher at low concentrations. The author felt that the increase in Ct product at low concentrations was due to detoxification and that the practical usefulness of the Ct formula was not affected by this, provided it was used within certain concentration limits.

Cordier and Cordier [44] exposed cats and guinea pigs to phosgene at concentrations of 20-25 mg/cu m (5.0-6.25 ppm) and 10-15 mg/cu m (2.5-3.75 ppm) repeatedly over several weeks. The duration of each exposure was 10 minutes. The interval between exposures was 24 hours, and the number of exposures varied from 2 to 41. Examination of the animals concentrated on body weight, organ weight, and microscopic examination of the lungs. After exposure at 20-25 mg/cu m, all animals developed pulmonary lesions, although signs of these were not detected while the animals were alive. Microscopic examination of the 15 cats exposed indicated that all but two had some degree of pulmonary edema. The remaining two showed other lung abnormalities. The degree of lung damage did not show any increase with increasing number of exposures. Therefore the authors concluded that there is no cumulative effect of phosgene at this concentration when the duration of exposure is short and the animals are given time to recover between exposures. Both cats and guinea pigs were exposed to phosgene at the lower range of concentrations of 10-15 mg/cu m. Upon microscopic examination, pulmonary edema was found in 3 of 6 cats and in none of 6 guinea pigs. Other lung changes were found, but, in general, the effect on the pulmonary alveoli was considered to be insignificant. The authors concluded that this concentration, inhaled daily for 10 minutes, seems to be the minimal concentration capable of creating edematous pulmonary zones. This minimum effect level, expressed as a Ct product (25-37.5 ppm-minutes) concurs with the minimum effect level of 30 ppm-minutes later found by Rinehart and Hatch [41] in experiments with rats using pulmonary uptake of carbon monoxide and ether to measure effect.

Koontz [45] gassed dogs with phosgene at the minimum lethal dose (undefined by the author) and then studied 95 of those that survived. One-third died or were killed by other dogs during the course of the experiment. The other two-thirds were killed at intervals from 2 to 60 weeks. About one-half of the dogs showed no or only minor lesions. Those with more significant abnormalities showed transient bronchial plugging and adjacent atelectasis. Most of the lungs took on a more normal appearance as the time from recovery increased.

Durlacher and Bunting [46] exposed 31 dogs to phosgene at concentrations averaging 0.29 mg/ liter (72.0 ppm) for 30 minutes. The animals were given a variety of treatments, including oxygen, transfusions, or venesection. The most striking findings were consolidation of one or more lobes of the lungs 4-9 days after exposure. The authors noted that "pulmonary organization occurred...and caused high mortality in spite of oxygen therapy." The oxygen therapy consisted of maintenance in an atmosphere of 60% oxygen when the arterial oxygen saturation was below 80%. No specific time for initiation of therapy other than "after exposure" was given.

Gross et al [47] described their findings concerning pulmonary reactions to toxic gases. They noted that the proliferative lesions produced by phosgene, chlorine, sulfur dioxide, nitrogen dioxide, ozone, and crotonaldehyde differed only quantitatively on a histologic basis. It appeared probable to the authors that, with a proper adjustment of the concentration, even the quantitative difference could be eliminated. They concluded that deep lung irritants preferentially attacked the respiratory bronchioles because of delayed clearance in that region.

In 1920, Underhill [31] exposed dogs to phosgene and noted the development of pulmonary edema which was maximal at 24-36 hours and resolved in animals surviving 10 days or more. He concluded that the minimum lethal concentration of phosgene for dogs was 310-350 mg/cu m (75-87 ppm). He found that dogs that survived for 3 days usually recovered. He also concluded that recovery from gassing increased the likelihood of death from regassing of dogs, which differs from the findings of Box and Cullumbine [40] in rats. Underhill explained that tolerance is demonstrable only with low concentrations; it does not decrease subsequent reactions to lethal concentrations. Winternitz et al [48] presented detailed information on the pathology found in these animals at autopsy.

Long and Hatch [29] reported that a reduction in the rate of respiratory uptake of carbon monoxide was an early and sensitive test of pulmonary impairment following exposure to pulmonary irritants. The test was developed using unanesthetized rats and phosgene as the test irritant. The animals were exposed to phosgene for 30 minutes at the following levels: 0.5-1, 1-2, 2-3, 3-4, and 4-5 ppm. The responses included a decrease in pulmonary uptake in CO which was progressive for 6-8 hours. followed by gradual recovery. They found that their test detected changes even at the lowest level of phosgene exposure (0.5-1 ppm) in the absence of microscopic changes at autopsy.

Boyd and Perry [30] exposed rabbits to phosgene for 30 minutes at a concentration of 270 mg/cu m (67 ppm). They reported a latent period of several hours following exposure. After the latent period, pulmonary edema developed.

Noweir et al [49] exposed rats to decomposition products of carbon tetrachloride at its TLV (10 ppm) and demonstrated [9] that up to 10 ppm of phosgene could be produced by thermal decomposition of this level of carbon tetrachloride. Thermal decomposition was achieved by passing a stream of carbon tetrachloride over a variety of hot surfaces including iron and glass, as well as open flames. Animals were exposed for 12 or 60 minutes to phosgene at concentrations of 10 or 2 ppm allowing an equal Ct of 120 ppm-minutes. Mixtures of decomposition products were tested as well. No marked potentiation of each irritant's effects upon the others was discovered. They found that chlorine, chlorine dioxide, and hydrogen chloride as well as phosgene contributed to respiratory damage.

Winternitz et al [50] studied the comparative pathology of acute phosgene poisoning. They reported that the pathologic findings of acute phosgene poisoning were similar in goats, dogs, monkeys, rabbits, guinea pigs, rats, and mice. These findings consisted primarily of pulmonary edema which increased in severity with the length of survival of the species. The most susceptible species, monkeys and guinea pigs, died prior to the development of pulmonary edema as severe as that seen in the dog or goat.

The basic mechanism of action by which phosgene produces lung damage has, as yet, not been established. The original supposition that liberated HCl was the toxic agent was never proved. A number of experiments carried out in World War II appear to have disproved the liberated HCl hypothesis and shown that phosgene affects tissues because the carbonyl group combines with free amines of cell enzymes or other critical substances. [51] A more recent theory is that of Ivanhoe and Meyers [52] who exposed rabbits to

phosgene at concentrations ranging from 50 ppm for 14 minutes to 200 ppm for 25 minutes. Their results showed a marked decrease in sympathetic nervous system activity in exposed animals. The authors concluded that phosgene toxicity was an example of acute pulmonary edema resulting from a hypoactive-sympathetic or neuroparalytic state in the host. This is corroborated, in part, by the work of Frosolono [53] who studied rat lungs by electron microscopy after exposures of 1,000 ppm-minutes to 4,320 ppm-minutes. The author noted interstitial edema as the common denominator of phosgene poisoning and felt that the autonomic nervous system might indeed play a significant role.

Cameron and Foss [54] exposed a group of animals to phosgene at an average concentration of 4.38 mg/cu m (1.1 ppm) for 5 hours/day for 5 days. The animal exposure group consisted of 20 mice, 10 rats, 10 rabbits, 2 cats, and 2 goats. After 24 hours, 50% of the mice were dead (10/20); after 48 hours, another 8 died, resulting in a casualty rate of 90% in 48 hours (18/20). All mice showed marked mottling of lungs with congestion, edema, and what was described as emphysema. Two rabbits died after 48 hours (2/20). On examination, one showed large areas of collapse in the lung with congestion and edema. The other rabbit showed some edema and congestion. The remaining animals survived and were killed at the end of the 5 days of exposure. Microscopic examination of the lungs of 37 of the animals showed that 22 (59%) had lung changes graded as severe, 15 (41%) had mild lung changes. Severe lesions were found in the cat, rabbits, guinea pigs, and mice. Goats and rats were much less affected. Edema was present in 35 of the 37 examined (95%), with severe edema in 12 animals, moderate edema in 13, and slight edema in 10. All species showed some degree of edema.

In a subsequent study, Cameron et al [55] exposed a group of animals to phosgene at an average concentration of 3.47 mg/cu m (0.86 ppm) for a single 5-hour exposure. The animal exposure group consisted of 20 mice, 10 rats, 10 guinea pigs, 10 rabbits, 2 cats, 2 monkeys, and 2 goats. On the morning following exposure, 10% of the rats (1/10) and 60% of the mice (12/20) were dead. There were no other casualties, although one cat and one monkey were very ill with considerable labored breathing. All survivors of the experiment were killed on the morning following exposure. All animals were then autopsied and one lung from each animal was fixed in formalin for sectioning. Upon examination, 54 out of 56 animals (96.4%) showed microscopic evidence of pulmonary involvement which was severe in 29 animals (39%), mild in 17 (31%), and slight in 16 (30%). The most frequent lung change noted was edema.

In another study, Cameron et al [56] reported the results of exposing a variety of animals to phosgene at an average concentration of 0.9 mg/cu m (0.2 ppm) for 5 hours daily for 5 consecutive days. The experimental group consisted of 20 mice, 10 rats, 10 guinea pigs, 10 rabbits, 2 cats, and 2 goats. No deaths occurred during the exposures. Except for some labored breathing noted in the cats and in one goat, the other animals showed little evidence of distress. At autopsy, pulmonary lesions were seen in 67% of the animals. In the opinion of the investigators, the great majority of such lesions were slight and of little significance. Discounting the more susceptible animals (guinea pigs) and correcting for the normal incidence of disease in laboratory animals, the authors estimated that probably between 5 and 10% of the animals showed moderately severe lesions. Pulmonary edema was noted in 41% of the animals but was

considered to be slight in most cases. In 6 animals (1 rabbit, 1 mouse, 1 rat, and 3 guinea pigs), it was extensive. Acute bronchitis was noted in 22% of the animals and bronchial regeneration in 20%. Their results are shown in Table III-3.

In their summary statement, the authors [56] advanced the opinion that there is little doubt that repeated exposure at low concentrations (0.9 mg/cu m) induces damage to the lungs but that such damage was rarely severe. Seemingly in contradiction with this, they also stated that, at this concentration, some fairly severe changes are found in the lungs of experimental animals.

TABLE III-3

SEVERITY OF LUNG LESIONS AFTER EXPOSURE TO 0.2 PPM PHOSGENE, 5 HOURS DAILY FOR 5 CONSECUTIVE DAYS

	Goats	Cats	Rabbits	G. pigs	Rats	Mice	Total	%
Total Number of Animals	2	2	10	10	10	20	54	
Severe lesions	0	0	0	1	1	0	2	4
Mild lesions	0	0	1	3	1	1	6	11
Very slight lesions	0	1	5	6	3	13	28	52
No lesions	2	1	4	0	5	6	18	33
Incidence of pulmonary edema	0	1	5(1)	7(3)	2(1)	7(1)	22	41
Incidence of severe bronchitis	0	1	5	5	1	0	12	22
Incidence of bronchial regeneration	0	0	4	5	1	1	11	20
Incidence of broncho-pneumonia	0	0	0	1	1	0	2	4

Figures in parentheses under pulmonary edema indicate number of animals showing fairly severe edema.

From reference 56

Correlation of Exposure and Effects

Phosgene is known historically as a respiratory poison used to disable large masses of soldiers. It is no longer used as a military weapon but has become an important industrial chemical. The focus of impairment to the health of those who are exposed to high concentrations of the gas has therefore shifted from the military to industry. Epidemiologic studies [38, AF Myers, written communication, November 1974] have shown no ill effects definitely attributable to phosgene in workers exposed to phosgene at an average of 0.125 ppm or less for considerable periods. However, the investigations of Levina and Kurando [38] did not mention studying the possibility of pulmonary disease, and the Myers communication indicated that, most of the time, levels were actually much lower than 0.125 ppm.

Animal studies, for the most part, have attempted to duplicate the war gas or accidental overexposure situation where there is exposure to phosgene at high concentrations for relatively short periods. These studies, summarized in Table III-4, [29,30,31,39,40,41,42,45,46,48] have shown a fairly similar picture, ie, animals dying immediately show severe pulmonary epithelial and capillary destruction, and animals surviving show variable amounts of bronchiolitis, pneumonitis, bronchial plugging, atelectasis, pulmonary consolidation, pneumonia, and emphysema.

The one animal study [56] devoted to long-term, repeated exposure to phosgene at low concentrations produced pulmonary edema in 41% of the animals. After correcting for the normal incidence of disease in laboratory animals, 5-10% of the animals had moderately severe lesions.

Human exposures to phosgene reported in the literature (summarized in Table III-5) consist of many instances of acute overexposure. The work of Galdston et al [28,35] is the best substantiated in the American literature and gives details of pulmonary function studies in 11 workers with single acute or repeated exposures to phosgene at unknown concentrations. Unfortunately, other pulmonary irritants were sometimes involved.

Galdston et al [35] gave evidence that repeated exposures to phosgene can result in residual pulmonary problems. This paper reports on 5 workers who were studied in detail, 2 of whom had abnormal chest films. It is difficult to extrapolate the results found in these workers to what might be expected in the general population of workers exposed to phosgene over long periods of time.

Levina et al [36] found no pulmonary abnormalities in Soviet workers exposed to 1-2 mg/cu m of phosgene for over a 6-month period. Other inhalants apparently caused hematologic abnormalities. Unfortunately, no mention is made of any pulmonary function studies done on these workers.

In summary, there are no truly pertinent data in the scientific literature concerned with long-term effects on humans exposed to phosgene at low concentrations. Animal data show a 5-10% incidence of severe pulmonary problems in animals exposed at 0.2 ppm. Despite Cherkes' [26] statement that the dog is the animal most resembling man in terms of susceptibility to phosgene, neither Cherkes nor any other investigator has offered any concrete data to support this contention. In fact, Winternitz et al [50] concluded that, based upon pathologic findings, phosgene lung changes were basically similar in all the species studied. Referring to investigations of others, Cucinell [57] has stated that, at least in terms

of lethality, man is about as susceptible as the mouse. But he also pointed out that data with which to correlate the toxicity of phosgene in man to that in laboratory animals at low concentrations do not exist.

Carcinogenicity, Mutagenicity, and Teratogenicity

Data on other possible effects of toxic chemicals, such as carcinogenicity, mutagenicity, or teratogenicity have not been reported for phosgene, and there is no analogy on which to postulate such effects on long-term, low-level exposure. However, with the likely ability of phosgene at high concentrations to cause extensive damage to lung tissue, it is conceivable that among survivors of such exposures occasional neoplasia might occur as the consequence of regeneration of damaged tissue.

TABLE III-4

PHOSGENE INHALATION EXPOSURES AND EFFECTS--ANIMALS

Authors	Exposure Variables	Exposure Time	Effects
Frosolono [53]	Rats 1,000-4,320 ppm-min		Interstitial edema
Ivanhoe & Meyers [52]	Rabbits, 50-200 ppm	14-25 min	Decrease in sympathetic tone
Underhill [31] as reported by Winternitz et al [48]	Dogs, 44-120 ppm	30 min	Pulmonary edema, pneumonia, emphysema, death
Box & Cullumbine [40]	Rats 20 ppm	10 min	*
	Rats 55-100 ppm	"	Reduction in death rate from 74% to 33% by previous challenge
Durlacher & Bunting [46]	Dogs, 72 ppm	30 min	Pulmonary consolidation, death
Boyd & Perry [30]	Rabbits, 67 ppm	30 min	Pulmonary edema
Clay & Rossing [39]	Dogs 24-40 ppm	30 min 1 or 2 exposures at rate of 1-3/week	Acute bronchiolitis
	"	30 min 4-10 exposures at rate of 1-3/week	Chronic bronchiolitis
	"	30 min 30-40 exposures at rate of 1-3/week	Emphysema
Cordier & Cordier [44]	Cats and guinea pigs 2.5-6.25 ppm	10 min/day x 2-41 days	Pulmonary edema, bronchitis, bronchopneumonia, death

* Animals were gassed to determine effect of pregassing upon a later challenge

TABLE III-4 (CONTINUED)

PHOSGENE INHALATION EXPOSURES AND EFFECTS--ANIMALS

Authors	Exposure Variables	Exposure Time	Effects
Long & Hatch [29]	Rats, 0.5-5 ppm	30 min	Decreased pulmonary CO uptake
Rinehart & Hatch [41]	Rats, 0.5-4 ppm	5-480 min	Increased resistance to breathing decrease in diffusion capacity
Gross et al [42]	Rats, "	"	Chronic pneumonitis
Cameron & Foss [54]	Variety of animals, 1.1 ppm	5 hours/day x 5 days	Pulmonary edema, death
Cameron et al [55]	Variety of animals, 0.9 ppm	5 hours/day x 1 day	Pulmonary edema, death
Cameron et al [56]	Variety of animals 0.2 ppm	5 hours/day x 5 days	Pulmonary edema
Koontz [45]	Dogs, unknown	Unknown	Bronchial plugging and atelectasis

TABLE III-5

PHOSGENE INHALATION EXPOSURES AND EFFECTS--HUMANS

Authors	Exposure Variables	Exposure Time	Effects
Theiss & Goldmann [19]	a) Unknown	Brief	Pulmonary edema
	b) 1 mole of phosgene**	"	"
	c) Unknown	30 min	Pulmonary edema, death
Gerritsen & Buschmann [6]	a) " **	Indefinite	"
	b) " **	3 hours	Pulmonary edema
Spolyar et al [5]	Unknown (15 ppm)*, **	<3 1/2 hours	Pulmonary edema, death
Glass et al [21]	Unknown **	4 1/2 hours	Acute bronchitis
Everett & Overholt [23]	"	Brief	Pulmonary edema
Delepine [25]	a) Unknown	"	Bronchial irritation, death
	b) "	"	"
English [8]	Unknown **	8 hours	Bronchiolitis, reactivation of a duodenal ulcer
Seidelin [7]	Unknown **	Brief	Pulmonary edema
Stavrakis [27]	a) Unknown	"	"
	b) "	"	Pulmonary edema, death
Steel [34]	a) Unknown	"	Acute bronchitis and delirium
	b) "	"	Pulmonary edema and delirium
Derrick & Johnson [22]	Unknown **	"	Pulmonary edema, death

* Re-created exposure simulating accident

** Simultaneous exposure to chlorinated hydrocarbons