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**A STUDY OF THE EFFECTS OF CONTINUOUS INHALATION
OF HIGH CONCENTRATIONS OF OXYGEN AT
AMBIENT PRESSURE AND TEMPERATURE**

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U. S. ARMY CHEMICAL RESEARCH AND DEVELOPMENT
LABORATORIES
ARMY CHEMICAL CENTER, MARYLAND

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FOREWORD

Investigations of a study of the effects of continuous inhalation of high concentrations of oxygen at ambient pressure and temperature described herein were conducted by Francis W. Weir, Dale W. Bath, Paul Yevich, and Fred W. Oberst of the Directorate of Medical Research, U. S. Army Chemical Research and Development Laboratories, Army Chemical Center, Maryland. They were performed under Air Force Project No. 7165, "Health Hazards of Materials and Radiation," Task No. 716501, "Evaluation and Control of Toxic Chemical Materials." The contract monitor was Dr. Kenneth C. Back, Toxic Hazards Section, Physiology Branch, Biomedical Laboratory of the Aerospace Medical Laboratory. The experiments were started January 1960 and completed August 1960.

Animal experimentation was performed in accordance with the Rules for Animal Care established by the American Medical Association.

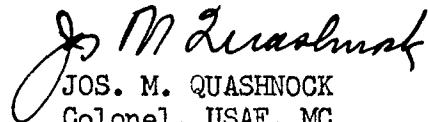
ABSTRACT

Investigations were carried out to determine the times of occurrence and progression of toxic effects in rats, and the times to death for various animal species exposed continuously to relatively pure oxygen at controlled environmental conditions and ambient pressures and temperatures.

Mice, rats, guinea pigs, dogs, and monkeys were exposed continuously to oxygen (95-99%) for 240 hours, unless interrupted by death. The initial toxic effects of exposure were labored breathing and lethargy which occurred after 15 to 20 hours in the rodents and 36 to 42 hours in the dogs. In the monkeys, these effects occurred considerably later, 72 to 96 hours.

Most animals dying during exposure showed extensive bilateral pleural effusions and pulmonary edema. Animals surviving 240 hours of oxygen exposure showed severe organ and tissue damage, including pulmonary edema, but did not show pleural effusion.

PUBLICATION REVIEW



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A STUDY ON THE EFFECTS OF CONTINUOUS INHALATION OF HIGH CONCENTRATIONS
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INTRODUCTION

The French investigator, Paul Bert, 1878 (4) was the first to show that a high oxygen concentration can kill many forms of organisms. Since that time the toxic effects of continuous exposure to high oxygen concentrations have been the subject of a large number of investigations (1,3,4,6,8,9,12) on experimental animals and a few on humans. These investigations indicate that the primary toxic action of high concentrations of oxygen at atmospheric pressures is restricted to irritation of the respiratory tract. The effects noted were believed to be due to the direct action of the oxygen, leading to pulmonary edema, atelectasis, extensive fibrosis of the alveolar walls, and death. Bean (1) pointed out that the pulmonary damage probably is not due to any single mechanism but is the result of several factors. In another article (2), Bean reported that deaths occurred in rats after a period of 45 hours of exposure to 90 to 98 per cent oxygen. His animals either died or were in a "terminal state" at the end of 70 hours of exposure. He found, without exception, that the thorax of each animal was filled with a clear, watery fluid, which clotted when exposed to air. The lungs were dark purple in color with few air-containing areas; they were of a rubbery consistency and sank in a fixing solution.

One of the most extensive experiments on oxygen toxicity in dogs was described by Paine, Lynn, and Keys (10). One of their dogs died after six hours exposure and showed pulmonary pathology. The average duration of survival in high oxygen concentrations was 39 hours. Other investigators (1,9) have found that dogs maintained in 98 per cent oxygen developed respiratory distress within 48 hours and died after about 60 hours. These variations in speed of action may possibly be explained by the differences in environmental conditions. For example, Hulpieu and Cole (7) found that increases in relative humidity combined with high temperature greatly increased the toxic effects of oxygen.

Experiments have been reported on human volunteers exposed continuously for 65 hours to 90 per cent oxygen at atmospheric pressure (1). The subjects were adversely affected by the exposure, and the experiment had to be discontinued because of severe respiratory distress.

The objective of the present investigation was to determine the times of occurrence and progression of toxic effects in rats exposed to relatively pure oxygen, and the times to death for various animal species at controlled environmental conditions and ambient pressures and temperatures.

MATERIALS AND METHODS

The exposure chamber was a modified gassing chamber of cubic shape with a volume of approximately 400 liters (fig. 1). It contained a small door for the introduction of animals. In addition, two openings with rubber gaskets were provided, so that the operator could insert both arms into the chamber and perform various manipulations without affecting the oxygen concentration. A wire-mesh screen floor was supported about 4 inches above the chamber floor over a removable tray containing a moisture absorbant. With this device, urine was absorbed and droppings were caught by the wire screen. Food and water were available to the animals ad libitum.

USP grade oxygen (97 - 99% purity by analysis) was introduced into the test chamber through a manifold system supplied from 4 cylinders (size 1-A). Rate of delivery of the O_2 into the chamber was approximately 20 liters per minute so that a slight positive pressure of about 5 mm Hg was maintained. The chamber-air was recirculated continuously by means of a blower-type pump through a system containing a condenser to remove excess moisture and Baralyme* to remove CO_2 before being returned to the chamber. The rate of circulation was 20 to 30 liters per minute. The relative humidity of the chamber was determined at hourly intervals by means of wet and dry bulb thermometers. The CO_2 content was measured continuously by passing a small stream of chamber-air through a Beckman model LB-1 medical gas analyzer. The oxygen concentration was determined on samples drawn from the chamber approximately once each hour during exposure, using a Beckman model E-2 paramagnetic oxygen analyzer.

The experiments in this study consisted of two parts.

1. Lt50's of Oxygen for Rats, Mice, Guinea Pigs, and Dogs

All animals were exposed continuously until death or for a maximum of 240 hours. The times to death were recorded and the Lt50's were calculated by the Bliss method (5). The species and the number of animals used are shown in table 1. The ranges for onset time of labored breathing and for death were determined. Similar experiments for rats of different sex and ages were carried out. These animals were divided into four groups of ten animals each. The sex and ages of the four groups were: (1) males, 8 weeks, (2) females, 8 weeks, (3) males, 6 months, and (4) females, 6 months.

*Produced by McGraw-Edison Company

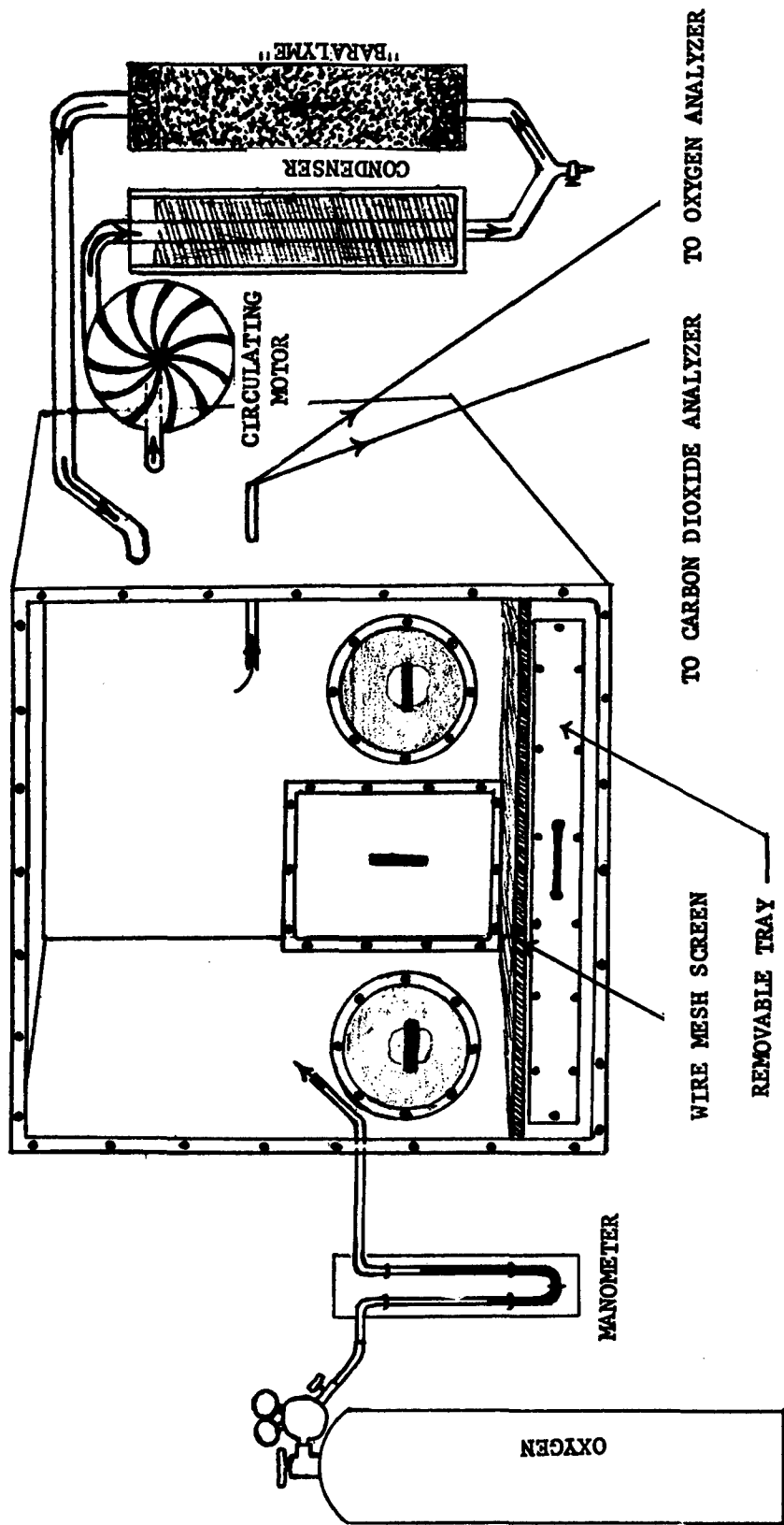


Figure 1. Oxygen Exposure Apparatus

TABLE 1

MORTALITY DATA FOR ANIMALS EXPOSED CONTINUOUSLY TO 95 TO 99 PER CENT OXYGEN

(Maximum Exposure Time Was 240 Hours)

Species	No of Animals	Times to Appearance of Labored Breathing hours	Range of Times to Death hours	Lt50 with 95% Confidence Limits hours	Slope of Time-response Curve (Bliss) $\frac{\text{log time}}{\text{probit \% mortality}}$	Final Mortality per cent
Mice	25	55 - 65	72 - 201	126 (114 - 138)	.10	100
Guinea Pigs	10	*	62 - 100	79 (66 - 94)	.07	100
Dogs	5	36 - 42	47 - 149	74 (43 - 127)	.19	100
Monkeys	2	70 - 75	150 - 216			100
Rats, Male, 8 weeks	20	15 - 20	53 - 72	65 (26 - 165)	.05	75
Effects of Sex & Age						
Rats, Male, 8 weeks	10	*	48 - 65	56 (54 - 58)	.06	100
Rats, Male, 6 months	10	*	51 - 66	57 (55 - 58)	.04	90
Rats, Female, 8 weeks	10	*	45 - 77	57 (53 - 60)	.08	90
Rats, Female, 6 months	10	*	49 - 70	59 (57 - 61)	.05	90
Rats (All Data Combined)	60		48 - 77	60	.06	87

* Data not recorded

2. Observations of Toxic Signs and Pathological Changes in Organs and Tissues

a. Rats

(1) Toxic Signs

Twenty 8-week-old male rats were exposed continuously to oxygen for 240 hours to determine the occurrence and the time of the onset of toxic effects during the course of exposure.

(2) Pathology

Those rats which survived the 240-hour oxygen exposure were sacrificed on the 5th day after exposure for examination of organs and tissues. Rats dying during the 240-hour exposure period were examined immediately after death for organ and tissue changes. Unexposed animals serving as controls were sacrificed from time to time during the 240-hour exposure period for purposes of comparison with exposed animals.

Progression of pathological changes in organs and tissues during oxygen exposure was also evaluated. Two 8-week-old male rats chosen at random were withdrawn at 2-hour intervals from 2 to 48 hours during exposure and were sacrificed along with control animals for gross tissue and organ examination. The hearts and lungs were removed for microscopic study.

b. Mice, Guinea Pigs, and Dogs

Twenty-five adult female mice, 10 three-month-old male guinea pigs, and 5 young beagle dogs (4 males and 1 female) were exposed continuously to oxygen till death. The mice and guinea pigs were exposed as a group, while the dogs were exposed individually. Occurrence of toxic signs were recorded.

All animals were examined for pathological changes.

c. Monkeys

Two young, adult, male Sooty-Mangabey monkeys were exposed individually to oxygen until death. They were observed for occurrence of various toxic signs; time of onset of these effects was recorded. Immediately after death, gross examinations of the tissues and organs were made. Microscopic examinations were made of the heart, lungs, pancreas, liver, and spleen.

RESULTS

The mean chamber oxygen concentration was 98 (range 95 to 99) per cent; average CO₂, 0.10 (range 0.01 to 0.25) per cent; relative humidity, 50 (range 30 to 70) per cent; and temperatures 25° (range 23° to 28°)C.

1. Lt50's of Oxygen for Rats, Mice, Guinea Pigs, and Dogs

The Lt50 values with the slopes of the time-response curves for each of the animal species are shown in table 1. The times to labored breathing, the range for times to death, and similar data showing the effect of sex and age of rats on these values are also included. The mortalities for the 8-week-old females, the 6-month-old males, and the 6-month-old females were 90 per cent. The range for times to death of animals in these three groups was 45 to 77 hours. One animal in each group survived the 240-hour exposure. For the 8-week-old males, the mortality was 100 per cent. There were no significant differences in the Lt50's and the slopes of the time-response curves.

2. Observations of Toxic Signs and Pathological Changes

a. Rats

(1) Toxic Signs

A flushed coloration of the nose, ears, feet and scrotum of the rats appeared almost immediately after inhalation of pure oxygen. After 15 to 20 hours, rapid, labored breathing developed, followed by lethargy. The animals maintained a curled-up position, had piloerection, and appeared unkempt. After about 36 hours, a reddish exudate was secreted from the eyes of some of the exposed animals. Respiratory distress progressively increased and the animals became prostrate. Deaths began to occur after 53 hours and continued through the 72nd hour of exposure, when 15 out of 20 rats had died. At the time of death, an amber fluid drained from their nostrils. The dead animals were immediately withdrawn from the chamber and examined for pathological changes. After about 100 hours of exposure, the five surviving animals began to show signs of recovery. Daily food and water consumption, which had progressively declined, began to increase. There was an increase in general activity with improvement in the appearance of each animal, although they were still lethargic and showed labored breathing.

At the end of 240 hours of exposure, the concentration of oxygen was progressively decreased over a period of about four hours to atmospheric oxygen concentration. During the post-exposure period the

rats' activity increased; their pelts became smooth and clean, and the respiratory pattern became normal. The five survivors were sacrificed 5 days after the exposure.

(2) Pathology

The apical lobes of lungs from rats surviving 240 hours exposure to oxygen and sacrificed 5 days after the exposure were consolidated. No pleural effusion was found. Microscopically, the degree of lung damage varied greatly among the different animals. Pulmonary edema was present in all. Large macrophages were seen in the alveolar spaces of these animals. Some of the alveolar walls were thickened, in several cases to the point of obliteration of the lumen. The adventitia of the blood vessels was edematous and showed a loose, fibrous network. Emphysema and dilatation of the tracheo-bronchial tree were observed.

Examination of the animals that died during exposure showed extensive, bilateral, pleural effusion which clotted firmly after incision. In some instances, the thoracic cavity was completely filled with the fluid. The lungs appeared to be collapsed and were dull red in color. When placed in a fixative, they immediately sank to the bottom of the container. Microscopically, there was severe pulmonary edema.

The lobes from the lungs of the control animals were pink and crepitant, and the thoracic cavities were free of exudate. Murine pneumonia was found in a few of these animals. No significant changes were found in other organs and tissues examined.

Groups of two rats exposed for periods of 2 to 48 hours and sacrificed immediately thereafter showed rather wide variations in times of onset of morphological changes. The lungs of the animals appeared normal until 4 to 6 hours of exposure when traces of edema were found in a few animals. The severity of the edema progressed with exposure time. The edema became noticeable in the alveolar wall and there was an appearance of a stringy exudate in the alveolar spaces. Considerable edema was seen in the walls of the pulmonary vein after 24 to 28 hours of exposure. Necrosis of the pulmonary vein deep within the lungs was present at the 30th hour of exposure. Thickening of the walls of the arterioles had developed by 36 to 44 hours. The heart showed an increase of endomysial elements with necrosis of cardiac muscle fibers, especially in large focal areas of the ventricles. At 48 hours, the edema of the adventitia of the trachea and of the bronchial tree was very severe. Control animals did not show any tissue changes that were not within normal limits.

b. Mice

All deaths occurred between 72 and 201 hours. Seventeen of the 25 animals died between 72 and 134 hours, seven more died between 150 and 173 hours, and the last animal died after 201 hours of exposure. All animals examined on death had extensive bilateral pleural effusion. The pathological changes in organs and tissues were similar to those seen in rats. Necrosis of the pulmonary veins and interstitial edema were quite pronounced.

c. Guinea Pigs

All of the guinea pigs were dead after 100 hours of continuous exposure. The toxic signs and pathological changes in organs and tissues were similar to those found in rats.

d. Dogs

(1) Toxic Signs

During the first 24 to 36 hours of exposure, the dogs showed a flushed coloration of the skin. They were active and behaved normally. Food and water consumption were normal. As the exposure continued, their activity decreased. After 36 to 42 hours, breathing became labored, eyes appeared bloodshot, and tremors were noted in the hind legs. After 44 to 48 hours of exposure, food and water consumption decreased, and breathing was very rapid and deep with forceful exhalations. Auscultation revealed a rasping, gurgling noise in the chest cavity. Several times during this period the animals discharged a yellow frothy vomitus. Deaths occurred between 47 and 149 hours.

(2) Pathology

On opening the chest, large bilateral pleural effusions were found. Rather large, bright red areas were seen in both the right and left apical lobes of the lungs. Portions of the lobes appeared to be consolidated. The apical lobes contained areas which were grayish in color and glistened. The tracheal and bronchial trees were filled with a white, frothy exudate. The apex of the heart showed hemorrhages in several of the animals. The auricles appeared normal. In all dogs, the tissues surrounding the trachea, bronchial tree, pulmonary vessels, and those attached to the heart appeared gelatinous. The stomachs of three dogs contained blood. In one dog, blood was found on the surface of the dura. Microscopic examination showed extensive edema in the tissues of the lungs and bronchial trees as well as of the alveolar walls. The alveolar spaces contained a pink-staining, stringy exudate.

e. Monkeys

(1) Toxic Signs

The skin in the thoracic and abdominal regions on two monkeys became flushed within two to three hours of exposure. During the first 72 to 96 hours, the animals were very active. Daily food and water consumption were normal, and they responded normally to external stimuli. After 96 hours of exposure, they became progressively more lethargic. Respiration became difficult and progressed to deep, gasping, oral breathing. They drank copious amounts of water, and their food intake was decreased to a low level. Approximately 24 hours before they died, a clear fluid drained from their nostrils, and a foamy exudate came from their mouths. Respiration was very rapid and was mostly through the mouth. Their eyes had a glassy appearance. Deaths occurred at the end of 150 and 216 hours of exposure.

(2) Pathology

Gross examination of the tissues and organs of these animals revealed no significant pathological changes in the eyes, nasal passages, mouth, heart, spleen, liver, and kidneys. The thoracic cavity was free of excess fluid. All lobes of the lungs had a dull gray color with glistening surfaces.

Microscopic examination of the heart revealed necrosis of the muscle bundles with a possible increase in cellular elements. The lymphatics of the bronchial tree were dilated. All sections showed alveolar wall thickening. The alveolar wall epithelium showed swollen, vesicular nuclei in some areas. The alveolar spaces were filled with fibrinous material. Also, at the periphery of the lobes, there was hyalinization of the alveolar walls and extensive emphysema. The acini of the pancreas were necrotic. The sinusoids of the liver were dilated. The splenic sinusoids were free of blood, but showed some proliferation of the stromal elements.

DISCUSSION

The toxic signs and morphologic changes in organs and tissues of various animal species were very similar to those reported by other investigators (1,9). In some instances, it was difficult to compare the results of our work with that of other investigators because of variations in experimental technique and environmental conditions. In all instances, it is evident that the major pathology was found in the thoracic cavity. Most animals that died during exposure had pleural effusion and pulmonary edema. After 44 to 48 hours of exposure a rasping, gurgling noise could be heard by auscultation of the chest of dogs,

indicating the presence of excess fluid in the lung. No pleural effusion was found in the chest cavity of the two monkeys at autopsy. No attempt was made to auscultate the chest during exposure. It is possible that they, too, had pleural effusions present at some time during the exposure which was reabsorbed before death, the exact cause of death being undetermined.

It is of interest that the times to death of most animals occurred within a short period of each other. The animals which survived beyond this period usually tolerated an extraordinarily long exposure, 240 hours. For some reason these animals became adapted to pure oxygen. Among a group of 20 rats, 75 per cent died between 53 and 72 hours. The remaining 5 animals survived the 240-hour exposure. Smith et al. (11), reported that adaptation does take place in the lungs of rats on prolonged exposure to high oxygen concentrations.

The most significant difference in pathology between those animals dying during exposure and the survivors was the presence of pleural effusion in the former. Very little free fluid was present in the chest of the survivors. It appeared that the amount of damage in tissues and organs was the same in those dying and survivors. The same observation was made in the 40 rats studied for effect of age and sex on oxygen toxicity. Thirty-seven of these animals died between 45 and 77 hours. There were three rats that survived the 240-hour exposure. These rats showed severe organ and tissue damage and pulmonary edema similar to those dying during exposure, but did not have the abundance of pleural effusion. It is possible that these animals had pleural effusion early in the course of exposure but for an unknown reason, resorption of this fluid may have taken place and thus extended the survival time. The survivors appeared as sick as non-survivors during the early phase of the exposure but gradually began to show signs of general improvement during the last few days of exposure. At present no adequate explanation can be given for the pleural effusion and pulmonary edema development during long periods of exposure to pure oxygen.

SUMMARY

Mice, rats, guinea pigs, dogs and monkeys were exposed continuously to oxygen (95-99%) for 240 hours, unless interrupted by death. The initial toxic effects of oxygen were labored breathing and lethargy which occurred after 15 to 20 hours in the rats and 36 to 42 hours in the dogs. In the monkeys, these effects occurred considerably later, 72 to 96 hours. Sex and age differences of rats did not significantly affect the toxicity of oxygen.

Most animals dying during exposure showed extensive bilateral pleural effusions and pulmonary edema. Microscopically, other features were emphysema and dilatation of the tracheo-bronchial tree. Animals surviving 240 hours of oxygen exposure showed severe organ and tissue damage, including pulmonary edema, but did not show pleural effusion. The adventitia of the tracheo-bronchial tree and of the large blood vessels of the lungs was edematous. Necrosis of the pulmonary vein and thickening of the pulmonary arterioles were also seen.

Times to death in animals varied over a wide range and only a few rats survived the 240-hour exposure period. All other animal species died before the end of this period.

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<p>ASD TR 61-664</p> <p>U. S. Army Chemical Research and Development Laboratories, Army Chemical Center, Maryland</p> <p>A STUDY OF THE EFFECTS OF CONTINUOUS INHALATION OF HIGH CONCENTRATIONS OF OXYGEN AT AMBIENT PRESSURE AND TEMPERATURE, by F. W. Weir, D. W. Bath, P. Yevich, and F. W. Oberst. December 1961. 18p. incl. illus., table. (Proj. 7165; Task 716501) Unclassified report</p> <p>Investigations were carried out to determine the times of occurrence and progression of toxic effects in rats, and the times to death for various animal species exposed continuously to relatively pure oxygen at controlled environmental conditions and ambient (<i>over</i>)</p>	<p>UNCLASSIFIED</p> <p>I. Weir, F. W. II. Bath, D. W. III. Yevich, P. IV. Oberst, F. W. V. Aeronautical Systems Division, Aerospace Medical Laboratory, Wright-Patterson Air Force Base, Ohio</p> <p>VI. MIPR No. (33-616) 60-33</p> <p>UNCLASSIFIED</p>	<p>ASD TR 61-664</p> <p>U. S. Army Chemical Research and Development Laboratories, Army Chemical Center, Maryland</p> <p>A STUDY OF THE EFFECTS OF CONTINUOUS INHALATION OF HIGH CONCENTRATIONS OF OXYGEN AT AMBIENT PRESSURE AND TEMPERATURE, by F. W. Weir, D. W. Bath, P. Yevich, and F. W. Oberst. December 1961. 18p. incl. illus., table. (Proj. 7165; Task 716501) Unclassified report</p> <p>Investigations were carried out to determine the times of occurrence and progression of toxic effects in rats, and the times to death for various animal species exposed continuously to relatively pure oxygen at controlled environmental conditions and ambient (<i>over</i>)</p>	<p>UNCLASSIFIED</p> <p>I. Weir, F. W. II. Bath, D. W. III. Yevich, P. IV. Oberst, F. W. V. Aeronautical Systems Division, Aerospace Medical Laboratory, Wright-Patterson Air Force Base, Ohio</p> <p>VI. MIPR No. (33-616) 60-33</p> <p>UNCLASSIFIED</p>	<p>UNCLASSIFIED</p> <p>I. Weir, F. W. II. Bath, D. W. III. Yevich, P. IV. Oberst, F. W. V. Aeronautical Systems Division, Aerospace Medical Laboratory, Wright-Patterson Air Force Base, Ohio</p> <p>VI. MIPR No. (33-616) 60-33</p> <p>UNCLASSIFIED</p>
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