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Chemical Research and Development Laboratories lopment Laboratories
Technical Report port

CRDLR 3226

The Humar Assessment of EA 1729 and EA 1729 and
EA 3528 by the Inhalation Route (U) on Route (U)

by

James S. Ketchum sum
George K. Aghajanian ajanian
Oscar H. L. Bing ing

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July 1964 CRDLR 3226

THE HUMAN ASSESSMENT OF EA 1729 AND EA 3528 BY THE INHALATION ROUTE (U)

by

James S. Ketchum
George K. Aghajanian
Oscar H. L. Bing

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Edgewood Arsenal, Maryland

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(U) FOREWORD

This work was conducted under Project 1C522301A079, Non-Defense Medical Aspects of Chemical Agents (U). The work was started in March 1963 and completed in April 1964.

Acknowledgments

The assistance of the Aerosol Branch and the Clinical Investigation Branch is gratefully acknowledged.

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(C) DIGEST

A study of the inhalation effectiveness of agent EA 1729 (d-l agent EA 1729 (d-lysergic acid diethylamide) and its maleate salt was conducted in which retained ed in which retained doses ranging from 0.3 to 7.8 μg/kg were administered to 60 military volunts 60 military volunteers.

The ED50 for EA 1729 by the inhalation route is 5.8 (2.5 to route is 5.8 (2.5 to 13.5) μg/kg retained dose. The ECT50 is 55 (34 to 90) mg min/cu m, calcu g min/cu m, calculated at a minute volume of 10 liters. The ED50 and ECT50 for the maleate sa for the maleate salt would be 1/3 greater on a formula weight basis, i.e., 7.7 μg/kg and e., 7.7 μg/kg and 73 mg min/cu m, respectively.

Onset time for the effective aerosol dose is about 15 min, pe is about 15 min, peak time about 1-1/2 hr, and partial recovery time about 5-1/2 hr. Full recove 2 hr. Full recovery requires at least 12 hr.

The safety factor in man cannot be stated with certainty. d with certainty. If man resembles most other animals in his toxicological response. the ratio response. the ratio of lethal to effective dose would be very high; however, there is no direct there is no direct information about lethality in man.

If a correction is made for differences in formula weight, in formula weight, the effectiveness of the maleate and free base forms of the agent by inhala the agent by inhalation is roughly the same.

There is a tendency to cough during inhalation of the malea alation of the maleate at higher concentrations, but in the few instances in which this occurred, which this occurred, there was no change in the retained dose.

By the aerosol dissemination technique employed, it was s employed, it was shown that the effectiveness of the aerosol route is 0.25 to 0.30 that of the or to 0.30 that of the oral or intravenous routes.

Prior exposure to the agent does not significantly influenc nificantly influence the numerical facility performance decrement observed when an equivalen when an equivalent dose is given 2 weeks later.

(U) CONTENTS

(C) THE HUMAN ASSESSMENT OF EA 1729 AND EA 3528 BY THE INHALATION ROUTE (U)

I. (C) INTRODUCTION.

(C) This report summarizes the results of recent investigations by the Psychopharmacology Branch of the Clinical Research Division into the aerosol effectiveness of EA 1729 and EA 3528, the free base and maleate forms, respectively, of d-lysergic acid diethylamide (LSD25).

(U) LSD25 has been well known to pharmacologists for more than 20 years as the most potent of all psychochemicals. Because of its interest to clinicians as well as research scientists, it has been extensively used and studied.

(U) In small doses (about 0.5 μg/kg, orally), effects are generally noted within half an hour and persist for at least 4 to 8 hr. The following features are commonly observed or described:

1. Euphoria, giggling.
2. Increased nervous tension, restlessness.
3. Increased sensitivity to minor stimuli.
4. Distractability, indecisiveness.
5. Feelings of strangeness, unreality.
6. Passivity, indifference.

(U) Larger doses (1 to 2 μg/kg, orally) cause more profound effects, detectable within 15 min and disappearing for the most part after about 12 hr. These may include:

1. Loss of control over thoughts and inability to focus attention.
2. Marked feelings of unreality, strangeness, detachment, altered identity.
3. Perceptual distortions: fluctuations in apparent size, shape, color, distance, and texture of surfaces; hyperacusis, synesthesia, kaleidoscopic imagery, hallucinations.

4. Disturbances in body image, feelings of electricity,"butterflies," abdominal spasms, pressure in head and chest, coldness, trembling, changes in size, shape, or consistency of body parts, etc.

5. Various "secondary" symptoms: paranoid suspiciousness, delusions, outbursts of hostility, sudden assaultiveness, muteness, immobility, pacing, laughter, sobbing, etc.

(C) In a series of field trials in 1958, volunteers at Fort Bragg, N. C., were assigned a variety of team missions to be carried out after the ingestion of 150 μg/man of LSD25. These tasks included reporting of meteorological information, fire direction control, artillery control surveying, and antiaircraft tracking. In these cases, the dose given resulted in loss of effectiveness sufficient to constitute failure in the mission, as judged by XVIII Airborne Corps evaluation teams.

(C) In the 1961 report,* summarizing the results of these and other clinical studies of the effectiveness of LSD25, the author concluded that incapacitation by the oral route could be achieved with doses as low as 1 μg/kg.

(C) In 1963, a variety of preliminary studies on LSD25 (including the free base various salts**) were resumed with the ultimate aim of establishing the aerosol effectiveness of this agent. The following initial conclusions were reached:

1. Both the maleate and the free base were effective aerosols but it was not possible to say which, if either, was superior.† The maleate sometimes induced coughing.

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* (U) Sim, Van M. CRDLR 3074. Clinical Investigation of EA 1729 (U). June 1961. SECRET Report.

** (C) EA 1729: free base of LSD25; EA 1653: tartrate salt; and EA 3528: maleate salt.

† (C) To facilitate comparison of effectiveness of the various forms of LSD, it was decided to express the dose in terms of the free base, which has a molecular weight of 323. Since the tartrate (EA 1653) and the maleate (EA 3528) salts have formula weights of 430 and 439, respectively, doses of either salt must be multiplied by 0.74 or 0.75 to convert them to the free base equivalent.

2. Plasma levels of LSD25 could be measured reliably and used as a basis for comparing absorption of various forms of the drug by different routes of administration. The performance and plasma level values of an intravenous study (figure 1) were later used in effectiveness comparisons with the inhalation route.

3. The degree of response was related positively to both the aerosol retained dose and the plasma level, but considerable variability was present among the individuals exposed to similar doses.

4. The aerosol retained dose and the plasma level were highly correlated, indicating that absorption is highly predictable from the retained dose (figure 2).

5. Further inhalation studies were required to provide sufficient observations to permit adequate statistical analysis of dose-response relationships.

(U) The final aerosol test series employed both free base and maleate. The data from these tests together with those already obtained during the preliminary test series were combined in an attempt to answer the following questions:

1. What are the ED50 and the ECT50 for these compounds by the inhalation route?

2. What are the onset times, peak times, and durations of action of these compounds when given by aerosol?

3. What are the estimated safety factors for these agents?

4 Is there any difference in potency between the free base and the maleate on a molecule-for-molecule basis?

5. Is the coughing tendency observed earlier with the maleate a consistent finding and does it have practical significance?

6. What is the relative potency of these agents when the inhalation, oral, and intravenous routes are compared?

7. Does the response to a second dose differ from the response to an equivalent first dose?

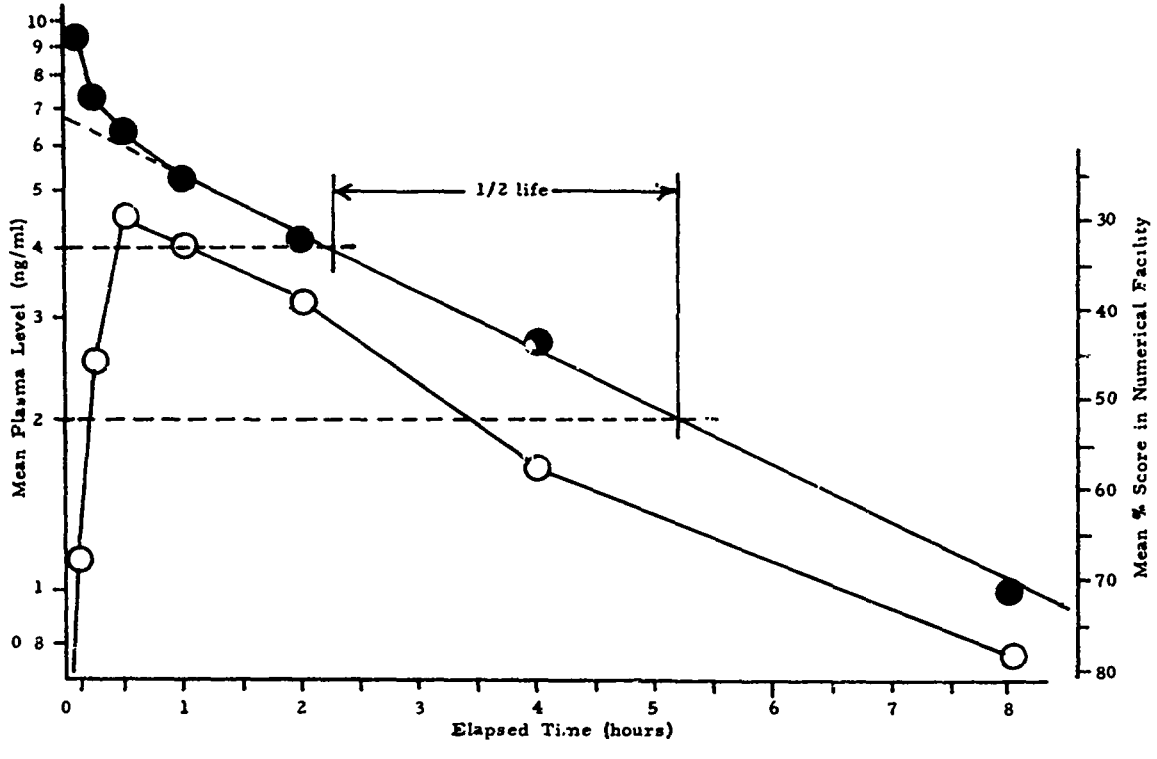


FIGURE 1

SERIAL PLASMA LEVELS EA 1653 VERSUS SERIAL PERFORMANCE SCORES (U)

(U) Each dot represents the mean value for five subjects receiving the tartrate iv. Dose was equivalent to 2.0 μg/kg of the free base. Plasma level is plotted against a log scale. Closed dots = plasma levels; open dots = percent numerical facility scores.

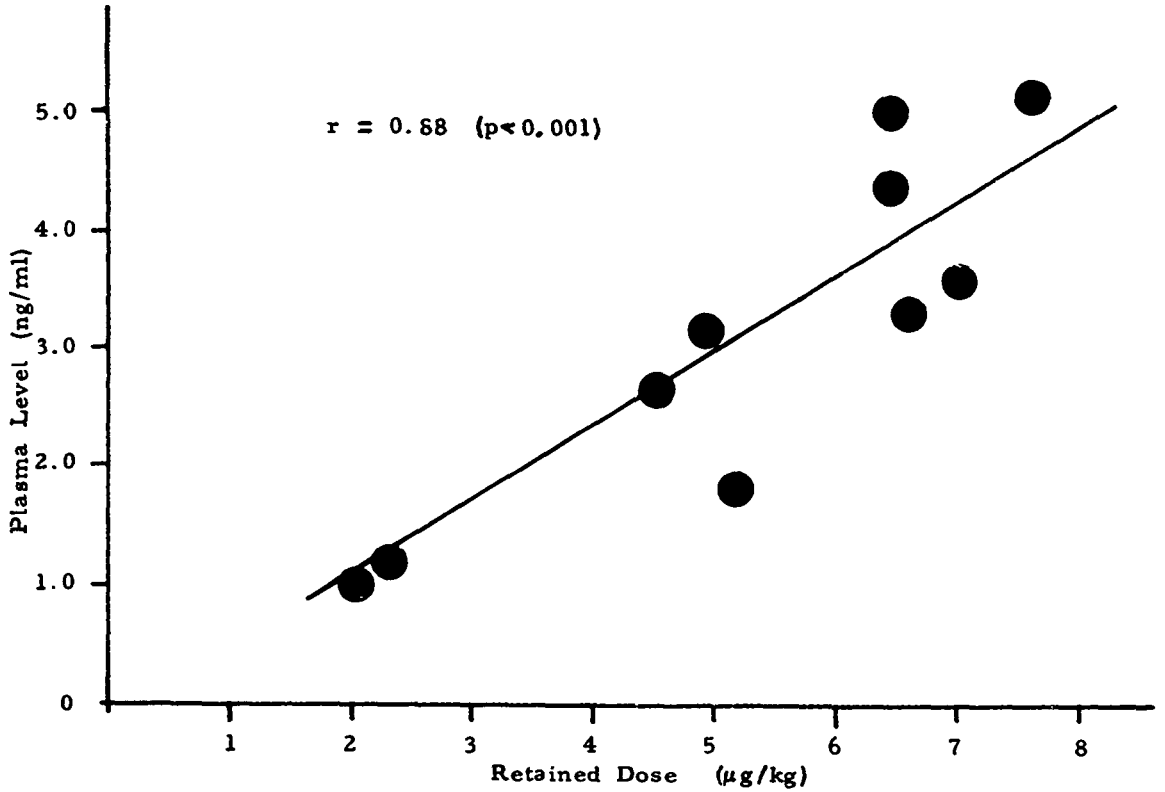


FIGURE 2

AEROSOL RETAINED DOSE VERSUS PLASMA LEVEL (U)

(U) Plasma levels are the means of samples taken at 1 and 2 hr following inhalation of EA 3528. Retained doses are expressed as free base equivalent.

(U) In keeping with the above expressed aims, the following features were included in the test plan for this series:

1. To provide a sufficient sample, there were to be 16 exposures to each form of the agent (table 1); however, for technical reasons a second exposure was not completed in two subjects.

2. To facilitate comparisons between maleate and free base, matched equivalent doses were used.

(U) TABLE I

DESIGN FOR TEST SERIES

March-April 1964

Name	Target dose	First dose	Second dose
Joh	2.0	2.0 F	2.0 M
Rod		2.1 M	2.5 F
Kra		2.1 M	2.7 F
Pro		2.2 F	---
Got	3.0	3.0 F	2.7 M
Hug		3.2 F	3.5 M
Wai		3.5 M	3.6 F
Ada		3.5 M	3.7 F
Dar	4.5	4.1 M	4.0 F
Win		4.4 M	4.1 F
Gol		4.5 F	4.9 M
Hou		4.7 F	4.9 M
Bat	6.8	6.8 F	---
Nee		6.9 F	6.9 M
Hyt		7.1 M	7.1 F
Nea		7.8 M	7.6 F

NOTE: Doses are retained doses in μg/kg, expressed as free base equivalent. M = maleate; F = free base. The second dose in each case was intended to equal the actual first dose, rather than the initial target dose.

3. To control response variability, each man was to be exposed twice, once to each form of the agent, with a 2-week interval between exposures; the second dose was to be matched to the first.

4. To avoid effects attributable to the order of exposure to the two forms of the agent, a counterbalanced design was employed.

5. To provide an adequate, but not excessively broad, dose range, there were four target doses: 2.0, 3.0, 4.5, and 6.8μg/kg, representing a logarithmic series with a constant increment of 50% between levels.

6. To establish a clinical criterion for effectiveness, a standardized brief interview was conducted at a specific time following exposure. This was rated in accordance with a specified rating system." Effectiveness" does not imply military incapacitation.

7. To permit quantitative pharmacologic comparisons of free base and maleate, the plasma assay and the Numerical Facility (NF) subtest of the Texas Battery were employed.

8. To reduce bias, a double-blind arrangement was followed so that the clinical rating was made without knowledge of dose or performance scores.

II. (U) METHODS.

A. Selection and Management of Volunteers.

1. Screening and Selection.

Sixteen subjects were selected from a group of 45 on the basis of a psychiatric interview. All had previously received a complete physical examination, laboratory studies, including an EEG and a Minnesota Multiphasic Personality Inventory, and an interview by the screening psychologist.

2. Briefing and Supervision.

Following selection, the 16 subjects were assembled and the program was explained to them in general terms. They were told there would be two aerosol tests and additional psychological and other test activities during the intervening and subsequent periods. All the men readily agreed to participate.

Arrangements were made for the members of the group to be assigned to the same set of squad rooms, and a senior Master Sergeant with extensive neuropsychiatric training and experience was assigned a room in the same area. Each individual was also assigned a specific partner from among his roommates with whom he would always be scheduled on any test he was to undergo. Liaison with NCO supervisor was facilitated by requiring each volunteer subject to complete a short checklist (appendix A) twice daily, the results of which were tabulated by the supervisor.

During the 6-week test period, biweekly meetings were scheduled with the psychiatrist, at which time the men were given an opportunity to learn of the progress of the study and to give their opinions about any aspect of the program.

B. Description of Measurements Used.

1. Clinical Rating of Severity.

A clinical rating of severity was developed, based upon the independent judgment of the two psychiatrists. A scale of 0-3, corresponding to no effect, mild, moderate, and severe, respectively, was employed. Although in all the aerosol series, a double-blind procedure was adhered to, both raters had access to all clinical information, including NF scores, during the preliminary series; however, it was decided that NF scores might influence the judgment of the raters and they were accordingly withheld during the later test series. Interrater reliability in both cases was approximately 0.80 by rank order correlation.

The following procedure was adhered to during the later series:

a. A standard interview was constructed, to be administered at 0105 experimental time by one of the two psychiatrists on the team. This interview, which normally required 5 to 8 min to complete, consisted of questions designed to bring out evidence of disorientation, difficulty in mental calculation, inattentiveness, loss of expressive fluency, disturbances in visual perception or in bodily sensations, and inability to reproduce a simple geometric pattern from memory. The interviews were recorded on videotape and rated at a convenient time later in the study.

b. In rating the interviews, primary drug effects were considered, rather than "secondary" behavioral features (such as paranoid ideation, depression, hostility, etc.). This distinction is based on an earlier study in which it was concluded the so-called primary effects are

dose related whereas the secondary phenomena are not.* The primary effects included an essential difficulty in directing the train of thought (i.e., in concentrating) and a distortion of visual perception (e.g., shifting, rolling or undulating appearance to the walls of the room). Bodily sensations of tension, tingling, trembling, and hypersensitivity, as well as distortions (changes in size, shape, texture, weight, or consistency of body parts), were also considered to be manifestations of primary drug effect. An overall rating, emphasizing the thinking difficulty, was assigned to each case, using the following rating scale:

Rating		Intensity of drug effect
0	= =	none
0-1	=	barely discernible
1	=	mild
1-2	=	mild to moderate
2	=	moderate
2-3	=	moderate to severe
3	=	severe

Since two ratings were averaged in each case to produce a single rating, the following average ratings resulted:

Defined as not effective	Defined as effective
0.0	2.2
0.2	2.5
0.5	2.8
0.8	3.0
1.0	
1.2	
1.5	
1.8	
2.0	

* Klee, Gerald D., Bertino, Joseph, Weintraub, Walter, and Callaway, Enoch. The Influence of Varying Doses on the Effects of Lysergic Acid Diethylamide (LSD-25) In Humans, J. Nervous and Mental Disease 132:404 (1961).

c. Ratings of 2.2 or higher were decided in advance to be indicative of an effective dose. It is important to note that the "effective" dose is not necessarily equivalent to the "incapacitating" dose. (To regard them as synonymous plainly requires some unusually broad assumptions.) "Effective" as used here arbitrarily means the effects are considered to be more than moderate in intensity by a crude clinical rating system.

d. By way of further clarification, the terms moderate and severe were intended to be applied as follows:

(1) Moderate Intensity (Rating of "2"). If the subject displays some slowing in his performance of serial subtraction (as compared with control performance) and makes several errors or hesitates for long periods in the middle of the task, he is considered to be showing moderate difficulty in thinking. In addition, there are usually definite alterations in visual perception (e.g., shimmering or oozing appearance to flat surfaces, fluctuations in light intensity, etc.). There may also be some changes in body image (e.g., feelings of lightness, tingling, coldness, increase in muscle tone, etc.).

(2) Severe Intensity (Rating of "3"). Serial subtraction is either impossible or only one or two subtractions are performed, with great effort and considerable delay, even with encouragement. If able to communicate the visual distortions he is experiencing, the subject will generally describe movements of an oscillatory type, with larger amplitude than that seen with lesser effects. His body may feel as if it is charged with electricity, about to burst; his stomach may be seized with intermittent nauseating contractions; and he may feel as if he is "in a fog," changing in size or shape or composition. Usually, he is only capable of brief phrases, which he repeats several times; or at times he can only nod, or smile in a perplexed manner, in response to questions. It may be noted that despite these profound effects subjects are not stuporous or disoriented.

2. Numerical Facility Test:

This is a speed-accuracy test in the performance of addition problems (see sample in appendix B) which are available in 20 forms of equal difficulty. The subject is given 3 min to complete as many problems as possible, and the score is the number of correct solutions divided by the baseline score, yielding a percentage. The baseline is calculated by taking the mean of the five highest scores of the ten baseline trials, which are obtained over a 2-day period prior to exposure. Because some slight practice effect continues to elevate subsequent scores, a new baseline (the mean of

the 5 highest scores from the original 10 and an additional 2 trials given just prior to the second exposure) is calculated for use during the second experiment. The scheduling of the NF test is shown on the Aerosol Protocol to be found in appendix C.

3. Abramson Checklist.

In the course of extensive investigations with LSD25, Abramson and his associates developed a list of symptoms commonly described by subjects.* He has indicated that low and high doses could be distinguished through the simple expedient of counting the number of positive replies given by the subject when questioned as to the presence or absence of each of 76 symptoms. A sample of the questionnaire form and the schedule followed in administering it are both to be found in appendix D. In actual use, with the nurse reading the questions to the subject and recording the positive replies, about 5 min are required for its completion.

4. Behavior Checklist.

This is a list of 27 behavioral signs, originally developed for BZ, but carried over to other agents for the purpose of comparison. The sample and schedule for use are shown in appendix E. To produce a single score, items that were assumed to reflect positive drug effects were given a plus sign and those that reflect absence of drug effect (i.e., indicate normal behavior) were assigned a minus sign. The summation of ratings for the 27 items (adding 6 for calibration) was used as a score in subsequent data analysis.

5. Behavioral Notes.

As in all psychochemical studies requiring nurses to be in attendance, frequent descriptive entries by the nurse in the clinical record are considered highly important. Four to six typewritten pages of such observations are generally collected in the course of a 24-hr study of this type.

* Abramson, H. A., Jarvik, M. E., Kaufman, M. R., Kornetsky, C., Levine, A., and Wagner, M. Lysergic Acid Diethylamide (LSD-25). I. Physiological and Perceptual Responses. J. Psychol. 39:3 (1955).

6. Draw-a-Man Test.

This is a 3-min procedure that has been included in many psychochemical studies during the past 3 years. A quantitative scoring system for these drawings is still undergoing development.

7. Heart Rate and Blood Pressure.

These measures are in the schedule primarily for safety purposes.

8. Pupil Size.

Various techniques for the recording of pupil size have been employed in previous studies within the Division, but none have proved entirely satisfactory. In this test series, a technique was introduced entailing the use of a binocular telescope with direct reading of pupil size from a millimeter scale positioned along the horizontal diameter of the pupil.

9. EEG Studies.

A single EEG was carried out at 0130 experimental time. Spontaneous activity and the effect of single flash and repetitive photic stimulation (photic driving) were compared with control records. The results of this study will be reported in a separate publication by the investigator responsible for this phase of the project.

10. Plasma Levels of Agent.

A 12-ml blood sample was taken at 0100 and 0200 hr experimental time. Bloods were centrifuged and plasma was removed and frozen. Plasma samples (5 ml) were later assayed according to a modification of Axelrod's spectrofluorometric method.* Details will be submitted in a separate report.

* Axelrod, Julius, Brady, Roscoe O., Witkop, Bernard, and Evarts, Edward V. The Distribution and Metabolism of Lysergic Acid Diethylamide. Annals N. Y. Acad. Sciences 66:435 (1957).

11. Neurological Measurement of Accommodation and Convergence.

The change in accommodative convergence ratios observed in preliminary studies with LSD25 was studied in this series in the hope that it would prove a sensitive indicator of dose. The results will be presented elsewhere by the investigator responsible for these studies.

C. Technique of Exposure.

Subjects were trained to breathe in conformity with a standard pattern that assured a rate of 15 breaths per minute and a minute volume of approximately 10 liters. The method, developed previously for BZ inhalation studies, employs an oscilloscopic display of the respiratory activity. The subject endeavors to make the beam track a prescribed curve of inspiration and expiration superimposed on the oscilloscope screen. Rate is established by sweep time of the beam. Vertical deflection is produced by air flow across a detector situated in the orifice of the face mask. With minimal practice, stable breathing patterns are easily achieved.

Because of the possibility that coughing might occur during inhalation, subjects were instructed in all cases that if the urge to cough occurred, they should in no case break contact with the mask, but cough into the system if necessary.

The agent, both maleate and free base, was generated as a water solution in droplet form; average particle size being 0.8μ. Concentration in air was usually less than 20 μg/liter, and exposure time from 1 to 4 min. Retention was calculated by direct measurement of concentration differences between inspired and expired air. This difference was multiplied by the total volume breathed. Drug retained in apparatus was then subtracted to give total retained dose per man.

D. Tabulation of Data.

Following the typing and collation of individual case records, selected information was abstracted from the records and entered on code sheets. After punch cards were prepared from these sheets, the cases were sorted in order of retained dose and certain columns of data were extracted in list form as shown in table 2. The cards were also used to prepare paper tape inputs for computer analysis. Complete analysis will require considerable time, and further statistical findings will be summarized in a future supplement to this report.

(U)

TABLE 4

ABSTRACTED NUMERICAL DATA FOR ALL 60 INHALATION EXPOSURES

Case number	Name	Form of agent*	Retained dose	First or second exposure	Ct	Plasma level		Score on numerical facility					Average clinical rating
						1 hour	2 hour	Experimental time 0050	0130	0200	0230	0330	
			µg/kg			µg/liter		%					
370	Che	M	0.3	1	03	-	-	090	090	-	092	086	0.0
358	Bel	M	1 3	1	15	-	-	099	099	-	-	105	1.0
361	Lur	M	1.4	1	10	-	-	084	093	-	066	094	1.5
366	Bro	M	1.5	1	20	-	-	029	045	-	062	045	2.0
359	Del	M	1.9	1	17	-	-	081	090	-	078	075	1.0
367	Fen	M	1.9	1	19	-	-	084	071	-	069	071	2.0
468	Joh	F	2.0	1	20	1.5	0.0	052	048	-	048	072	1.0
482	Joh	M	2.0	2	18	1.7	0.8	056	064	060	076	084	1.0
421	Hef	F	2.0	1	15	1.4	0.7	092	066	-	082	076	1.0
470	Rod	M	2 1	1	22	1.1	1.2	072	089	085	093	085	1.5
460	Kra	M	2.1	1	[illegible]	1.2	1.0	072	056	066	093	064	2.0
458	Pro	F	2.2	1	7[illegible]	1.3	1.4	096	054	060	071	065	0.8
423	Cox	F	2 3	1	25	1.2	1.2	056	058	-	052	054	2.2
484	Rod	F	2.5	2	28	1.8	1.8	086	076	083	086	086	1.5
363	Spr	M	2.6	1	24	-	-	049	069	-	049	047	2.2
473	Kra	F	2 7	2	22	1.6	0.5	069	086	083	083	084	1.0
472	Got	M	2.7	2	29	1.2	0.3	079	063	056	079	087	2.2
362	Mcp	M	2.7	1	33	-	-	056	040	-	065	062	2.2
456	Got	F	3.0	1	33	0.8	0.7	071	071	079	063	085	0.8
394	Stu	F	3.1	1	31	-	-	032	032	-	-	060	3.0
466	Hug	F	3.2	1	3[illegible]	1.5	1.0	079	092	082	088	085	1.8
462	Whi	M	3.5	1	[illegible]	.3	1.0	070	057	089	089	092	2.0
479	Hug	M	3.5	2	3	.0	1.2	086	083	117	092	101	2.0
463	Ada	M	3.5	1	26	2.5	2.5	043	050	069	071	087	1.2
476	Whi	F	3.6	2	40	1.4	0.9	050	054	061	079	086	1.2
365	Smi	M	3.6	1	41	-	-	069	065	-	085	081	1.0
475	Ada	F	3.7	2	37	1.6	1.8	078	067	072	074	085	2.0
364	Ino	M	3.8	1	41	-	-	078	087	-	092	100	1.0
369	Has	M	3.8	1	55	-	-	038	031	-	035	063	2.0
474	Dar	F	4 0	2	41	1.7	1.8	093	093	090	110	097	0.8
478	Wil	F	4.1	2	52	1.9	0.9	042	036	056	044	072	2.2
459	Dar	M	4.1	1	19	2.7	2.1	067	070	077	080	094	1.5
371	Thr	M	4.1	1	33	-	-	081	100	-	066	026	2.2
395	Tho	F	4.1	1	40	-	-	028	011	-	000	006	2.5
368	Foj	M	4.2	1	47	-	-	058	048	-	055	069	2.0
464	Win	M	4.4	1	43	1.4	1.7	031	030	044	036	056	2.5
455	Gol	F	4.5	1	35	1.8	0.9	068	057	060	053	063	1.2
422	Whi	F	4.5	1	44	3.1	2.3	053	045	-	066	069	1.5
360	Kea	M	4.5	1	23	-	-	000	004	-	009	024	3.0
465	Hou	F	4.7	1	32	2.3	1.5	064	068	064	062	067	1.2
480	Hou	M	4.9	2	33	2.5	2.5	092	084	089	080	106	1.2
471	Gol	M	4.9	2	53	3.0	2.7	068	040	035	045	043	2.0
428	Mor	F	4.9	1	30	3.6	2.9	038	040	-	070	041	1.8
372	And	M	5 0	1	64	-	-	054	038	-	056	056	2.0
396	Tro	F	5.0	1	50	-	-	049	069	-	077	074	2.0
426	Woo	F	5.1	1	35	2.2	1.5	069	065	-	059	084	2.0
373	Osh	M	5 3	1	64	-	-	060	054	-	038	076	2.0
393	Sou	F	6.0	1	74	-	-	055	000	-	025	055	3.0
427	Jon	F	6.4	1	56	5.3	4.8	000	000	-	000	000	3.0
430	Rup	F	6.4	1	66	4.7	4.2	047	002	-	042	042	2.8
425	Whe	F	6 6	1	71	3.5	3.1	000	000	-	000	020	3.0
457	Bat	F	6.8	1	65	3.0	1.8	000	004	037	000	015	2.8
467	Nee	F	6.9	1	58	2.0	1.2	045	047	053	072	090	2.0
481	Nee	M	6.9	2	69	3.3	2.5	048	012	033	042	029	2.5
424	Hyt	F	7.0	1	65	4.2	3.9	068	059	-	062	066	2.5
477	Hyt	F	7.1	2	64	5.9	4.4	020	008	034	026	034	3.0
461	Hyt	M	7 1	1	62	3.2	2.2	000	009	012	003	015	3.0
429	Rei	F	7.6	1	64	6.0	4.5	009	012	-	029	077	2.0
469	Nea	M	7.8	1	74	4.4	2.8	017	023	032	038	049	1.8
483	Nea	F	7.6	2	74	6.2	3.4	001	028	031	030	052	2.5

* M = maleate; F = free base. Retained dose is in µg/kg, expressed as free base equivalent.

III. (C) RESULTS.

(U) The results are presented and discussed in terms of the specific questions raised at the initiation of this study.

A. (C) What is the ED50 and the ECT50 for LSD25 by the Inhalation Route ?

As shown in tables 3 and 4, the estimated values (expressed as free base equivalen) are as follows:

ED50 = 5.8 μg/kg
(95% confidence limits: 2.5 to 13.5)

ECT50 = 55 mg min/cu m
(95% confidence limits: 34 to 90)

(Because of the greater formula weight of the maleate salt, the ED50 and ECT50 for it would be 7.7 μg/kg and 73 mg min/cu m, respectively.)

The effective dose, based on a clinical rating as defined in the Methods Section, cannot be equated with military incapacitation. Effective was defined here only to mean greater than moderate clinical drug effect.

B. (C) What are the Onset Times, Peak Times, and Durations of Action of the Effective Inhalation Dose?

Onset time is defined here as that time at which performance on the NF test fell below 75% of baseline. Clinically, this represents definite impairment in mental efficiency.

Employing this criterion, the onset time for the effective dose may be interpolated to approximately 15 min (figure 3). Peak time is about 1-1/2 hr. Partial recovery time (time at which scores return to 75% or higher) is about 5-1/2 hr, and "full" recovery time (100% or higher) is between 8 and 12 hr.

As shown in figure 1, the half-life of the drug following intravenous injection is about 3 hr. The percent decrease from 1 to 2 hr is 22%. In the inhalation cases, blood levels were measured at 1 and 2 hr, and with the maleate, the blood level dropped an average of 23% from the first to the second hour, while the average decrease for the free base was 28%. This would indicate a half-life of 155 and 130 min, respectively, for the maleate and the free base. It seems unlikely that the half-life for the free base would be

TABLE 3

PROBIT ANALYSIS OF EFFECTIVE DOSE

Mean dose*	Responses
1.67	0/10
2.59	5/10
3.62	0/10
4.32	5/10
5.39	3/10
7.16	7/10

Criterion: clinical rating 2.2 or higher

Solution: **
Slope = 2.52
Standard error of slope = 0.94

ED50 = 5.8 (2.5 to 13.5)

* All doses are retained dose in μg/kg of free base equivalent.

** Bliss method used for statistical solution.

TABLE 4

PROBIT ANALYSIS OF EFFECTIVE CT

Mean Ct*	Responses
14.6	0/10
20.1	3/10
33.8	3/10
41.1	3/10
56.3	4/10
68.6	7/10

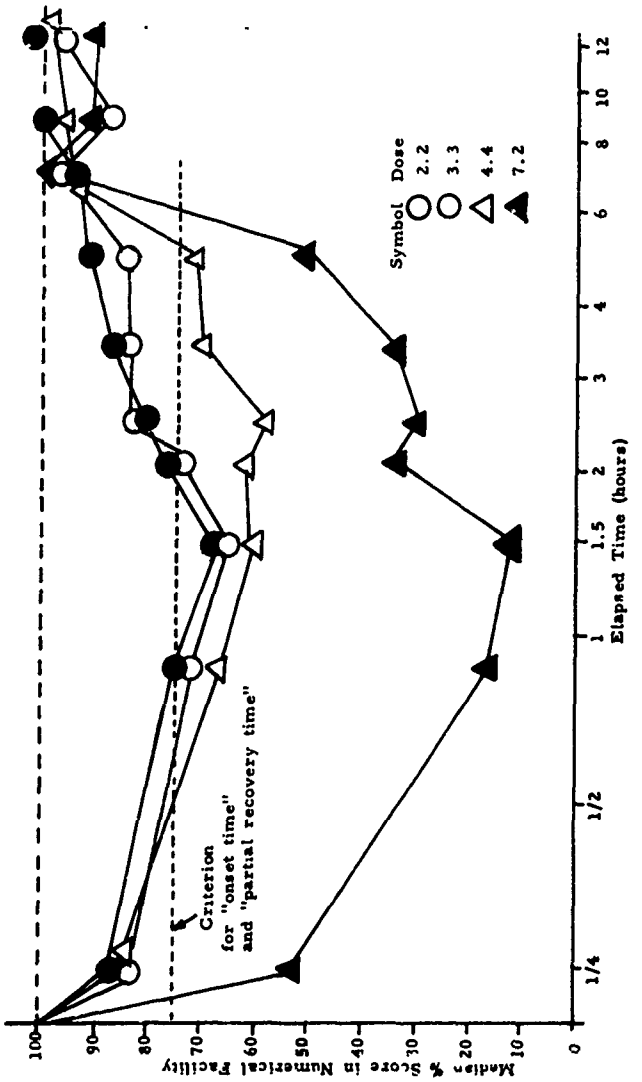
Criterion: clinical rating 2.2 or higher

Solution: **
Slope = 2.42
Standard error of slope = 0.83

ECT50 = 55 (34 to 90)

* All doses are expressed as concentration x time (milligrams per cubic meter x minutes of exposure.) Minute volumes are 10 liters/min.

** The Bliss method is used for statistical solution.



FIGURE

THE EFFECT OF DOSE ON SERIAL NUMERICAL FACILITY PERFORMANCE

Dose values are mean retained doses (μg/kg) expressed as free base equivalent. Each dose group consists of 7 to 8 subjects. Points plotted represent median scores for each group.

shorter by the inhalation route than the intravenous route, and it may well be that these differences are not significant. Also, it should be noted that a half-life estimate based on only two times of measurement is not fully acceptable, since there is no assurance that equilibration has been completed. If a compromise figure of 150 min is used, the prediction would be that less than 10% of the original blood concentration at the time of equilibration would remain at 10 hr. This corresponds to the time of nearly "complete" recovery (100% on NF) from effects (figure 4).

C. (C) What is the Estimated Safety Factor for the Agent?

The safety factor for an incapacitating agent has been defined as the ratio between the LD1 and the ED50. Since no direct information is available concerning the lethality of the compound in man, it is difficult to assume a value for the LD50 and, of course, the LD1 is unknown.

With the exception of the rabbit, all animal species tested have demonstrated unusually high lethal to effective ratios; as high as several thousand in the monkey. If man has a toxicological response to this agent similar to most animals then there would be a wide margin of safety.

D. (C) Is There Any Difference in Potency Between the Free Base and the Maleate on a Molecule-for-Molecule Basis?

None of the comparisons made in this study reveal any distinct differences between the two forms of LSD25 as far as potency is concerned. As can be seen in figures 4, 5, 6, and 7, the distribution of maleate response is completely overlapping with those for the free base. No consistent tendency for one form to show greater correlations between dose and response variables is discernible (table 5). The average dose/plasma level ratios for the two forms are virtually identical, as shown in table 6.

A comparison of the NF scores and blood levels at 1 hr for the maleate exposures with those for the free base (using only those 14 cases that were exposed to both forms in nearly equal dosage) reveals no difference of any consequence (table 7).

Thus, all the evidence so far examined indicates that if one allows for differences in formula weight, the free base and the maleate are equally effective by the inhalation route.

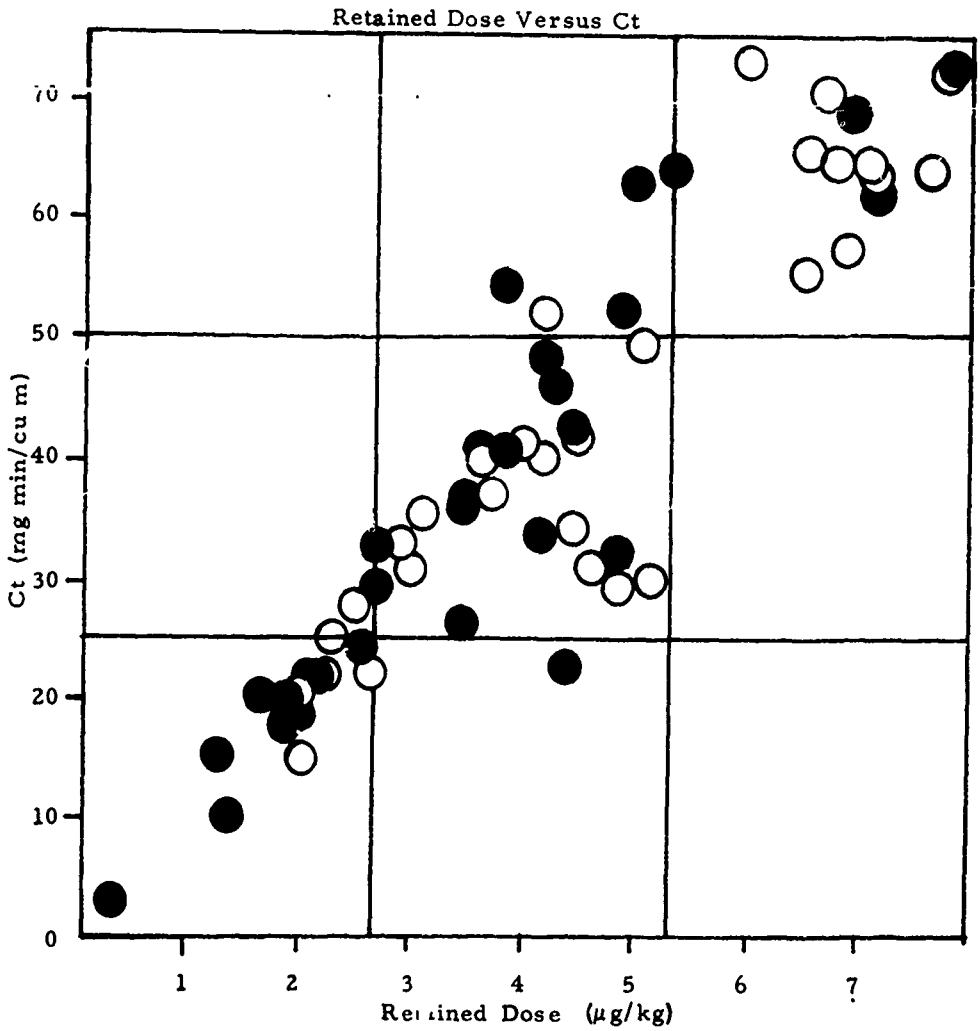


FIGURE 4

RETAINED DOSE VERSUS CT (U)

(U) Both retained doses and Ct values are expressed in terms of free base equivalent. Black dots = maleate; white dots = free base.

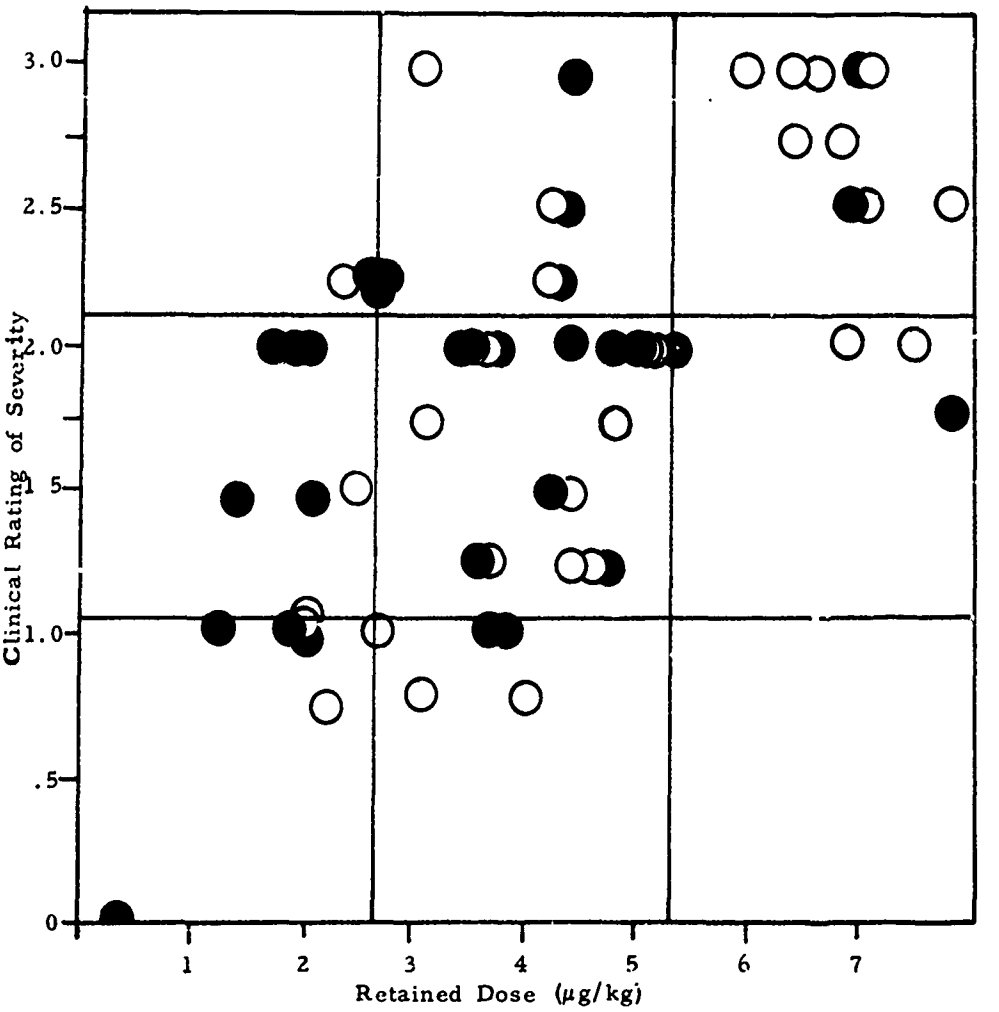


FIGURE 5

RETAINED DOSE VERSUS CLINICAL RATING OF SEVERITY (U)

(U) Retained doses are expressed in terms of free base equivalent. Black dots = maleate; white dots = free base.

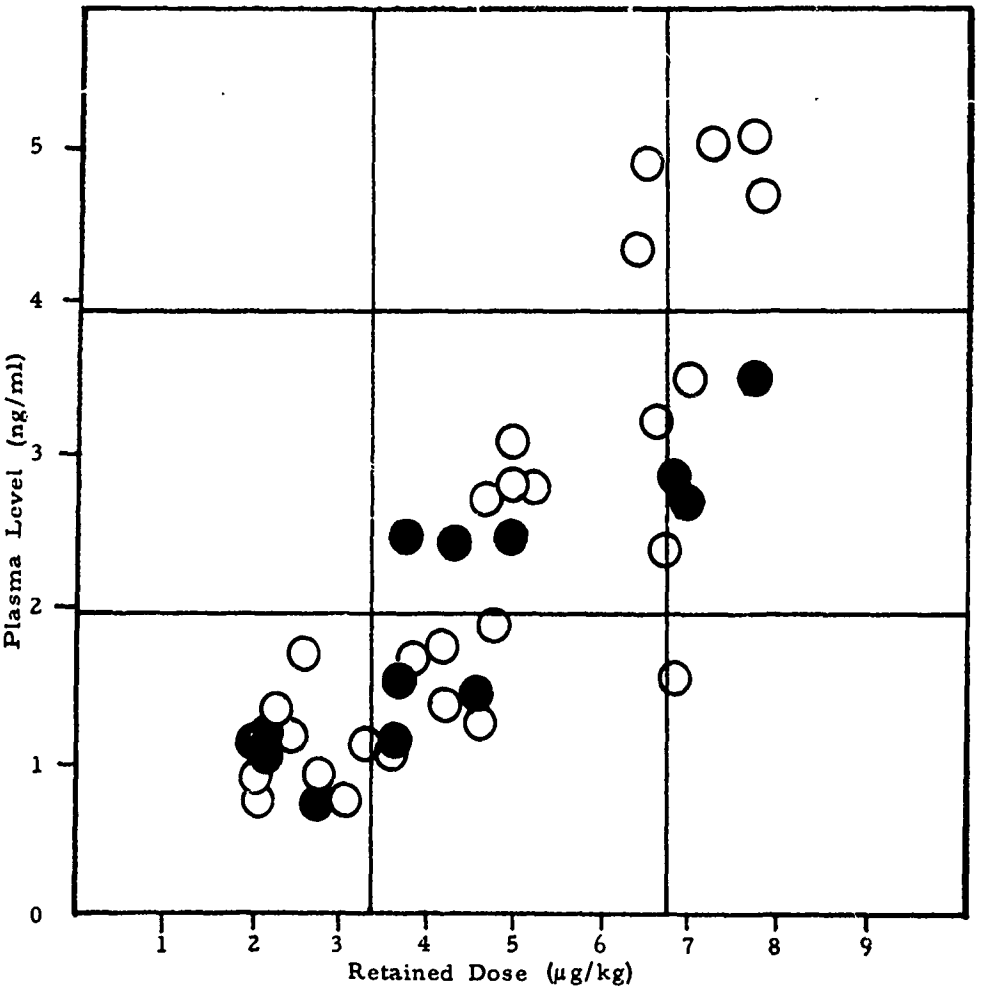


FIGURE 6

RETAINED DOSE VERSUS PLASMA LEVEL (U)

(U) Plasma levels are the mean of the 1- and 2-hr values. Retained dose is expressed as free base equivalent. Black dots = maleate; white dots = free base.

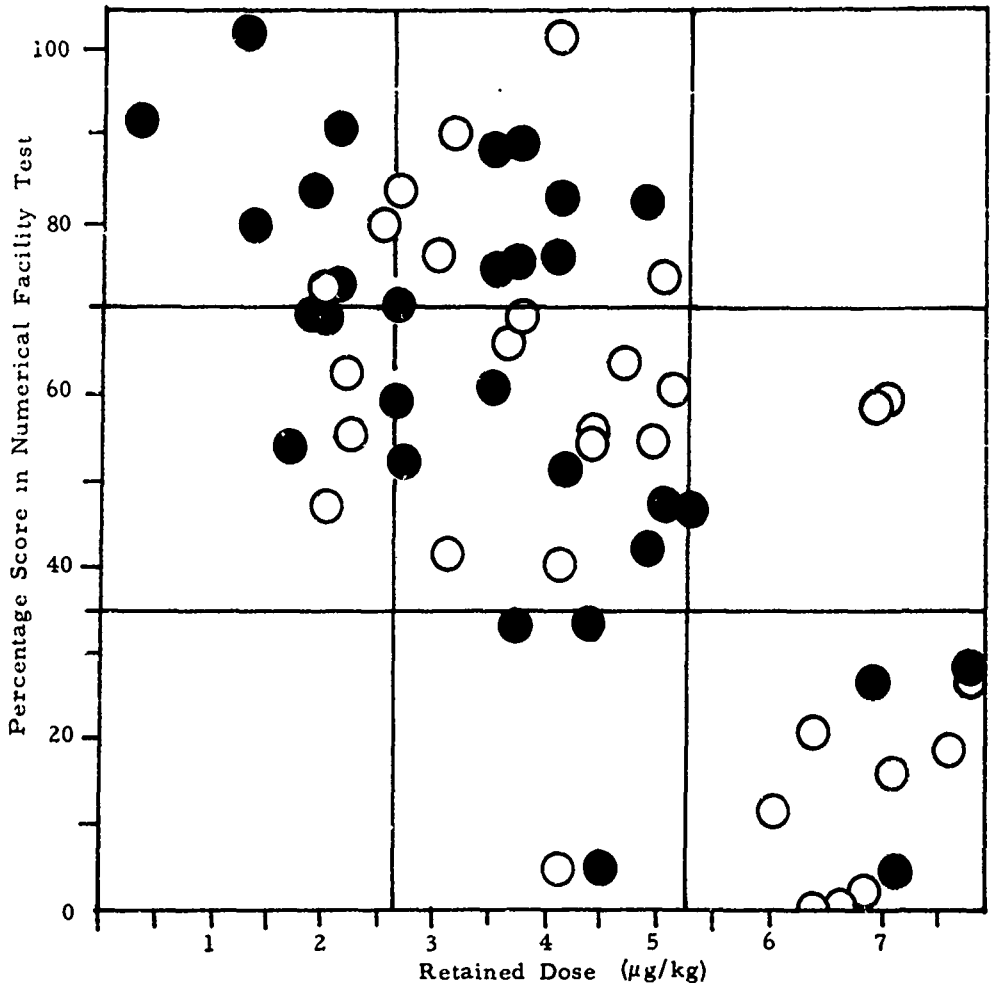


FIGURE 7

RETAINED DOSE VERSUS NUMERICAL FACILITY (U)

(U) Retained doses are expressed as free base equivalent. Percentage scores represent the mean of the 0130 and 0230 scores for each individual. Black dots = maleate; white dots = free base.

(C)

TABLE 5

CORRELATIONS (U)

		Maleate	Free base
Retained dose versus:			
1.	Ct	0.95**	0.94**
2.	Plasma level (1 hr)	0.88**	0.80**
3.	Plasma level (2 hr)	0.77*	0.69*
4.	Numerical facility, % (0050)	-0.64	-0.80**
5.	Numerical facility, % (0130)	-0.75*	-0.68*
6.	Numerical facility, % (0205)	-0.62	-0.83**
7.	Numerical facility, % (0230)	-0.81**	-0.63*
8.	Numerical facility, % (0325)	-0.67*	-0.59
9.	Pupil size (0045)	-0.09	-0.11
10.	Pupil size (0120)	0.48	0.36
11.	Pupil size (0220)	0.12	0.05
12.	Pupil size (0320)	-0.01	-0.11
13.	Heart rate (0045)	0.42	0.39
14.	Heart rate (0120)	0.58	0.51
15.	Heart rate (0220)	0.29	0.57
16.	Heart rate (0320)	0.53	0.28
17.	Behavior check list (0030)	0.57	0.62*
18.	Behavior check list (0125)	0.70*	0.38
19.	Abramson check list (0040)	0.15	0.11
20.	Abramson check list (0125)	0.24	0.22
21.	Abramson check list (0225)	0.49	-0.03
22.	EEG severity	0.21	-0.11
23.	Accommodative convergence ratio change	0.64	-0.16
24.	Clinical severity rating	0.48	0.78**

Note: (U) Except for items 22 and 23, the number of subjects = 14 for the maleate and 16 for the free base. A single asterisk indicates significance at the 0.01 level, two asterisks indicates the 0.001 level.

(C)

TABLE 6

COMPARISON OF PLASMA LEVELS (0100) AND NUMERICAL FACILITY SCORES (0050) AT EQUIVALENT DOSES OF MALEATE AND FREE BASE (U)

Mean dose	EA 3528 (maleate)		EA 1729 (free base)	
	Numerical facility	Plasma level	Numerical facility	Plasma level
µg/kg	%	ng/ml	%	ng/ml
2.2	56	1.7	52	1.5
	72	1.1	86	1.8
	72	1.2	69	1.6
3.3	79	1.2	71	0.8
	86	2.0	79	1.5
	70	1.3	50	1.4
	43	2.5	78	1.6
4.4	67	2.7	93	1.7
	31	1.4	42	1.9
	68	3.0	68	1.8
	92	2.5	64	2.3
7.2	48	3.3	45	2.0
	0	3.2	20	5.9
	17	4.4	1	6.2
Means:	57.2	2.25	58.4	2.28

(C) TABLE 7

COMPARISON OF RATIOS (RETAINED DOSE/PLASMA LEVEL) AT VARIOUS DOSE LEVELS OF MALEATE AND FREE BASE (U)

EA 3528 (maleate)				EA 1729 (free base)			
Number of subjects	Mean dose	Mean plasma level	Ratio	Number of subjects	Mean dose	Mean plasma level	Ratio
	µg/kg	ng/ml			µg/kg	ng/ml	
5	2.5	1.4	1.8	5	2.2	1.1	2.0
				5	3.9	1.4	2.8
4	4.1	1.7	2.4	6	4.0	1.9	2.1
				5	6.4	3.7	1.7
5	6.2	2.9	2.1	5	6.9	3.7	1.9
Mean ratio = 2.1				Mean ratio = 2.1			

NOTE: (U), Administered by inhalation route. Doses are expressed as free base equivalent. Plasma levels are the mean values of the 1- and 2-hr determinations.

E. (C) Is the Coughing Tendency Observed Earlier With the Maleate a Consistent Finding and Does It Have Practical Significance?

The answer to this question would appear to be no, at least not at the concentrations used in this study. Two subjects out of 14 did cough in the presence of the maleate aerosol, while none of those exposed to the free base displayed this symptom. A few others reported a mildly irritating sensation in the throat. This was confirmed by one of the investigators who took several breaths of the same concentration that elicited the coughing and noted a dust-like sensation in the back of the throat. The concentration of agent that caused both instances of coughing was the highest used in the entire series (approximately 20 μg/liter). It is, therefore, possible that some coughing would be produced if the agent were disseminated at higher concentrations; however, this may not be of any great practical importance because the two subjects who coughed were able to continue breathing the aerosol and had the usual retention of the drug.

F. (U) What is the Relative Effectiveness of the Inhalation Route, Compared to the Oral and Intravenous Routes?

1. Oral Versus Aerosol: Figure 8 illustrates the method used to estimate the ratio of effectiveness for these two routes. NF percent scores at 1.5 and 2.5 hr following exposure were averaged for each subject, and the subjects were grouped according to dose. The mean score for each group was plotted and a linear relationship was observed between dose and response values. The ratio between the slopes of the best fitting lines is defined to be the effectiveness ratio. This ratio is approximately 3.75.

2. Intravenous Versus Aerosol: Figure 9 shows a similar technique again applied to the NF percent scores. Only one intravenous dose group of five subjects was available. The same subjects, however, were also exposed to the same material by the inhalation route. The small sample size is, therefore, partially compensated for by the elimination of most of the sampling error. One hundred percent performance of NF at a dose of 0.0 is assumed to anchor one end of a linear regression line. The ratio of the slopes here is 3.9.

In figure 10, an alternative calculation is shown, based on the plasma levels plotted against dose in the same cases. The ratio obtained by this method is 3.7.

On the basis of these ratios, it seems probable that the oral and intravenous routes are roughly equal in effectiveness, and the inhalation route is 25% to 30% as effective as either.

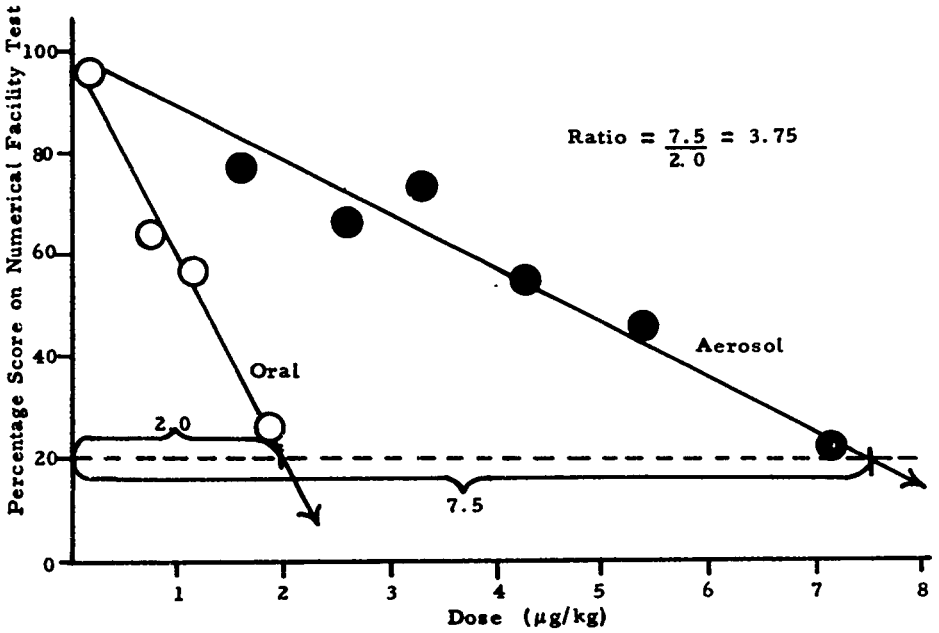


FIGURE 8

METHOD OF ESTIMATING RELATIVE EFFECTIVENESS OF ORAL VERSUS AEROSOL ROUTE BY NUMERICAL FACILITY

Aerosol scores represent medians for 6 groups of 10 subjects each. Each subject's score is the mean of 0130 and 0230 scores, regardless of route. Aerosol doses are retained doses expressed as free base equivalent. Oral doses are also expressed as free base equivalent. Oral scores represent medians for 4 groups containing 4, 4, 13,and 7 subjects, respectively.

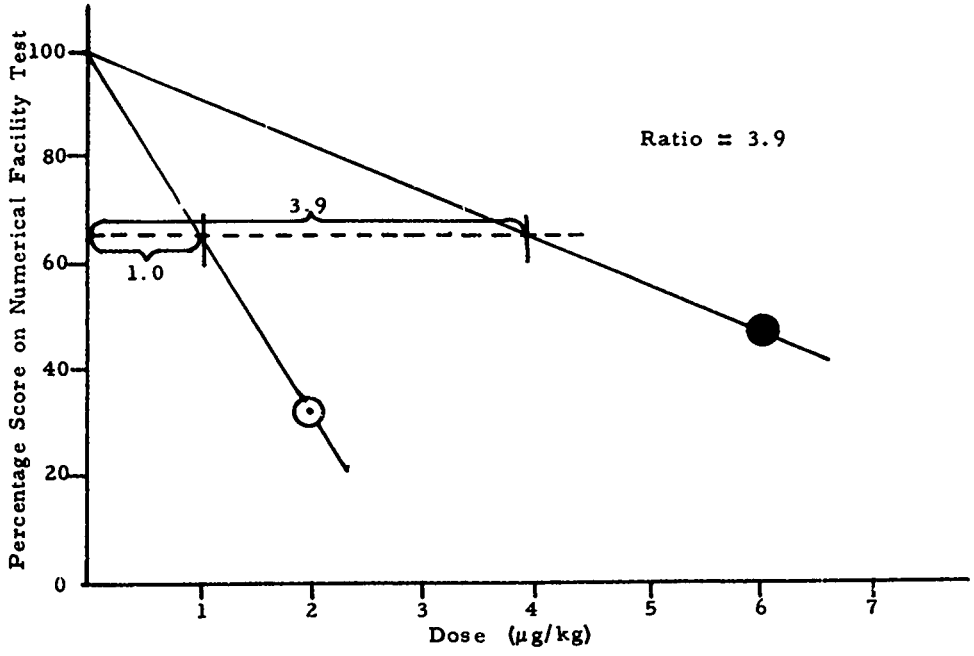


FIGURE 9

METHOD OF ESTIMATING RELATIVE EFFECTIVENESS OF IV VERSUS AEROSOL ROUTE BY NUMERICAL FACILITY SCORES

The white dot represents the mean percent score for 5 subjects who received 2.0 µg/kg of free base iv. The black dot represents mean score for the same 5 subjects who received a mean retained dose of 6.0 µg/kg free base. A linear dose response regression line is assumed from the previous figure's demonstration of linearity in the case of the oral and aerosol routes.

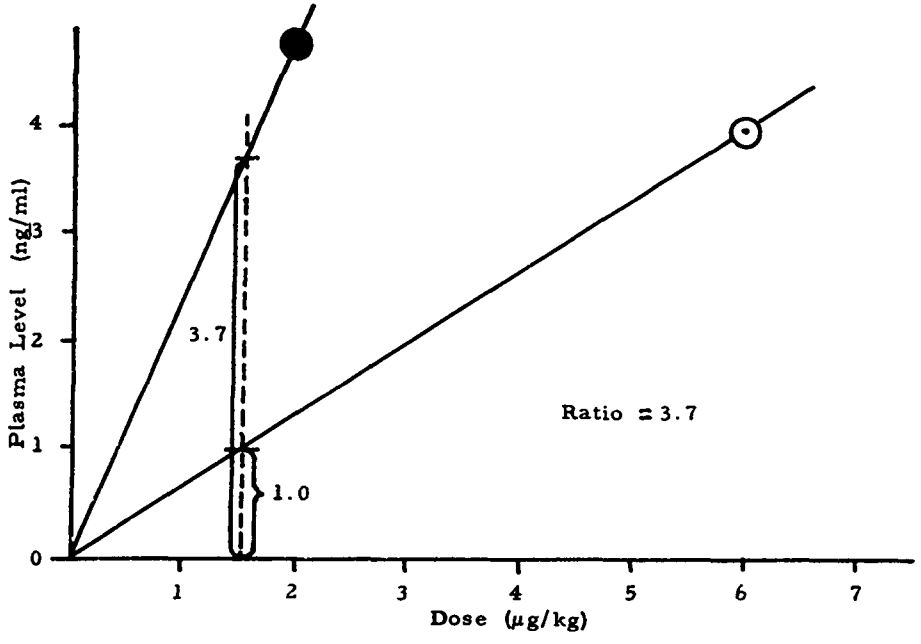


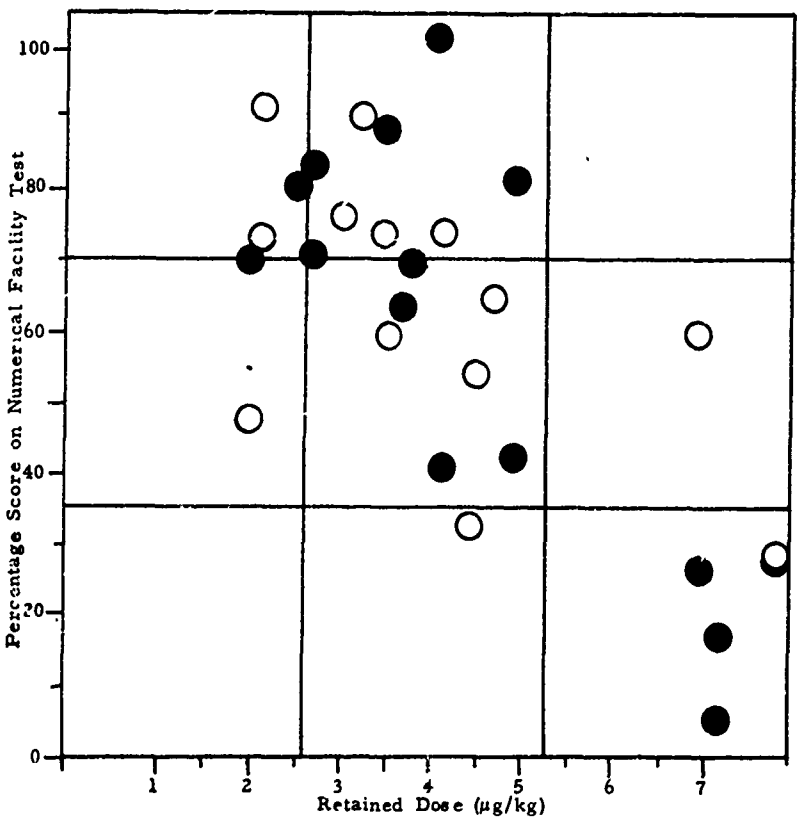
FIGURE 10

METHOD OF ESTIMATING RELATIVE EFFECTIVENESS OF IV VERSUS AEROSOL ROUTE BY PLASMA LEVELS

The white dot represents the mean plasma level for 5 subjects exposed to a mean aerosol retained dose of 6.0 μg/kg of the free base. Each subject's plasma level, in turn, represents the mean of the 1- and 2-hr values. The black dot represents the mean plasma level (similarly determined) for the same 5 subjects after exposure to 2.0 μg/kg of the tartrate (in free base equivalent) by the iv route. A linear regression line passing through the origin is assumed from previously demonstrated linear relationship between dose and blood level (see figure 7).

G. (U) Does the Response to a Second Dose Differ From an Equivalent First Dose?

Figure 11 shows no apparent differences in NF percent scores for the 14 subjects who were each exposed to the agent on two occasions.



RETAINED DOSE VERSUS NUMERICAL FACILITY
COMPARISON BETWEEN FIRST AND SECOND DOSE EFFECTS

Retained doses are expressed as free base equivalent.
White dots = first exposures; black dots = second exposures.

IV. (C) CONCLUSIONS.

The ED50 for EA 1729 by the inhalation route is 5.8 (2.5 to 13.5) μg/kg retained dose. The ECT50 is 55 (34 to 90) mg min/cu m, calculated at a minute volume of 10 liters. The ED50 and ECT50 for the maleate salt would be 1/3 greater on a formula weight basis, i.e., 7.7 μg/kg and 73 mg min/cu m, respectively.

Onset time for the effective aerosol dose is about 15 min, peak time about 1-1/2 hr, and partial recovery time about 5-1/2 hr. Full recovery requires at least 12 hr.

The safety factor in man cannot be stated with certainty. If man resembles most other animals in his toxicological response, the ratio of lethal to effective dose would be very high; however, there is no direct information about lethality in man.

If a correction is made for differences in formula weight, the effectiveness of the maleate and free base forms of the agent by inhalation is roughly the same.

There is a tendency to cough during inhalation of the maleate at higher concentrations, but in the few instances in which this occurred, there was no change in the retained dose.

By the aerosol dissemination technique employed, it was shown that the effectiveness of the aerosol route is 0.25 to 0.30 that of the oral or intravenous routes.

Prior exposure to the agent does not significantly influence the numerical facility performance decrement observed when an equivalent dose is given 2 weeks later.

(U)

APPENDIX A

SELF CHECKLIST

Name

Date

Day: S M T W T F S

A.M. Items:

1. Hours of sleep last night: ____
2. Last night I slept. ____
   a. Less soundly than usual
   b. As soundly as usual
   c. More soundly than usual
3. Last night I dreamed: ____
   a. Not at all
   b Occasionally
   c. Frequently
4. Today I feel: ____
   a. Tired
   b. Normally rested
   c. Full of pep
5. I think today will be: ____
   a. One of my bad days
   b. An average day
   c. One of my good days

P.M. Items:

6. Today the time seemed to pass: ____
   a. Slowly
   b. At the usual pace
   c. Quickly
7. In general it was: ____
   a. One of my bad days
   b. An average day
   c. One of my good days
8. The things I did were: ____
   a. Pretty boring
   b. Routine with a few high spots
   c. Quite interesting
9. Right now I'm: ____
   a. Quite tired
   b. Not really tired
   c. Full of pep
10. During the day I found I was: ____
    a. Very relaxed
    b. Quite keyed up and jittery
    c. Somewhere in between

COMMENT:

(This part is optional. Write down anything you think may interest the research staff.) (Use other side if necessary)

APPENDIX B

NUMERICAL FACILITY TEST

Form NF-6

66	14	68	20	64	5	7	68	14	17
67	90	5	46	19	26	97	71	65	53
40	84	51	78	58	93	10	86	52	77
73	97	70	88	85	68	58	21	55	56
14	11	90	79	60	23	85	74	71	19
64	75	33	97	15	22	9	54	87	71
5	73	96	51	6	35	98	87	37	59
71	88	2	40	15	85	42	66	78	36
95	5	74	14	93	15	99	47	22	50
86	90	19	2	20	13	64	54	41	72
11	52	7	4	1	92	61	73	26	12
5	27	60	2	90	3	71	32	78	41
65	41	62	33	10	51	62	98	63	94
9	14	93	31	75	59	99	11	6	96
68	86	55	8	6	77	6	12	55	26
76	22	59	39	40	59	51	44	13	44
83	98	33	54	78	56	29	95	8	95
20	12	82	16	78	78	16	92	27	27
37	22	43	49	89	6	93	63	1	36
90	8	90	36	62	83	15	16	50	99
53	51	35	37	93	2	49	84	18	79
81	86	91	71	56	96	83	60	17	69
13	66	29	95	83	45	48	62	88	61
29	32	70	67	13	8	43	71	30	10
39	92	13	13	27	64	36	46	71	78
35	33	80	20	92	13	92	40	44	71
1	98	3	2	79	5	88	80	91	32

Subject_____ Examiner_____ Date_____

(U)

APPENDIX C

AEROSOL PROTOCOL

Real Time	Exp. Time	Check*	Procedure
	0010		S.C.L. (Symptom Check-List) (1)
	0015		NF (Numerical Facility)
	0020		HR and PS (Heart Rate and Pupil Size)
	0030		B.C.L. (Behavior Check-List)
	0040		S.C.L. (2)
	0045		HR and PS
	0050		D.A.M. (Draw-A-Man) and NF
	0100		Draw Blood
	0105		TV Interview
	0120		HR and PS
	0125		S.C.L. (3)
	0130		D.A.M. and NF
	0135		EEG and B.C.L.
	0200		Draw Blood
	0205		NF
	0220		HR and PS
	0225		S.C.L. (4)
	0230		D.A.M. and NF
	0240		TV Interview (B.C.L.)
	0320		HR and PS
	0325		NF
	0450		HR and PS
	0455		S.C.L. (5)
	0500		D.A.M. and NF
	0510		B.C.L.
	0650		HR and PS
	0655		S.C.L. (6)
	0700		D.A.M. and NF
	0710		B.C.L.
	0850		HR and PS
	0900		NF
	1220		HR and PS
	1225		S.C.L. (7)
	1230		D.A.M. and NF
	1720		HR and PS
	1730		NF
	2220		HR and PS
	2230		NF
	2300		Write Personal Account of Test
	2400		Complete Check List

* Check when completed.

(U) APPENDIX D

ABRAMSON CHECKLIST

Subject _____ Dosage _____ Date _____

	Experimental Time: 0010	0040	0125	0225	0455	0655	1225
1. Do you feel ill in any way?							
2. Are you nauseated?							
3. Have you a feeling of ch ing?							
4. Is salivation increa							
5. Or decreased ?							
6. Is your appetite inc							
7. Or decreased?							
8. Do you have a dry taste in your mouth?							
9. Do you have a funny taste in your mouth?							
10. Is it a bitter taste?							
11. Are your lips numb?							
12. Or drawn back as if you were smiling?							
13. Does your head ache?							
14. Are things moving about you?							
15. Do you feel dizzy?							
16. Or unsteady?							
17. Is there difficulty in breathing?							

APPENDIX D (contd)

18. Have you passed more urine than usual?							
19. Are you aware of your heartbeat?							
20. Is it faster than usual?							
21. Are you sweating?							
22. Are you hot?							
23. Or cold?							
24. Are you palms moist?							
25. Or dry?							
26. Or cold?							
27. Is your skin sensitive?							
28. Do you have funny feelings on your skin?							
29. Do your hands and feet feel peculiar?							
30. Do they feel heavy?							
31. Or light?							
32. Is there pressure in your ears?							
33. Is your hearing abnormal?							
34. Is it more acute than usual?							
35. Is your eysight blurred?							
36. Do you have difficulty in focusing your vision?							
37. Do you see double?							

APPENDIX D (contd)

38. Are shapes and colors altered in any way?							
39. Does light bother you?							
40. Do things seem too close?							
41. Or too far away?							
42. Do you tremble inside?							
43. Do you feel weak?							
44. Or fatigued?							
45. Do you feel drowsy?							
46. Do you feel as if in a dream?							
47. Are you anxious?							
48. Do you tremble outside?							
49. Are you nervous?							
50. Are you afraid?							
51. Do you feel confused?							
52. Do you feel different since you have had the medicine?							
53. Do you see any lights with your eyes closed?							
54. Do people appear to be larger?							
55. Do people appear to be smaller?							
56. Do you see any colors with your eyes closed?							

APPENDIX D (contd)

57. Do things appear to move nearer and closer as you watch them?							
58. Do your hands feel clumsy?							
59. Do you feel nappy?							
60. Do you feel sad?							
61. Do you feel bored?							
62. Do questions bother you?							
63. Do you want to be alone?							
64. Do you want to be with people?							
65. Do you feel the medicine?							
66. Is the feeling from the medicine stronger?							
67. Is the feeling from the medicine weaker?							
68. Is it hard to concentrate?							
69. Do you have pains in the stomach?							
70. Have you felt that you need to move your bowels?							
71. Do your hands and feet change size as you look at them?							
72. Do your hands and feet change shape as you look at them?							
73. Do your hands and feet change color as you look at them?							

APPENDIX D (contd)

74. Do you feel that your hands, feet or any other part of your body is no longer a part?							
75. Have you seen any colors on the wall?							
76. Have you seen things like a fantastic Walt Disney movie?							

APPENDIX E

BEHAVIOR CHECK LIST

NAME _____ DATE _____
SERIAL NUMBER _____ PAGE _____

	REAL TIME							
	EXPER. TIME							
Mostly asleep or lying down								
Quite restless and active								
Picking at specks or clothing								
Exploring walls								
Can obey simple request								
Speaks without being spoken to								
Pleasant and friendly								
Suspicious, cautious, hesitant								
Negativistic, irritable, or hostile								
Makes comments of paranoid nature								
Interested in TV, magazines, etc								
Hallucinating								
Speech is nonsensical at times								
Confabulates								
Seems quite normal								
Short attention span								
Confused as to place								
Confused as to time and date								
Confused as to person								
Impared recent memory								
Tends to stumble								
Poor coordination								
Tends to undress								
Cannot button clothing								
Complains about vision								
Complains of dry mouth								
Complains of weakness in legs								

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ABSTRACT

1. ORIGINATING ACTIVITY - U. S. Army Edgewood Arsenal Chemical Research and Development Laboratories, Edgewood Arsenal, Maryland - Clinical Research Division.

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2b. GROUP - GROUP 4, DOWNGRADED AT 3 YEAR INTERVALS; DECLASSIFIED AFTER 12 YEARS

3. REPORT TITLE - THE HUMAN ASSESSMENT OF EA 1729 AND EA 3528 BY THE INHALATION ROUTE (U)

4. DESCRIPTIVE NOTES - The work was started in March 1963 and completed in April 1964

5. AUTHORS - Ketchum, James S., Aghajanian, George K., Bing, Oscar H. L.

6. REPORT DATE - July 1964

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11. SUPPLEMENTARY NOTES - Nondefense medical aspects of chemical agents (U)

12. SPONSORING ACTIVITY -

13. ABSTRACT

(C) This report summarizes the results of recent investigations, by the Psychopharmacology Branch of the Clinical Research Division into the aerosol effectiveness of EA 1729 and EA 3528. The ED50 for EA 1729 by inhalation is 5.8 μg/kg retained dose. The ECT50 is 55 mg min/cu m. The ED50 and ECT50 for EA 1653 is one third greater, because of the weight of the maleate. On a molecule-for-molecule basis, EA 1729 and EA 1653 are equally potent. Onset time for the effective dose is 15 min, peak time 1-1/2hr, and partial recovery time about 5-1/2 hr. The effectiveness of the aerosol route appears to be about 0.25 to 0.30 that of the oral or intravenous routes.

14. KEYWORDS

Incapacitation
Effectiveness
Plasma levels
Retained dose
Hallucinations
Numerical facility test
Clinical rating
Human assessments
Psychopharmacology
EA 1729
EA 3528
EA 1653
Inhalation
ED50
ECT50
Toxicological response
Dissemination
Chemical agents
LSD25