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HEPATOTOXIC POTENCY OF VARIOUS CHLORINATED HYDROCARBON VAPORS RELATIVE TO THEIR NARCOTIC AND LETHAL POTENCIES IN MICE			
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Patent Status	***Date Issued***	***Page Count***	***Lab Report Code***
No Action Required	24 January 1968	32	HET K-002516-017
Geographic Location	***Department***	***Archive Number***	
N. America	TERC		

Abstract

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Biochemical Research Laboratory

The Dow Chemical Company

BC T2.2-151-1

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File: T2.2-151-1
Chg.: 1219
Date: 1-24-68
By: P. J. Gehring

Signed P. J. Gehring Checked D. K. Rowe 1-29-68

ABSTRACT

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HEPATOTOXIC POTENCY OF VARIOUS CHLORINATED HYDROCARBON VAPORS RELATIVE TO THEIR NARCOTIC AND LETHAL POTENCIES IN MICE

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Running Title: Hepatoxicity of Chlorinated Hydrocarbons

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Although a voluminous amount of data depicting the hepatotoxicity of chlorinated hydrocarbons is available, only a few studies have been reported that quantitatively relate hepatotoxicity to other biological effects. Since the effects of these compounds on the liver is a primary concern in assessing their toxicity, it is important to characterize the specificity of their hepatotoxic activity. To do this, it is necessary to obtain quantal dose-response data for the hepatotoxic potency of the chlorinated hydrocarbons and relate it to the quantal dose-response data for other biological effects of these compounds.

Because of the tedium encountered in determining whether morphological alteration of the liver has been induced by a chlorinated hydrocarbon as well as the difficulty in translating the results into quantal dose-response data, other means of assessing liver damage have been used. Prolongation of pentobarbital anesthesia (Plaa et al., 1958) and sulfobromophthalein (BSP) retention (Kutol and Plaa, 1962) have been used to quantitate hepatotoxicity. Recently, Klaassen and Plaa (1966) determined the relative hepatotoxic activity of 1,1,1-trichloroethane, chloroform, dichloromethane, trichloroethylene, tetrachloroethylene, carbon tetrachloride, and 1,1,2-trichloroethane in mice using BSP retention and elevated serum glutamic-pyruvic transaminase (SGPT) as indications of liver damage. In their study, the chlorinated hydrocarbons were administered by intraperitoneal injection. They found that the elevation of SGPT was a more sensitive indicator

of the hepatic damage induced by these compounds than was BSP retention.

Since some of these compounds cause severe writhing and even massive peritonitis following intraperitoneal injection, it is conceivable that the local irritation may alter or even negate the validity of the results. Aside from this possible pitfall, exposure by vapor inhalation seemed more appropriate because human beings are more likely to receive these materials by this route. Therefore, the primary purpose of the present investigation was to obtain similar data from mice exposed to the vapors of these same compounds and compare it to the data obtained using intraperitoneal injection. A secondary purpose was to explore the feasibility of using this methodology to quantify the hepatotoxic potency of new hepatotoxic agents thereby permitting comparison of one material with another.

In order to compare the results obtained from this study with those obtained by Klaassen and Plaa (1966), the experiments were repeated in which carbon tetrachloride, tetrachloroethylene, and 1,1,1-trichloroethane were administered by intraperitoneal injection.

METHODS:

Female Swiss-Webster white mice weighing 20-35 g were used 7 to 21 days after arrival in the laboratory.

The chlorinated hydrocarbons employed were: 1,1,1-trichloroethane, chloroform, dichloromethane, trichloroethylene, tetrachloroethylene, carbon tetrachloride and 1,1,2-trichloroethane. All were center-cut fractions containing less than 0.5% impurities.

Vapor inhalation studies were done using the equipment described by Irish and Adams (1940) and Rowe et al. (1952). The exposure chamber was a 160 liter cubical (20 x 20 x 20 inches) made with a Monel® frame. The sides of the chamber, including the door, are glass. The door which makes up one side of the chamber is sealed with a Silicone® rubber gasket; it is fitted with quick opening latches.

The desired vapor concentration was attained by metering the liquid chlorinated hydrocarbon at a constant rate into a tube, heat being applied at the point of vaporization as needed to affect complete volatilization. All air entering the chamber passes through this tube and enters the chamber through a manifold located at the front of the top of the chamber. The chamber is exhausted through a similar manifold located at the bottom of the rear of the chamber. A constant air flow was maintained during each exposure, the lowest rate being about 17 liters per minute and the highest being about 30 liters per minute. The chamber is also equipped with a quick-opening valve and inlet pipe of a rapid

exhaust system which allows the vapor exposure to be terminated within one minute.

The top of the chamber has two rubber stoppered tubes, 3.5 inches in diameter. One of the rubber stoppered tubes is used to quickly put animals into or to withdraw animals from the chamber. This method of introducing and withdrawing animals from the chamber has been shown to cause very little change in the concentration of vapor in the chamber. The other tube has a rubber stopper with two holes that are fitted with Silicone® tubing. These Silicone® tubes permit air to be continuously circulated through the cell of an infrared spectrophotometer thus maintaining a closed system but still allowing a continuous analysis of the vapor concentration in the chamber. The path length of cells for the infrared spectrophotometer was 1 cm, 2 cm, or 10 cm depending on the vapor being analyzed.

If there was more than a 7% change in the desired vapor concentration during an exposure, the data were not used and the exposure was repeated. Mice exposed to chlorinated hydrocarbon vapor for less than two hours were put into the chamber through the tube in the top of the chamber. This procedure caused less than a 7% reduction in the desired concentration. However, in experiments requiring an exposure duration greater than two hours, the mice were placed in the chamber using the door. This latter procedure caused less than a 30% reduction in vapor concentration.

The desired vapor concentration was re-established in less than 10 minutes.

Some experiments with carbon tetrachloride required exposure durations as short as three seconds. This was accomplished by placing the mice into a wire cylindrical cage which could be introduced and withdrawn from the chamber through the tube.

The dose of chlorinated hydrocarbon received by an animal during the course of an exposure is a function of vapor concentration, duration, respiratory rate and tidal volume, as well as other parameters which influence the passage of vapor from the alveolar air through the alveolar membrane into the blood. In the experiments described herein, attention was given to only the vapor concentration and exposure duration. The vapor concentration was maintained constant and the exposure duration was varied. This methodology was chosen because of convenience. Varying the concentration would require more time to adjust and standardize the equipment to deliver the desired concentration.

In these experiments, a vapor concentration of each compound was used which would, based on previous studies, be expected to kill 50% of the animals between 9 and 12 hours of continuous exposure.

When 1,1,1-trichloroethane, carbon tetrachloride and tetrachloroethylene were administered by intraperitoneal injection,

they were made up in corn oil to deliver the desired dose in a final volume of 0.01 ml/gm.

Lethality:

During the course of an exposure, the mice were repeatedly observed through the glass walled exposure chamber. The number of dead mice and the exposure duration were recorded. The time after the initiation of an exposure when respiratory movements ceased was considered the time of death for each mouse. The percent of dead mice as a function of time was determined from which the median lethal time (LT_{50}) was calculated. In those experiments in which agents were given by intraperitoneal injection, the number of deaths were recorded at the end of 24 hours.

Anesthesia:

The duration of time between the initiation of an exposure and onset of anesthesia was also recorded for each mouse. Onset of anesthesia was considered to be the time at which the mouse became immobilized. With the exception of dichloromethane, the time required for immobilization of each mouse occurred within narrow temporal limits and only infrequently would a mouse again become mobile. With dichloromethane, the induction of anesthesia was slow making it difficult to assess the time at which immobilization occurred. Therefore, the bottoms of the cages in which the mice were kept were marked off in four-inch squares. In order for

a mouse to be judged immobile, the mouse had to remain within the same square for the remainder of the experiment.

Hepatic Damage:

Twenty-four hours after the beginning of an exposure or the injection of an agent, a 0.5 to 1.0 ml blood sample was obtained from each mouse by cardiac puncture using a syringe that had been rinsed with a solution of sodium heparin (10,000 units/ml). For this procedure, the mice were anesthetized with methoxyflurane. The SGPT was determined using the method of Reitman and Frankel (1957) as specified in the Sigma Technical Bulletin 505, (1964).

The mean and standard deviation for the SGPT of 254 air-exposed control mice was 26.7 ± 13.6 Reitman-Frankel units; therefore, a value for the SGPT greater than 54 Reitman-Frankel units was considered the upper limit of the normal range. The 254 control mice are a composite of groups of control mice that were air-exposed concurrently with each group of mice exposed to the vapor of a chlorinated hydrocarbon. The percent of mice having a significant elevation of SGPT as a function of exposure duration was determined and compared with similar data for anesthesia and lethality.

In a similar manner, quantal dose-response data were obtained for mice given 1,1,1-trichloroethane, carbon tetrachloride, and tetrachloroethylene by intraperitoneal injection. In 50 mice treated with corn oil, the mean SGPT activity was 24.4 ± (SD) 14.7

Reitman-Frankel units. Therefore, in these experiments, SGPT values greater than 54 Reitman-Frankel units were considered abnormal and indicative of a significant change.

Statistics:

All statistical analyses were done according to the method of Litchfield and Wilcoxon (1949).

RESULTS

Intraperitoneal administration of 1,1,1-trichloroethane, carbon tetrachloride, and tetrachloroethylene. Before undertaking vapor inhalation experiments, quantal dose-response data for the lethality and hepatotoxicity of 1,1,1-trichloroethane, carbon tetrachloride, and tetrachloroethylene following intraperitoneal injection were obtained. The doses of each of these agents required to cause death and a significant SGPT elevation in 50% of the treated animals within 24 hours are shown in Table 1. Klaassen ard Plaa (1966) indicate that the deaths occurring within 24 hours after the intraperitoneal injection of these agents are narcotic deaths. Assuming this hypothesis to be correct, the dose required to cause death in 50% of the mice divided by the dose required to cause an abnormal elevation of the SGPT in 50% of the mice (LD_{50}/ED_{50}) gives a potency ratio which is indicative of an agent's capacity to cause hepatic damage relative to its ability to cause anesthesia. Table 2 depicts the results obtained by Klaassen and

Plaa (1966) for these compounds, as well as for the other compounds reported in this study. The similarity of the results presented in Tables 1 and 2 assures that, aside from the method of administering the agents to the mice, the methodology used in the vapor inhalation experiments should provide comparable results. It should be noted that in our studies the dose-response curve for liver dysfunction ascertained by SGPT activity and the curve for lethality of carbon tetrachloride when given by intraperitoneal injection were not parallel.

Carbon Tetrachloride by Vapor Inhalation: A vapor concentration of 8,500 ppm carbon tetrachloride killed 50% of the mice after 690 minutes of continuous exposure. Therefore, quantal dose-response data for SGPT activity, anesthesia and lethality were obtained as a function of time at this concentration. These data are shown in Figure 1 as the percent response (expressed as probability) as a function of the logarithm of the exposure duration. Although a single line can be drawn to represent significant increases in SGPT and anesthesia, the lethality is better represented by two straight lines. This suggests that the mechanism responsible for causing the death of mice exposed continuously for 300 to 600 minutes is different than when exposures are longer. The LT_{50} and the ET_{50} values for anesthesia and increased SGPT activity are given in Table 3.

Chloroform by Vapor Inhalation: Chloroform at a vapor concentration of 4,500 ppm killed 50% of the mice in 560 minutes of continuous exposure. Using this concentration, the quantal dose-response data shown in Figure 2 were obtained. The ET_{50}'s for anesthesia and SGPT elevation, together with the LT_{50} are presented in Table 3. The line of best fit for an abnormal SGPT elevation is not parallel with the lines of best fit for anesthesia and lethality (Figure 2). Therefore, a potency ratio with statistical significance cannot be calculated. The data in Figure 2 show chloroform to be a potent hepatotoxin which causes hepatic damage at exposure durations smaller than those needed to induce anesthesia.

1,1,2-Trichloroethane by Vapor Inhalation: A vapor concentration of 3,750 ppm was used in this study. The quantal dose-response data are depicted in Figure 3 and the ET_{50} values for SGPT elevation and anesthesia and LT_{50} value, together with the potency ratios, are given in Table 3. At this vapor concentration, the time required to cause a significant SGPT elevation essentially coincided with the time required to cause anesthesia. Thus, 1,1,2-trichloroethane, although a less specific hepatotoxin than either carbon tetrachloride or chloroform, must still be considered a potent hepatotoxin.

Tetrachloroethylene by Vapor Inhalation: A vapor concentration of 3,700 ppm was used in experiments with tetrachloroethylene. The results are presented in Figure 4 and Table 3. The

data indicate that the duration of exposure needed to cause a significant elevation of SGPT is considerably larger than that needed to produce anesthesia. Indeed, durations of exposure long enough to kill some of the mice were required to cause SGPT elevation in a significant number of the survivors.

Since a selected population of mice, the survivors, were used for SGPT determinations, the statistical data concerning this parameter are not strictly correct. However, the fraction of surviving mice having an elevated SGPT when compared with the fraction of mice that died remains indicative of an agent's capacity for causing liver damage.

Trichloroethylene by Vapor Inhalation: The experiments on trichloroethylene were carried out using a vapor concentration of 5,500 ppm. The results are given in Figure 5 and Table 3. The similarity in the data obtained for this compound and tetrachloroethylene negates any further need for interpretation of the results. Both materials have a similar hepatotoxic specificity.

Dichloromethane by Vapor Inhalation: At a vapor concentration of 13,500 ppm, the quantal dose-response data for anesthesia, lethality and SGPT elevation are presented in Figure 6 and Table 3. The quantal dose-response data for the fractions of surviving mice having an elevated SGPT are essentially the same as those for the death, indicating that this compound is a less potent hepatotoxin than either trichloroethylene or tetrachloroethylene.

1,1,1-Trichloroethane by Vapor Inhalation: In this study the vapor concentration of 1,1,1-trichloroethane was the same as that used in the experiments with dichloromethane, 13,500 ppm. The data are presented in Figure 7 and Table 3. This compound, like dichloromethane, apparently has very little capacity to cause hepatic damage. At the same exposure duration, it was found that the percent of surviving mice having a significant SGPT elevation was equal to or smaller than the percent of deaths. Since the surviving mice may represent a less susceptible population it can only be concluded that exposure durations equal to or greater than those necessary to cause death are needed to induce a significant SGPT elevation. Thus, the ET_{50} for SGPT elevation as well as the potency ratios in Table 3 were calculated from the data for lethality and represent limits.

DISCUSSION

In order to compare the toxicity of chlorinated hydrocarbons, they could be ranked according to the absolute dose required to produce a given effect such as death, anesthesia, SGPT elevation. A more meaningful approach is to relate the capacity of an agent to cause damage to a particular organ and its capacity to produce other biological effects. These relationships can then be used to rank the agent relative to other agents possessing the same activities. By comparing the ratios of the doses of chlorinated hydrocarbons required to cause an elevation of SGPT and

and death in 50% of the treated mice, LD_{50}/ED_{50}, Klaassen and Plaa (1966) were able to rank the following materials in the order of their decreasing capacity to cause liver dysfunction: carbon tetrachloride; chloroform; 1,1,2-trichloroethane; tetrachloroethylene; trichloroethylene; dichloromethane; and 1,1,1-trichloroethane. In their study, interpretation is clouded because the agents were administered by intraperitoneal injection which does not represent a common means of exposure. Therefore, it seemed desirable to repeat their experiments administering the compounds by vapor inhalation rather than by injection. Comparing the results reported herein, Table 3, with those reported by Klaassen and Plaa (1966), Table 2, it is clear the rank is maintained in spite of considerable quantitative differences.

Aside from the confirmation of the results presented by Klaassen and Plaa (1966), this study illustrates some advantages in using vapor inhalation instead of intraperitoneal injection for assessing the physiological potency of these agents. Not only is it possible to obtain a comparison of the capacity of an agent to cause liver dysfunction relative to its capacity to cause death, but also to its capacity for inducing anesthesia. Thus, it is possible to evaluate the likelihood that an individual acutely exposed to the vapor of any one of these agents has experienced liver damage by knowing of the degree of narcosis experienced. In defining a safe environmental concentration of a chlorinated hydrocarbon, little attention to its effect on the liver is warranted if it requires a near lethal dose to cause

significant liver dysfunction. Examples of materials of this type are tetrachloroethylene, trichloroethylene, dichloromethane, and 1,1,1-trichloroethane. Time could be better spent by detecting and protecting against other adverse effects. With a compound such as 1,1,2-trichloroethane, it is necessary to consider both its hepatotoxic activity and narcotic activity in determining a safe environmental vapor concentration. On the other hand, chloroform and particularly carbon tetrachloride represent compounds whose specificity for causing liver damage necessitates primary consideration in determining a safe environmental vapor concentration. In this light, it would be useful if other detectable signs of biological activity, harmful and unharmful, were available to compare with the three used in this study.

A technical advantage afforded by using vapor inhalation to expose mice to these and other agents is that a single group of mice can be used to obtain quantal dose-response data for both anesthesia and lethality. This is possible because the independent variable is time. The dependent variable, unconsciousness and death, can be obtained by observation. Thus, less time is needed to obtain the quantal dose-response data for these parameters and fewer animals are required.

SUMMARY

Hepatic damage was determined in mice by serum glutamic-pyruvic transaminase (SGPT) activity 24 hours following single

exposures to the vapor concentrations of carbon tetrachloride, chloroform, 1,1,2-trichloroethane, tetrachloroethylene, trichloroethylene, dichloromethane, and 1,1,1-trichloroethane expected to kill 50% of the animals in 9 to 12 hours of continuous exposure. Maintaining a constant vapor concentration, the fractions of mice having a significant elevation of SGPT was expressed as a function of exposure duration and compared to similar expressions for the onset of anesthesia and lethality. A median effective exposure duration for an increase in SGPT activity was calculated and expressed as a ratio of the median effective exposure durations for lethality and anesthesia. The ratios obtained for each agent were then ranked and used to illustrate the capacity of each compound for inducing liver damage relative to anesthesia and lethality. Carbon tetrachloride and chloroform were found to be potent hepatotoxins inducing liver damage prior to the onset of anesthesia. 1,1,2-Trichloroethane is a moderate hepatotoxin that requires exposure durations long enough to induce anesthesia before causing hepatic damage. The remaining compounds studied required exposure durations approaching those or longer than those necessary to cause death before hepatic damage could be ascertained by a significant SGPT elevation. Since the data presented herein were obtained following single exposures to the vapors of the various compounds, they are not necessarily indicative of the hepatic damage that may be induced by repeated low level exposures.

LEGENDS FOR FIGURES

Figure 1: Carbon Tetrachloride Vapor, 8,500 ppm. Percent (expressed as probability) of mice anesthetized □— - —□, dead ·——·, or having a significant SGPT elevation Δ— — —Δ, as a function of the $\log_{10}$ duration of exposure. Each point for anesthesia and lethality was obtained using a single group of 30 mice; the number in each group used to obtain the points for SGPT activity is given in parenthesis.

Figure 2: Chloroform Vapor, 4,500 ppm. Percent (expressed as probability) of mice anesthetized □— - —□, dead ·——·, or having a significant SGPT elevation Δ— — —Δ, as a function of the $\log_{10}$ duration of exposure. Each point for anesthesia was obtained using a single group of 10 mice while each point for lethality was obtained using a single group of 20 mice; group size used for determining SGPT activity is indicated in parenthesis.

Figure 3: 1,1,2-Trichloroethane Vapor, 3,750 ppm. Percent (expressed as probability) of mice anesthetized □— - —□, dead ·——·, or having a significant SGPT elevation Δ— — —Δ, as a function of the $\log_{10}$ duration of exposure. A single group of 20 mice was used to obtain each experimental point for anesthesia and

lethality. The number of mice in each group used for determining SGPT activity is indicated in parenthesis.

Figure 4: Tetrachloroethylene Vapor, 3,700 ppm. Percent (expressed as probability) of mice anesthetized □—-—□, dead ·——·, or having a significant SGPT elevation Δ—-—Δ, as a function of the $\log_{10}$ duration of exposure. A single group of eight mice was used to determine the anesthetic response; lethality was determined using group sizes varying from 20 to 94 mice. The number of mice per group used to determine SGPT activity is indicated in parenthesis.

Figure 5: Trichloroethylene Vapor, 5,500 ppm. Percent (expressed as probability) of mice anesthetized □—-—□, dead ·——·, or having a significant SGPT elevation Δ—-—Δ, as a function of the $\log_{10}$ duration of exposure. A single group of 19 mice was used to obtain each point for lethality; a single group of 20 mice was used to obtain each point for anesthesia. The number of mice per group used to determine SGPT activity is indicated in parenthesis.

Figure 6: Dichloromethane Vapor, 13,500 ppm. Percent (expressed as probability) of mice anesthetized □—-—□, dead ·——·, or having a significant SGPT elevation Δ—-—Δ,

as a function of the $\log_{10}$ duration of exposure. Each point for anesthesia was determined using a single group of 20 mice; lethality was determined using a single group of 40 mice. For SGPT activity, individual group size is indicated in parenthesis.

Figure 7: 1,1,1-Trichloroethane Vapor, 13,500 ppm. Percent (expressed as probability) of mice anesthetized □—-—□, dead ·——·, or having a significant SGPT elevation Δ— — —Δ, as a function of the $\log_{10}$ duration of exposure. Each experimental point for anesthesia and lethality was calculated using composite groups of 20 to 135 mice. Individual group sizes used to obtain SGPT activity are indicated in parenthesis.

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ACKNOWLEDGEMENTS

Thanks are expressed to Miss Carol Hendrick, Mrs. Susan Ellis and Mrs. Joyce Buerge for their technical assistance.

TABLE 1

LD_{50} VALUES AND ED_{50} VALUES FOR ELEVATION OF SERUM GLUTAMIC-PYRUVIC TRANSAMINASE (SGPT) ACTIVITY FOR MICE FOLLOWING INTRAPERITONEAL INJECTION OF 1,1,1-TRICHLOROETHANE, CARBON TETRACHLORIDE, AND TETRACHLOROETHYLENE

Compound	24 Hour LD_{50}, m mole/kg	SGPT Activity[a] ED_{50}, m mole/kg	SGPT Activity Potency Ratio[b]
Carbon Tetrachloride	30.4 (26.7-34.6)[c]	0.19 (.12-.29)	160[d]
1,1,1-Trichloroethane	35.2 (32.4-38.4)	21.8 (19.8-24)	1.62 (1.43-1.83)
Tetrachloroethylene	34.2 (30.3-38.7)	24.0 (21.3-26.8)	1.43 (1.21-1.67)

[a] SGPT activity was determined 24 hours after treatment.

[b] The "potency ratio" is LD_{50}/ED_{50}.

[c] The 0.95 confidence limits in parentheses.

[d] Curves deviated from parallelism; therefore, a statistically valid potency ratio cannot be calculated.

TABLE 2[a]

SUMMARY OF LD_{50} VALUES AND ED_{50} VALUES FOR THE ELEVATION OF SERUM GLUTAMIC-PYRUVIC TRANSAMINASE (SGPT) ACTIVITY FOR MICE FOLLOWING INTRAPERITONEAL INJECTION OF CHLORINATED HYDROCARBONS

Compound	24 Hour LD_{50}, m mole/kg	SGPT Activity[b] ED_{50}, m mole/kg	SGPT Activity Potency Ratio[c]
Chloroform	14 (12-15)[d]	2.3 (1.9-2.8)	6.4 (3.8-10.9)
1,1,1-Trichloro ethane	37 (31-44)	25 (20-31)	1.5 (1.2-2.0)
Dichloromethane	23 (17-31)	e	---
1,1,2-Trichloro-ethane	3.7 (3.0-4.7)	1.8 (0.8-1.6)	3.4 (2.3-5.1)
Trichloroethylene	24 (18-31)	18 (14-21)	1.4 (1.1-2.2)
Tetrachloroethylene	28 (23-34)	28 (22-35)	0.98[f]
Carbon Tetrachloride	28 (25-31)	0.10 (0.006-0.016)	280 (170-440)

[a] Klaassen and Plaa (1966).

[b] SGPT activity was determined 24 hours after treatment.

[c] The "potency ratio" is the ratio of the LD_{50} to the ED_{50}.

[d] The 95% confidence limits are in parentheses.

[e] No increase in SGPT activity.

[f] Does not differ significantly from 1.0.

TABLE 3

SUMMARY OF LT_{50} VALUES FOR MICE EXPOSED CONTINUOUSLY TO THE VAPOR OF CHLORINATED HYDROCARBONS AND ET_{50} VALUES FOR THE ONSET OF ANESTHESIA AND ELEVATION OF THE SERUM GLUTAMIC-PYRUVIC TRANSAMINASE (SGPT) ACTIVITY

Compound	Vapor[a] Conc., ppm	LT_{50}, Minute	Anesthetic ET_{50}, Minute	SGPT Activity ET_{50}, Minute	Potency Ratio: $\frac{ET_{50}\ Anesthetic}{ET_{50}\ SGPT\ Activity}$	Potency Ratio: $\frac{LT_{50}}{ET_{50}\ SGPT\ Activity}$
Carbon Tetrachloride[c]	8,500	850 (759-952)[b] 680 (666-693)	21.0 (18.3-24.2)	0.155 (0.119-0.202)	136 (100-182)	$\frac{5480}{4390}$[d] (4170-7300)
Chloroform	4,500	560 (540-585)	35.0 (31.0-39.6)	13.5 (10.1-18.1)	2.6[d]	41.5[d]
1,1,2-Trichloroethane	3,750	600 (556-648)	18.0 (15.4-21.0)	17.5 (15.2-20.5)	1.0[e]	33.3 (28.4-39.0)
Tetrachloroethylene	3,700	730 (707-752)	24.0 (20.2-28.6)	470 (379-583)	0.052 (0.038-0.068)	1.55 (1.26-1.91)
Trichloroethylene	5,500	585 (548-626)	46.0 (40.9-51.8)	400 (336-475)	0.115 (0.094-0.141)	1.46 (1.22-1.75)
Dichloromethane	13,500	640 (622-658)	128 (116-141)	730 (615-870)	0.175 (0.145-0.213)	1.0[e]
1,1,1-Trichloroethane	13,500	595 (578-615)	16.3 (15.4-17.2)	≥595 (578-615)[f]	≤0.027 (0.025-0.029)[f]	≤1.0[f]

[a] These concentrations were chosen because they cause 50% lethality between 9 and 12 hours of continuous exposure.

[b] The 95% confidence limits are in parenthesis.

[c] Two lines best represented the lethality data for carbon tetrachloride. LT_{50} values given in this table were calculated from data represented by line 1 and 2, respectively, Figure 1.

[d] The lines representing quantal dose-response data for the indicated parameters deviated from parallelism; therefore, the ratio expressed is not statistically valid.

[e] No significant difference in potency.

[f] Longer exposure durations are needed to elevate the SGPT than to cause death (Figure 7). Since surviving mice do not represent a random population, these values were calculated using the lethality data in place of the SGPT data and represent limits.

FIGURE 1

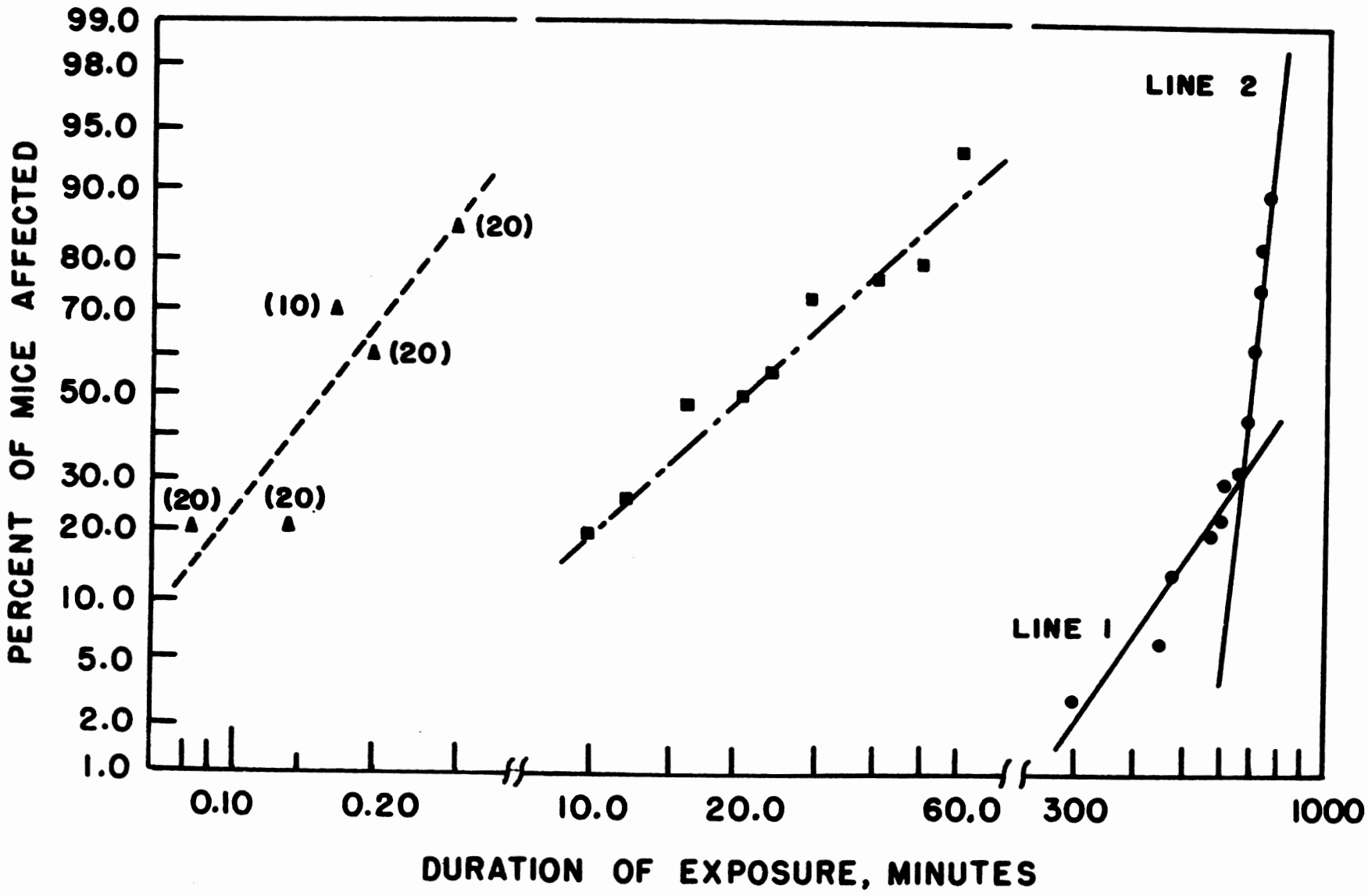


FIGURE 2

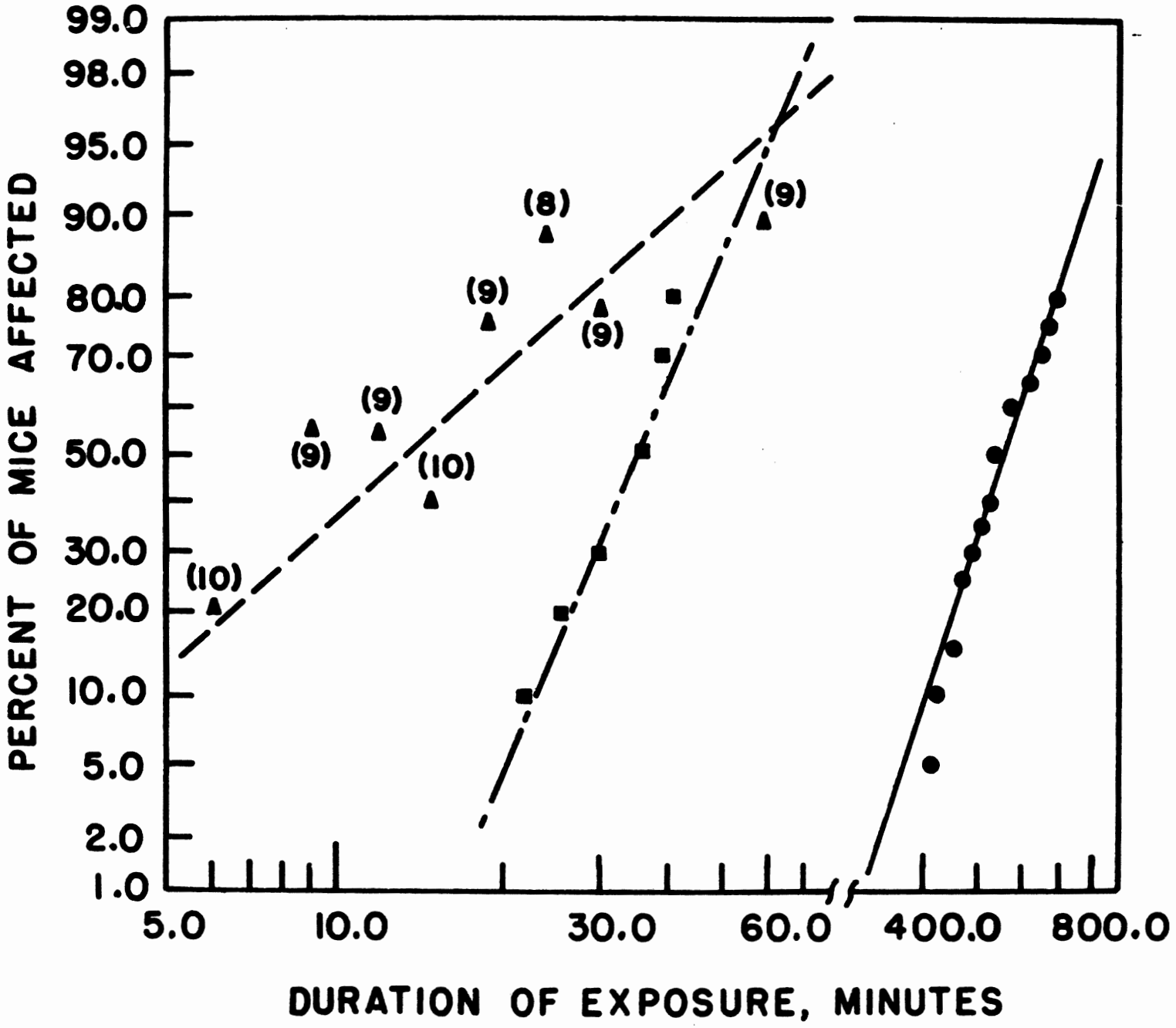
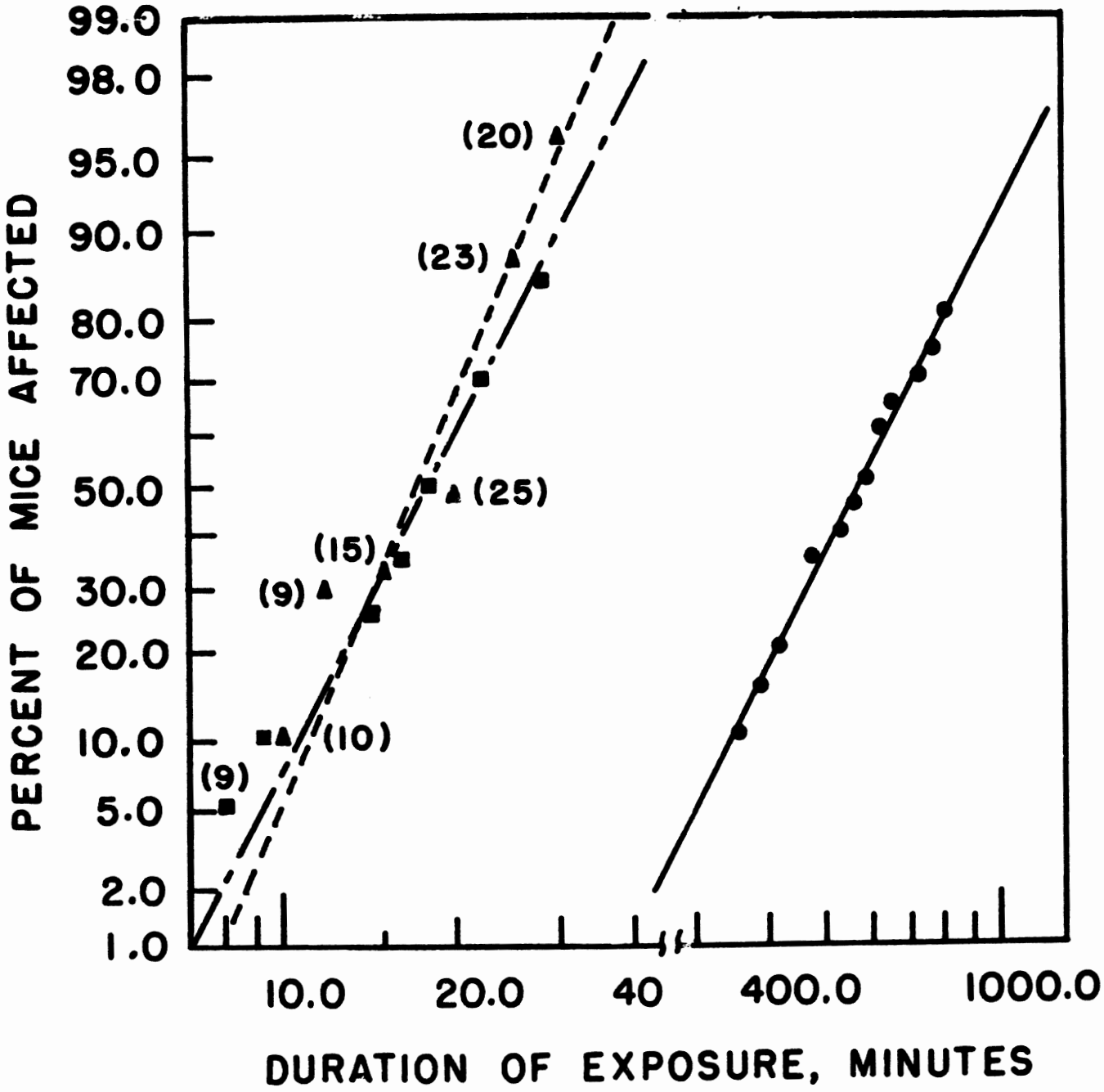


FIGURE 3



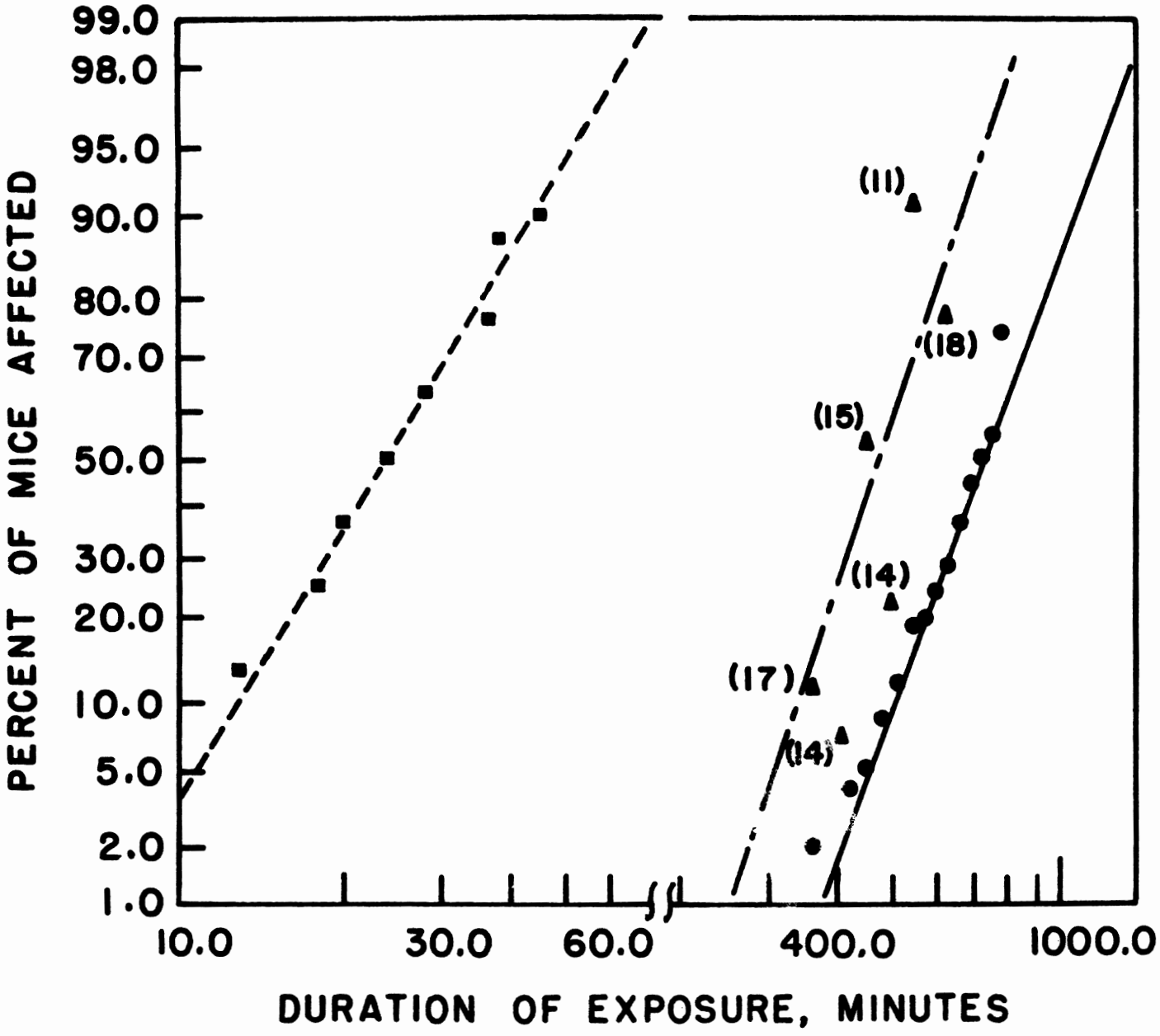


FIGURE 5

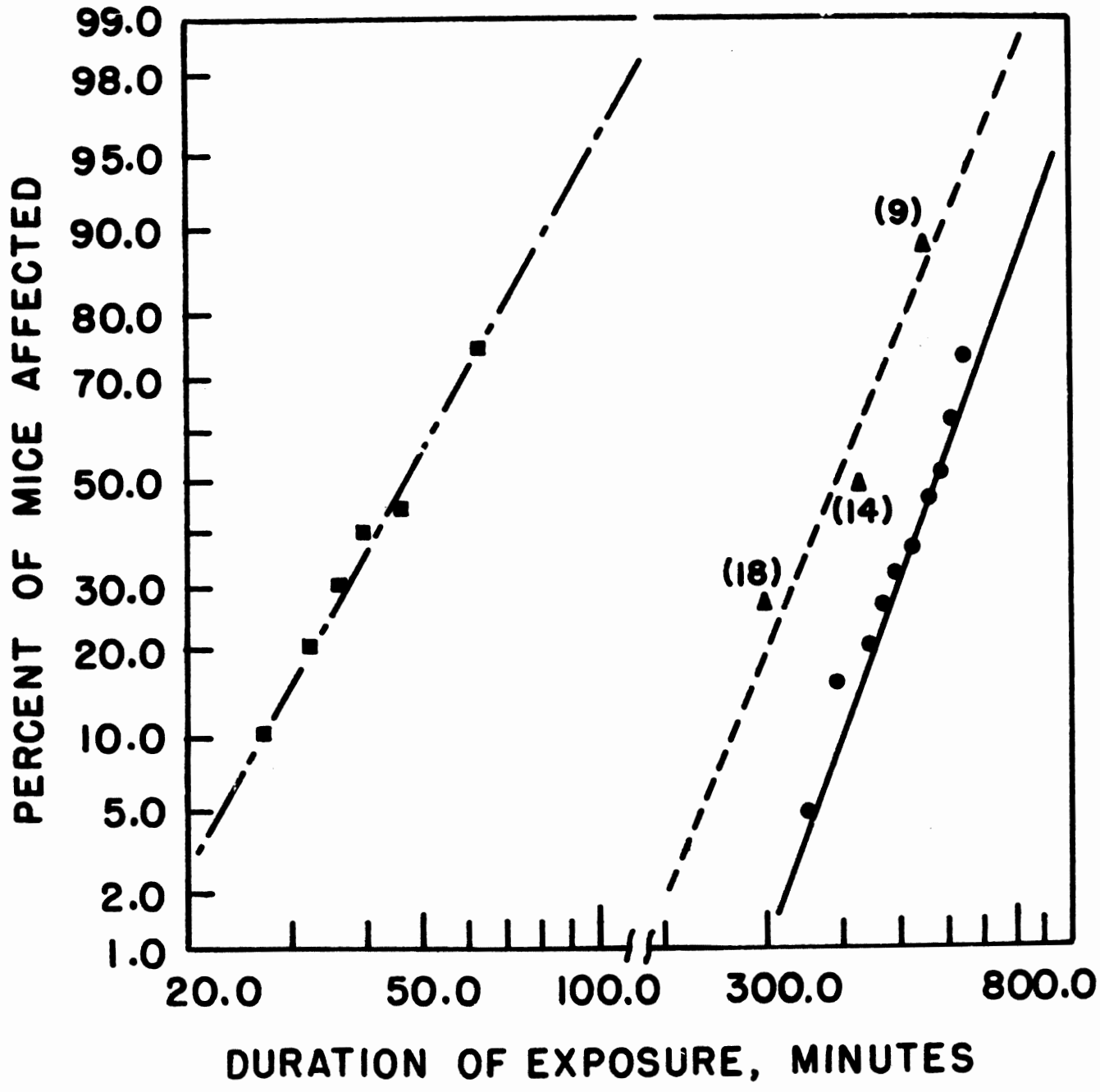


FIGURE 6

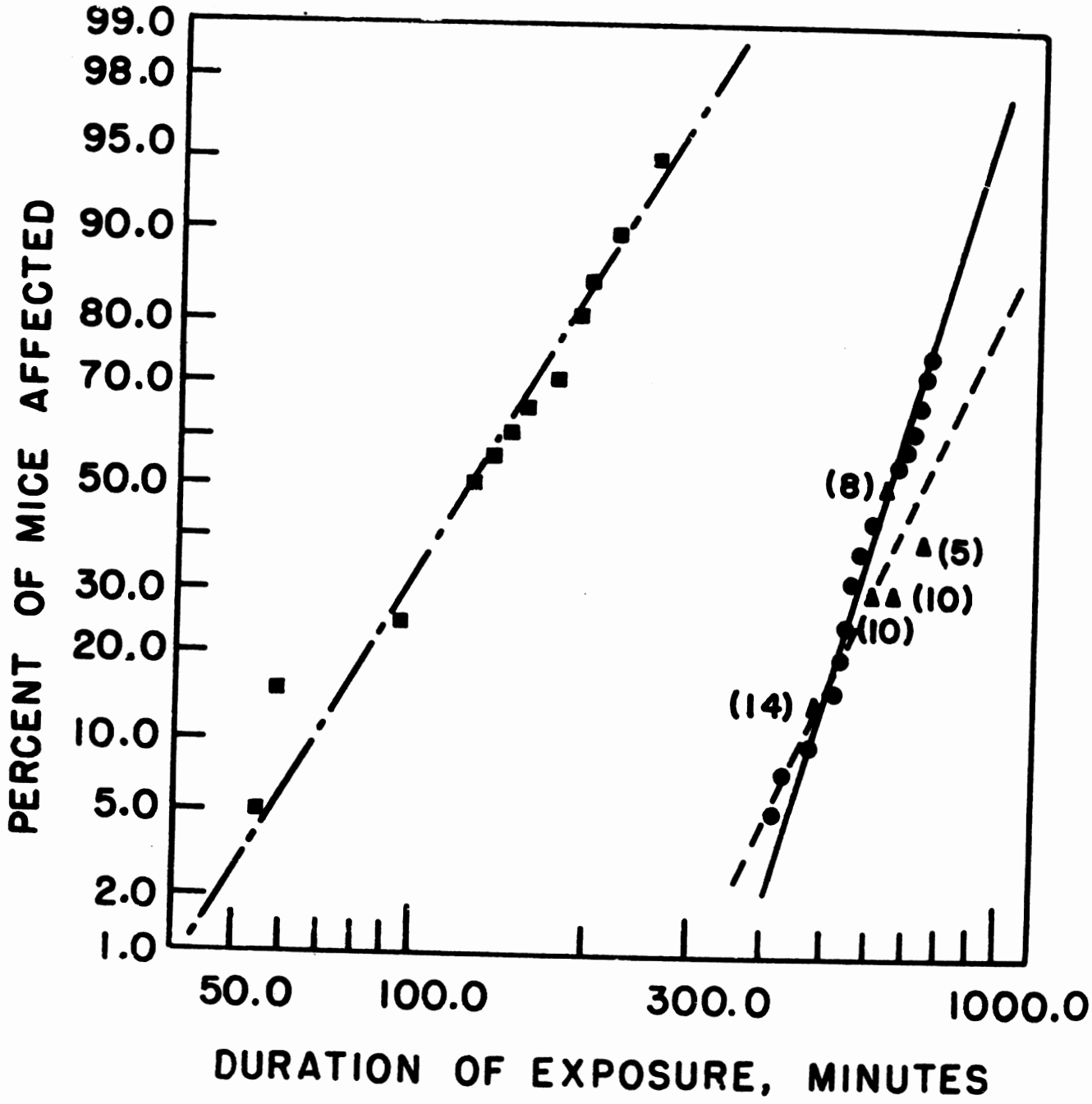


FIGURE 7