AD

US Army Edgewood Arsenal
Chemical Research and Development Laboratories

Technical Report

CRDLR 3348

Pharmacotoxic Evaluation of Nine Vehicles Administered Intraperitoneally to Mice

by

Elmer G. Worthley
C. Donald Schott

December 1965

EDGEWOOD ARSENAL, MARYLAND 21010

CRDLR 3348

PHARMACOTOXIC EVALUATION OF NINE VEHICLES ADMINISTERED INTRAPERITONEALLY TO MICE

by

Elmer G. Worthley
C. Donald Schott

Experimental Medicine Division
Directorate of Medical Research

December 1965

US Army Edgewood Arsenal
CHEMICAL RESEARCH AND DEVELOPMENT LABORATORIES
Edgewood Arsenal, Maryland 21010

FOREWORD

The work described in this report was authorized under Project 1C622401A097, Medical Defense Aspects of Chemical Agents (U). The work was started in May 1964 and completed in August 1965.

In conducting the research described in this report, the investigators adhered to the "Principles of Laboratory Animal Care" as established by the National Society for Medical Research.

Acknowledgments

The authors are indebted to Pfc Gerhard A. Hauptmann for his excellent technical assistance during these studies and to Dr. Bruno Papirmeister for helpful criticism and assistance in preparation of the manuscript.

Notices

The information in this report has been cleared for release to the general public.

Disclaimer

The findings in this report are not to be construed as an official Department of the Army position, unless so designated by other authorized documents.

Disposition

When this report has served its purpose, DESTROY it.

DIGEST

The purpose of the present study was to determine the LD100 (lethal dose for 100% of the test population), LD50 (lethal dose for 50% of the test population), and ED0 (highest dose at which no effects are seen in any of the test population) for intraperitoneal injections of nine solvents into mice.

A comparison of the toxicity (ED0, LD50, and LD100) of these solvents showed their descending order of toxicity to be: (1) 100% ethanol, (2) 100% polyethylene glycol-200, (3) 100% propylene glycol, (4) 100% dimethyl sulfoxide, (5) 100% sterol diluent, (6) distilled water, (7) 0.5% methylcellulose solution, (8) isotonic saline solution, and (9) 3.0% polyvinylpyrrolidone solution suspended in isotonic saline solution.

CONTENTS

LIST OF TABLES

LIST OF FIGURES

PHARMACOTOXIC EVALUATION OF NINE VEHICLES ADMINISTERED INTRAPERITONEALLY TO MICE

I. INTRODUCTION.

Choosing a vehicle for resuspension of ethanol extracts is a bothersome problem faced by the Natural Products Laboratory. Resuspended ethanol extracts are not injected intravenously because a true solution is not usually obtained; hence, fatal occlusion of pulmonary arteries by masses of suspended material could result. Pulmonary capillaries cannot pass the larger particles; i.e., those 20μ or larger in diameter.[1] As a result, all ethanol extracts are administered intraperitoneally. Aqueous or any other extracts are also administered intraperitoneally when the extract fails to go into solution upon resuspension in isotonic saline.

Any active principle that may be present in a crude extract is probably already so diluted that any "interesting symptoms" displayed by mice may not occur until a dose as high as 150 mg/kg is reached. Usually, the crude extract material must not be concentrated in excess of 100 mg/ml because it may clog the syringe. The vehicle (diluent) should have a high ED0 (highest dose at which no effects are seen in any of the test population) because, if it causes a reaction in the test animal, it may be impossible to distinguish a symptom caused by the crude extract from that caused by a pharmacologically active solvent.

The purpose of the present study was to determine the LD100 (lethal dose for 100% of the test population), LD50 (lethal dose for 50% of the test population), and ED0 for intraperitoneal injections into mice of the following nine solvents: (1) 100% ethanol, (2) 100% polyethylene glycol-200, (3) 100% propylene glycol, (4) 100% dimethyl sulfoxide, (5) 100% sterol diluent, (6) distilled water, (7) 0.5% methylcellulose solution, (8) isotonic saline solution, and (9) 3.0% polyvinylpyrrolidone suspended in isotonic saline solution.

II. METHODS AND MATERIALS.

Replicate groups of 10 male, Swiss albino, Caesarean-derived mice were given each solvent intraperitoneally (at 0.167 common or Briggsian log dose intervals to base 10 at lethal-dose levels and 0.5 common or Briggsian log dose intervals to base 10 at effective-dose levels) and retained

for observation (up to 5 days) until death or until normal activity returned. The room temperature was 24° to 28°C, with the humidity ranging from 20% to 30% during the day and from 60% to 70% during the night. The mice (in groups of 20) were housed overnight in plastic-bottomed, metal-topped cages (9 by 19 by 5 in.) prior to injection. After administration of the vehicle, the mice were transferred to smaller, plastic-bottomed, metal-topped cages (6 by 11 by 5 in.) in groups of five for observation. Food and water were available ad libitum. The weight range of the mice was 20 to 30 gm. Time of injection, reactions displayed, and time of death were observed and recorded. The solvents with their empirical formulas are as follows[2-4]:

Name of solvent	Empirical formula
Ethanol	CH_3CH_3OH
Propylene glycol	$CH_2OHCHOHCH_3$
Polyethylene glycol-200	$HOCH_2(OCH_2CH_2)_nOH$
Dimethyl sulfoxide	$(CH_3)_2SO$
Polyvinylpyrrolidone	$(-CH_2CHC_6H_4NO-)_n$
Methylcellulose (4,000 cp; type HG 65, Dow Chemical)	$(R_nOCH_3)_x$ R_n = glucose chain
Sterol diluent:	
Benzyl alcohol	$C_6H_5CH_2OH$
Polysorbate 80; Tween 80; Span; polyoxyethylene sorbitan monooleate	Complex mixture of polyethylene ethers of mixed partial oleic esters of sorbital anhydrides $(C_6H_{10}O_6R; C_6H_{12}O_5R; C_7H_9O_5R)_n$ R = fatty acid residue
Sodium carboxymethylcellulose	$(R_nOCH_2COONa)_x$; R_n = glucose chain Solubility depends upon degree of substitution of carboxy groups
Saline solution	$NaCl \cdot H_2O$
Distilled water	H_2O

III. RESULTS.

The present study has shown that the descending order of toxicity of the solvents is as follows: (1) 100% ethanol, (2) 100% polyethylene glycol-200, (3) 100% propylene glycol, (4) 100% dimethyl sulfoxide, (5) 100% sterol diluent, (6) distilled water, (7) 0.5% methylcellulose solution, (8) isotonic saline solution, and (9) 3.0% polyvinylpyrrolidone (tables 1, 2, and 3 and figure). Detailed toxicity data on each solvent are referred to in the appendix.

TABLE 1

ESTIMATED LETHAL AND EFFECTIVE DOSE LEVELS OF SOLVENTS TESTED

Solvent*	LD100	LD50	ED0
		ml/kg	
Polyvinylpyrrolidone	>316.0	>316.0	31.6
Isotonic saline solution	>316.0	>316.0	21.4
Methylcellulose (0.5%)	316.0	275.0	1.0
Distilled water	316.0	190.0	14.7
Sterol diluent	147.0	123.5	10.0
Dimethyl sulfoxide	14.7	11.0	0.32
Propylene glycol	14.7	10.0	0.1
Polyethylene glycol-200	10.0	7.5	1.0
Ethanol	3.2	1.23	0.1

* Administered intraperitoneally in mice.

TABLE 2

NUMBER OF DEATHS OUT OF EACH SET OF 10 MICE TESTED AT VARIOUS DOSE LEVELS

Dose intraperitoneal	Solvent*								
	A	B	C	D	E	F	G	H	I
ml/kg									
0.1	—	—	—	—	—	—	0/10	—	0/10
0.32	—	—	—	—	—	0/10	0/10	—	0/10
1.0	—	—	0/10	—	—	0/10	0/10	0/10	1/10
1.5	—	—	—	—	—	—	—	—	10/10
2.1	—	—	—	—	—	—	—	—	8/10
3.2	—	—	0/10	—	—	0/10	—	0/10	10/10
4.6	—	—	—	—	—	—	—	0/10	—
6.8	—	—	—	—	—	0/10	0/10	4/10	10/10
10.0	—	—	—	—	0/10	4/10	5/10	10/10	—
14.7	—	—	—	0/10	—	10/10	10/10	—	—
21.4	—	0/10	—	—	—	—	—	10/10	—
31.6	0/10	0/10	—	0/10	0/10	—	—	—	—
46.5	—	—	—	—	—	—	—	—	—
68.0	0/10	—	—	—	—	—	—	—	—
100.0	—	—	—	0/10	0/10	—	—	—	—
147.0	—	—	0/10	0/10	10/10	—	—	—	—
214.0	—	—	2/10	8/10	10/10	—	—	—	—
316.0	0/10	0/10	10/10	10/10	—	—	—	—	—

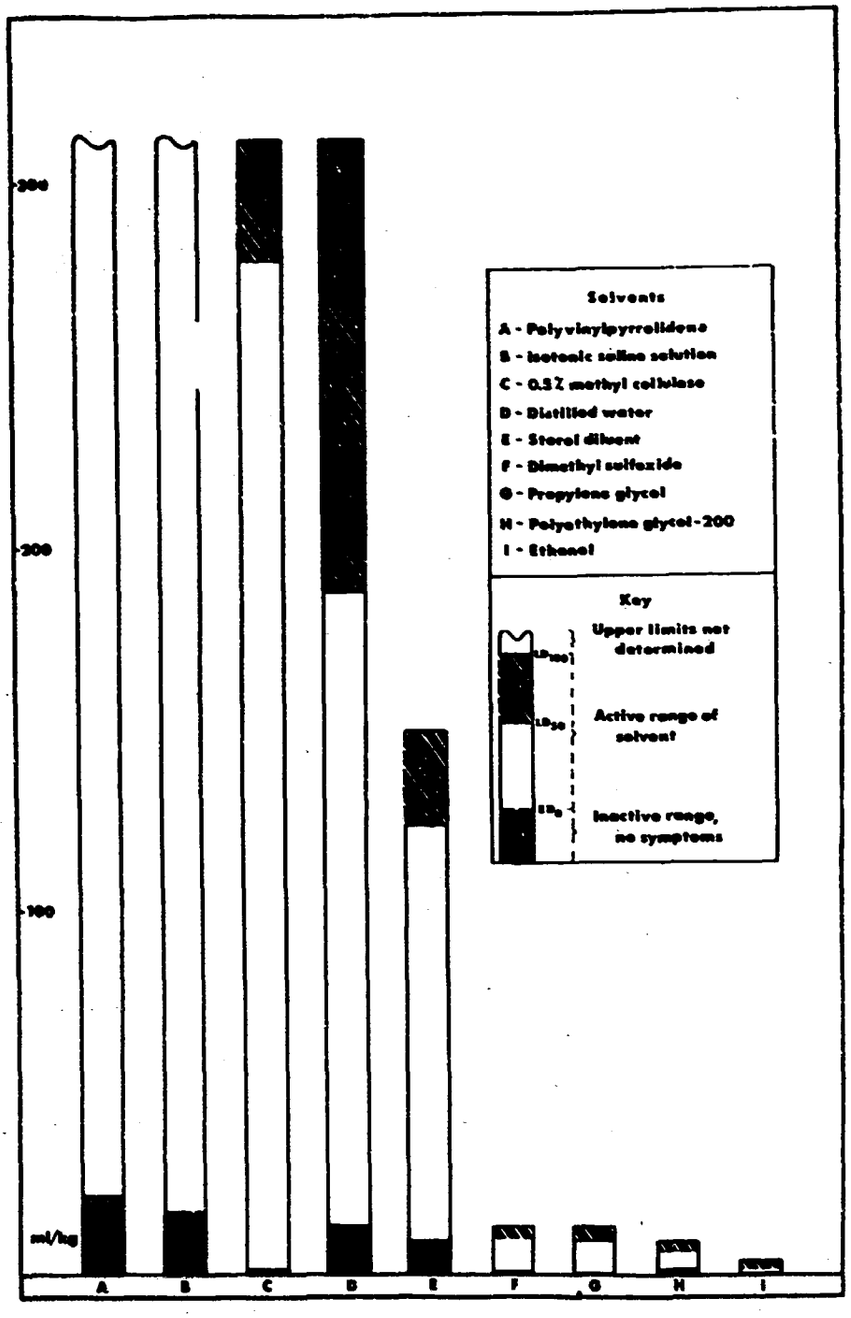
* A = polyvinylpyrrolidone; B = isotonic saline solution; C = 0.5% methylcellulose; D = distilled water; E = sterol diluent; F = dimethyl sulfoxide; G = propylene glycol; H = polyethylene glycol-200; I = ethanol.

TABLE 3

NUMBER OF MICE SHOWING REACTIONS OUT OF EACH SET OF 10 MICE TESTED

Dose intra-peritoneal	Solvent*								
	A	B	C	D	E	F	G	H	I
ml/kg									
0.1	—	—	—	—	—	—	0/10	—	0/10
0.32	—	—	—	—	—	0/10	10/10	—	3/10
1.0	—	—	0/10	—	—	10/10	10/10	0/10	10/10
1.5	—	—	—	—	—	—	—	—	10/10
2.1	—	—	—	—	—	—	—	—	10/10
3.2	—	—	10/10	—	—	10/10	—	10/10	10/10
4.6	—	—	—	—	—	—	—	10/10	—
6.8	—	—	—	—	—	10/10	10/10	10/10	10/10
10.0	—	—	—	—	0/10	10/10	10/10	10/10	—
14.7	—	—	—	0/10	—	10/10	10/10	—	—
21.4	—	0/10	—	—	—	—	—	10/10	—
31.6	0/10	10/10	—	9/10	6/10	—	—	—	—
46.5	—	—	—	—	—	—	—	—	—
68.0	8/10	—	—	—	—	—	—	—	—
100.0	—	—	—	10/10	10/10	—	—	—	—
147.0	—	—	10/10	10/10	10/10	—	—	—	—
214.0	—	—	10/10	10/10	10/10	—	—	—	—
316.0	10/10	10/10	10/10	10/10	—	—	—	—	—

* A = polyvinylpyrrolidone; B = isotonic saline solution; C = 0.5% methyl-cellulose; D = distilled water; E = sterol diluent; F = dimethyl sulfoxide; G = propylene glycol; H = polyethylene glycol-200; I = ethanol.



FIGURE

ACTIVITY OF NINE SOLVENTS INJECTED INTRAPERITONEALLY IN MICE

IV. DISCUSSION.

A. Sterol Diluent.

The present authors chose sterol diluent for use in routine administration of extracts in most quantities to animals because it has good solvent properties[5] and is not very toxic (LD50 = 147.0 ml/kg, ED0 = 10.0 ml/kg). This mixture of benzyl alcohol, Tween 80, sodium carboxymethylcellulose, saline, and water is used routinely for the resuspension of extracts that will not go into solution with saline. Macht[6,7] lists the toxicity of benzyl alcohol as about 2.0 gm/kg, which is about the amount present in toxic doses of sterol diluent. Symptoms or death after the administration of benzyl alcohol occur very rapidly (10 to 20 min),[8] as they did after the administration of sterol diluent in the present studies; hence, the toxicity of sterol diluent is attributed to benzyl alcohol. The rapidity of the toxic action of sterol diluent facilitates the evaluation of suspended materials, because any symptoms caused by the solvent will have occurred within 15 to 20 min. One could, therefore, administer more than 10.0 ml/kg (ED0) to mice and still be sure that any signs observed after 30 min were caused by the extract. This is probably true for doses up to 30 ml/kg.

B. Methylcellulose (0.5%).

Possessing good emulsifying properties,[5] methylcellulose has also been demonstrated to be highly effective when used to resuspend certain types of crystals; e.g., sulfur particles.[9] Methylcellulose is not very toxic (LD50 = 275.0 ml/kg, ED0 = 1.0 ml/kg), but it can cause decreased locomotor activity at low doses. When sterol diluent fails to give a good solution or suspension of crude extract, 0.5% methylcellulose is used. The present authors do not use it routinely because of its low ED0 and because sterol diluent possesses better solvent properties.

C. Polyvinylpyrrolidone (3.0%).

The least toxic of the solvents tested (LD50 = >316.0 ml/kg, ED0 = 31.6 ml/kg), polyvinylpyrrolidone is occasionally used in conjunction with sterol diluent when ethanol extracts are difficult to resuspend. Inherent intraperitoneal toxicity could not be determined because of the volume of fluid required. It is also doubtful that inherent intravenous toxicity could be demonstrated easily because this material is so nontoxic. Polyvinylpyrrolidone is commonly used as a human plasma extender.[2]

D. Saline Solution.

Saline solution is not very toxic when administered intraperitoneally in the doses tested (LD50 = >316.0 ml/kg, ED0 = 21.4 ml/kg). It is used routinely for suspending aqueous extracts instead of polyvinylpyrrolidone because it is more easily obtained and easier to work with. Saline solution does not possess the proper solvent characteristics for resuspending extracts other than water. Inherent intraperitoneal toxicity could not be determined because of the volume of fluid required. Intravenous toxicity can, however, be demonstrated.[10]

E. Distilled Water.

Although more toxic when administered intraperitoneally than saline solution, distilled water (LD50 = 190.0 ml/kg, ED0 = 14.7 ml/kg) can also be used for routine resuspension of aqueous extracts. Rowntree[11] has described the effects of large quantities of water when administered to mammals. The same effects were observed in mice at dose levels higher than 100 ml/kg. Distilled water is not used for resuspension of ethanol extracts because it does not have the proper solvent characteristics.

F. Dimethyl Sulfoxide (100%).

Dimethyl sulfoxide is toxic when administered intraperitoneally (LD50 = 11.0 ml/kg, ED0 = 0.3 ml/kg), but it has excellent solvent characteristics and many potential uses.[12] It can be used in small concentrations to aid in the dissolving of difficult extracts, but it is not suitable for use as a vehicle because it is too toxic and highly irritating. Dimethyl sulfoxide causes reversible hemolytic anemia and can cause discomfort because of heat released when it is injected (i.e., from the heat of the solution when mixing with water).[13] Caujolle and coworkers[14] found that 50% dimethyl sulfoxide has an LD50 of 17.7 gm/kg when administered intraperitoneally to mice.

G. Polyethylene Glycol-200 (100%).

Polyethylene glycol-200 is toxic when administered intraperitoneally (LD50 = 7.5 ml/kg, ED0 = 1.0 ml/kg). Shideman and Procita[15] administered polyethylene glycol-400 to mice intraperitoneally and found the LD50 to be 9.2 gm/kg. Highly viscous, polyethylene glycol-200 is also too toxic for use as a vehicle when administered intravenously or intraperitoneally; however, it is five to six times less toxic when administered orally, and it could be used

as a vehicle by this route.[16,17] The LD50 of polyethylene glycol (mol wt = 3,600) when administered intragastrically to rats and guinea pigs is 50.0 gm/kg.[18] When administered intravenously or intraperitoneally, polyethylene glycol causes hemolysis of red blood cells and serious kidney damage.[16,19] When administered orally or intragastrically, however, only very small amounts reach the bloodstream, and it is not as damaging to the test animal.

H. Propylene Glycol (100%).

Similar to polyethylene glycol in that it is not very toxic when administered orally,[19] propylene glycol is up to six times more toxic when administered intravenously or intraperitoneally (ip LD50 = 10.0 ml/kg, ED0 = 0.1 ml/kg).[20] Davis and Jenner[21] report an LD50 of 11.4 gm/kg, and Lampe and Easterday[22] report an LD50 of 9.7 gm/kg. of propylene glycol administered intraperitoneally to mice. The high viscosity and toxicity of propylene glycol (100%) make it undesirable for resuspending extracts that are to be injected.

I. Ethanol (100%).

Ethanol (100%) is the most toxic of the nine solvents tested (LD50 = 1.2 ml/kg, ED0 = 0.1 ml/kg). Reactions displayed by mice at non-lethal dose levels lasted up to 4 hr. Latven and Molitar[23] report that 95% ethanol was one of the most toxic and irritating solvents they tested intravenously in mice.

V. CONCLUSIONS.

A comparison of the toxicity (ED0, LD50, and LD100) of these solvents showed their descending order of toxicity to be: (1) 100% ethanol, (2) 100% polyethylene glycol-200, (3) 100% propylene glycol, (4) 100% dimethyl sulfoxide, (5) 100% sterol diluent, (6) distilled water, (7) 0.5% methyl-cellulose solution, (8) isotonic saline solution, and (9) 3.0% polyvinylpyrrolidone solution suspended in isotonic saline solution.

LITERATURE CITED

1. Easterday, O. Evaluation of Natural Products Monthly Progress Report: Preliminary Investigation of Embolization. Hazleton Laboratories, Inc., Falls Church, Virginia. Report Group No. 8, 1V: 11-20. March 1964.

2. Cutting, W. F. Handbook of Pharmacology. pp 200, 201. 2nd ed. Appleton-Century-Crofts, New York. 1964.

3. Sax, N. I. Dangerous Properties of Industrial Materials. Reinhold Publishing Company, New York. 1957.

4. Strecker, P. G. The Merck Index of Chemicals and Drugs. 7th ed. Merck and Company, Inc., Rahway, New Jersey. 1960.

5. Goldstein, S. W. Cellulose Derivatives as Aids in Extemporaneous Compounding. J. Am. Pharm. Assoc. Pract. Pharm. Ed. 14, 111 (1953).

6. Macht, D. I. A Toxicological Study of Some Alcohols. J. Pharmacol. Exptl. Therap. 16, 1 (1920-1921).

7. Macht, D. I. Study of Benzyl Alcohol as Local Anesthetic. Ibid. 11, 263 (1918).

8. Nahum, L. H., and Hoff, L. H. The Mechanism of Sudden Death in Experimental Acute Benzol Poisoning. Ibid. 50, 336 (1934).

9. Jaggard, M. H., and Zopf, L. C. The Cellulose Ethers and the Polyethylene Glycol Stearates as Suspending Agents. J. Am. Pharm. Assoc. Pract. Pharm. Ed. 14, 218 (1953).

10. Vincent, S., and Thompson, J. H. Saline Injections. J. Pharmacol. Exptl. Therap. 36, 107 (1928).

11. Rowntree, L. G. The Effects on Mammals of the Administration of Excessive Quantities of Water. Ibid. 24 (1), 135 (1924).

12. Rosenbaum, E. E., et al. Dimethyl Sulfoxide in Musculoskeletal Disorders. J. Am. Med. Assoc. 192 (4), 109 (1965).

13. Rosenkrantz, H., et al. Dimethyl Sulfoxide: Its Steroid Solubility and Endocrinologic and Pharmacologic-Toxicologic Characteristics. Cancer Chemotherapy Rept. No. 31, 7 (September 1963).

14. Caujolle, M. F., et al. Pharmacodynamie-Toxicité et Aptitudes Pharmacologiques du Dimethylsulfoxide. Compt. Rend. 258, 2224 (February 1964).

15. Shideman, F. E., and Procita, L. Some Pharmacological Actions of Polypropylene Glycols of Average Molecular Weight 400, 750, 1200, and 2000. J. Pharmacol. Exptl. Therap. 103, 293 (1951).

16. Curme, G. O., and Johnston, F. Glycols. American Chemical Society Monograph. Series 114. ch. 15. Reinhold Publishing Corporation, New York. 1953.

17. Gleason, M. N., Gosselin, R. E., and Hodge, H. C. Clinical Toxicology of Commercial Products. The Williams and Wilkins Company, Baltimore. 1936.

18. Smyth, H. F. The Single Dose Toxicity of Some Glycols and Derivatives. Arch. Environ. Health 23 (6), 259 (1941).

19. Sollmann, T. A Manual of Pharmacology and Its Applications to Therapeutics and Toxicology. pp 128, 129. 8th ed. W. B. Saunders Company, Philadelphia. 1957.

20. Weatherby, J. H., and Haag, H. B. Toxicity of Propylene Glycol. J. Am. Pharm. Assoc. Pract. Pharm. Ed. 27, 466 (1938).

21. Davis, K. J., and Jenner, P. M. Toxicity of Three Drug Solvents. Toxicol. Appl. Pharmacol. 1, 576 (1959).

22. Lampe, K. F., and Easterday, O. D. A Note on the Contraindication to Propylene Glycol, as a Solvent in Toxicity Studies. J. Am. Pharm. Assoc. Sci. Ed. 42 (7), 445 (1953).

23. Latven, A. R., and Molitar, H. Comparison of the Toxic, Hypnotic and Irritating Properties of Eight Organic Solvents. J. Pharmacol. Exptl. Therap. 65, 89 (1939).

APPENDIX

REFERENCES IN THE LITERATURE PERTAINING TO THE VEHICLES STUDIED

Solution	Animal	Sex	Injection route a/	LD100	LD50	Reference
%						
			A. Ethanol			
70	Mouse	— b/	Iv	5.0 c/	4.0 b/	1
70	Mouse	—	Oral	17.0 c/	14.5 c/	1
70	Mouse	—	Sc	18.0 c/	14.5 c/	1
95	Mouse	—	Iv	3.0 c/	2.5 c/	1
95	Mouse	—	Oral	14.0 c/	12.0 c/	1
95	Mouse	—	Sc	12.0 c/	10.5 c/	1
30	Rat	—	Ip	—	5.0 gm/kg	2
30	Rabbit	—	Oral	—	7.5 gm/kg	2
			B. Polyethylene Glycol (mol wt = 1,250)			
50	Rat	—	Ig	—	51.3 gm/kg	3
			C. Polyethylene Glycol (mol wt = 3,600)			
50	Rat	—	Ig	—	50.0 gm/kg	3
50	Guinea pig	—	Ig	—	50.0 gm/kg	3
			D. Polyethylene Glycol-400			
100	Mouse	—	Ip	—	9.2 gm/kg	4
			E. Polyethylene Glycol-1000			
100	Mouse	—	Ip	—	2.0 gm/kg	4

a/ Iv = intravenous; sc = subcutaneous; ip = intraperitoneal; and ig = intragastric.

b/ Dash (—) indicates sex not recorded in reference.

c/ Units not given.

APPENDIX (contd)

Solution %	Animal	Sex	Injection route a/	LD100	LD50	Reference
			F. Polyethylene Glycol-4000			
100	Mouse	—	Ip	—	8.0 gm/kg	4
			G. Propylene Glycol			
100	Mouse	Male	Ip	—	11.4 gm/kg	5
100	Mouse	Male	Ip	—	9.7 gm/kg	6
50	Guinea pig	Male	Ig	—	18.4 gm/kg	3
50	Rat	Male	Ig	—	16.4 gm/kg	3
100	Mouse	Female	Ip	—	9.7 gm/kg	7
—	Mouse	Both	Ig	—	23.9 ml/kg	8
—	Rat	Both	Ig	—	21.0 ml/kg	8
—	Guinea pig	Both	Ig	—	18.9 ml/kg	8
100	Mouse	— b/	Iv	8.0 c/	1.0 c/	1
100	Mouse	—	Oral	26.0 c/	22.0 c/	1
100	Mouse	—	Sc	24.0 c/	18.5 c/	1
			H. Dimethyl Sulfoxide			
50	Rat	—	Ip	—	12.0 gm/kg	9
50	Mouse	—	Iv	—	8.9 gm/kg	9
50	Mouse	—	Ip	—	17.7 gm/kg	9
100	Mouse	—	Iv	—	5.8 gm/kg	10
100	Rat	—	Iv	—	5.4 gm/kg	10
100	Mouse	—	Oral	—	21.4 gm/kg	10
100	Rat	—	Oral	—	28.3 gm/kg	10
100	Mouse	Both	Iv	—	3.8 gm/kg	11
100	Rat	Both	Iv	—	5.3 gm/kg	11
100	Mouse	Both	Sc	—	20.5 gm/kg	11
100	Rat	Both	Sc	—	20.5 gm/kg	11

a/ Iv = intravenous; sc = subcutaneous; ip = intraperitoneal; and ig = intragastric.

b/ Dash (—) indicates sex not recorded in reference.

c/ Units not given.

APPENDIX (contd)

Solution	Animal	Sex	Injection route	LD100	LD50	Reference
%						
I. Sodium Carboxymethylcellulose						
No toxicity data						12, 13
J. Methylcellulose						
No toxicity data						12, 13
K. Polyvinylpyrrolidone						
Not toxic						13
L. Water						
Toxic in excessive amounts						14
M. Saline						
Not toxic						15

LITERATURE CITED

1. Latven, A. R., and Molitar, H. Comparison of the Toxic, Hypnotic and Irritating Properties of Eight Organic Solvents. J. Pharmacol. Exptl. Therap. 65, 89 (1939).

2. Bauer, C. W., and Wasson, L. A. Sugar Free and Non-Glycogenetic Preparations for Use by Diabetic Persons. J. Am. Pharm. Assoc. Pract. Pharm. Ed. 10, 296 (1949).

3. Smyth, H. F. The Single Dose Toxicity of Some Glycols and Derivatives. Arch. Environ. Health 23 (6), 259 (1941).

4. Shideman, F. E., and Procita, L. Some Pharmacological Actions of Polypropylene Glycols of Average Molecular Weight 400, 750, 1200, and 2000. J. Pharmacol. Exptl. Therap. 103, 293 (1951).

5. Davis, K. J., and Jenner, P. M. Toxicity of Three Drug Solvents. Toxicol. Appl. Pharmacol. 1, 576 (1959).

6. Lampe, K. F., and Easterday, O. D. A Note on the Contraindication to Propylene Glycol, as a Solvent in Toxicity Studies. J. Am. Pharm. Assoc. Sci. Ed. 42 (7), 445 (1953).

7. Karel, L., et al. The Intraperitoneal Toxicity of Some Glycols, Glycol Ethers, and Phthalates in Mice. J. Pharmacol. Exptl. Therap. 90, 338 (1947).

8. Laug, E. P., et al. The Toxicology of Some Glycols and Derivatives. Arch. Environ. Health 21 (5), 173 (1939).

9. Caujolle, M. F., et al. Pharmacodynamie-Toxicité et Aptitudes Pharmacologiques du Dimethylsulfoxide. Compt. Rend. 258, 2224 (February 1964).

10. Wilson, J. E., et al. A Toxologic Study of Dimethyl Sulfoxide. Toxicol. Appl. Pharmacol. 7, 104 (1965).

11. Rosenkrantz, H., et al. Dimethyl Sulfoxide: Its Steroid Solubility and Endocrinologic and Pharmacologic-Toxicologic Characteristics. Cancer Chemotherapy Rept. No. 31, 7 (September 1963).

12. Goldstein, S. W. Cellulose Derivatives as Aids in Extemporaneous Compounding. J. Am. Pharm. Assoc. Pract. Pharm. Ed. 14, 111 (1953).

13. Cutting W. F. Handbook of Pharmacology. pp 200, 201. 2nd ed. Appleton-Century-Crofts, New York. 1964.

14. Rowntree, L. G. The Effects on Mammals of the Administration of Excessive Quantities of Water. J. Pharmacol. Exptl. Therap. 24 (1), 135 (1924).

15. Vincent, S., and Thompson, J. H. Saline Injections. Ibid. 36, 107 (1928).

UNCLASSIFIED
Security Classification

024715

DOCUMENT CONTROL DATA - R&D

(Security classification of title, body of abstract and indexing annotation must be entered when the overall report is classified)

1. ORIGINATING ACTIVITY (Corporate author)
US Army Edgewood Arsenal Chemical Research and Development Laboratories, Edgewood Arsenal, Md 21010 Experimental Medicine Division

2a. REPORT SECURITY CLASSIFICATION
UNCLASSIFIED

2b GROUP
N/A

3. REPORT TITLE
PHARMACOTOXIC EVALUATION OF NINE VEHICLES ADMINISTERED INTRAPERITONEALLY TO MICE

4. DESCRIPTIVE NOTES (Type of report and inclusive dates)
This work was started in May 1964 and completed in August 1965.

5. AUTHOR(S) (Last name, first name, initial)
Worthley, Elmer G. Schott, C. Donald

6. REPORT DATE	7a. TOTAL NO. OF PAGES	7b. NO. OF REFS
December 1965	025	027

8a. CONTRACT OR GRANT NO.

b. PROJECT NO.
1C622401A097

c. Task No.

d. Work Unit.

9a. ORIGINATOR'S REPORT NUMBER(S)
CRDLR 3348

9b. OTHER REPORT NO(S) (Any other numbers that may be assigned this report)
N/A

10. AVAILABILITY/LIMITATION NOTICES
Qualified requesters may obtain copies of this report from Defense Documentation Center, Cameron Station, Alexandria, Virginia 22314

11. SUPPLEMENTARY NOTES
Medical defense aspects of chemical agents

12. SPONSORING MILITARY ACTIVITY
N/A

13. ABSTRACT

A comparison of the toxicity (ED0, LD50, and LD100) of nine solvents injected intraperitoneally into mice showed their descending order of toxicity to be as follows: (1) 100% ethanol, (2) 100% polyethylene glycol-200, (3) 100% propylene glycol, (4) 100% dimethyl sulfoxide, (5) 100% sterol diluent, (6) distilled water, (7) 0.5% methyl cellulose solution, (8) isotonic saline solution, and (9) 3.0% polyvinylpyrrolidone solution suspended in isotonic saline solution.

14 KEYWORDS

Evaluation	Pharmacotoxicological	Dimethyl sulfoxide
Mice	Medical aspects	Intraperitoneal administration
Concentration	Ethanol	Polyethylene glycol-200
Sterol diluent	Distilled water	Methyl cellulose solution
Propylene glycol	ED0	Isotonic saline solution
LD50	ID100	
Polyvinylpyrrolidone solution		

DD FORM 1 JAN 64 1473

UNCLASSIFIED
Security Classification