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(Project: A 10.2)

PHOSGENE.
MEDIAN LETHAL CONCENTRATIONS FOR MICE:
2- AND 30-MINUTE EXPOSURES.

AD-B957 358

By

S. D. Silver
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PHOSGENE.
MEDIAN LETHAL CONCENTRATIONS FOR MICE;
2- AND 30-MINUTE EXPOSURES.

ABSTRACT

Object.

The object of project A 10.2 is to determine the toxicity of various substances in order to estimate their value as possible war agents.

The object of the work described in this report was to determine the median lethal concentrations of phosgene for white mice for exposure periods of 2 and 30 min. and an observation period of ten days. The work was done in order to secure additional data for comparison of the toxicity of cyanogen chloride, hydrocyanic acid and phosgene.

Results.

The results of 9 runs, using an exposure period of 2 min. and an observation period of 10 days, are as follows:

Analytical concn. mg./l.	Fraction dead	Per cent deaths
1.22	3/20	15
1.50	3/20	15
1.68	0/20	0
1.88	8/20	40
2.08	9/20	45
2.36	15/20	75
2.65	9/20	45
2.87	12/20	60
2.99	14/20	70

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The results of 8 runs, using an exposure period of 30 min. and an observation period of 10 days, are as follows:

Analytical conc. mg./l.	Fraction dead	Per cent deaths
0.055	5/20	25
0.071	4/20	20
0.11	6/20	30
0.132	12/20	60
0.138	17/20	85
0.160	17/20	85
0.171	19/20	95
0.217	19/20	95

Conclusions.

1. The median lethal concentration of phosgene for white mice, for an exposure period of 2 min. and an observation period of 10 days, is 2.35 mg./l., with an average deviation of 0.25 mg./l.

2. The median lethal concentration of phosgene for mice, for an exposure period of 30 min. and an observation period of 10 days, is 0.112 mg./l., with an average deviation of 0.016 mg./l.

Recommendations.

None, since the work was done in connection with that on cyanogen chloride (see E.A.T.R. 341).

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PHOSGENE.
MEDIAN LETHAL CONCENTRATIONS FOR MICE: 2- AND 30-MINUTE EXPOSURES.

I. INTRODUCTION.

The object of project A 10.2 is to determine the toxicity of various substances in order to estimate their value as possible war agents.

The object of the work described in this report was to determine the median lethal concentrations of phosgene for white mice for exposure periods of 2 and 30 min. and an observation period of ten days. The work was done in order to secure additional data for comparison of the toxicity of cyanogen chloride, hydrocyanic acid and phosgene*.

II. HISTORICAL.

Phosgene is a well known war agent and much work has already been done on it. However, the only reliable information on its median lethal concentrations for mice is rather meager. Wells (E.A.T.R. 119) gives its m.l.c. for a 10-min. exposure and a 5-day observation period as 0.366 mg./l. Miller and Gross (B.M. XXXII, 57) report 0.073 mg./l. as the m.l.c. for a 30-min. exposure and a 10-day observation period.

The m.l.c. of phosgene for dogs for various exposure periods is reported by Armstrong and Witherspoon (E.A.M.R.D. 15). Their conclusions are as follows:

Time of exposure seconds	M.l.c. mg./l.
30	16.19
60	8.41
180 (3 min.)	1.51
300 (5 min.)	0.85
450 (7-1/2 min.)	0.62

* 4th ind., CWS 400.112/137 secret, OG, EA, May 1, 1941, to C, CWS on basic letter, same file, OG, EA, March 6, 1941, subject, A 3.5-1 E.A.T.R. 340, HCN, Stability in Shell, Status Report, 1940, to C, CWS.

[redacted]

No record can be found reporting the m.l.c. of phosgene for mice exposed for periods of less than 10 min.

III. EXPERIMENTAL.

A. Material.

The phosgene used was obtained from the Toxic Gas Yard. Analysis by the Analytical Dept. of the Research Division showed it to be of the following composition:

Phosgene	98.92%
HCl	0.64%
Cl_2	0.04%
Residue	0.001%

B. Animals.

The white mice used in these experiments were healthy stock purchased from dealers. Mice from two lots, no. 23 and 24, were used. Twenty-five mice from each lot were set aside as controls in order to establish the normal daily death rate. Data pertaining to these mice are tabulated below:

Run	Lot used	Date received	Observation period days	Daily death rate %
1-7	23	7/9/41	16	0.0
8-17	24	7/15/41	21	0.19

C. Apparatus.

All apparatus is shown in photo. 8798.

D. Procedure.

The airflow through the gassing chamber was started and adjusted to 250 l./min. The phosgene was introduced from a cylinder through a flowmeter (adjusted to a predetermined pressure differential for each run by means of the pressure equalizer) into a five-liter mixing bowl, and thence into the upper right-hand front corner of the chamber. From the equation $t_{99} = \frac{4.6 \times \text{chamber vol.}}{\text{airflow}}$, we find that the concentration in a 386-l. chamber with an airflow of 250 l./min. reaches 99% of equilibrium concentration after 7.1 min. Accordingly, sampling was started after 8-1/2 minutes had elapsed; the mice were introduced at the tenth minute and exposed for either two or thirty minutes.

The interior of the chamber was sprayed with protective lacquer before runs were started. After 20 runs had been made, slight corrosion of the chamber walls was observed.

Samples of the gas-air mixture were aspirated at the rate of 1 l./min. through a Vigreux-type bubbler containing 35 ml. of aqueous 5% sodium peroxide. The volume of the sample of gas-air mixture drawn for the two-minute gassings was 10 l. on the wet meter; for the 30-min. runs 30 to 50 l. were taken. The true volume was calculated from the formula:

$$\text{True volume} = \frac{(\text{barometer reading} - \text{wet meter manometer reading})}{\text{barometer reading}} \times \text{observed vol.}$$

In order to test the efficiency of the absorbing system, two of the bubblers, in series, were each filled with 25 ml. of 5% sodium peroxide, and 10 l. of gas-air mixture (concentration 2.63 mg./l.) were drawn through them at the relatively high rate of 1.8 l./min. No halogen was found in the second bubbler.

After each sample had been drawn from the chamber, the contents of the bubbler were transferred quantitatively to a 250-ml. glass-stoppered Erlenmeyer flask and boiled for twenty minutes to decompose the peroxide. After being cooled, the solution was analyzed for chlorides by a modification of the Volhard method. A slight excess of 1:1 nitric acid (free of nitrous acid and oxides of nitrogen), a measured excess of standard silver nitrate (approx. 0.02 M), and a few drops of nitrobenzene were added. The flask was shaken vigorously to floccuate the silver chloride. The excess of silver nitrate was titrated with standard potassium thiocyanate (approx. 0.02 M), using ferric alum as indicator.

The concentration of phosgene was calculated by use of the following formula:

$$\text{Anal. concn.(mg./l.)} = \frac{(\text{ml.}AgNO_3 \times \text{N.F.*}) - (\text{ml.}KCNS \times \text{N.F.*}))}{\text{true volume}} \times 49.5$$

In order to test the analytical procedure under operating conditions two samples of gas-air mixture were withdrawn on succeeding days (7/21/41 and 7/22/41), the settings on the flowmeters remaining unchanged. Ten-liter samples were drawn. The empty mouse carriage was introduced into, and withdrawn from, the chamber in the normal fashion during sampling. The analytical concentrations on these runs were 2.59 and 2.50 mg./l., respectively. These were regarded as satisfactory checks.

---

* = normality factor.

E. Results.

The results of the two-min. runs are tabulated in table 1.

Table 1

Toxicity of Phosgene to Mice; 2-min. Exposure

Run no.	Date 1941	Anal. concn. mg./l.	Immed.*	Daily deaths (cumulative) 1	2	3	4	5	6	7	8	9	10	10 day %
1	7-14	1.22	0	0	1	2	2	2	2	2	3	3	3	15
4	7-14	1.50	0	2	3	3	3	3	3	3	3	3	3	15
2	7-14	1.68	0	0	0	0	0	0	0	0	0	0	0	0
3	7-14	1.88	0	5	8	8	8	8	8	8	8	8	8	40
5	7-15	2.08	0	8	9	9	9	9	9	9	9	9	9	45
15	7-21	2.36	0	13	13	13	14	14	15	15	15	15	15	75
6	7-15	2.65	0	7	8	8	8	8	8	9	9	9	9	45
16	7-22	2.87	0	11	12	12	12	12	12	12	12	12	12	60
7	7-15	2.99	0	10	14	14	14	14	14	14	14	14	14	70

The results of the thirty-min. exposures are tabulated in table 2.

Table 2

Toxicity of Phosgene to Mice; 30-min. Exposure

Run no.	Date 1941	Anal. concn. mg./l.	Immed.*	Daily deaths (cumulative) 1	2	3	4	5	6	7	8	9	10	10 day %
11	7-18	0.058	0	2	4	4	5	5	5	5	5	5	5	25
13	7-31	0.071	0	3	4	4	4	4	4	4	4	4	4	20
12	7-18	0.11	0	0	5	6	6	6	6	6	6	6	6	30
8	7-17	0.132	0	11	12	12	12	12	12	12	12	12	12	60
17	7-22	0.138	0	16	17	17	17	17	17	17	17	17	17	85
14	7-21	0.160	0	16	16	17	17	17	17	17	17	17	17	85
9	7-17	0.171	0	19	19	19	19	19	19	19	19	19	19	95
10	7-17	0.217	0	17	17	17	18	19	19	19	19	19	19	95

* Deaths were classed as immediate if they occurred during the exposure period or within 1 hr. thereafter.

Upon introduction into the gassing chamber for the 2-min. exposures, the mice became excited. The eyes were half-closed and the mice were observed to be scratching their noses. Within one minute they invariably became quiet and were apparently holding their breaths. At about 1-1/2 minutes some lacrimation was usually noticeable.

Among the mice exposed for 30 min., a moderate amount of lacrimation was noticed. The mice did not hold their breaths for extended periods of time, but their breathing was shallow. Some gasping was observed.

Microscopic examination was made of sections from the lungs of two mice from run 10 (30-min. exposure to a concentration of 0.217 mg./l.) which had died between 16 and 17 hours after exposure. In the major portion of the alveoli a pinkish-red, finely granular material was found. The alveolar walls were thick in some areas and thin in others. The capillaries were distended with red cells. Areas of emphysema were found; however, this condition was more marked near the pleura. The bronchioles contained pinkish red, finely granular material such as was found in the alveoli. In several of the bronchioles the epithelium had sloughed and was lying in the lumen of the bronchiole.

Microscopic examination showed a marked edema of the lungs, sloughing of the bronchiole epithelium and congestion of the lungs.

IV. DISCUSSION.

A. Concentration data.

Only analytical concentrations were used in this work. In order to set up the wide range of concentrations necessary for the toxicity determinations a number of different phosgene flowmeters were utilized. This made it highly impractical to calibrate each one for the purpose of calculating the nominal concentrations. The use of two absorption bubblers in series showed that all the agent was collected in the first one, and the method of analysis was one approved and suggested by the Analytical Department of the Research Division. It is, therefore, considered that the analytical concentrations give a true picture of actual conditions in the gassing chamber.

B. Known sources of error.

	Per cent error
1. Chemical and physical.	
a. Purity of phosgene 98.92%	1.08
b. Nominal concentrations were not used	
c. Analytical concentration $C_a = m/v$	
m = weight found by analysis depending on titrative volume.	
Near m.l.c. volume = 25 ± 0.05 ml. (2-min. exposure)	0.2
Near m.l.c. volume = 4 ± 0.05 ml. (30-min. exposure)	1.25
v = volume of sample = 10 ± 0.01 l. (2-min exposure)	0.1
v = volume of sample = 30 ± 0.01 l. (30-min. exposure)	0.033
2. Biologic.	
a. Animals	
Lot 23, 10-day death rate 0.0%	indeterminable
Lot 24, " " " 1.9%	"
Physiologic variations due to differences in age, sex, nutritional history, etc.	"

C. Median lethal concentrations.

From table 1 the concentrations were plotted against the per cent 10-day deaths (chart 1). The median lethal concentration for a 2-min. exposure was read from chart 1 to be 2.35 mg./l., with an average deviation of 0.25 mg./l. From table 2 the concentrations were plotted against the per cent 10-day deaths (chart 2). The median lethal concentration for a 30-min. exposure was read from chart 2 to be 0.113 mg./l., with an average deviation of 0.016 mg./l. The average deviation is used as a measure of the internal consistencies of charts 1 and 2.

A comparison of ct values for the two different exposure times as well as for the 10-min exposure as reported in E.A.T.R. 119 follows.

[redacted]

Exposure time (t), in min.	2	10	30
Median lethal concn. (c), in mg./l.	2.35	0.375	0.112
ct	4.70	3.75	3.36

It appears that the ct value is fairly constant. The high value in the 2-min. exposure run might be ascribed to the fact that the mice seemed to hold their breaths for an appreciable part of the exposure.

V. CONCLUSIONS.

1. The median lethal concentration of phosgene for white mice, for an exposure period of 2 min. and an observation period of 10 days, is 2.35 mg./l., with an average deviation of 0.25 mg./l.

2. The median lethal concentration of phosgene for mice, for an exposure period of 30 min. and an observation period of 10 days, is 0.112 mg./l., with an average deviation of 0.016 mg./l.

VI. RECOMMENDATIONS.

None, since the work was done in connection with that on cyanogen chloride (see E.A.T.R. 341).

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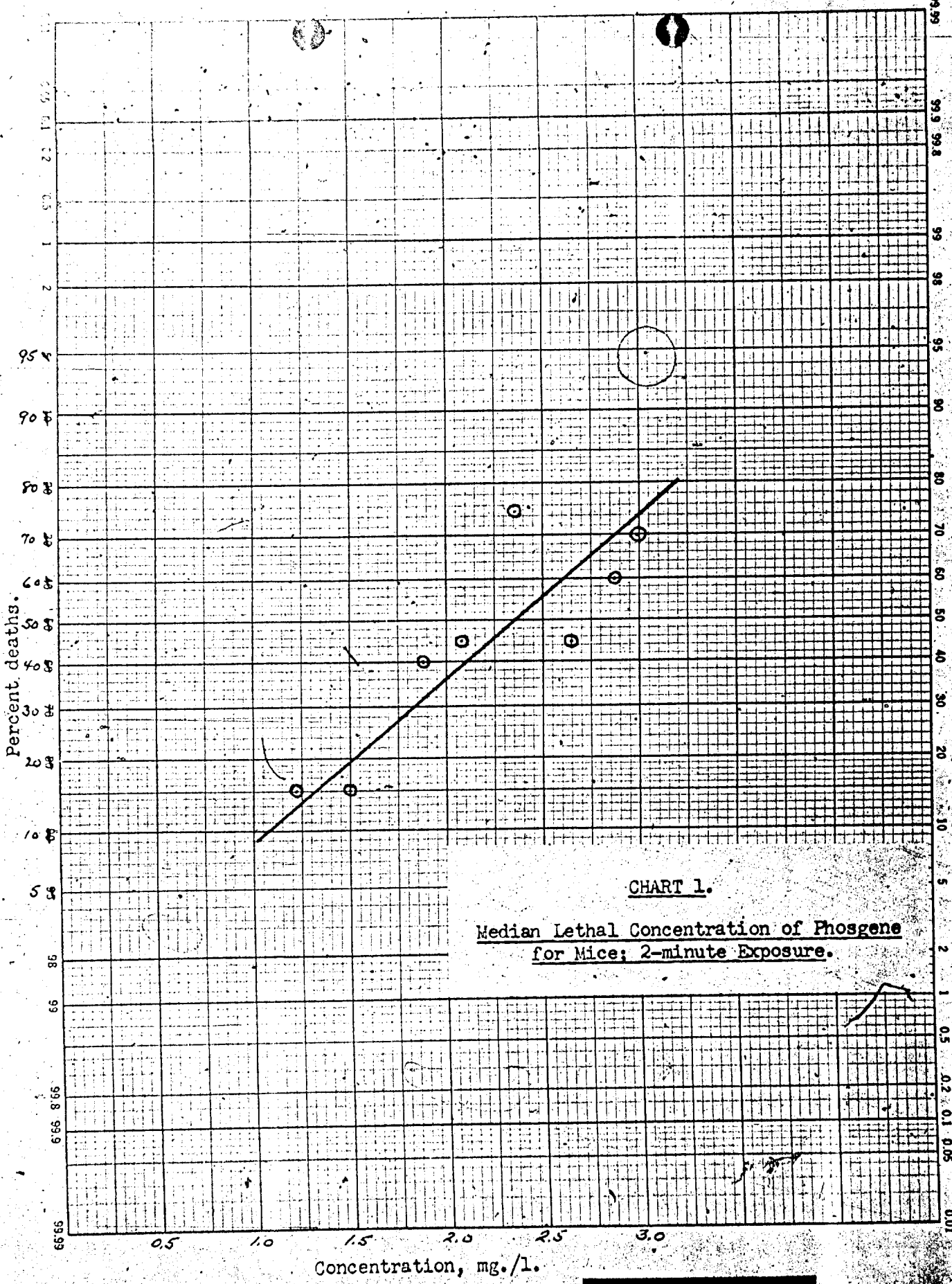

CHART 1.

Median Lethal Concentration of Phosgene for Mice; 2-minute Exposure.

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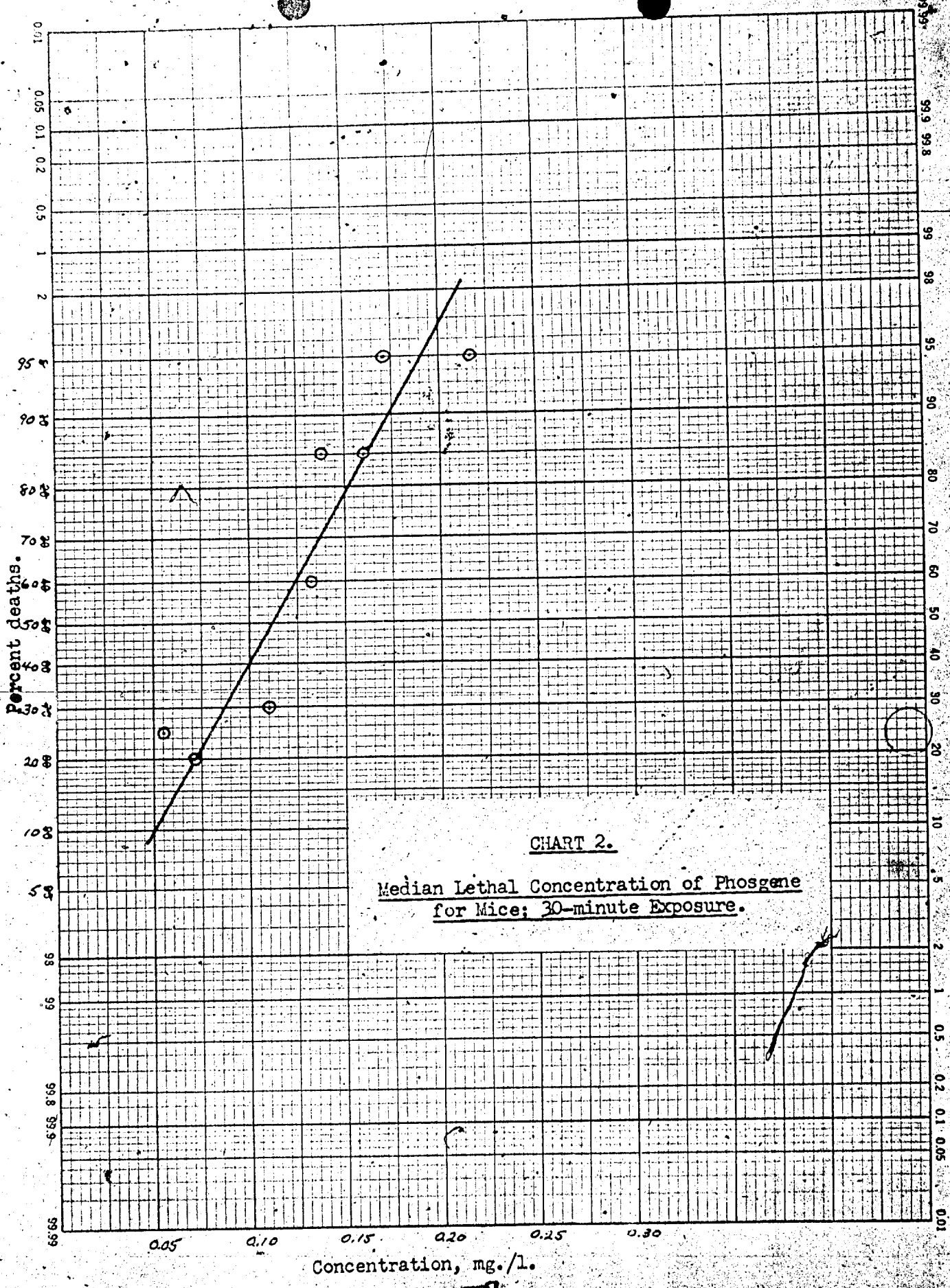
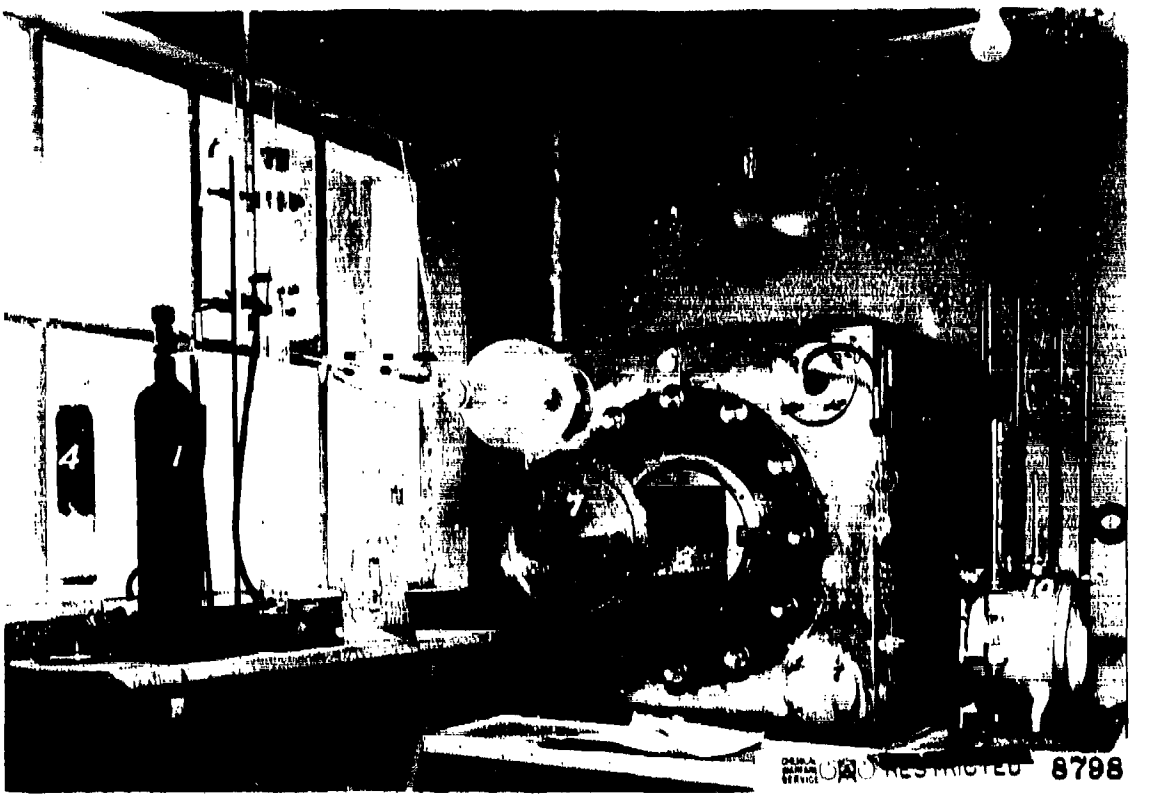


CHART 2.

Median Lethal Concentration of Phosgene for Mice; 30-minute Exposure.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