

# The Comparative Toxicity and Cathartic Efficiency of Disodium Tartrate and Fumarate, and Magnesium Fumarate, for the Mouse and Rabbit\*

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The availability of fumarate, at this time of serious and increasing shortage in the supply of tartrate, has suggested a comparative survey of the two salts for extent of parallelism in toxicity. Because a considerable use of tartrate is as a saline laxative, the relative cathartic efficiency of fumarate also has been determined.

## EXPERIMENTAL

*Comparative Toxicity for the Mouse.*—Titration was made for the dosage tending to produce one death in ten ( $LD_{10}$ ), as summarized in Table I.

The salts compared were supplied by Chas. Pfizer and Co. as crystalline preparations with molecular weights of 160 (disodium fumarate), 230 (disodium tartrate) and 228 (magnesium fumarate) and were given in 25% aqueous solution.

The dosages reported are in terms of individual weight. The average weight was between 22 and 23 Gm. The mice were white, of mixed strain and sex, non-fasting and selected only to the extent that use of animals in recognizably poor condition was avoided. A tuberculin syringe fitted into a 16-gauge needle, ground sufficiently blunt at the tip to permit harmless insertion into the mouth and throat for a distance of 1 inch, was used for the feedings. Not more than 0.3 cc. was given at one time. Death as a result of feeding accidents was infrequent and distinguishable from death as an effect of the ingested solutions.

The intestines, at death, were distended with fluid. The average weight loss by the survivors was approximately 8 per cent. Ninety per cent of the deaths occurred within 24 hrs.

*Toxicity for the Rabbit.*—Table II reports a titration for amount of substance producing sublethal impairment in ability to respond to the demands imposed on function by chilling.

The rabbits used were non-fasting New Zealand White males with an average weight between 2.5 and 3.0 Kg. They were not free of the low-grade infections and infestations common to rabbits secured from dealers but had temperatures and weights within the normal range at time of use.

The sodium chloride was Mallinckrodt, C.P. All of the salts were given in 25% aqueous solution, with additional water available.

The warming time is the number of minutes required for a spontaneous recovery of 3 degrees of body temperature by rabbits chilled to 96° F. as described in reference (1). Normally, from 28 to 40 minutes are required in the absence of factors producing change. The warming time tends to shorten during serial chilling (2). It tends to be an average of 6 to 7 minutes shorter following a second chilling before complete recovery from a first and may remain shortened, after two consecutive chillings, for more than 24 hrs. Actions tending to depress or impair functional efficiency cause the warming time to lengthen, instead of shorten, on re-chilling (2-4). A lengthening exceeding 40% may be described as "serious" since, in an infected rabbit, it markedly reduces the chance for survival (1-4).

The average dosages producing unmistakable but sublethal effect on function as indicated by the warming time test were 21† (sodium chloride), 19 (disodium fumarate), 16 (disodium tartrate) and 11 (magnesium fumarate) mM/Kg. These levels compare with the following  $LD_{10}$  levels found in the mouse: 23 (disodium fumarate), 19 (disodium tartrate) and 10 (magnesium fumarate) mM/Kg.

† See the notations to Tables I and II.

Table I.—The Comparative Mortality Following Single Feedings of Graded Amounts of Disodium Tartrate, Disodium Fumarate and Magnesium Fumarate, to the Mouse

Substance given	Amount, mM/Kg. <sup>a</sup> Range	Av.	Mortality	Approx. $LD_{10}$ , mM/Kg.
Water, only	...	..	0/96	..
Disodium fumarate	10-19	15	2/52	23
	20-29	25	4/32	
	30-34	33	6/24	
	36-48	43	13/29	
Disodium tartrate	50-66	54	10/14	19
	7-15	12	2/30	
	16-23	20	4/35	
Magnesium fumarate	24-43	30	15/51	10
	6-12	8	3/36	
	13-21	15	8/35	
	22-30	28	14/25	
	32-43	36	18/23	
	48-88	63	10/11	

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<sup>a</sup> Millimoles per kilogram. For conversion to Gm./Kg., multiply by the molecular weight as given in the adjoining text, and divide by 1000.

Table II.—The Effects of Single Feedings of Sodium Chloride, Disodium Fumarate and Tartrate and Magnesium Fumarate on the Ability of the Rabbit to Warm up after Chilling

Substance Given	Amount, mM/Kg.		Number of Rabbits	Per Cent with a Warming Time >40% Longer		Per Cent Deaths		Per Cent Excreting Fluid with the Feces
	Range	Av.		2 Hrs. after	24 Hrs. after	In <24 Hrs.	36-48 Hrs.	
None <sup>a</sup>	..	..	17	0	0	0	0	0
Sodium chloride	1-16 <sup>b</sup>	7	9	0	0	0	0	0
	17-25	21	7	43	14	0	0	14
	26-45	32	7	86	(0) <sup>c</sup>	43	0	0
Disodium fumarate	2-13	7	8	0	0	0	0	0
	15-23	19	7	29	14	0	0	86
	27-38	33	5	80	(0) <sup>c</sup>	80	0	60
Disodium tartrate	1-12	6	7	0	0	0	0	0
	15-17	16	6	0	17	0	0	0
	20-27	23	7	43	(67) <sup>c</sup>	14	43	43
Magnesium fumarate	9-13	11	22	14	9	0	0	0

<sup>a</sup> Controls. Water and salt were available but not forced.

<sup>b</sup> On a basis of 2 moles of chloride equaling 1 of tartrate, etc.

For conversion of the sodium chloride figures to Gm./Kg., multiply by 0.116, not 0.058.

<sup>c</sup> This figure covers only those of the group not already dead or moribund at the time of the 24-hr. determination.

The effect produced on the warming time by disodium tartrate differed from that produced by the chloride and fumarate in speed of development. Instead of being maximal shortly after ingestion, with rapid subsidence in the absence of fatality, it did not become maximal until the second day. The deaths following single feedings of sodium chloride and fumarate occurred within 24 hrs. Three-fourths of the deaths following tartrate ingestion were during the second day after feeding. Disodium fumarate had a greater tendency to produce fluid excretion with the feces than was observed for disodium tartrate.

The experiment summarized in Table III was undertaken on the presumption that a continuing serious interference with function must culminate in death.

Table III.—Comparative Mortality Following Repeated Feedings of Sodium Chloride and Disodium Fumarate and Tartrate to the Rabbit

Substance	Av. No. of Consecutive Daily Feedings	Amount, mM/Kg. <sup>a</sup>		Mortality
		Range	Av.	
Sodium chloride	13	1-9 <sup>b</sup>	5	0/5
	11	17-25	20	0/4
Disodium fumarate	28	2-13	5	0/14
	17, 2 <sup>c</sup>	18-23	20	3/6
Disodium tartrate	17	2-7	5	0/3
	19, 6	15-17	16	3/6

<sup>a</sup> See note *b* to Table II.

<sup>b</sup> The amount given each rabbit was held constant but was increased from rabbit to rabbit, in each group, over the range indicated.

<sup>c</sup> The figure before the comma refers to the survivors. That following the comma refers to the non-survivors.

The amounts of disodium fumarate and tartrate found to produce a substantial effect on the warming time but no deaths, following a single feeding, produced an incidence of three deaths in six on repeated feeding.

No significantly marked change was detectable in the warming time, weight, blood non-protein nitro-

gen, creatinine, red cell count or white cell count of the rabbits surviving more than ten repeated feedings.

Seven rabbits sacrificed following 36 consecutive daily feedings, each, of 4 mM/Kg. of disodium fumarate showed no consistently manifested, clearly relevant evidence of injury on gross examination. The results accruing from the gross post-mortem examinations of the fatalities were equally uninterpretable because of the predominance of death within 48 hrs. and during the night, the presence of complicating low-grade infections and infestations and the small total numbers under comparison.

*Comparative Cathartic Efficiency for the Mouse.*—Titration was made as indicated in Table IV for the dosages producing equivalent shortening of the average time elapsing before the defection of softened feces, and feces containing charcoal, following feedings of the compared substances together with water and a "test meal" (5).

The mice were not given food after the noon feeding of the day preceding. Fifteen minutes prior to test, 0.15 cc. of water was given in the way described for the toxicity estimations. The test feeding consisted of 0.1 cc. of a mucilage of gum acacia admixed with a thick suspension of charcoal and not more than 0.15 cc. of the salt under test dissolved to a concentration of not more than 25% in water. Following the test feeding, the mice were placed in individual cages floored with white paper. Examination was made of each cage at 15-min. intervals for the presence of soft feces or feces containing charcoal. Water was continuously available. No mouse was used for test more frequently than once in 7-10 days.

The average time elapsing before the first appearance of softened feces was shortened 40% by 1.9 mM/Kg. of magnesium fumarate, 2.7 mM/Kg. of disodium fumarate and 7.4 mM/Kg. of disodium tartrate. The average time before first appearance of charcoal was shortened 15% by approximately

Table IV.—Comparative Effectiveness of Magnesium and Sodium Fumarates and of Sodium Tartrate for Producing Softening of the Fecal Contents and Accelerated Dejection in Mice Given Test Feedings of Charcoal Suspended in Water and Gum Acacia

Substance Given	Amount, mM/Kg.	Number of Mice	Av. Time in Hours of First Appearance in the Feces of:	
			Softening	Charcoal
Water, <sup>a</sup> gum acacia alone	. .	146	2.84 ± 0.06 <sup>b</sup>	3.25 ± 0.04
Magnesium fumarate	3.7	113	1.32 ± 0.04	2.75 ± 0.05
	1.9	56	1.62 ± 0.09	2.93 ± 0.09
	0.9	41	1.81 ± 0.13	2.93 ± 0.12
Disodium fumarate	10.6	32	1.47 ± 0.08	2.36 ± 0.09
	5.3	39	1.36 ± 0.09	2.48 ± 0.09
	2.7	35	1.64 ± 0.14	3.00 ± 0.12
Disodium tartrate	7.4	31	1.65 ± 0.10	2.57 ± 0.09
	3.7	39	2.46 ± 0.16	3.28 ± 0.10

<sup>a</sup> The amount of water given would come to more than a quart if given proportionately to a man.

<sup>b</sup> Probable error as computed from Peter's formula (J. W. Mellor, "Higher Mathematics, etc." (1926), Longmans, Green and Co., New York.)

3.7 mM/Kg. of magnesium fumarate, 4 mM/Kg. of disodium fumarate and 6.5 mM/Kg. of disodium tartrate.

The ratio between the dosage producing a 15% shortening of the "charcoal time" and that producing one death in ten was, for magnesium fumarate and disodium tartrate, near  $\frac{1}{8}$  and, for disodium fumarate, near  $\frac{1}{6}$ .

*Correlative Literature.*—Weiss, Downs and Corson (10) report the death of one of two rabbits given 28 and 32 mM/Kg. of sodium fumarate and an additional rabbit given 22 mM/Kg. of sodium tartrate. Death was produced in comparable dosage by sodium citrate, malate, lactate, sulfate and chloride. Sodium potassium tartrate failed to produce grossly apparent injury and little microscopic evidence of injury when fed by Underhill, Wells and Goldschmidt (6) to one fasting rabbit in a dosage of 12 mM/Kg. and to two non-fasting rabbits in dosages of 11 and 13 mM/Kg. Kidney injuries leading to death within 36 hrs. followed feedings of 17–25 mM/Kg. The action on the kidneys was interpreted by Rose (7) to be associated with slow or incomplete oxidation. "Readily oxidizable substances are probably burned to carbon dioxide and water without exerting detrimental renal effects. Acids which are oxidized with difficulty may be disposed of by excretion only. In the course of the body's efforts to eliminate them, damage to the kidney cells may result." Underhill, Leonard, Gross and Jaleski (8) found no indication of oxidation or other alteration of parenterally given tartrate in its passage through the body.

Fumarate is reported to be more readily oxidized than tartrate and actively utilized by tissue as a source of energy (9).

#### SUMMARY

Disodium fumarate proved to be, on a mole for mole basis, 20% less toxic for the mouse and rabbit than disodium tartrate. Neither substance had a toxicity for the rabbit greatly exceeding that of sodium chloride. Both had an effect on function,

measured by the warming time test, which led to fatality on continued feeding in amounts within the range producing the function-impairing effect. Consecutive daily feedings at levels below this range were without significant effect on weight, blood non-protein nitrogen, creatinine, red cell count or white cell count. Disodium tartrate, at levels within the critical range, showed evidence of a delayed toxic effect not observed with the chloride or fumarate. Disodium fumarate produced evidence of cathartic effect on the mouse and rabbit in amounts smaller than were required for equivalent effect by disodium tartrate. Magnesium fumarate, with a cathartic efficiency for the mouse exceeding that of disodium fumarate, had an off-setting, greater toxicity.

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