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A STUDY OF THE CEILING LEVEL OF PHOSGENE

Samuel A. Cucinell

Edgewood Arsenal
Edgewood, Maryland

April 1973

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by

Samuel A. Cucinell, M.D., LTC, MC

Biomedical Laboratory

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13. ABSTRACT

Existing information on the toxicity of phosgene was reviewed and an estimate of the phosgene concentration which would have no deleterious effects on persons working regularly with the agent and on people living in the surrounding areas was developed in this report. A review of the literature since 1941 reveals no concentration of phosgene so low as not to cause pathologic changes in experimental animals. There are no data with which to correlate the toxicity of phosgene in man to that in laboratory animals at low concentrations, but estimates made during World War I are that the LCt_{50} for man is 3,200 mg min/cu m (2-min exposure). The measured LCt_{50} is 8,400 mg min/cu m for a 1-minute exposure in the dog and 3,450 mg min/cu m for a 1-minute exposure in the mouse. So, at least in terms of lethality, man is about as susceptible as the mouse and twice as vulnerable as the dog. The monkey is peculiarly sensitive to phosgene, with a 1-minute LCt_{50} of approximately 1,000 mg min/cu m. The threshold limit value (TLV) of phosgene adopted by the American Conference of Governmental Industrial Hygienists (ACGIH) for 1971 is 0.1 part per million (ppm) or 0.4 mg/cu m. This figure is based upon data obtained by the Chemical Warfare Service prior to 1921 that indicated 1 ppm of phosgene may be safe for prolonged exposure. After evaluating the available data, it is proposed that: (1) The concentration not to be exceeded during a daily 8-hour exposure of workers (healthy adults medically evaluated and cleared for duty) be established as 0.08 mg/cu m (0.02 ppm), and (2) The concentration not to be exceeded for the general population be established as 0.0025 mg/cu m (0.0006 ppm).

14. KEYWORDS

Phosgene	Pneumonitis
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Samuel A. Cucinell, M. D., LTC, MC

Medical Research Division
Biomedical Laboratory

April 1973

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Task No. 1W662710AD2502

DEPARTMENT OF THE ARMY
Headquarters, Edgewood Arsenal
Aberdeen Proving Ground, Maryland 21010

FOREWORD

The work described in this report was authorized under Project No. 1W662710AD2502, Medical Defense Against Chemical Agents, Prophylaxis and Therapy for Lethal Agents. This work was started in November 1971 and completed in May 1972.

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DIGEST

Existing information on the toxicity of phosgene was reviewed and an estimate of the phosgene concentration which would have no deleterious effects on persons working regularly with the agent and on people living in the surrounding areas was developed in this report.

A review of the literature since 1941 reveals no concentration of phosgene so low as not to cause pathologic changes in experimental animals. There are no data with which to correlate the toxicity of phosgene in man to that in laboratory animals at low concentrations, but estimates made during World War I are that the LCt_{50} for man is 3,200 mg min/cu m (2-min exposure). The measured LCt_{50} is 8,400 mg min/cu m for a 1-minute exposure in the dog and 3,450 mg min/cu m for a 1-minute exposure in the mouse. So, at least in terms of lethality, man is about as susceptible as the mouse and twice as vulnerable as the dog. The monkey is peculiarly sensitive to phosgene, with a 1-minute LCt_{50} of approximately 1,000 mg min/cu m.

The threshold limit value (TLV) of phosgene adopted by the American Conference of Governmental Industrial Hygienists (ACGIH) for 1971 is 0.1 part per million (ppm) or 0.4 mg/cu m. This figure is based upon data obtained by the Chemical Warfare Service prior to 1921 that indicated 1 ppm of phosgene may be safe for prolonged exposure.

After evaluating the available data, it is proposed that:

1. The concentration not to be exceeded during a daily 8-hour exposure of workers (healthy adults medically evaluated and cleared for duty) be established as 0.08 mg/cu m (0.02 ppm), and

2. The concentration not to be exceeded for the general population be established as 0.0025 mg/cu m (0.0006 ppm).

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FIGURE

Lower Airway Resistance During and After Chronic Exposure of Dogs to 24-40 ppm Phosgene for 30 Minutes Three Times a Week . . . 12

A STUDY OF THE CEILING LEVEL OF PHOSGENE

I. INTRODUCTION.

Existing information on the toxicity of phosgene was reviewed and an estimate of that phosgene concentration, which will have no deliterious effects on persons working regularly with the compound, and on people living in the surrounding areas was developed.

II. BACKGROUND.

The threshold limit value (TLV)* of phosgene adopted by the American Conference of Governmental Industrial Hygienists (ACGIH) for 1971 is 0.1 part per million (ppm), or 0.4 mg/cu m.[1] This figure is based upon data obtained by the Chemical Warfare Service prior to 1921 that indicated that 1 ppm of phosgene may be safe for prolonged exposure.** The figure is also based upon recent work which has shown that concentrations as low as 0.5 ppm for 2 hours caused definite pathological changes in the lungs of rats sacrificed 96 hours postexposure (table I).[2] Some abnormalities were considered to be present 3 months after rats had been exposed to 2 ppm for 80 minutes.

However, no studies done on experimental animals have demonstrated a concentration of phosgene so low that it caused no pathologic changes. Even exposure to 0.8 mg/cu m (0.2 ppm) of phosgene for 5 hours per day for 5 consecutive days caused evidence of pulmonary edema in 41% of the animals (goats, cats, rabbits, guinea pigs, rats, mice; table II).[3] Extensive lung lesions were present in 4% of the animals. Exposure of the same species to 1 ppm (4 mg/cu m) 5 hours daily for 5 consecutive days caused lesions in the lung that were "likely to give rise in man to serious clinical symptoms.[3,4] At this concentration the dose in cats even caused hemoconcentration and leucocytosis. In addition, ciliary function was depressed by 1.0 ppm phosgene, while the lachrymators brombenzylnitrile (CA) and diphenylaminochloroarsine (DM) had no such effects, even at high concentrations.[3] The TLV for man is 1/10 to 1/5 of that concentration known to produce pathological changes in animal lungs. In the absence of negative experiments and based on the preceding chronic studies, it is possible that 0.4 mg/cu m (0.1 ppm) may cause biological damage over prolonged periods of time.

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*Threshold limit values refer to airborne concentrations of substances and represent conditions under which it is believed that nearly all workers may be repeatedly exposed day after day without adverse effects. As the abbreviation TLV is closely associated with standards established by the ACGIH, we have avoided its use in connection with standards proposed by this laboratory.

** References 3-7 probably were not available to the ACGIH.

[1] Documentation of the Threshold Limit Values for Substances in Workroom Air. Third Edition. American Conference of Governmental Industrial Hygienist. Cincinnati, Ohio. 1971

[2] Gross, P., Rinehart, W. E., and Hatch, T. Chronic Pneumonitis Caused by Phosgene. Arch. Environ. Health. 10, 768-775 (1965).

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Table I. Pneumonitis Caused by Phosgene in Rats

CT	C	T	Chron. Pneum.[a]	CT	C	T	Chron. Pneum.[a]
ppm × time	ppm[b]	min.		ppm × time	ppm	min.	
13	1.3	10	0	108	0.9	120	0,F
15	1.5	10	0	120	1.0	120	++,P
24	0.8	30	+	120	1.0	120	+
27	0.9	30	+	120	1.5	80	+
33	1.1	30	+	180	0.5	360	+
36	1.2	30	+	180	0.5	360	+
40	1.0	40	+	180	1.0	180	+
48	0.8	60	++	180	1.5	120	+++,P
48	0.8	60	+,P	192	1.2	160	++
54	0.9	60	++,P	198	1.1	180	+++
60	0.5	120	+	210	1.0	210	++
84	1.4	60	+++,P	228	1.9	120	++
88	1.1	80	+	240	0.5	480	++,P
90	0.5	180	+	240	0.5	480	++
90	0.5	180	++	240	0.5	480	+++,P
90	0.5	180	+	240	1.0	24	++
99	1.1	90	+	264	1.1	240	++,P
90	1.5	60	+++	342	1.9	180	++,P
96	0.8	120	+++	360	1.0	360	+,F

a/ 0, no chronic pneumonitis; +, slight chronic pneumonitis; ++, moderate chronic pneumonitis; +++, severe chronic pneumonitis; P, acute pneumonia; F, fibrinous pneumonia.

b/ 1 ppm = 4 mg/cu m

Table II. Severity of Lung Lesions After Repeated Exposure to 0.2 ppm (0.8 mg/cu m) Phosgene[a/]

	Goats	Cats	Rabbits	Guinea pigs	Rats	Mice	Total	%
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
Frequency of Pulmonary Edema								
Edema present	0	1	5(1)	7(3)	2(1)	7(1)	22	41
Edema absent	2	1	5	3	8	13	32	59
Frequency of Acute Bronchitis								
Bronchitis present	0	1	5	5	1	0	12	22
Bronchitis absent	2	1	5	5	9	20	42	78
Frequency of Bronchial Regeneration								
Regeneration present	0	0	4	5	1	1	11	20
Regeneration absent	2	2	6	5	9	19	43	80
Frequency of Acute Bronchopneumonia								
Bronchopneumonia present	0	0	0	1	1	0	2	4
Bronchopneumonia absent	2	2	10	9	9	20	52	96

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

a/ Exposed 5 hours per day for 5 consecutive days.

Although there are no data with which to correlate the toxicity of phosgene in man to that in laboratory animals at low concentrations, there have been estimates made by observers in World War I that the LCt_{50} for man is 3,200 mg min/cu m (2-minute exposure; table III).[5,6] The measured LCt_{50} is 8,400 mg min/cu m for a 1-minute exposure in the dog and 3,450 mg min/cu m for a 1-minute exposure in the mouse. So, at least in terms of lethality, man is about as susceptible as the mouse and twice as vulnerable as the dog. The monkey is peculiarly sensitive to phosgene, with a 1-minute LCt_{50} of approximately 1,000 mg min/cu m.

III. CRITICAL EXAMINATION OF DATA ON PHOSGENE

A. Effect of Temperature on Toxicity of Phosgene.

All data given up to this point were obtained at unspecified temperatures (presumably room temperature). There is an indication that the mouse at least at high dosage levels, is more susceptible to phosgene when ambient temperature is either lower or higher than normal room temperature.[5] There was a tenfold increase in the toxicity of phosgene in mice kept at 8°C compared with those maintained at 27°C. The exact interpretation of these data is questionable. The limits set by the ACGIH for the TLV are for room temperature, but in the development of safe concentrations the range of outdoor temperatures must be considered.

Studies in dogs demonstrate no consistent changes in toxicity with changes in temperature and humidity (table IV).[7] No data are available on the effects of humidity and altitude on the toxicity of phosgene.

B. Effects Related to Toxicity: Chronic Disease.

1. Caused by Phosgene.

It is generally accepted that phosgene, as well as other pulmonary irritants, is responsible for the development of chronic lung disease in man as well as emphysema and obliterative bronchiolitis in dogs.[8,9] There are no quantitative data available on what dosage might

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5 Medical Division Status Summaries. CWS Field Lab Memo 1-4-5, p. 305. 1944. UNCLASSIFIED Report.

6 Chasis, H. Phosgene. Review of the Literature on the Effect of Exposure in Man and Experimental Animals. Contract W-49-036-CWS-1. 1944. UNCLASSIFIED Report.

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Table III. Toxicity of Phosgene

Animal	Time	LCt_{50}
	min	mg min/cu m
Mouse	1	3,450
	30	3,400
Rat	1	6,500
	30	1,400
Guinea pig	1	2,800
	30	2,200
Monkey	1	1,000
	30	1,000
Dog	1	8,400
	20	4,200
Man	2	3,200

Table IV. Effects of Temperature on Phosgene Toxicity in the Dog

[540 mg/cu m (135 ppm) X 20 min]

No. dogs	Dry bulb	Humidity	48 hr. deaths	Mortality
	°F	%		%
30	43	42	23	76.7
28	52	55	19	67.8
31	60	55	20	64.5
30	70	55	26	86.6
29	80	55	21	72.4
30	80	35	23	76.7
19	80	72	16	84.5
29	80	82	22	75.9
28	90	55	23	82.2

cause permanent lung damage in man. However, it has been experimentally demonstrated that 80-160 mg/cu m (20-40 ppm) for 30 minutes, given to dogs every other day for 1 week, causes increases in lower airway resistance and, with continued exposure, permanent pathophysiologic changes within the lung (figure).[8] These concentrations, however, are recognized as toxic (20 X a pneumonitis-producing dose, table 1), and their exact relationship to disease in man is unknown. In these studies lung function had not completely returned to normal 13 weeks following exposure. Nitrogen washout studies (emphysematous changes) showed the greatest abnormality at week 13, while airway resistance had almost returned to normal by this time. Studies of this type were designed to obtain an experimental model of chronic emphysema. No experimental studies have been performed to determine the effects of chronic low dosage exposure to phosgene on pulmonary function tests in laboratory animals. The effects of chronic low doses of phosgene upon the lung in animals or man in situations where there are no acute symptoms from phosgene are not known.

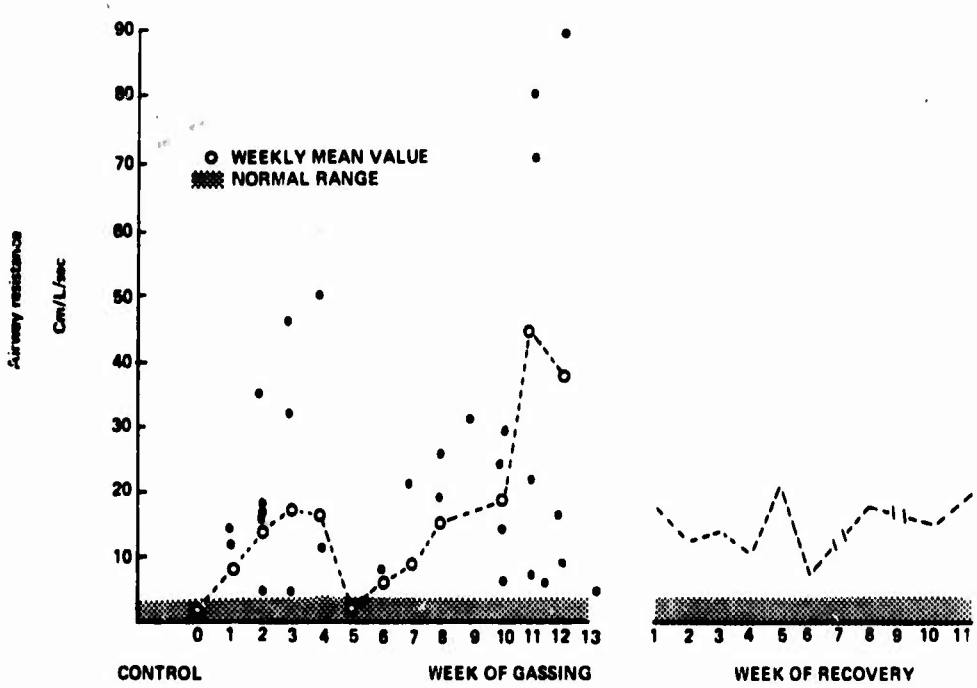

Figure. Lower Airway Resistance During and After Chronic Exposure of Dogs to 24-40 ppm Phosgene for 30 Minutes Three Times a Week

2. Aggravated by Phosgene.

No data have been generated to indicate that people with chronic respiratory diseases have an increased susceptibility to acute or chronic phosgene poisoning. It is assumed that people working around phosgene will have been prescreened and will not have, or be subject to, respiratory diseases (normal alphatrypsin inhibitory factor in the blood).[10] Russian investigators evaluated the general health of people who worked with isocyanate.[11] Among the pollutants in the factory atmosphere were phosgene, 0.1 ppm (0.4 mg/cu m); hexamethylene diisocyanate, 0-0.1 ppm, hexamethylene diamine, 0.05-0.81 ppm; chlorobenzene, 0.6-8.0 ppm; and dinyl, 0-4.6 ppm. There was a strong indication of abnormalities in the hearts, lungs, and livers of the workers. It is impossible to say how much of this was attributable to phosgene.

C. Factors Affecting Toxicity: Development of Tolerance to Phosgene.

Guinea pigs treated with low doses of phosgene [10 mg/cu m (1.5 ppm) X 10 min] for 7 days became relatively resistant to toxic levels [140 mg/cu m (35 ppm) X 10 min].[12] Repeated exposure of cats to phosgene, 10-15 mg/cu m (1.5-3.8 ppm) or 20-25 mg/cu m (5-6 ppm), for 10 minutes everyday caused no greater lung damage after 40 days than after 2 days.[13] They were able to tolerate a total Ct of 9,000 mg min/cu m (total time, 400 min) even though the LCt_{50} for cats is about 2,000 mg min/cu m for 1 minute.

There is some evidence that 1 ppm of phosgene produces tolerance to other irritants.[12] Rats exposed for 6 hours to this concentration were capable of surviving Ct's of ozone and nitrogen dioxide that killed almost all rats not previously exposed to phosgene (table V).[14] The exact mechanism of this tolerance is unknown. However, there was no increased resistance to phosgene itself. Tolerance to lethal doses of phosgene is felt by some to represent a manifestation of pathologic changes in the lungs. No information is available on the development of tolerance in man.

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Table V. Effect of Phosgene on Development of Tolerance to Other Gases (Rats)

First dose of phosgene	Second dose of phosgene	Dose of NO_2	Dose of O_3	Mortality
ppm (6 hr)	ppm (30 min)	ppm (30 min)	ppm (30 min)	
1.02 ± 0.0	18.2 b/	--	--	19/20 a/
18.2 ± 2.66	--	--	--	20/20 c/
		212.0 ± 5.04	--	19/20
1.03 ± 0.0	--	212.0 ± 5.04 b/	--	2/20
		--	48.0 ± 1.31	18/20
1.08 ± 0.03	--	--	48.0 ± 1.31 b/	2/20

a/ After second dose of phosgene
b/ Four days after phosgene
c/ After first dose of phosgene

IV. CONCLUSIONS.

1. The current ACGIH standard of 0.1 ppm may be too high for an 8-hour work day, 5 days per week, at room temperature. However, no adverse effects of the TLV of 0.1 ppm have been reported in the English language. It is recognized that ambient concentrations of phosgene in industrial situations in the United States are considerably below the TLV. Industrial intoxication by phosgene has been due to accidental exposure to a high concentration.

2. Some adjustments in the acceptable level for the general population must be made for a continuous 24-hour-a-day exposure, as compared to single or intermittent exposures. (Note: Animals tolerate intermittent better than continuous exposure to phosgene.)

3. There is no consistent pattern of response to phosgene in animals with temperature variations. The CL proposed applies to all environmental temperatures. (There are no data on the influence of altitude or humidity.) The effects of activity, causing increased respiratory minute volume, may be significant but are unknown at present.

4. Although high doses of phosgene can cause chronic lung disease in man and animals, it is not known whether low doses of phosgene will aggravate pre-existing conditions or cause lung disease.

V. RECOMMENDATIONS.

A. Estimation of the Ceiling Level of Phosgene.

Since the lowest experimental values available for chronic exposure suggest that 0.8 mg/cu m (0.2 ppm) for 5 hours for 5 days may cause slight changes in the lung, it would seem that a value of 0.1 ppm (0.4 mg/cu m) would not give a sufficiently large margin of safety. If a tenfold safety margin is used, then the ceiling level (concentration not to be exceeded) for working personnel for an 8-hour day, 5 days per week, at sea level would be 0.08 mg/cu m (0.02 ppm). Because the data on the effects of temperature on the toxicity of phosgene are contradictory and because there is no known theoretical reason for temperature to have a great effect, it is proposed that the ceiling level of 0.08 mg/cu m (0.02 ppm) be used in the range of environmental temperatures. In support of the suggested ceiling level of phosgene, one may propose that a Ct of 10 ppm min (40 mg min/cu m) (table I) is safe and this application of Haber's law* is valid. Then, considering a 480-minute day for workers, the ceiling level would be 0.08 mg/cu m (0.02 ppm). This is the same figure obtained from applying a tenfold safety margin to the TLV.

B. Special Situations.

For a 24-hour-a-day exposure, it is proposed that the ceiling level would be lowered by about one-third to 0.025 mg/cu m (0.006 ppm). An additional tenfold safety margin is recommended for situations in which people of all ages and states of health or disease (general population) may be exposed [0.0025 mg/cu m (0.0006 ppm)].

* Effect = Concentration X duration of exposure.

C. **Recapitulation.**

In summary, it is proposed that

1. The ceiling level* for a daily 8-hour exposure of workers (healthy adults medically evaluated and cleared for duty) be established as 0.08 mg/cu m (0.02 ppm), and

2. The ceiling level for the general population be established as 0.0025 mg/cu m (0.0006 ppm).

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* It is expected that in the event of accidental discharge of phosgene leading to concentrations in excess of the ceiling level for any period of time, corrective action will be taken before any additional phosgene is processed.

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