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Toxicology of the Citric Acid Esters: Tributyl Citrate, Acetyl Tributyl Citrate, Triethyl Citrate, and Acetyl Triethyl Citrate[1]

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Various citrate esters have been under consideration as plasticizers in materials used for packaging food. The possibility that certain foods might be contaminated by them called for an investigation of the potential hazards of their ingestion. This forms the subject of the present study.

METHODS

Four citrate esters were studied. All were clear, colorless, oily fluids; the physical constants of the compounds are shown in Table 1.

TABLE 1
PHYSICAL CONSTANTS OF FOUR CITRATE ESTERS

Physical constants	Tributyl citrate (TBC)	Acetyl tributyl citrate (ATBC)	Triethyl citrate (TEC)	Acetyl triethyl citrate (ATEC)
Molecular weight	360.4	402.5	276.3	318.3
Specific gravity, 25/25° C	1.042	1.048	1.136	1.135
Flash point, ° C	185	204	155	188
Pour point, ° C	—62	—60	—46	—43
Viscosity 25° C, cps	31.9	42.7	35.2	53.7
Boiling point at 1 mm Hg, ° C	170	173	127	132
Sol. in water 25° C g/100 ml	Insol.	Insol.	6.50	0.72

The experiments were not planned to provide a complete pharmacologic profile of these compounds, but, for the most part, to supply the kind of

1 This study was supported by the toxicology fund of the Department of Pharmacology to which contributions were made by several industrial groups including Chas. Pfizer & Co., Inc., who also supplied the materials.

information which would have the most direct bearing on the problems of their intended application. Since the possible hazards would occur under conditions of oral ingestion, all doses were administered by the gastrointestinal route. The plan of the experiments followed the general lines, with some modification, as described by Lehman *et al.* (1955).

The following items were investigated: (1) LD_{50}, (2) symptoms and course of poisoning, (3) onset and duration of action, (4) cumulation, (5) effect on growth and nutrition, (6) effect on urine, (7) effect on blood elements, (8) effect on blood chemistry, (9) effect on heart and circulation, (10) effect on neuromuscular conduction, (11) gross changes in abdominal and thoracic structures, and (12) histological changes in abdominal and thoracic structures. In relation to some of the phenomena, the study included the acute effects of the single dose, the changes that might develop over a period of several weeks, and the cumulative effects of repeated daily doses over a period of several weeks ("short-term" dosage). Two hundred and fifty rats (Wistar) and ninety-five cats were used in this study.

RESULTS

Tributyl Citrate and Acetyl Tributyl Citrate (Rats)

Effect of one dose. Each of these compounds was administered by stomach tube to a group of five rats, in doses ranging from 10 to 30 cc per kilogram, and observed for gross effects on appearance and behavior for 21 days. Shortly after administration, the material began to leak from the rectum. The animals appeared somewhat sluggish but recovered promptly and in the ensuing 3 weeks of observation, showed no signs suggesting systemic toxicity. In view of the fact that the largest doses corresponded to approximately 2 l of the material for an average human, it did not seem profitable to pursue further this phase of the study of acute toxicity in rats with the tributyl (TBC) and acetyl tributyl (ATBC) citrates.

Effect of "short-term" feeding on growth. The effect on nutrition and growth was studied in a 6-week feeding experiment in twenty-two immature rats, 21 days old, ten males and twelve females, arranged in five groups, usually of four rats each. The animals had free access to food and water. The diet consisted of Big Red Dog Food pellets (manufactured by the Cooperative Grange League Federation Exchange of Ithaca, New York) reported to contain 22% protein and 3% fat. The citrates were thoroughly mixed with the food in concentrations of 5 and

10%. The animals were weighed at weekly intervals. The results are shown in Fig. 1. The 5% diet had no deleterious effect on the growth curve. The 10% diet tended to depress it, an effect which may be due to frequent diarrhea with the higher concentration.

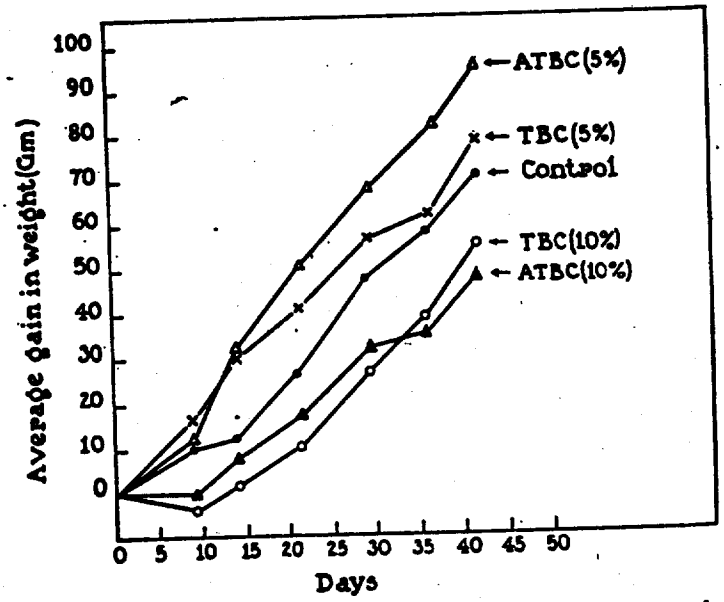

FIG. 1. Effect of various concentrations of tributyl citrate and acetyl tributyl citrate in the diet on the growth curve of immature rats.

Effect of "short-term" feeding on blood count. During this feeding experiment, a complete blood count was made at the start and again after 4 and 8 weeks. Table 2 shows the results with fourteen treated rats and four simultaneous controls. There are very wide fluctuations in the red cell count, white cell count, and differential, but no conspicuous differences between the control values and after treatment.

Gross and histological effects. At the end of the 8-week period of feeding with diets containing 5 and 10% concentrations of TBC and ATBC, eight of the rats were sacrificed, in addition to two simultaneous controls. There were no gross abnormalities in the thoracic or abdominal organs. Forty histological sections including the heart, lungs, gastrointestinal tract, liver, pancreas, spleen, and kidneys were indistinguishable from the controls.

TABLE 2

EFFECT ON BLOOD OF 8-WEEK FEEDING WITH DIET CONTAINING TRIBUTYL AND ACETYL TRIBUTYL CITRATES IN RATS

Concentration in diet (%)	Time (months)	Rats	Counts	RBC (in millions) Average	RBC (in millions) Range	WBC (in thousands) Average	WBC (in thousands) Range	Differential (in per cent) Polys Average	Polys Range	Lymphos Average	Lymphos Range	Monos Average	Monos Range	Eosinos Average	Eosinos Range	Basos Average	Basos Range
Control																	
Controls	0	4	4	7.9	7.2–9.3	20.1	12.0–27.0	21	12–33	75	61–87	2.5	0–5	1.0	0–3	—	—
	1	4	4	9.6	8.3–10.7	31.2	22.2–40.0	9	4–12	89	84–95	1.3	0–4	0.6	0–1	—	—
	2	4	4	9.4	8.3–10.6	42.6	38.4–46.1	11	7–14	86	83–88	1.8	1–3	1.0	0–4	—	—
Tributyl citrate																	
5	0	1	1	7.2	—	31.6	—	30	—	70	—	—	—	—	—	—	—
	1	3	3	8.6	7.9–9.3	38.7	26.7–52.0	9	4–18	89	82–94	1.3	0–4	0.6	0–2	—	—
	2	3	3	8.5	8.1–8.9	38.5	32.7–45.9	19	17–20	78	76–82	2.6	0–5	0.6	0–1	—	—
10	0	2	2	6.2	6.0–6.5	18.0	17.3–18.8	8	2–14	91	86–95	1.5	0–3	—	—	—	—
	1	3	3	8.4	7.5–9.1	26.3	21.6–28.8	9	1–19	88	76–98	2.3	1–4	0.6	0–1	—	—
	2	3	3	9.3	8.3–10.4	38.4	36.0–41.2	11	7–14	85	81–90	3.0	2–4	1.0	—	0.3	0–1
Acetyl tributyl citrate																	
5	0	3	3	6.3	5.5–6.8	16.0	10.0–17.7	15	14–15	80	78–81	4.0	3–5	2.0	1–3	—	—
	1	4	4	8.4	7.3–9.1	31.3	19.2–42.3	15	9–23	81	71–87	4.5	0–10	0.3	0–1	—	—
	2	4	4	8.8	7.7–10.4	38.5	27.5–62.8	27	10–50	70	40–88	2.5	0–6	1.3	0–4	—	—
10	0	4	4	7.9	6.5–9.1	30.1	13.3–39.4	21	2–30	77	68–96	1.0	0–2	1.0	0–2	—	—
	1	4	4	9.3	9.0–9.5	40.3	24.7–57.9	10	3–17	87	81–92	1.3	1–2	1.5	1–3	—	—
	2	4	4	9.9	9.4–10.5	42.9	33.8–50.8	11	6–16	86	77–91	1.3	0–2	1.3	0–3	1.0	0–2

Triethyl Citrate (TEC) and Acetyl Triethyl Citrate (ATEC) (Rats)

Acute toxicity. Doses ranging from 5 to 15 cc per kilogram were administered by stomach tube to 165 rats. The results are summarized in Table 3. The effects of the two compounds were indistinguishable. The signs included weakness, depression, ataxia, hyperexcitability, unrest, urinary dribbling, irregular and labored respiration, and in the advanced phase of poisoning convulsions appeared in some of the animals. Their absorption was fairly rapid; signs, depending on the dose, appeared within a few minutes. The course of their poisoning was also fairly rapid, progressing to advanced stages within an hour or so and terminating either in death in about 2 hours to 3 days or in apparent recovery in about 15 hours to 4 days.

The LD_{50} was not established with precision, but the data in Table 3 indicate that it lies at about 7 cc per kilogram for both materials. This would correspond to an oral dose of about 500 cc in a man of 70 kg.

Effect on growth. The effect on nutrition and growth was studied with a group of fifty-three immature rats, 21 days old, including twenty-five males and twenty-eight females. They were divided into seven approximately equal groups: (1) control group receiving the diet alone; (2) three groups receiving the diet containing TEC in concentrations of 0.5, 1.0, and 2.0%, respectively; and (3) three groups receiving the diet containing ATEC, also in concentrations of 0.5, 1.0, and 2.0%. The diet was similar to the one described above. The animals were weighed at weekly intervals. The feeding covered a period of 6 weeks. A urine examination and complete blood count were made at the start, after 3 weeks, and again after 6 weeks of feeding.

The average weight of all the rats at the beginning was 85 g, 11% more for the heaviest group and 23% less for the lightest. Preliminary experiments with this colony showed that at 100 g, each consumed approximately 20 g of food per day. The several diets, therefore, represented an approximate daily consumption of 1, 2, and 4 g/kg, respectively, of each compound in the early period of the feeding experiment. An epidemic of pneumonia in the rat colony during this experiment resulted in the loss of about one-third of the animals (similar loss among the controls), thus reducing to thirty-six the number supplying the final data. These are charted in Figs. 2 and 3 which show that TEC and ATEC given in the daily food in doses up to about 50% of the LD_{50} for 6 weeks had no material effect on growth in the rat. The absence of any

TABLE 3

ACUTE TOXICITY AND CURVE OF ACTION OF TRIETHYL AND ACETYL TRIETHYL CITRATES IN RATS AND CATS

Dose (cc/kg)	Number died/used	Per cent mortality	Species	Time (average)		
				To onset of effects (min)	To recovery (hours)	To death (hours)
			Triethyl citrate			
15	1/1	100	Rats	3	—	7.5
14	1/1	100	Rats	3	—	15
13	5/5	100	Rats	6.6	—	15.2
12.5	3/4	75	Rats	7	36	85
12	4/5	80	Rats	6.4	40	26
10	4/5	80	Rats	2.4	16	6.7
8.5	4/5	80	Rats	23	—	1.8
8	12/16	75	Rats	18.6	15.5	6.3
7.5	19/20	95	Rats	28.2	36	8.4
7	6/15	40	Rats	13.1	8.9	13.6
6	7/15	46.7	Rats	32	34.5	11.3
5	3/10	30	Rats	88	36	30.7
9	3/3	100	Cats	10.7	—	3.5
8	3/3	100	Cats	8	—	3.0
7	2/2	100	Cats	6.5	—	4.6
6	1/1	100	Cats	4	—	1.5
5	4/4	100	Cats	11.2	—	4.1
4	3/4	75	Cats	20.6	108	31.2
3	0/3	0	Cats	16.2	16.7	—
2	1/5	20	Cats	14	4.6	64
1	0/5	0	Cats	50	14	—
			Acetyl triethyl citrate			
12	1/1	100	Rats	10	—	2.3
10	5/6	83	Rats	11.7	60	19.9
9	6/10	60	Rats	26.6	37	39
8	4/6	66.7	Rats	11.5	49	16
7	4/5	80	Rats	15	39	21
6	9/20	45	Rats	26.6	21.8	15.4
5.5	3/10	30	Rats	90	18	19.1
5	0/5	0	Rats	53	14.6	—
9.5	3/3	100	Cats	18	—	30.3
9	4/4	100	Cats	15	—	21.3
8.5	3/4	75	Cats	14.3	28	27.3
8	2/3	66	Cats	12	39	41.5
7.5	1/4	25	Cats	18	33	39
7	0/2	0	Cats	20	17.5	—
5	0/2	0	Cats	19	16.5	—

toxic effects is probably to be explained by the protracted ingestion, as in the case of the daily food intake and by the interference of food with the process of absorption.

Effect on blood count. During this feeding experiment a complete blood count and differential was made at the start, again in 4 weeks and 8 weeks—a total of 68 counts. The results are summarized in Table 4.

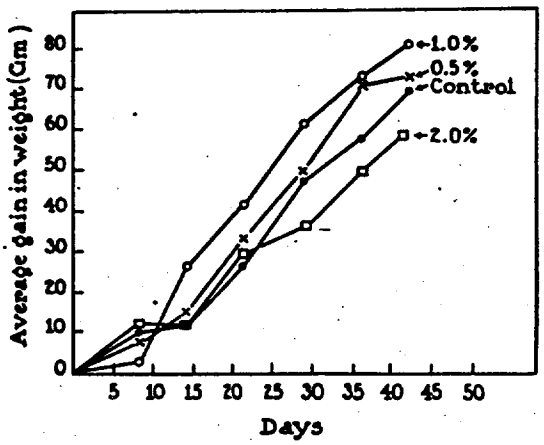

FIG. 2. Effect of various concentrations of triethyl citrate in the diet on the growth curve of immature rats.

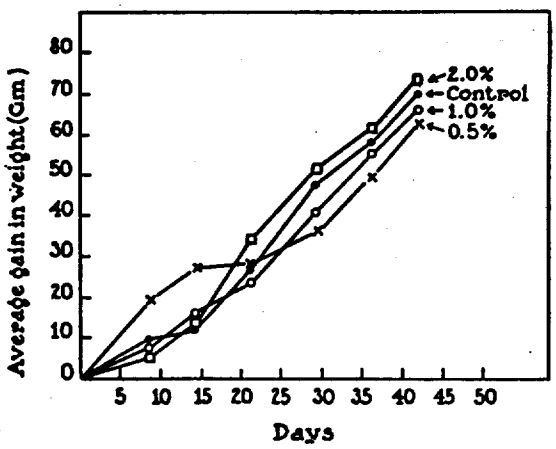

FIG. 3. Effect of various concentrations of acetyl triethyl citrate in the diet on the growth curve of immature rats.

TABLE 4

EFFECT IN RATS OF 8-WEEK FEEDING WITH DIET CONTAINING TRIETHYL AND ACETYL TRIETHYL CITRATES

Concentration in diet (%)	Time (months)	Rats	Counts	RBC (in millions) Average	RBC (in millions) Range	WBC (in thousands) Average	WBC (in thousands) Range	Differential (in per cent) Polys Average	Polys Range	Lymphos Average	Lymphos Range	Monos Average	Monos Range	Eosinos Average	Eosinos Range	Basos Average	Basos Range
Triethyl citrate																	
0.5	0	3	3	6.7	6.0–7.3	14.5	10.3–22.0	18	7–34	81	66–90	0.6	0–2	0.3	0–1	—	—
	1	4	4	8.6	8.0–10.0	32.1	20.5–45.5	12	2–22	84	75–96	4.0	1–8	0.3	0–1	—	—
	2	3	3	9.5	8.4–10.6	46.1	33.0–59.3	14	9–19	81	67–91	2.0	0–6	2.3	0–7	0.3	0–1
1.0	0	4	4	6.2	5.1–7.6	22.0	16.5–31.3	23	21–25	71	65–76	5.6	2–13	0.3	0–1	—	—
	1	4	4	8.9	7.9–10.7	28.3	23.3–36.0	13	6–24	85	76–91	3.5	3–4	—	—	—	—
	2	4	4	9.9	8.8–10.8	22.6	20.3–27.0	12	5–23	84	69–92	1.3	0–3	1.5	0–3	0.8	0–2
2.0	0	2	2	7.1	5.9–8.3	11.1	9.0–13.2	40	—	60	—	—	—	—	—	—	—
	1	3	3	10.1	9.9–10.6	32.5	19.9–51.7	6	4–8	90	90–90	3.7	2–5	0.5	0–1	—	—
	2	3	3	9.1	8.6–9.5	35.4	23.5–50.8	15	8–26	82	68–89	1.3	0–2	1.0	1–1	1.3	0–3
Acetyl triethyl citrate																	
0.5	0	3	3	6.7	6.0–7.3	22.0	16.0–26.2	23	12–42	75	57–85	1.0	0–3	0.6	0–1	—	—
	1	3	3	8.2	7.5–9.3	20.8	16.9–26.8	30	15–45	69	54–83	1.5	1–2	—	—	—	—
	2	3	3	10.9	9.1–13.6	30.6	25.0–33.8	14	11–18	82	80–86	1.6	1–2	2.0	1–4	—	—
1.0	0	3	3	7.9	6.5–9.0	26.8	19.1–31.3	25	10–40	70	60–80	0.3	0–1	—	—	—	—
	1	4	4	9.1	7.8–10.5	24.4	20.0–30.3	12	7–17	85	76–89	3.5	0–7	—	—	0.3	0–1
	2	2	2	10.1	9.4–11.1	36.5	22.0–48.5	19	11–27	75	67–87	3.5	0–7	1.3	0–3	1.5	0–4
2.0	0	3	3	8.2	7.5–8.6	18.6	12.5–28.9	16	11–26	82	74–88	0.3	0–1	—	—	—	—
	1	3	3	10.0	9.3–10.6	24.0	17.6–31.0	7	2–16	90	78–97	2.6	0–6	0.3	0–1	—	—
	2	2	2	10.3	10.1–10.5	33.2	24.4–42.0	6	1–11	91	84–97	2.5	2–3	—	—	1.0	0–2

As may be seen, there was no material effect on the red cell count, white cell count, or differential.

Gross and histological effects. Of the thirty-six rats, fourteen were sacrificed at the end of the 8-week feeding period. There were no gross abnormalities in the thoracic and abdominal organs. Sixty-three histological sections including the heart, lungs, gastrointestinal tract, liver, pancreas, spleen, and kidneys were indistinguishable from those of the controls.

Tributyl Citrate and Acetyl Tributyl Citrate (Cats)

Effect of one dose. For this purpose, twelve cats were used, including two as simultaneous controls. After food had been withheld for 24 hours, each compound was given to a group of four cats by stomach tube in doses from 30 to 50 cc/kg. This corresponds to about 2–3.4 liters for a man of average size. The animals showed signs of slight nausea, and within a few hours they developed a diarrhea with oozing of the oily material from the rectum. The diarrhea subsided in less than 24 hours in all but one (50 cc tributyl citrate per kilogram) in which some diarrhea was still present on the following day. The animals were observed for periods up to 2 months. There were no signs of systemic toxicity as judged by the general appearance and behavior of the animals.

In each of two cats, given a dose of 50 cc/kg, the following additional tests were made for 2 months at intervals of 2 weeks: blood counts, blood chemistry, and urine. The results of these tests, which include two untreated cats maintained under the same conditions, are summarized in Table 5. As may be seen, there were no effects on the blood count, hemoglobin, sugar, nonprotein nitrogen, or creatinine. Sixteen specimens of urine examined during this period showed no abnormalities in specific gravity, albumin, sugar, pH, or microscopic formed elements.

Effect of daily doses for 8 weeks. Each of two cats received either TBC or ATBC in doses of 5 cc/kg by stomach tube daily for a period of 2 months. Observations and tests were made at weekly intervals, for a total of 207 tests. The results, which include two cats that served as simultaneous controls, are summarized in Table 6. No change was manifest in appearance and behavior of the animals, and no effect was observed on the urine, blood chemistry, or blood count. The treated animals showed a decline of approximately 30% in body weight which may be due to the loose bowel movements which most of them developed.

TABLE 5

EFFECT IN CATS ON BLOOD COUNT, BLOOD SUGAR, AND BLOOD NITROGEN OVER A PERIOD OF 8 WEEKS OF ONE ORAL DOSE OF THE FOUR CITRATE ESTERS

	RBC (in millions)		WBC (in thousands)		Hemoglobin (g)		Blood sugar (mg %)		Blood NPN (mg %)		Blood creatinine (mg %)	
Citrate dose	First	Last	First	Last	First	Last	First	Last	First	Last	First	Last
Controls	9.1	10.6	30	20.5	10.4	13.3	64	80.5	48	42	2.9	2.3
Tributyl (50 cc/kg)	7.1	7.4	25	66	8.8	10.3	95	93	53	38	2.3	2.2
Acetyl tributyl (50 cc/kg)	7.0	6.3	40	20	8.8	10.3	80	91	43	39	2.3	2.2
Triethyl (5 cc/kg)	8.1	7.9	17	19	10.3	10.0	91	85	44	40	2.3	2.2
Acetyl triethyl (5 cc/kg)	8.3	9.1	21	22	12.1	12.5	91	85	48	43	2.3	2.1

TABLE 6

EFFECT IN CATS OF DAILY DOSES FOR 8 WEEKS OF TRIETHYL AND ACETYL TRIETHYL CITRATES

Citrate	Controls	Tributyl	Acetyl tributyl	Triethyl	Acetyl triethyl
Dose	—	5.0 cc/kg	5.0 cc/kg	0.3 cc/kg	0.5 cc/kg
Number of values	12	9	9	12	11
Weight (kg)					
First	3.2	3.1	3.1	3.1	3.1
Last	3.2	2.5	2.1	3.1	2.7
Average	3.2	2.7	2.4	3.0	2.8
RBC (in millions)					
First	9.0	9.7	8.6	8.3	8.5
Last	8.2	7.9	6.5	10.2	8.5
Average	9.8	8.3	7.7	9.1	8.3
WBC (in thousands)					
First	24.0	18.4	17.2	25.9	26.6
Last	14.7	21.4	14.4	24.9	21.5
Average	20.6	19.9	15.5	23.8	25.6
Hemoglobin (g)					
First	11.3	12.8	10.5	11.2	10.8
Last	12.3	11.5	8.3	12.3	10.5
Average	14.4	11.2	9.6	12.2	11.5
Blood sugar (mg %)					
First	150.5	108.5	129.5	117.0	116.0
Last	116.5	96.8	151.5	109.5	137.5
Average	113.0	132.1	142.7	128.5	134.0
Blood NPN					
First	43.5	36.5	42.8	48.5	40.0
Last	35.8	43.9	40.0	36.8	43.8
Average	43.8	38.9	39.0	43.1	42.5
Blood creatinine (mg %)					
First	2.4	2.3	2.2	2.7	2.3
Last	2.1	2.1	2.0	2.2	2.1
Average	2.2	2.2	2.1	2.5	2.3

Triethyl Citrate and Acetyl Triethyl Citrate (Cats)

Acute toxicity. Observations on the signs, extent, and course of poisoning were made in fifty-two cats following doses of 1–9.5 cc/kg, given by stomach tube 24 hours after the last feeding. The signs con-

sisted of nausea, vomiting, ataxia, weakness, muscle twitching, tremors, reflex hyperexcitability, lowering of body temperature, gasping and shallow respiration, prostration, convulsions, respiratory failure, and death. Some of the details are summarized in Table 3. The absorption of both compounds was fairly rapid, signs usually appearing within a few minutes. The course of the poisoning, as judged by the manifest signs in the intact animals, was also fairly rapid, progressing to advanced stages within an hour or so and terminating in death in about 2 hours to 2 days, or apparent recovery in about 4 hours to 3 days. As will be seen later, the disappearance of manifest signs of poisoning can be deceptive, since the poisoning persists for a much longer time. TEC appears to be approximately twice as potent as ATEC in the cat, the approximate LD_{50} being about 3.5 cc/kg and 7.0 cc/kg, respectively.

Postmortem examination of these animals showed no acute gross abnormalities in the thoracic or abdominal organs which could account for the toxic effects.

Additional tests were made in two cats: weight, blood counts, hemoglobin, blood nitrogen, and urine, at intervals of 2 weeks for 2 months. One received TEC by stomach tube and the other ATEC, in doses of 5 cc/kg. These produced severe poisoning, but both cats recovered and the tests were continued. The results are summarized in Table 5 and include two animals which served as simultaneous controls. As may be seen, these doses produced no conspicuous delayed effects over a period of 2 months.

Effect of daily doses for 8 weeks. The effect of small daily doses of the two compounds was studied in six cats for a period of 8 weeks. The tests were made at intervals of 7–10 days during the 2-month period. The doses were 0.25 cc/kg in the case of TEC and 0.5 cc in the case of ATEC, representing for each compound approximately 7% of the LD_{50}, given by stomach tube. The results are summarized in Table 6. They indicate no clear differences between the controls and treated animals with respect to weight, blood count, hemoglobin, blood sugar, and blood nitrogen.

Thirty-eight electrocardiograms of the six cats, taken at various intervals during the course, showed considerable fluctuations in the T-waves, but no changes in the treated animals that were not observed in the control animals of this series.

Mild symptoms of poisoning appeared after the fourth or fifth doses:

weakness, ataxia, and depression progressed to a fairly advanced degree, but all animals survived the entire 8-week period of treatment. They recovered and appeared normal within 1–4 days after the doses were discontinued.

The six cats were sacrificed at the end of the experiment. Postmortem examination of the thoracic and abdominal organs showed no gross abnormalities.

Cumulative effects. The experiments described in the foregoing section showed evidence of cumulation with daily doses as low as approximately 7% of the LD_{50} of TEC and ATEC. This phenomenon was studied further with larger doses in each of twelve cats. One group of three cats received approximately 50% of an LD_{50} by stomach tube daily, and another group, approximately 25% of an LD_{50} every 4 hours, in the case of both compounds. The usual signs of poisoning developed and progressed with the repetition of the doses. The results are summarized in Table 7. The behavior of the two compounds was similar. All the

TABLE 7

CUMULATION OF TRIETHYL AND ACETYL TRIETHYL CITRATES IN CATS

		Individual dose			Average total dose range		
Citrate	Number of cats	Frequency	cc/kg	Per cent LD_{50} (approx.)	Number	cc/kg	No. of LD_{50} which proved fatal
Triethyl	3	Daily	2	50	8(2–17)	16(4–34)	4.6
Triethyl	3	Every 4 hours	1	25	9(8–10)	9(8–10)	2.6
Acetyl triethyl	3	Daily	4	50	8(6–9)	32(24–36)	4.3
Acetyl triethyl	3	Every 4 hours	2	25	7(5–8)	14(10–16)	1.9

animals died. Those that received the 25% dose at intervals of 4 hours required an average of about two times an LD_{50}, and those with the 50% dose at daily intervals required an average of about four times the LD_{50}. It is clear that it takes longer than 4 hours to recover from about one-fourth of the LD_{50} and longer than 24 hours to recover from about one-half of the LD_{50}.

Effect on blood pressure and heart. Experiments were performed in five cats, two with the triethyl (6 and 9 cc/kg) and three with the acetyl triethyl compound (6, 9, and 12 cc/kg). These are in the range of doses

which prove fatal. After the dose was administered by stomach tube, the animal was placed on an animal board and prepared for recording on a smoked drum the blood pressure from the carotid artery. The effect on the heart was recorded frequently by electrocardiograms. In the five experiments, 76 electrocardiograms were taken. The results showed that both drugs cause progressive lowering of the blood pressure to shock levels. The pressure frequently remained at levels below 100 mm Hg during the last hour or two.

The electrocardiograms showed progressive slowing of the heart from the rapid rates of about 200 or over in the control, to rates in the range of about 150 a minute. In one animal with each of the compounds, there was progressive lowering of the T-wave, and in one with acetyl triethyl citrate, there was also progressive depression of the R-T segment. During the period when the respiration was active there were no changes in rhythm. The respiration ceased before the heart, and the heart could be seen beating when the chest was opened. After the respiration ceased, the heart became slower, A-V conduction became prolonged, with elevation of the R-T segments. These changes are in all probability the result of asphyxia, and as the asphyxia continued the rhythm became irregular and ectopic beats appeared.

There were 158 additional electrocardiograms taken in various stages of acute poisoning in the experiments previously described (56 in fifteen cats with triethyl and 102 in twenty-seven cats with acetyl triethyl citrate). The changes were similar to those described above. In animals that survived, tracings showed no persistence of effects in the electrocardiogram after 1–3 days.

Effect on neuromuscular conduction. When respiration ceased in the above five cats, and in twelve cats of another series, the chests were opened immediately and the phrenic nerves stimulated by an electric shock from an inductorium. A sustained contraction of the diaphragm resulted, similar to that in normal animals which succumb to ether or hemorrhage. In each of the above five cats, the sciatic nerve was exposed and also stimulated with a shock from an inductorium at the instant the respiration ceased. There was here also a vigorous and sustained contraction of the muscles, similar to that in untreated controls. These responses to stimulation of the phrenic and sciatic nerves indicate the absence of any material interference with neuromuscular transmission during advanced poisoning by triethyl and acetyl triethyl citrates.

Comparison of cat and rat. It may be noted that the symptoms of acute poisoning, the speed of absorption, and duration of action of TEC and ATEC were substantially similar in the cat and rat. The tributyl and acetyl tributyl citrates are nontoxic in both species in doses corresponding to nearly 3.5 l for a man of about 70 kg. By comparison, the triethyl and acetyl triethyl citrates are quite potent. Vomiting occurred in some of the animals receiving these compounds, usually in 30 minutes to 3 hours, occasionally as early as 10 minutes. Those that vomited and survived were excluded from the estimation of the LD_{50}. The two compounds are about equally potent in the rat, the LD_{50} being about 7 cc/kg and similar for ATEC in the cat. The latter, however, is about one-half as toxic as TEC in the cat, since the LD_{50} is approximately 3.5 cc/kg for TEC. The larger dose corresponds to about 500 cc, and the smaller to about 250 cc, for a man of about 70 kg.

Attention is called to the facts that all the materials were tested by the oral route, that the nontoxic tributyl compounds are insoluble, and that the most toxic triethyl citrate is the most soluble (Table 1). Their differences in systemic potency may represent difference in absorption; however, this explanation is in need of proof.

DISCUSSION

The foregoing experiments provide only a suggestive account of the mechanism of the systemic action of triethyl and acetyl triethyl citrates. There is no evidence on the tributyl compounds as they produced no conspicuous systemic effects even after massive oral doses.

An action on the central nervous system may explain all the major signs of poisoning and the fatal effect: vomiting, unrest, ataxia, hyperexcitability, convulsions, vasomotor depression with circulatory failure, respiratory disturbances, depression of respiration, and death with primary cessation of respiration. The indications are against significant synaptic blockade in the diaphragm and skeletal muscles. Contributions to the observed effects from a direct peripheral action on the heart and blood vessels cannot be excluded.

It remains to be established whether these citrate esters exert a specific action as such. Their effects and the course of poisoning resemble closely those common to the citrate ion when introduced into the circulation, due to calcium privation from the formation of the soluble and poorly dissociable complex of citrate with calcium (Adams, 1944).

SUMMARY

1. Some pharmacologic and toxic properties of four citrate esters, tributyl (TBC), acetyl tributyl (ATBC), triethyl (TEC), and acetyl triethyl (ATEC) citrates, administered by the gastrointestinal route have been studied in 250 rats and 95 cats.

2. The two tributyl citrates are nontoxic by the oral route in the rat and cat. They produced no local gastrointestinal irritation and no systemic effects in large single doses as high as those corresponding to more than 3 l for a man of average weight. They proved inactive also when mixed with the diet and fed for 2 months in daily amounts as high as those corresponding to 1.4 l daily for a man of average weight. This inactivity may be due to their insolubility, which may interfere with absorption.

3. By comparison, the two triethyl citrates are quite potent and in most respects similar in the rat and cat.

4. The oral LD_{50} is approximately 7.0 cc/kg for TEC and ATEC (rat) and ATEC (cat), but only approximately 3.5 cc/kg for TEC in the cat.

5. The absorption of TEC and ATEC is rapid in both species, effects appearing in a few minutes, advancing rapidly to fatality in a few hours or a day or two. When taken in the diet, large doses may be consumed daily for several weeks without toxic effects.

6. Their duration of action is fairly brief, signs of poisoning subsiding in a few hours to a few days. Some of the action of these compounds remains for some time beyond the manifest effects, as shown by cumulation from repeated doses.

7. Feeding these four citrate esters mixed with the diet in large daily doses for 6–8 weeks results in no deleterious effect on growth and nutrition and no effects on the blood count, hemoglobin, blood sugar, blood nitrogen, gross or histological appearance of the thoracic and abdominal organs.

8. The toxic effects and the course of TEC and ATEC poisoning, studied here in greater detail in the cat, resemble those of the citrate ion introduced into the circulation, resulting in deionization of calcium and the effects of hypocalcemia.

References

Adams, W. E., Thornton, T. F., and Allen, J. G. (1944). The danger and prevention of citrate intoxication in massive transfusions of whole blood. *Ann. Surg.* **120**, 656-669.

Lehman, A. J., Patterson, W. I., Davidow, B., Hagan, E. C., Woodard, G., Lang, E. P., Frawley, J. P., Fitzhugh, O. G., Bourke, A. R., Draize, J. H., Nelson, A. A., and Vos, B. J. (1955). Procedures for the appraisal of the toxicity of chemicals in foods, drugs and cosmetics. *Food Drug Cosmetic Law J.* **10**, 679-748.

REPORT

THE CITRATES

GRAS Review Branch (BF - 335)
Bureau of Foods
Food and Drug Administration
200 C Street, SW
Washington, D. C. 20204

Submitted to Att: Mr. Alan Spiher
Project Manager

Date April 17, 1973

Laboratory No. 1216

Submitted by:

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THE CITRATES

Compound	Accession No.	CAS Reg. No.
SODIUM CITRATE	571	000068042
CALCIUM CITRATE	119	000813945
POTASSIUM CITRATE	495	006100056
TRIETHYL CITRATE	665	000077930
STEARYL CITRATE	626	001337344
TRI-ISOPROPYL CITRATE	339	977050977
MONOISOPROPYL CITRATE	427	977051367

TABLE OF CONTENTS

SODIUM CITRATE

Summary - Toxicological Information

The acute toxicity of sodium citrate is as follows: mouse (oral) 7.12g/kg (292); rat (intraperitoneally) 1.85g/kg (148); rabbit (intravenously) 517.44 mg (148); dog (intravenously) 0.20g/kg (258); and human (intravenously) theoretical - 6.5g/kg (258).

Acute toxic signs seen after various routes of administration are: increased activity, hyperpnea, vasodilation, salivation, clonic-tonic convulsions, cyanosis (148), decreased blood pressure, heart rate (347, 377), blood calcium (66, 74 and 377), decreased intestinal peristaltic activity (347), decreased cardiac output and contractile force (43), and death (148). The toxicity is dependent on the speed of the injection and blood concentration of the sodium citrate (258).

Repeated subcutaneous injections of a 4% sodium citrate solution into dogs results in an increased urinary calcium excretion with a concomitant decrease in blood calcium levels (136).

There were no long term studies found in the literature on sodium citrate.

Special studies demonstrate that sodium citrate prevents inactivation of penicillin in the stomach of humans by gastric HCl (309); increases the incorporation of glycine-1-^{14}C into rabbit liver and muscle proteins (204); prevents renal lithiasis and nephritis caused by ethylene glycol in rats (433); causes the

remission of lymphangiomas (in children) within one to two months, if sclerosing injections (1cc of a 60% solution) are used (56); and causes tumor cell death (at 30mg/kg) in rats with Walker Carcinosarcoma and Pliss lymphosarcoma, and will reduce growth and transplantability as well (317).

Sodium citrate is an effective treatment in heavy metal toxicosis, by preventing death from lethal doses of uranium nitrate (100, 102), lead (225, 263), radiothorium and strontium (365) in rats and in humans by increasing the excretion rates of these metals, and stimulates kidney repair of heavy metal induced damage.

This compound has varied effects on coli bacteria, for it will inhibit their phagocytosis of leucocytes in vitro, if the concentration of the sodium citrate is 220 mg % (2). E. coli will show growth inhibition if the sodium citrate (0.1 M) is added to a growth stimulating medium (182). While cultures of E coli supposedly killed by heat, chlorine, zephiran, and H_2O_2 were found to have viable cells present after they were inoculated with sodium citrate (163).

Infectivity of tuberculosis and other microorganisms is enhanced if sodium citrate (1%) is added to the diet (104 , 105). The resistance to infection is decreased due to a change in metabolism induced by an altered diet.

Digitalis induced cardiac arrhythmias in dogs and humans can be eliminated by sodium citrate given intravenously (0.5 - 1.4g in dogs, and 2g in humans) (396).

A total of 15,098,337 pounds of sodium citrate was used in the United States in 1970 as reported in an NAS/FEMA study.

SODIUM CITRATE

Chemical Information

I. Nomenclature (Merck Index, p. 957) (254a)

A. Common Name

(none)

B. Chemical Name

Sodium Citrate

Trisodium Citrate

C. Trade Name

Citrosodine

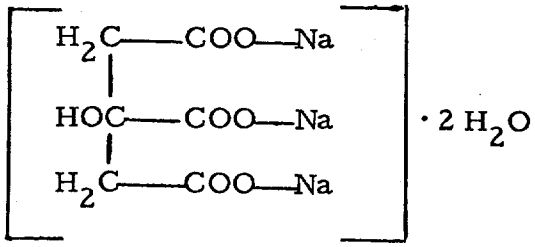
Citnatin

D. Chemical Abstracts Unique Registry Number
000068042

II. Empirical Formula (Food Chemicals Codex, p. 614) (120a)

$C_6H_5Na_3O_7 \cdot 2H_2O$

III. Structural Formula



IV. Molecular Weight (120a)

294.10

V. Specifications (254a)

A. Chemical

Anhydrous salt 87.75%

H_2O 12.25%

Anhydrous citric acid 65.31%

Anhydrous: C 27.92%

H 1.95%

Na 26.73%

O 43.40%

B. Food Grade (120a)

Assay. Not less than 99% of $C_6H_5Na_3O_7$, calculated on the anhydrous basis.

Water. Anhydrous citrate, not more than 1%; sodium citrate dihydrate, between 10 and 13%.

Limits of Impurities

Alkalinity. Passes Test.

Arsenic (as As). Not more than 3 parts per million (0.0003%).

Heavy metals (as Pb). Not more than 10 parts per million (0.001%).

C. Official Compendia

Food Chemical Codex - First Edition. p. 614. (120a)

VI. Descriptions (254a)

A. General Characteristics

White, odorless crystals, granules or powder; cool, saline taste.

B. Physical Properties

Sodium citrate is anhydrous or contains two molecules of water of crystallization.

Stable in air.

Becomes anhydrous at 150°.

Soluble in 1.3 parts water, 0.6 part boiling water.

Insoluble in alcohol.

The aqueous solution is slightly alkaline to litmus. pH about 8.

C. Stability in containers (120a)

Store in tight containers

VII. Analytical Methods

Determination by colormetric titration (189, 466)

Dichromate oxidation followed by electrometric back-ditration of excess dichromate. (220).

Ion-exchange separation of citrate/citric acid mixture followed by sodium hydroxide/phenolphthalein ditration. (42).

Ion-exchange isolation of sodium citrate from other sodium and potassium salt mixtures followed by its colormetric determination (288).

VIII. Occurrence and Levels found in:

A. Plant

Ubiquitous

B. Animal

Ubiquitous

C. Synthetics

No accessible data in available literature

D. Natural inorganic source

Ubiquitous

SODIUM CITRATE

Biological Data

I. Acute Toxicity

Animal	Route	Material	LD_{50} mg/kg **	Ref.
Mouse	Oral	Sodium citrate	7.12g/kg	(292)
Mouse	I.P.	Sodium citrate	2.67 - 3.90g/kg	(415)
Mouse	I.P.	Sodium citrate	2.23g/kg	(148)
Mouse	I.P.	Di-sodium citrate	2.38g/kg	(148)
Mouse	I.P.	Tri-sodium citrate	1.87g/kg	(148)
Mouse	I.P.	Citric Acid	960	(148)
Mouse	I.V.	Sodium citrate	69.62	(148)
Mouse	I.V.	Di-sodium citrate	95.1	(148)
Mouse	I.V.	Tri-sodium citrate	224.40	(148)
Mouse	I.V.	Citric Acid	42.22	(148)
Mouse	I.V.	Sodium citrate (MTD)*	0.25g/kg	(375)
Rat	I.V.	Sodium citrate (MTD)*	0.25g/kg	(375)
Rat	I.P.	Sodium citrate	1.85g/kg	(148)
Rat	I.P.	Di-sodium citrate	2.31g/kg	(148)
Rat	I.P.	Tri-sodium citrate	2.04g/kg	(148)
Rat	I.P.	Citric Acid	883.20	(148)
Rabbit	I.V.	Sodium citrate	517.44	(148)
Rabbit	I.V.	Di-sodium citrate	563.09	(148)

* Maximum Tolerated Dose

** Except as noted

Animal	Route	Material	LD_{50} mg/kg **	Ref.
Rabbit	I.V.	Tri-sodium citrate	591.60	(148)
Rabbit	I.V.	Citric Acid	330.24	(148)
Rabbit	I.V.	Sodium citrate (MTD)*	0.13g/kg	(258)
Dog	I.V.	Sodium citrate	0.20g/kg	(258)
Human	I.V.	Sodium citrate	6.5g/kg (theoretical)	(258)

* Maximum Tolerated Dose
** Except as noted

II. Short Term Studies

Subcutaneous injections of a 4% sodium citrate solution into dogs causes an increase in urinary Ca^{+2} excretion with a concomitant decrease in blood Ca^{+2} levels. Repeated subcutaneous injections into puppies and rats leads to changes similar to those observed after large doses of parathyroid hormone (136).

Rats in a 21 day feeding study were protected from renal lithiasis and tubular nephritis which would normally be induced from the addition of 1% ethylene glycol to their drinking water, if 7.5% sodium citrate were incorporated into their diet (433).

III. Long Term Studies

(none)

IV. Special Studies

Trisodium citrate combined with penicillin - calcium prevents the inactivation of the drug by HCl in the stomach of humans. (309).

Sodium citrate given orally to rats will increase the blood concentration of tetracycline if both are ingested at the same time (426).

Sodium citrate concentrations of 4 to 8 M stimulates the incorporation of glycine-1-^{14}C into rabbit liver, muscle proteins, and lipids (204).

Gruber (148) says that the injection of sodium citrate into mice, rats and rabbits, leads to increased activity, hyperpnea, peripheral vasodilation, salivation, muscle twitching, clonic-tonic convulsions, cyanosis, Cheyne-Stokes respiration and death; citrate intoxication doesn't occur. Mikulicz-Radecki says the toxicity is dependent on blood concentration and speed of the injection. The lethal doses are 50% higher than the MTD (258). Payne (308) and others (57 and 59) also agree.

Sodium citrate when injected into the cat paralyzes the cardiac vagus nerve by blocking nerve impulses at the synapses between pre-and post-ganglionic fibers. This effect lasts for 20-30 minutes. Reduced blood pressure, heart rate and respiration are also observed. Reduced blood Ca^{+2} seems to be the primary factor and concomitant treatment with calcium chloride will prevent this reaction. The blood Ca^{+2} binds to the citrate moiety (377).

Cicardo (66) also found a decrease of blood calcium when he injected sodium citrate either intracisternally or intraventricularly into anesthetized dogs which precipitated a marked hypotension and respiratory stimulation. Respiratory paralysis and death occurred with repeated injections. The hypertension is caused by excitation of the vasomotor centers and is eliminated after cervical spinal cord section (69).

Classen, et. al., (74) observed a dose and time dependent decrease of blood calcium level with infusions (10-50mg/min) of sodium citrate, in cats and shock symptoms appeared with death due to respiratory arrest.

Infusions of isotonic sodium citrate solution into the carotid sinus, (animal not stated) which was excluded from the circulation, caused respiratory arrest and decreased blood pressure (347).

Popescu found that sodium citrate given intravenously to the dog produced increased respiratory reflexes with a decrease of intestinal tone and peristaltic activity, and an increase in the splenic contractive reflex (315).

Bunker (43) studied the hemodynamic effects of infusing sodium citrate in six humans and in 9 dogs. He used multiple rapid infusions of citrated blood and observed a marked circulatory depression, decreased pulse pressure, decrease in cardiac output, decreased left ventricular work,

and evidence of hypocalcemia in man. Additionally, the dog evidenced a marked decrease of ventricular contractile force and marked elevations of ventricular and diastolic pressure.

Castro treated pediatric lymphangiomas with sclerosing injections of sodium citrate (a 60% solution). He have single injections of 1 cc once per week or 2 weeks directly into the tumor (56). The tumors disappeared within one to two months.

Sodium citrate at a concentration of greater than 30mg/kg causes tumor cell death in rats with Walker carcinosarcoma and the Pliss lympho-sarcoma (as suspensions). Doses of sodium citrate at 6, 10, 30, and 100 mg/g inhibited the transplantability and growth as well. The effects were proportional to the sodium citrate concentration (317).

Rosenblum observed that sodium citrate at 5mg/ml (in vitro) increased the viscosity of blood with a concomitant red cell shrinkage. This will not occur if 9mg/ml sodium citrate and ACD solution are used (342).

Sodium citrate at 0.001 M stimulates the in vitro secretion of insulin in rabbit pancreas slices (337).

Sodium citrate appears highly effective in treating heavy metal toxicity. Donnelly and Holman found that the repair and regeneration of kidney tubular epithelium in dogs injured by UNO_2 were facilitated and led to the

recovery of 92% of the animals so treated with sodium citrate (100). When 20 dogs were given 5.0 mg/kg of uranium nitrate, 19 of them survived when sodium citrate (0.23 g/kg/day for 5 to 10 days) was given intravenously. The sodium citrate was effective when administered as late as 67 hours after the uranium nitrate. The sodium citrate keeps carbohydrate metabolism functioning while recovery takes place (102).

The urinary and fecal excretion of lead in humans after long term exposure to lead, before, and during the administration of 15 g of sodium citrate per day. Statistically significant increases in urinary and fecal excretion of lead occurred with a concomitant decrease in blood lead in 8 out of 9 of the patients (225).

At one half and 72 hours following radio-thorium and strontium treatment, rats were given intraperitoneal injections of sodium citrate. Urinary excretion of the two isotopes was increased 3 times for the former and 2 times for the latter within 24 hours. Fecal excretion was unaffected. Liver, mesenteric lymph node, pancreas and spleen concentrations were all markedly reduced in the sodium citrate treated animals when compared with the controls (365).

A combination of sodium citrate and calcium gluconate used in rats, was found to be very effective in eliminating ^{134}Ce. In a 9 day study control rats eliminated 40% while the treated rats excreted (feces and urine) 80% of the isotope. Necrosis would occur at the injection site if sodium citrate alone was administered intramuscularly (351).

Sodium citrate is an effective antidote to a lethal dose of lead in guinea pigs (263). This material alters white cell physiology; for sodium citrate at a concentration of 110 mg % will markedly inhibit leucocytic phagocytosis of coli bacteria. While 220 mg % causes 100% inhibition, a dose of 2.5 mg % produces no effects (2).

Digitalis induced cardiac arrhythmias in dogs could be converted if intravenous injections of sodium citrate (0.6 - 1.4 g) were given. Similar results were obtained with humans (1.2 - 2 g) (396).

Sodium citrate has a wide variety of effects on microorganisms. The addition of sodium citrate (0.1%) to ground beef increases the lethality of gamma radiation to Clostridium botulinum spores (6), and enhances the effectiveness of heat (131° F for 35 min.) in killing Salmonella anatum (survival was 9 cells or less per ml of test material) (10).

Sodium citrate (0.1 M) inhibits the growth of E. coli in a growth stimulating medium. This occurred with S. typhosa (0.02 M) and with Streptococcus pyogenes var. aureus, and with Mycobacterium avicum (182).

Suspensions of E. coli strain B/r which were supposedly killed by heat, chlorine, zephiran and H_2O_2 were found to have viable cells present after they were inoculated with sodium citrate. This was not the case

if the cell suspension was inoculated in buffer or in nutrient broth. The reactivation may be due to a resynthesis of enzymes and the restarting of cyclic processes (163).

Sodium citrate at a concentration of 0.5 M prevents DNA degradation following x-radiation to E. coli. It also decreases the lethal effects and increases percentage of survival as well (214).

Sodium citrate enhances the infectivity of T-B in the mouse. The metabolism is affected through an altered diet causing an altered resistance to infection (104). It was also noted that the morbidity and mortality of mice infected with Micrococcus pyogenes var. aureus, Klebsiella pneumoniae, and Salmonella enteridis were increased if they were pretreated with a 1% sodium citrate solution in their diets. This decrease in resistance manifested itself by the presence of bacteremia, and greater numbers of bacteria within the spleen and liver. The mice became increasingly susceptible to the endotoxins of variuos gram-negative bacteria and tubercle bacilli (105).

SODIUM CITRATE

Biochemical Aspects

III. Metabolism and Excretion

Krebs Cycle

CALCIUM CITRATE

Summary - Toxicological Information

Acute oral toxicity data is not available within the current literature.

Adult rabbits were fed a mixture of rice and wheat bran for several days. Increased bone deposition was seen if the diet was supplemented with calcium citrate (494).

A glycerophosphate mixture of calcium citrate (3.6mg/kg) hastened the appearance of pathologic knee joint changes in rats fed a rachitogenic diet. If the calcium citrate/glycerophosphate mixture was omitted from the diet, these rachitic changes would normally occur in 20 days (489).

Wether lambs fed a calculogenic diet showed a decreased incidence of bladder calculi when their diets were supplemented with calcium citrate. These animals showed increased magnesium and phosphorus excretion (fecally) as compared with control animals who had bladder calculi (497).

Special studies with this substance reveal it to act synergistically with strychnine, codeine and caffeine enhancing the convulsant activities (511).

Ionic calcium absorption can be greatly enhanced in people with decreased gastric acidity if 25 mg/kg/day is given (496).

A total of 4,305 pounds of calcium citrate was used in the United States in 1970 as reported in an NAS/FEMA study.

CALCIUM CITRATE

Chemical Information

I. Nomenclature (Food Chemical Codex, p. 110) (120a)

A. Common Name

(none)

B. Chemical Name

Calcium Citrate

C. Trade Name

(none)

D. Chemical Abstracts Service Unique Registry Number

00081 3945

II. Empirical Formula (Merck Index, p. 191) (254a)

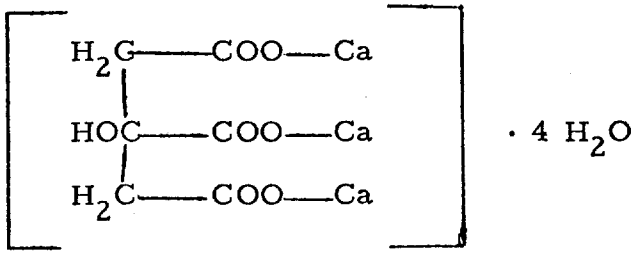
Anhydrous

$Ca_3(C_6H_5O_7)_2$

Tetrahydrate

$Ca_3(C_6H_5O_7)_2 \cdot 4H_2O$

III Structural Formula



IV. Molecular Weight

Anhydrous (254a)

498.44

Tetrahydrate (120a)

570.51

V. Specifications

A. Chemical (254a)

C 28.91%

H 2.02%

Ca 24.12%

O 44.94%

B. Food Grade (120a)

Assay. Not less than 97.5% of $Ca_3(C_6H_5O_7)_2$ after drying.

Loss on drying. Between 10 and 13.3%.

Limits of Impurities

Arsenic (as As). Not more than 3 parts per million (0.0003%).

Heavy metals (as Pb). Not more than 20 parts per million (0.002%).

Lead. Not more than 10 parts per million (0.001%).

C. Official Compendia

Food Chemical Codex - First Edition. p. 110. (120a)

VI. Description

A. General Characteristics (120a)

A fine, white, odorless powder.

B. Physical Properties (254a)

Loses most of its water at 100° and all at 120°.

Soluble in 1050 parts cold water; somewhat more soluble in hot water.

Insoluble in alcohol.

C. Stability in containers (120a)

Store in well-closed containers.

VII. Analytical Methods (120a)

Identification by gravimetry

VIII. Occurrences and Levels found in:

A. Plants

No accessible data in available literature

B. Animals

1% in bone (475a)

C. Synthetics

No accessible data in available literature

D. Natural Inorganic Sources

No accessible data in available literature

CALCIUM CITRATE

Biological Data

I. Acute Toxicity

(none)

II. Short Term Studies

Adult rabbits fed a rice and wheat bran mixture for several days with added calcium citrate showed increased bone deposition (494).

III. Long Term Studies

Rats fed a rachitogenic diet developed rachitic changes of the knee joints after 20 days. However, if calcium citrate (3.6 mg/day) was added to this diet, pathological changes occurred instead on the 8th day. This could be prevented if irradiated yeast were also incorporated into the diet (489).

The incidence of bladder calculi (0-4%) was greatly reduced in wether lambs fed a calculogenic diet, supplemented with calcium citrate. In contrast, 80% of the lambs fed a similar diet, supplemented with vitamin D_3 showed bladder calculi (497).

IV. Special Studies

Calcium citrate injected intravenously into the ear vein of rabbits acts synergistically to decrease the amounts of strychnine, caffeine and codeine needed to induce convulsions. Conversely, it increases the amounts of phenol, pyramidine and picrotoxin needed to induce the same effect (511).

Pure citric acid-calcium complex compounds have been found to decrease blood calcium, and weaken bone structure (514).

Ionic calcium absorption can be enhanced greatly in people with decreased gastric acidity if 25 mg/kg/day of calcium citrate is given (496).

CALCIUM CITRATE

Biochemical Aspects

III. Metabolism and Excretion

Krebs Cycle

POTASSIUM CITRATE

Summary - Toxicological Information

The acute intravenous toxicity for potassium citrate is 167 mg/kg in dogs (533). Values for other species are lacking, as are results of short and long term studies in the current literature on this substance.

This substance injected intravenously as a 2.5% solution, can cause cardiac arrest (534, 548, 556, 568) and myocardial necrosis in dogs and humans. One study (567) revealed, however, an absence of such myocardial damage.

In contrast, potassium citrate in a 30% solution is also used in resuscitating dog and guinea pig hearts (556, 568) after cardiac arrest, and is effective in reducing digitalin toxicity in dogs (517) and in guinea pigs (530).

Potassium citrate will also prevent ethylene glycol induced nephritis and renal lithiasis in rats if it is incorporated (at the 7.5% level) in the diet (565).

A total of 410,348 pounds of potassium citrate was used in the United States in 1970 as reported in an NAS/FEMA study.

POTASSIUM CITRATE

Chemical Information

I. Nomenclature (Food Chemicals Codex, p. 539) (120a)

A. Common Name

(none)

B. Chemical Name

Potassium Citrate

C. Trade Name

(none)

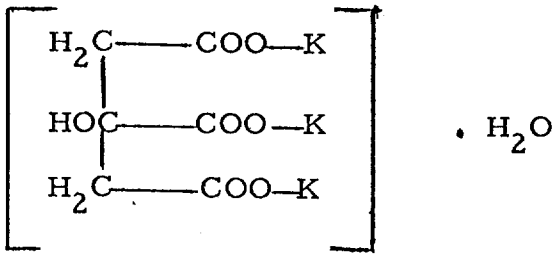
D. Chemical Abstracts Unique Registry Number

006100056

II. Empirical Formula (120a)

$C_6H_5K_3O_7 \cdot H_2O$

III. Structural Formula



IV. Molecular Weight (120a)

324.42

V. Specifications

A. Chemical (Merck Index, p. 853) (254a)

Anhydrous salt 94.47%

H_2O 5.53%

Anhydrous : C 23.52%

H 1.64%

O 36.55%

K 38.28%

B. Food Grade (120a)

Assay. Not less than 99% of $C_6H_5K_3O_7$ after drying.

Loss on drying. Between 3% and 6%.

Limits of Impurities

Alkalinity. Passes Test.

Arsenic (as As). Not more than 3 parts per million (0.0003%).

Heavy metals (as Pb). Not more than 10 parts per million (0.001%).

C. Official Compendia

Food Chemical Codex - First Edition. p. 539. (120a)

VI. Descriptions

A. General Characteristics (120a)

Transparent crystals, or a white, granular

powder. It is odorless, has a cooling, saline taste, and is deliquescent when exposed to moist air.

B. Physical Properties (254a)

Loses its water at 180°.

One gram dissolves in 0.65 ml in water; very slowly in 2.5 ml glycerol; almost insoluble in alcohol.

The aqueous solution is alkaline to litmus.

pH about 8.5.

C. Stability in Containers (120a)

Store in tight containers.

VII. Analytical Methods

Identification by precipitation methods. (120a p. 769).

Potassium - Colormetric determination (120a p. 539).

VIII Occurrence and Levels found in:

A. Plants

No accessible data in available literature

B. Animals

No accessible data in available literature

C. Synthetics

No accessible data in available literature

D. Natural inorganic sources

No accessible data in available literature

POTASSIUM CITRATE

Biological Data

I. Acute Toxicity

Animal	Route	Material	LD_{50} mg/kg	Ref.
Dog	Intravenous	Potassium Citrate	167	(533)

II. Short Term Studies

(none)

III. Long Term Studies

(none)

IV. Special Studies

Potassium citrate and sodium citrate in combination (517) reduced digitalis induced toxicity in dogs treated with a toxic dose of digitalis (60% deaths-control - 10% deaths in the treated group).

Potassium citrate alone is effective in reducing digitalin toxicity in guinea pigs, since the amount of digitalin required to cause cardiac arrest increases from 1.60 to 2.58 mg/kg (530).

Potassium citrate has been used to induce cardiac standstill. The principle side effects arising from its use are myocardial injury (532) and a decrease in cholinesterase and succinoxidase activities in dogs (534). Myocardial necrosis has also been observed in humans, as demonstrated in one study (548) wherein it was seen in 15 out of 19 patients treated with a 2.5% potassium citrate solution. Contrasting results were observed in the dog, when a 2.5% potassium citrate solution used to induce cardiac arrest failed to cause myocardial necrosis after 20 minutes of asystole (567).

This material can, in higher concentrations than used above, be used to restart a heart in asystole. One group of researchers has found a 30% potassium citrate solution to be more effective than potassium chloride in resuscitating dogs after cardiac arrest (568). Mechanical activity was observed to reappear faster on reperfusion, following induced cardiac arrest, if potassium citrate, rather than Sealy's mixture, A. C. D. solution, acetylcholine, anoxia or hyperthermia or even potassium citrate itself were used to induce the arrest in isolated guinea pig hearts (556).

Male rats fed a normal diet with 1% ethylene glycol in the water for 21 days evidenced increased kidney weights ranging from 1.88 to 2.84 grams. If citric acid (5%) and potassium citrate dihydrate (7.5%) were incorporated into the diet, kidney wieghts did not increase in 21 days. Blood urea was also increased with the first diet and remained unchanged with the second diet. Renal lithiasis and tubular nephritis were also seen, but were absent when the citrate

was introduced. It appears that the potassium citrate prevents the ethylene glycol induced nephritis and the precipitation of calcium oxalate (565).

POTASSIUM CITRATE

Biochemical Aspects

III. Metabolism and Excretion

Krebs Cycle

TRIETHYL CITRATE

Summary - Toxicological Information

Data on acute, short and long term effects of triethyl citrate are lacking.

Results of pharmacologic studies demonstrate that triethyl citrate induces anesthetic effects and cardiovascular collapse when given intravenously to frogs, mice, rats, and rabbits (580).

Triethyl citrate added to mammalian cell cultures will inhibit their growth (583).

A total of 10,035 pounds of triethyl citrate was used in the United States in 1970 as reported in an NAS/FEMA study.

TRIETHYL CITRATE

Chemical Information

I. Nomenclature (Food Chemical Codex p. 702) (120a)

A. Common Names

Ethyl Citrate

B. Chemical Names

Triethyl Citrate

C. Trade Names

(none)

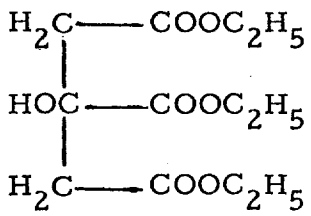
D. Chemical Abstracts Unique Registry Number

000077930

II. Empirical Formula (Food Chemical Codex p. 702) (120a)

$C_{12}H_{20}O_7$

III. Structural Formula



IV. Molecular Weight (120a)

276.29

V. Specifications

A. Chemical

(none)

B. Food Grade (120a)

Assay. Not less than 99% of $C_{12}H_{20}O_7$.

Limits of Impurities

Acidity (as citric acid). Not more than 0.02%.

Arsenic (as As). Not more than 3 parts per million (0.0003%).

Heavy metals (as Pb). Not more than 10 parts per million (0.001%).

Water. Not more than 0.25%.

C. Official Compendia

Food Chemicals Codex - First Edition p. 702. (120a)

VI. Description

A. General Characteristics

Triethyl citrate is an ester produced by the reaction of citric acid with ethyl alcohol, in which p-toluene sulfonic acid is utilized as a catalyst. * It is an odorless, practically colorless, oily liquid. It is slightly soluble in water, but is miscible with alcohol and with ether. (120a)

* Unidentified Company Specification Sheet

B. Physical Properties (254a)

Refractive index. Between 1.439 and 1.441

Specific gravity is approximately 1.137 at 20°.

Bitter, oily liquid, bp 294°c at 760 mm Hg.

Viscosity at 25°=35.2 centipoises.

Pour point 10°

Solubility in water about 6.9%

Solubility in peanut oil 0.8%.

C. Stability in Containers

Store in well-closed containers (120a)

VII Analytical Methods

Detection and estimation using gas-chromatography using mass spectrometric method. (581).

Extraction of triethyl citrate from egg white foam using ethyl ether, followed by GLC identification. (579).

VIII Occurrences and Levels found in:

A. Plants

No accessible data in available literature

B. Animals

No accessible data in available literature

C. Synthetics

No accessible data in available literature

D. Natural Inorganic Source

No accessible data in available literature

TRIETHYL CITRATE

Biological Data

I. Acute Toxicity

(none)

II. Short Term Studies

(none)

III. Long Term Studies

(none)

IV. Special Studies

Triethyl citrate given intravenously to mice, rats, frogs, and rabbits exerts a local anesthetic effect after contact with a nerve trunk. Stimulation of higher central nervous system centers is also seen. The dosage levels at which this effect is precipitated is not stated in current literature. However, one effect observed without species variation was that of cardiovascular collapse, indicative of some type of shock syndrome (580).

Cell cultures of mammalian cells will show growth inhibition if triethyl citrate is added to the culture medium (583).

TRIETHYL CITRATE

Biochemical Aspects

No accessible data in available literature.

STEARYL CITRATE

Summary - Toxicological Information

Acute oral toxicity for stearyl citrate (in 20% cottonseed oil) in the rat is greater than 5.4 g/kg (589).

No adverse effects were seen in rats and rabbits fed stearyl citrate at levels ranging from 1.3% to 10% of the total diet for 6 weeks (589). Rats fed this substance at the 1.9% and 9.5% levels did not manifest toxic signs during five generation reproduction studies (589).

Two year feeding studies in dogs fed stearyl citrate at the 10% level also failed to reveal adverse effects on growth, mortality and reproductive indices.

Special investigations on this compound have not been reported.

STEARYL MONOGLYCERIDYL CITRATE

Chemical Information

I. Nomenclature (Food Chemicals Codex, p. 667) (120a)

A. Common Name

(none)

B. Chemical Name

Stearyl Monoglyceridyl Citrate

C. Trade Name

(none)

D. Chemical Abstracts Unique Registry Number

001337344

II. Empirical Formula

No unique formula

III. Structural Formula

No unique formula

IV. Molecular Weight

No unique weight

V. Specifications (120a)

A. Chemical

Acid value. Between 40 and 52 meq/kg.

Total citric acid. Between 15 and 18 %.

Saponification value. Between 215 and 255.

B. Food Grade

Limits of Impurities

Arsenic (as As). Not more than 3 parts per million (0.0003%).

Heavy metals (as Pb). Not more than 10 parts per million (0.001%).

Residue on ignition. Not more than 0.1%.

Water. Not more than 0.25% .

C. Official Compendia

Food Chemical Codex - First Edition p. 667.(120a)

VI. Description (120a)

A. General Characteristics

A soft, practically tasteless, off-white to tan, waxy solid having a lard-like consistency.

B. Physical Properties

It is insoluble in water but is soluble in chloroform and in ethylene glycol. It is

prepared by a controlled chemical reaction from citric acid, monoglycerides of fatty acids (obtained by the glycerolysis of edible fats and oils or derived from fatty acids), and stearyl alcohol.

C. Stability in Containers

Store in well closed containers.

VII. Analytical Methods

Identification by precipitation method (120a p. 769). Stearyl Monoglyceridyl - Colormetric determination (120a, p. 667).

VIII. Occurrence and Levels found in:

A. Plants

No accessible data in available literature

B. Animal

No accessible data in available literature

C. Synthetics

No accessible data in available literature

D. Natural inorganic sources

No accessible data in available literature

STEARYL CITRATE

Biological Data

I. Acute Toxicity

Animal	Route	Material	LD_{50} mg/kg	Ref.
Rat	oral	Stearyl Citrate (in 20% cottonseed oil)	> 5400	(589)

II. Short Term Studies

Six week feeding studies in rats fed stearyl citrate at 0, 1.3, 2.5, 5.0 and 10%, and in rabbits at 2 and 10% of the total diet (589) failed to reveal any adverse effects on growth rate, mortality, histopathologic changes, fertility, gestation and lactation.

III. Long Term Studies

In 2 year feeding studies in dogs fed stearyl citrate as 10% of their diet, no adverse effects on growth rate, mortality, histopathologic changes, fertility, gestation and lactation were seen. Similarly during five generation reproduction studies with rats fed stearyl citrate in the diet either containing 1.9% or 9.5% levels showed no adverse effects in any of these catagories. This approximate 10% level of stearyl citrate is some 500 times greater than would be consumed in such a common food item such as margarine which might contain 0.15% of stearyl citrate and making up 15% by weight. (589).

Further biological and physiological data on this substance are lacking.

IV. Special Studies

(none)

STEARYL CITRATE

Biochemical Aspects

No accessible data in available literature.

TRI-ISOPROPYL CITRATE

Summary - Toxicological Information

The acute oral LD_{50} for isopropyl citrate (38% mono- and 62% di-glycerides in corn oil) in rats is greater than 20.7 g/kg. A significant vehicle effect is demonstrated in that the LD_{50} value decreases sharply (3.7 g/kg when the material is given orally to rats in 10% ethanol (591).

No adverse effects were reported following six week feeding studies in rats and rabbits fed isopropyl citrate at levels ranging from 1.68 to 22.5% of the total diet. Rats given this substance at the same level during a five generation reproduction study were without adverse effects as far as growth, reproductive indices, and survival were concerned (591). Dogs fed isopropyl citrate at the 2.8% level were likewise free from toxic signs during a two year feeding study.

Special studies with isopropyl citrate are lacking.

TRIISOPROPYL CITRATE

Chemical Information

I. Nomenclature

A. Common Name

(none)

B. Chemical Name

Tri-isopropyl citrate

C. Trade Name

(none)

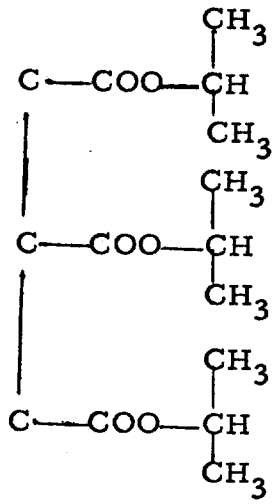
D. Chemical Abstracts Service Unique Registry Number

977050977

II. Empirical Formula

$C_{15}H_{21}O_6$

III. Structural Formula



All other chemical information not accessible in available literature.

TRIISOPROPYL CITRATE

Biological Data

I. Acute Toxicity

Animal	Route	Material	LD_{50} g/kg	Ref.
Rat	Oral	Isopropyl Citrate 38% mono-, 62% di-glycerides in corn oil	> 20.7	(591)
Rat	Oral	Isopropyl Citrate 75% in 10% ethanol	3.7 *	(591)

* The decrease in LD_{50} value appears to be the result of a vehicle effect.

II. Short Term Studies

Rats fed isopropyl citrate at 0, 1.68, 3.36, 7.00 and 14.00% of the diet for six weeks did not show any toxic effects. Rabbits fed isopropyl citrate at levels ranging from 1.9 to 22.5% for the same period likewise were free from toxic signs (591).

III. Long Term Studies

Dogs fed isopropyl citrate at the 2.8% level in the diet for 2 years were free of any adverse effects with respect to mortality, growth, pathological changes, fertility, gestation and lactation (591).

Rats fed isopropyl citrate at the 2.8% level in a five generation reproduction study were not adversely affected in any parameter. In conclusion this citrate

ester is considered harmless up to 1.1% of the total diet, and up to 500 times the level which would be ingested if margarine fat (0.02% isopropyl citrate) made up 15% of the diet by weight (591).

Further biological and physiological effects are lacking in the literature.

IV. Special Studies

(none)

TRI-ISOPROPYL CITRATE

Biochemical Aspects

No accessible data in available literature.

MONOISOPROPYL CITRATE

The current literature is devoid of any studies relating to the biological effects, chemical information or actions of this compound.

MONOISOPROPYL CITRATE

Chemical Information

I. Nomenclature

A. Common Name

(none)

B. Chemical Name

Monoisopropyl Citrate

C. Trade Name

(none)

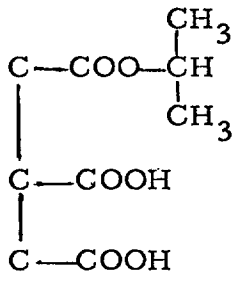
D. Chemical Abstracts Service Unique Registry Number

977051367

II. Empirical Formula

$C_9H_9O_6$

III. Structural Formula



All other chemcial information not accessable in available literature.

SODIUM CITRATE

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