assay of the commercial material would have shown this poor acceptance and permitted correction before undertaking an intensive and expensive field trial.

Limited experience with zinc phosphide has shown that material of the same chemical purity obtained from two different manufacturers varied greatly in palatability on laboratory as well as field-scale tests. The chemical assays did not reveal any cause for this variation.

In preliminary laboratory scale studies with other rodenticides, similar discrepancies in palatability and toxicity have been observed upon products which are of apparently identical chemical purity.

CONCLUSION.

Bioassays of rodenticides are necessary, since chemical assays often fail to indicate their physiological activities.

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THE TOXICITY OF PROPYLENE GLYCOL.*

BY HERBERT A. BRAUN AND GEORGE F. CARTLAND.

In recent years propylene glycol has assumed a position of somewhat increasing pharmaceutical interest as a vehicle and solvent. Seidenfeld and Hanzlik (1) have reported extensive toxicity studies in which propylene glycol is compared with glycerol and ethylene glycol. Hunt (2) has discussed the use of ethylene and propylene glycols as medicinal solvents and has shown that systemically propylene glycol is much less toxic than ethylene glycol.

We have compared the acute toxicities of propylene glycol and glycerol in rats by intramuscular, subcutaneous and intravenous injection and have obtained results which show satisfactory agreement with those obtained by Seidenfeld and Hanzlik (1). In addition, the acute and chronic toxicities of propylene glycol administered orally in rabbits have been studied.

The propylene glycol used in these studies is the Alpha Propylene Glycol (1, 2 Propane Diol).

Acute Toxicity.—Propylene glycol was injected in undiluted form intramuscularly and subcutaneously in rats. Parallel groups of rats were similarly injected with undiluted glycerol. With the large doses administered to establish the minimum fatal dose, all of the rats showed profound depression, analgesia and coma. With sub-lethal doses, the toxic symptoms persisted for a longer time in the glycerol-injected animals than in those injected with propylene glycol. In the larger doses, glycerol produced greater local tissue damage than was observed with propylene glycol in corresponding percentages of the M. L. D. The results of these experiments given in Table I show that propylene glycol is much less

* From the Research Laboratories, The Upjohn Company, Kalamazoo, Michigan.

toxic than glycerol. Intramuscularly, the M. L. D. for propylene glycol is 15.7 Gm. per Kg.; for glycerol, 7.6 Gm. per Kg. Subcutaneously, the M. L. D. for propylene glycol is 23.1 Gm. per Kg.; for glycerol, 15.1 Gm. per Kg.

The acture oral toxicity was determined, in rabbits, by administering a 20 per cent aqueous propylene glycol solution by stomach tube giving divided doses over a period of one hour. The toxic symptoms consist of increased respiratory rate, loss of equilibrium, profound depression, analgesia and coma. Death occurred in from 18 to 36 hours. The results given in Table I indicate that the M. L. D. of propylene glycol orally in rabbits is 20 Gm. per Kg.

TABLE I.—ACUTE TOXICITY OF PROPYLENE GLYCOL AND GLYCEROL IN RATS AND RABBITS.

Propylene Glycol.				Glycerol.			
Dose per Kg.		No. of	Per Cent	Dose per Kg.		No. of	Per Cent
Cc.	Gm.	Animals Used.	Mortality.	Cc.	Gm.	Animals Used.	Mortality.
			Intramuscular Injections in Rats.				
12	12.60	3	0	4	5.04	5	0
13	13.65	3	0	6	7.56	5	60
14	14.70	3	0	8	10.08	4	100
15	15.75	5	60	10	12.60	3	100
16	16.80	5	80	12	15.12	3	100
			Subcutaneous Injections in Rats.				
16	16.80	2	0	8	10.08	3	0
18	18.90	3	0	12	15.12	5	60
20	21.00	5	20	14	17.64	3	100
22	23.10	5	60	16	20.16	3	100
24	25.20	5	80	18	22.68	3	100
				20	25.20	2	100
			Oral Administration in Rabbits.				
15	15.75	2	0				
18	18.90	9	33				
19	19.95	7	86				
20	21.00	4	100				

The intravenous injection of propylene glycol in 20 rats indicated a minimum fatal dose of 18 cc. (18.90 Gm.) per Kg. This value shows satisfactory agreement with that given by Seidenfeld and Hanzlik of 16 cc. (16.8 Gm.) per Kg. intravenously in rats. The intravenous injection of undiluted propylene glycol produced rapid obliteration of the veins making administration very difficult. At doses of 16 to 19 cc. per Kg. intravenously, all the rats showed marked muscular tremors and later became comatose. Some of these symptoms may be due simply to the hypertoxicity of the undiluted propylene glycol.

Since the use of undiluted glycerin intravenously proved impracticable, a 50 per cent dilution was used. A series of 24 rats indicated that the minimum fatal dose for glycerol at this dilution was 6 cc. (7.56 Gm.).

Chronic Toxicity.—The toxicity of propylene glycol was studied by chronic oral administration in rabbits. Daily doses of 1 to 8 cc. (1.05 to 8.40 Gm.) per Kg. were administered by stomach tube as a 20 per cent aqueous solution of propylene glycol. The animals were weighed daily and the average body weights at successive 10-day periods are given in Table II. The experiment was continued for 50 days,

at the end of which time the animals were killed by the intravenous injection of magnesium sulfate. Comparison of the experimental animals with their controls showed no gross pathology which could be ascribed to the drug.

TABLE II.—CHRONIC ORAL TOXICITY OF PROPYLENE GLYCOL IN RABBITS.

Rabbit Number.	Dose per Kg. Daily. Cc.	Gm.	Initial Body Weight. Kg.	Average Body Weight at Successive 10-Day Periods. 1–10. Kg.	11–20. Kg.	21–30. Kg.	31–40. Kg.	41–50. Kg.
1	1	1.05	1.59	1.59	1.61	1.64	1.70	1.65
3	2	2.10	1.70	2.15	2.52	2.66	2.75	2.77
4	2	2.10	1.70	1.92	2.30	2.53	2.65	2.68
6	3	3.15	1.70	1.81	2.15	2.26	2.41	2.34
25	4	4.20	2.32	2.36	2.48	2.56	2.58	2.57
26	4	4.20	2.53	2.56	2.55	2.59	2.58	2.66
39	4	4.20	1.72	1.78	1.87	1.86	2.05	2.21
17	4	4.20	2.42	2.46	2.47	2.48	2.52	2.58
27	8	8.40	1.70	1.74	1.83	1.92	1.94	2.01
28	8	8.40	2.59	2.52	2.48	2.51	2.47	2.51
38	8	8.40	2.36	2.31	2.23	2.11	2.26	2.36
2	Control		1.81	1.88	1.86	1.88	1.89	1.83
11	"		1.81	1.89	2.13	2.45	2.64	2.75
7	"		1.81	2.00	2.40	2.59	2.69	2.68
5	"		1.70	1.92	2.30	2.20	2.69	2.70
24	"		1.98	2.12	2.31	2.45	2.60	2.79
55	"		1.94	2.04	2.06	2.00	2.00	2.07
50	"		2.00	2.16	2.17	2.24	2.32	2.54

The absence of any significant weight loss at the highest dosage and the satisfactory growth observed at the lower dosages indicate that daily doses of 4 to 8 cc. per Kg. are tolerated by the rabbit for a period of 50 days without any toxic symptoms other than slight anorexia. The highest dosage of 8 cc. per kilo represents the daily administration of 40 per cent of the fatal dose with no demonstrable cumulative effects. This lack of cumulative action in rabbits with a high percentage of the fatal dose of propylene glycol administered daily over a long period of time agrees with similar observations made in rats by Seidenfeld and Hanzlik (1) in which propylene glycol was added to the drinking water.

Local Irritation.—The low systemic toxicity observed for propylene glycol would indicate it to be a solvent of choice for certain medicinal preparations. It is an excellent solvent for a number of substances which are now administered in oil solution. However, the local pain caused by the injection of undiluted propylene glycol constitutes a serious handicap to its use in hypodermic preparations. Experiments on human subjects in our laboratories have shown that the subcutaneous injection of as little as 0.1 cc. of undiluted propylene glycol produces a very marked local burning sensation which, however, disappears in 5 to 10 minutes. When injected intramuscularly the local irritation appears to be no greater than that produced by oil.

SUMMARY.

The acute toxicity of propylene glycol has been compared to that of glycerol by intramuscular and subcutaneous injections in rats. The acute and chronic oral toxicity of propylene glycol has been studied in rabbits.

The M. L. D. for propylene glycol intramuscularly and subcutaneously in

rats is 15.7 and 23.1 Gm. per Kg., respectively, as compared to corresponding values of 7.6 and 15.1 Gm. per Kg., respectively, for glycerol.

In rabbits, the acutely fatal dose of propylene glycol by oral administration is 20 Gm. per Kg. Daily oral doses up to 8 cc. per Kg. administered for 50 days are tolerated by rabbits with no observed cumulative effects.

The low systemic toxicity of propylene glycol would recommend it as a solvent for certain medicinals. However, the severe, although transient, local irritation produced by its subcutaneous injection would appear to preclude its use in hypodermic preparations in undiluted form.

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DETECTION OF DIETHYLPHTHALATE IN WHISKIES AND OTHER ALCOHOLIC PRODUCTS.

(ELIMINATING SOURCES OF ERROR DUE TO FALSE POSITIVES AND THE 24-HOUR REQUIREMENT.)*

BY ISRAEL SCHWARTZ.[1]

Within the last years, mainly during prohibition, much has been published upon detection of diethylphthalate in alcoholic products. Its presence in a spirituous product was proof that industrial grade of alcohol was diverted for illicit use. Under Spiritus Frumenti U. S. P. X, listed among tests for denaturants, also was included the test for diethylphthalate. The U. S. P. XI now omits the test for diethylphthalate but retains the test for other denaturants. Apparently, the test for diethylphthalate was deleted because it was unreliable and therefore subject to criticism. Handy and Hoyt pointed out that many organic substances yield fluorescences, but those not due to diethylphthalate fade after 24 hours. It now is known that with such products as old bonded whiskies, rums, brandies, etc., fluorescent reactions are obtained with the U. S. P. X test which last more than 24 hours, sometimes a week or longer.

Denaturants still are a problem to be dealt with in testing alcoholic products, and routine tests for diethylphthalate should be included along with tests for other denaturants listed in U. S. P. XI. Ending of prohibition did not eliminate illicit practices, and products offered for consumption and containing denaturants are still with us. Such spurious products may represent prohibition left-overs brought out from concealment, or those due to diversion and "cleaning" of denatured alcohol, contamination, etc. Since the repeal, we found diethylphthalate in an imported rum offered through a very dependable concern. Investigation showed that its presence was due to filling machines previously used for bay rum, the latter legally containing diethylphthalate alcohol.

In certain types of cordials, diethylphthalate was found to be added as a "fixative." In this country such finding would be wrongly construed and injure

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* Scientific Section, A. PH. A., Portland meeting, 1935.

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