AD NUMBER: AD0151547
CLASSIFICATION CHANGES
TO: Unclassified
FROM: Confidential
AUTHORITY
Per DoD 5200.1 dtd 31 Dec 68

AD NUMBER: AD0151547
CLASSIFICATION CHANGES
TO: Confidential
FROM: Secret
AUTHORITY
Per DoD 5200.1 dtd 31 Dec 1959

SECRET

CHEMICAL WARFARE LABORATORIES

TECHNICAL REPORT

CWLR 2021

PSYCHOCHEMICAL PROGRAM (C)

Status Report as of 31 December 1955

by

E. Ross Hart

FC

3 May 1956

[redacted]

SECRET

Chemical Corps Research and Development Command
CHEMICAL WARFARE LABORATORIES
Army Chemical Center, Maryland

Chemical Warfare Laboratories Report No. 2021

Directorate of Medical Research

PSYCHOCHEMICAL PROGRAM (C)
STATUS REPORT AS OF 31 DECEMBER 1955

by

E. Ross Hart

Clinical Research Division

SECRET

Chemical Warfare Laboratories
Report No. 2021

APPROVED:

PSYCHOCHEMICAL PROGRAM (C)
STATUS REPORT AS OF 31 DECEMBER 1955

HERBERT R. DERRENCH
Colonel, Medical Corps
Director of Medical Research

Subprojects No. 4-08-02-018-01
4-08-03-016-05

SEYMOUR D. SILVER
Deputy Commander, Scientific Activities

Typed: 10 April 1956
sas

SECRET

Chemical Warfare Laboratories Report No. 2021

PSYCHOCHEMICAL PROGRAM (C)
STATUS REPORT AS OF 31 DECEMBER 1955

FORWARD

(U) This report summarizes toxicity data on 36 compounds and is one of a series of reports which will ultimately be consolidated and appear as sections of a single report. The ultimate report is expected to contain the following sections:

I. Introduction.
II. Chemical and Physical Properties of Compounds Studied.
III. Toxicity Evaluation in Animals.
IV. Detailed Pharmacologic Evaluation in Animals.
V. Experimental Evaluation in Laboratory Experiments on Humans.
VI. Evaluation on Humans in Military Situations.

Since this report on animal toxicity is the first of this series to be prepared certain introductory and background material is incorporated here which will be expanded in the Introduction Section of the completed report.

Chemical Warfare Laboratories Report No. 2021

PSYCHOCHEMICAL PROGRAM (C)
STATUS REPORT AS OF 31 DECEMBER 1955

INTRODUCTION

(C) In recent years major effort in the development of new CW agents has been directed toward more lethal agents. However, in certain military situations major advantage could be gained by the use of agents which produce mental derangement and through this pervert and render ineffective the complex coordinated activities required for military performance. Compounds which would fit this usage are referred to as psychochemical agents. It is considered feasible to use psychochemical agents for military use, and a research program concerned with the investigation and development of compounds for use as psychochemical agents is being carried out in the Chemical Warfare Laboratories under subprojects 4-08-02-018-01 Neurological Action of CW Agents, and 4-08-03-016-05 Psychochemical Agents. Applicable military characteristics for such agents were established and approved by Chemical Corps Technical Committee action (Reference CCTC Item 3060, 30 June 1955).

(C) The term psychochemical agent has never been adequately defined. An attempt will be made to do so here. Psychochemical agents may be considered to be compounds capable of deranging mental processes by one or more actions on the higher parts of the central nervous system, thereby producing in humans such symptoms as anxiety, irritability, distorted perceptions of time and space, hallucinations, feelings of unreality and dissociation from the immediate environment. This might or might not include loss of consciousness. Such compounds may well have other pharmacologic actions, such as effects upon the autonomic nervous system, but this would be of secondary importance. On the basis of present knowledge it would appear likely that such compounds would produce their effects upon the central nervous system in amounts very much lower than those required for lethal effects.

(C) A survey of the multitude of drugs included within the category of potential psychochemical agents has lead to concentrated study of three types: 1) mescaline and related compounds - because of their frank, full-blown, and characteristic hallucinatory effects; 2) lysergic acid diethylamide (LSD 25) and related compounds - because of their extreme potency in producing anxiety, hallucinations, and psychoses with an unusually wide margin between doses producing mental effects and lethal doses; and 3) the active ingredients of marijuana and related tetrahydrocannabinol derivatives - because of the novel type of long lasting central nervous system depression seen with relatively small doses of a few of these compounds.

(C) The complete attainment of various objectives in this program requires that the investigation of psychochemical agents be paralleled by investigation of compounds potentially useful in prevention or treatment

of the effects. Potential prophylactic and therapeutic compounds appear to categorize themselves into three groups: 1) sedatives, such as the barbiturates; 2) tranquilizers, such as chlorpromazine and reserpine; and 3) specific antidotes, one example of which may be azacyclonol (Frenquel).

(U) Pharmacologic evaluation in animals and in man will form the subjects of subsequent reports.

(C) A total of 45 compounds have to date been delivered to Clinical Research Division of these laboratories for study. These may be divided into 34 mescaline derivatives, two indoles, one aniline derivative, and 8 tetrahydrocannabinols. The mescaline group is most usefully subdivided according to the number and location of methoxy groups on the benzene ring. (One group of 8 has a methylene-dioxy linkage rather than two methoxy groups.) The individual members of these various groups differ in number and arrangement of carbon atoms in the alkyl chain between the benzene ring and the amino group.

(C) A formidable difficulty in the screening of suggested compounds has been the obvious necessity for testing in man at the earliest possible stage of investigation. To insure reasonable safety and to comply with legal requirements, toxicity is determined in 5 different species of experimental animals before trials are instituted in man. It is this toxicity study, reported in the form of LD50 and confidence limits (calculated according to the method of Litchfield and Wilcoxon), which forms the bulk of this report.

Toxicity Studies

(C) Of the total group of 45 compounds, 22 have been investigated for toxicity to the extent of determining LD50 in at least 5 species of animal. For 6 of these 22, work is incomplete. In 3 cases the supply of compound has been exhausted; in 3 others work is still in progress. An additional 14 compounds have been investigated for toxicity to the extent of determination of LD50 by intraperitoneal injection in mice. Part of this work was done under contract numbers DA18-108-CML-3968 and CML-5663 with the University of Michigan; the principal investigator being Dr. M. H. Seevers. An additional portion of the work was done in Field Toxicology Branch of these laboratories, and a further portion by personnel of Neurology Branch, these laboratories. All of these data together with the identifying numbers of the compounds and their structural formulae have been compiled in Table I. The reference note given at the extreme right of the table indicates the laboratory in which the work was done and the report where details may be found.

Comment on Toxicity Data

(S) These tabulated data which represent 120 determinations of LD50 on 36 different compounds in one or more of 7 species of animals represent a total utilization of more than 5,000 animals. It must be understood that no compound is accepted or rejected for further study on the basis of

toxicity determination. When sufficient information has been obtained to permit the calculation of the ratio of dose effective in producing disturbances to lethal dose then it will be the value of this ratio which will permit selection of compounds for further study, not the absolute magnitude of the dosages involved.

(U) Careful perusal of the table indicates that there is no single species which is consistently more sensitive or less sensitive. For economic reasons the accuracy of the LD50 determination in monkeys and in dogs is somewhat less than in smaller and less expensive animals. Examples could be cited where all species show approximately the same sensitivity to a compound and other examples could be cited where the lethal dose in one species is as much as 10 times the comparable dose for another species even though the route of administration is the same.

(C) It is unfortunately true that there is not yet enough work on a sufficient number of related compounds to permit any conclusions as to the relationship of chemical structure to toxicity.

Symptoms Produced by Various Compounds.

(C) The following compounds have been investigated only by intraperitoneal injections in mice and no symptomatology has been reported; 1290, 1291, 1302, 1303, 1305, 1312, 1313, 1314, 1320, 1321, 1323, 1324, 1325, and 1538.

(C) In addition, compound 1315 is presently under investigation. This investigation has not progressed to the point where statements can be made.

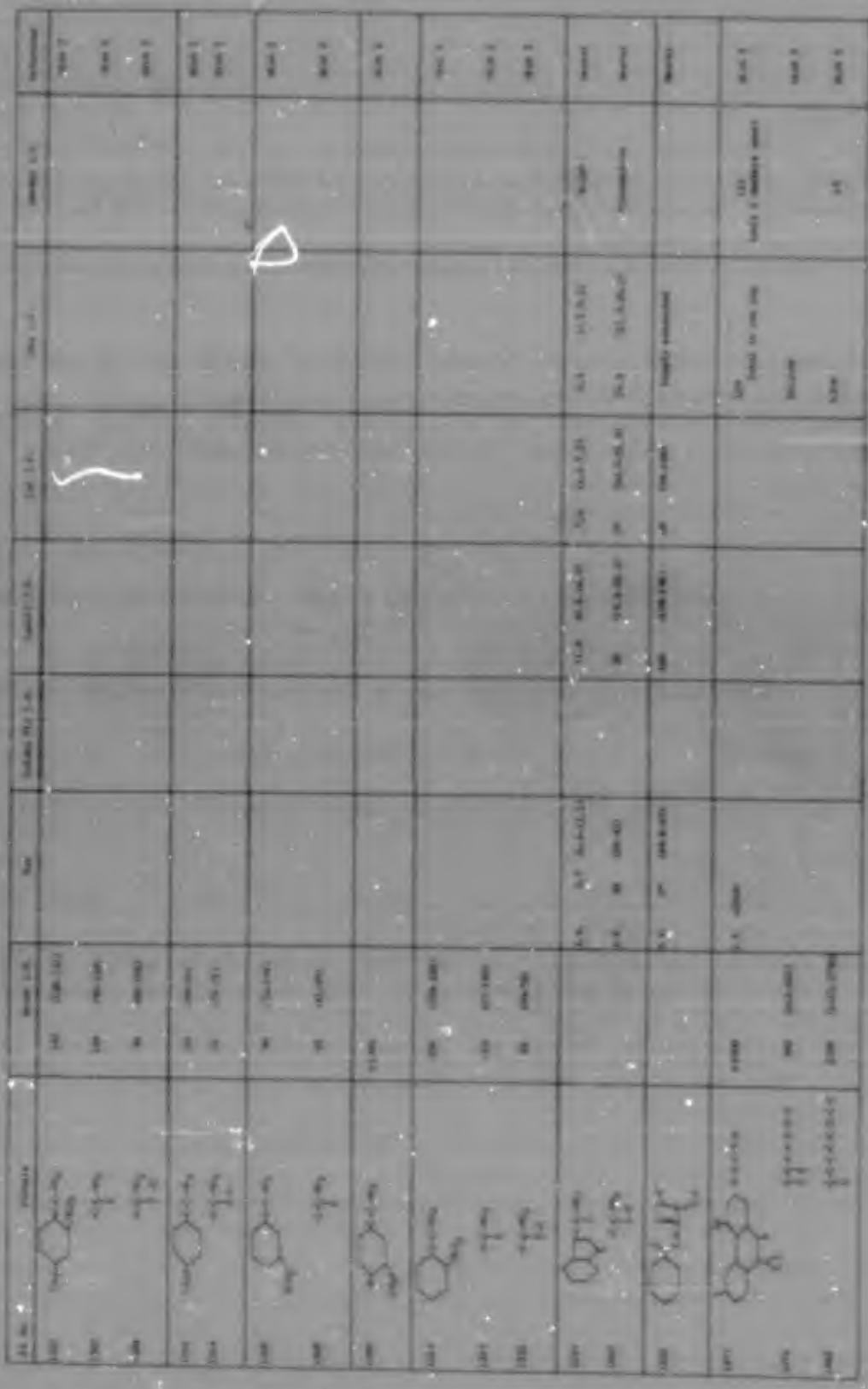
(S) For the other compounds there exist in reports from the University of Michigan or from Field Toxicology Branch, these laboratories, or Neurology Branch, these laboratories, details of the symptoms developed in animals being used for toxicity determinations. Except for the tetrahydrocannabinol derivatives, almost all of these compounds produce convulsions before death. In many cases hypersensitivity to stimuli, hyperactivity, tremors, or ataxia are reported in addition. The three tetrahydrocannabinol derivatives which have thus far been studied (1477, 1476, and 1465) all produced a depressant type response. Compound 1476 is conspicuous for its long duration of action.

(S) Behavior suggestive of hallucinations has been reported in dogs given 1304, 1505, and possibly, 1537. In cats this phenomenon has been observed following 1316, 1322 and 1539. In monkeys, this is reported after 1505. Difficulty in vision is reported in monkeys after 1475. This latter is inferred from the animal bumping into obstacles as he moves from place to place.

Table Six

Toxicity of Pyrethroids
(LC50 mg/kg; 24 hr treatment [unit])

Cl. No.	Formula	Musca d.v.	Aedes	Culex	Anopheles	Culex	Musca d.v.	Aedes	Reference
1206									Record
1207									Wright, A.
1208									Wright, B.
1209									Ryan, J.
1210									Ryan, C.
1211									Ryan, D.
1212									Ryan, E.
1213									Record
1214									Wright, A.
1215									Wright, B.
1216									Ryan, J.
1217									Ryan, C.
1218									Ryan, D.
1219									Ryan, E.
1220									Record
1221									Wright, A.
1222									Wright, B.
1223									Ryan, J.
1224									Ryan, C.
1225									Ryan, D.
1226									Ryan, E.



Distribution (7) 84 Copies Chemical Warfare Laboratories Report No. 2021

Copies

1-10 -Medical Library, Reports Section, Bldg. 355, Army Chemical Center, Maryland
11 -Executive Director, Coordinating Committee on Biological-Chemical Warfare, Office of Assistant Secretary of Defense, Research and Development, Room 3D 1050, The Pentagon, Washington 25, D. C., ATTN: Chief, Library Branch
12-14 -Chief Chemical Officer, Department of the Army, Washington 25, D. C.
15 -Commanding Officer, CmlC Research & Development Command, Washington 25, D. C., ATTN: Research Division
16 -The Director, Armed Forces Medical Library, 7th Street & Independence Avenue, SW, Washington 25, D. C.
17 -Chairman, Medical Research & Development Division, Office of The Surgeon General, Department of the Army, Washington 25, D. C.
18 -Commandant, Army Medical Service Graduate School, Walter Reed Army Medical Center, Washington 12, D. C.
19-21 -Commanding Officer, Chemical Corps Intelligence Agency, Building T-7, Gravelly Point, Washington 25, D. C.
22 -Chief, Bureau of Medicine & Surgery, Special Weapons Defense Division (Code 74), Navy Department, Washington 25, D. C.
23 -Chief, Bureau of Ships, Navy Department, Washington 25, D. C., ATTN Chief, Damage control, Ship Salvage & Personnel Protection Branch, Code 588
24 -Chief, Bureau of Ships, (Technical Library, Code 362), Navy Department, Washington 25, D. C.
25 -Director, Naval Research Laboratory, Washington 25, D. C. Code 6140
26 -Chief, Bureau of Ships, Department of the Navy, Washington 25, D. C., ATTN: Code 312
27 -Directorate of Research and Development, Headquarters, USAF, Washington 25, D. C., ATTN: AFDRD-HF
28 -Senior Special Weapons Defense Officer, Preventive Medicine Division, Office of The Surgeon General, USAF Headquarters, Washington 25, D. C.
29 -Colonel Walter A. Guild, Senior Army Representative, Department of Health, Education, and Welfare, Independence Ave. and 4th St., Room 5612, Washington 25, D. C.
30-34 -Director, Armed Services Technical Information Agency, Knott Building, Dayton 2, Ohio, ATTN: DSC-SD
35 -Executive Director, Operations Research Office, Department of the Army, The Johns Hopkins University, 7100 Connecticut Avenue, Chevy Chase, Maryland, ATTN: Librarian
36 -Headquarters, CONARC, Fort Monroe, Virginia, ATTN: Medical Section
37 -Commandant, Medical Field Service School, Fort Sam Houston, Texas
38 -Commanding Officer, Army Medical Research Laboratory, Fort Knox, Kentucky
39-40 -Commanding Officer, Cml C Training Command, Fort McClellan, Alabama

41 -Post Surgeon, Rocky Mountain Arsenal, Denver, Colorado
42 -Commanding Officer, Dugway Proving Ground, Dugway, Utah
43 -Commanding General, White Sands Proving Ground, Las Cruces, New Mexico, ATTN: Safety Director
44 -Commanding General, Ordnance Ammunition Center, US Army, Joliet, Illinois, ATTN: ORDLY-S
45 -Commanding Officer, Naval Medical Research Unit No. 1, Bldg. T-19, University of California, Berkeley 4, California
46 -U. S. Naval Radiological Defense Laboratory, San Francisco 24, California, ATTN: Director, Library Br., Code 3-222A
47 -Commanding Officer, U. S. Naval Air Rocket Test Station, Lake Denmark, Dover, New Jersey
48 -Lt Colonel Leonard C. Miller, Representative for Cml C, US Army Standardization Group, UK, Box 65, USN 100, FPO, New York, N. Y.
49 -Commander, Air Force Armament Center, Eglin Air Force Base, Florida, ATTN: ACXB
50 -Commander, Wright Air Development Center, Wright-Patterson Air Force Base, Ohio, ATTN: WCRDF-6
51 -Commander, Air Technical Intelligence Center, Wright-Patterson Air Force Base, Ohio, ATTN: ATISD-1b
52 -Headquarters, Air Materiel Command, Wright-Patterson Air Force Base, Ohio, Dayton, Ohio, ATTN: MCWB
53 -Headquarters, Air Materiel Command, Wright-Patterson Air Force Base, Dayton, Ohio, ATTN: MCD
54 -Commander, Headquarters, Air Research & Development Command, P. O. Box 1395, Baltimore 3, Md., ATTN: Directorate of Human Factors, RDTRH
55 -Commandant, USAF School of Aviation Medicine, Randolph Air Force Base, Randolph Field, Texas, ATTN: Research Secretariat
56 -The Surgeon, Headquarters, Tactical Air Command, Langley Air Force Base, Virginia
57 -Director, Project Big Ben, University of Pennsylvania, Philadelphia 4, Pa.
58-60 -Commanding General, Quartermaster Research and Development Center, Natick, Mass., ATTN: Technical Library
61 -Director, Air University Library, ATTN: AUL-6243, Maxwell Air Force Base, Alabama
62 -Commanding Officer, Army Environmental Health Laboratory, Bldg. 1235, Army Chemical Center, Maryland
63-66 -Commanding Officer, Chemical Warfare Laboratories, Bldg. 330, Army Chemical Center, Maryland, ATTN: Technical Library
67 -Commanding Officer, Naval Unit, Bldg. 51, Army Chemical Center, Md.
68 -President, Chemical Corps Board, Bldg. 483, Army Chemical Center, Maryland
69 -Operations Research Group, Building No. 483, Army Chemical Center, Maryland
70 -CONARC Liaison Office, Building No. 330, Army Chemical Center, Md.
71 -Air Force Development Field Representative, Building No. 330, Army Chemical Center, Maryland
72-77 -Canadian Army Technical Representative, Building No. 330, Army Chemical Center, Maryland

78-83 -British Liaison Officer, Building No. 330, Army Chemical Center Maryland

84 -Dr. V. Sim, Chief, Clinical Research Division, (THRU: Medical Library, Reports Section, Bldg. 355, Army Chemical Center, Md.)