Report on **Calcium Gluconate, Copper Gluconate, Ferrous Gluconate, Magnesium Gluconate, Sodium Gluconate & Zinc Gluconate** 2/4/74

#13

FDRL
FOOD AND DRUG
Research LABORATORIES, INC.

REPORT

CALCIUM GLUCONATE
Accession No. 122
CAS. Reg. No. 000299285

COPPER GLUCONATE
CAS. Reg. No. 000527093

FERROUS GLUCONATE
Accession No. 281
CAS. Reg. No. 000299296

MAGNESIUM GLUCONATE
CAS. Reg. No. 003632915

SODIUM GLUCONATE
Accession No. 573
CAS. Reg. No. 000527071

ZINC GLUCONATE
CAS. Reg. No. 004468024

Submitted to:

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

Attention:

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SUMMARY

In this review calcium gluconate, copper gluconate, iron (ferrous) gluconate, magnesium gluconate, sodium gluconate, and zinc gluconate are considered.

Calcium gluconate is used in sewage purification and to prevent caking in coffee powders. Medically, it is used in calcium deficiencies, but it may cause G.I. or cardiac disturbances. The veterinary profession uses calcium gluconate in treating milk fever in cattle, in pregnancy disease of sheep, in convulsions, lactation, eclampsia, and paraplegia in dogs and cats. It is also used in the treatment of magnesium, mercury, lead, and chloroform poisonings where the prompt action of calcium is desired.

The LD_{50} of calcium gluconate in various species, administered by various routes, is shown in Table I of the text. The i.v. tolerance in dogs when measured at the moment of vomiting was found to be 13.2 ± 1.7 mg of calcium/kg. But the administration to dogs of a dose of 10 mg of calcium/kg as calcium gluconate 3 times weekly for a period of 6 months did not reveal any abnormalities (22a).

Orally adminstered calcium gluconate reduces the hydrogen ion concentration of the blood and urine of rabbits, as the gluconic acid component is degraded by intestinal bacteria to organic acid. The degradation products of calcium gluconate by intestinal bacteria are lactic acid, formic acid, and butyric acid; these degradation products differ from sodium gluconate in that sodium gluconate degradation products also include acetic acid (4).

A 10% solution of calcium gluconate administered intravenously to the dog increased the blood pressure and pulse rate significantly and these hemodynamic changes persisted for 1 and 1/2 hours. There is a very small difference between an effective dose and a toxic dose of calcium gluconate and intravascular clotting is one of the greatest dangers facing intravenous calcium therapy in that it can suddenly be fatal (31a).

Orally administered to humans, 20 g of calcium gluconate caused abdominal stress, vomiting and diarrhea which was not observed when 10 g of calcium gluconate was administered. 10 g of calcium gluconate showed a very definite diuretic effect, and after medication the excretion of calcium in the urine was 2 to 5 mg hourly reaching a maximum in 4 hours (31b).

In two cases reported in this review, infants born with severe tetany were treated with intramuscular injections of calcium gluconate, and the calcium salts precipitated not only at the site of the injection, but also at remote points of the body. Therefore, there is uncertainty as to whether this is the safest method of treating tetany in newborns (45).

Sodium gluconate is used as a sequestering agent forming water soluble complexes with calcium in alkaline media and with iron in more neutral solutions, and is used in metal plating, mineral tanning of hides, mordanting fabrics, and in water paints. LD_{50} values were not found for sodium gluconate in this review, but mice subjected to thermal injury showed that sodium gluconate was very effective in the treatment of burn shock (48).

7.630 g of sodium gluconate per kg of body weight was the minimal lethal dose when a 0.5 normal solution was injected into the marginal

ear vein of the rabbit at a rate of 0.5 cc per kg. In the animals that survived the gluconate infusions, the heartbeat was not changed as to rhythm or intensity. In the animals that died, muscular contractions, to the point that they would stand, and death occurred 15 to 24 hours after the injection. Very dilute solutions (2.18 in 10 million ml) had a vasdilating action on the frog circulatory system and this vasodilation increased as the concentration of the solution increased to a concentration of 2.18 g in 100 ml (3).

600 mg/kg body weight of sodium gluconate in 25 ml of physiological saline administered intravenously to cats over a period of 30 minutes did not have any thrombolitic effects (8).

The LD_{50} values of ferrous gluconate, which is medically used in iron deficiency anemia, are shown for various routes and species in Table I of the text. 100 mg of iron/kg administered as ferrous gluconate produced a depression of growth rate in female rats but not in the male rats and did not produce any other pharmacologic effects in either of the sexes (40).

20 and 40 mg of iron/kg in the form of ferrous gluconate administered orally to cats produced emesis, and 450 mg of iron/kg in rabbits produced iron encrustation of the mucosa, superficial mucosal nucrosis and hepatitis of the liver (40).

During the first 3 weeks .1 ml, and for the following 14 weeks, 0.05 ml of a solution containing 75 mg of iron/ml as ferrous sodium gluconate was administered subcutaneously to mice and 5 tumors were induced at the injection site in the test animals between the 10th and 15th month. All of the tumors were spindle cell showing variable degrees of differentiation, but metastasis was found. Five untreated mice from

the control group developed malignant lymphomas (2).

Human patients suffering from hypochromic anemia responded well to doses ranging from 0.18 to 0.216 mg of iron daily in the form of ferrous gluconate. Symptomatically, most of the patients were apparently cured with the attainment of normal blood counts, but in some, profuse menstrual bleeding persisted after a normal blood count was reached. Several patients who had shown toxic reaction to other iron compounds were able to take the ferrous gluconate without any undue distress (44b).

Anemic patients administered a proprietary liquid ferrous gluconate preparation at a dose which contained 105 mg of iron per day supplemented with aureomycin hydrochloride, nicatinamide, riboflavin and Vitamin C, required 17.8 days to raise the hemoglobin value to normal (41a).

1.5 to 2.0 cc of a 10% magnesium gluconate solution administered subcutaneously to rats reduced the basal metabolism; the reduction reached its lowest point in the 3rd to 4th half hour interval of measurement. When sodium gluconate was administered at the same dosage level, there was no effect on basal metabolism (21).

20, 10, and 5 g magnesium gluconate administered orally produced a purgative action in rats, guinea pigs, and rabbits respectively, but this action was not observed when the magnesium gluconate was administered intravenously. After the oral administration, magnesium gluconate is absorbed rapidly and approximately 1/3 was recovered in the urine during the first 24 hours. The administration of 3 g per kg to rabbits intravenously produced magnesium narcosis which was easily reversed by the intravenous injection of $CaCO_2$ (34).

Hyperlipemic serum to which pieces of aorta obtained from rats were

added, revealed that the addition of magnesium gluconate greatly increased the lipolitic activity of the arterial wall. This led to the conclusion that an increase in the lipolysis in the arterial wall will result in a decrease in the atherogenic potential of lipids containing saturated fatty acids (32).

Pigeons fed an atherogenic diet for a period of 12 weeks and simultaneously administered magnesium gluconate at a dose of 100 mg/kg of body weight had a statistically significantly lower serum cholesterol level than the controls (37).

15 mg of copper gluconate administered intravenously produced ovulation in 8 of 10 rabbits. In humans, 100 to 200 mg of copper gluconate has been administered to patients suffering from anovulation without any subjective side effects being observed (14).

0.3 to 1.6 mg/kg of copper gluconate injected into the jugular vein of heifers accelerated the process of ovulation, the state of the uterus and the stages of development of follicles in the ovaries which caused the development of incomplete egg cells (11).

An average of 34.9 mg/kg per day of copper gluconate fed to rats for a period of 6 months had no adverse effect on food consumption, body weight gain, hemograms, urine analysis, or gross microscopic examination. Tissue analysis showed that there was an elevation in copper content in the kidneys of the animals. This dose level is estimated to be 1,100 times the daily consumption of copper gluconate in marketed products.*

In dogs, the administration of copper gluconate at a level of 60 mg/kg per day for a period of 6 months has been well tolerated. This is the equivalent of approximately 2,000 times the human exposure level for marketed products.*

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*Private Communication from unidentified source provided by the FDA.

Chemical Information

I. Nomenclature

A. Common Names (48, 41a, 43)

Calcium gluconate

Copper gluconate

Iron (ferrous) gluconate

Magnesium gluconate

Manganese gluconate

Sodium gluconate

Zinc gluconate

B. Chemical Names

Calcium gluconate

Copper gluconate

Cupric gluconate

Iron gluconate

Ferrous gluconate

Magnesium gluconate

Manganese gluconate

Sodium gluconate

Gluconic acid sodium salt

Zinc gluconate

C. Trade Names

Calcium gluconate

Calciofon; Colglucon; Ebucin; glucal; glucobiogen

Copper gluconate

No other trade names were encountered in the available literature.

Iron (ferrous) gluconate

Fergon; Ferlucon; Ferronicum; gluco-Ferrum; Irox; Nionate; Cerevon.

Magnesium gluconate

No other trade names were encountered in the available literature.

Manganese gluconate

No other trade names were encountered in the available literature.

Sodium gluconate
Pasexon 100 TS

Zinc gluconate

No other trade names were encountered in the available literature.

D. Chemical Abstracts Unique Registry Number

Calcium gluconate -	000299-28-5
Copper gluconate -	000527-09-3
Iron (ferrous) gluconate -	000299-29-6
Magnesium gluconate -	003632-91-5
Manganese gluconate -	006485-39-8
Sodium gluconate -	000527-07-1
Zinc gluconate -	004468-02-4

II. Empirical formula (48, 47, 16) *

Calcium gluconate

$C_{12}H_{22}CaO_{14}$

Copper gluconate

$C_{12}H_{22}Cu\ O_{14}$

Iron (ferrous) gluconate

$C_{12}H_{22}Fe\ O_{14} \cdot 2H_2O$

Magnesium gluconate

$(C_6H_{11}O_7)_x Mg \cdot yH_2O$

Manganese gluconate

$C_{12}H_{22}Mn\ O_{14} \cdot 2H_2O$

Sodium gluconate

$C_6H_{11}Na\ O_7$

Zinc gluconate

$C_{12}H_{22}Zn\ O_{14} \cdot 3H_2O$

III. Structural formula (47)

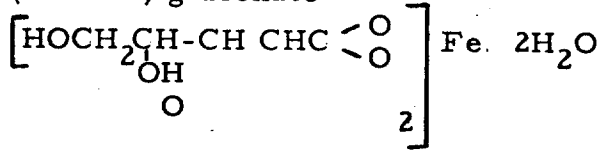
Calcium gluconate

$Ca\ [HOCH_2\ (CHOH)_4\ CO_2]_2$

Copper gluconate

$Cu\ [HOCH_2\ (CHOH)_4\ CO_2]_2$

Iron (ferrous) gluconate



$Fe \cdot 2H_2O$

Magnesium gluconate

$[CH_2OH\ (CHOH)_4\ COO]_x\ Mg \cdot yH_2O$

Manganese gluconate

$[CH_2OH\ (CHOH)_4\ COO]_2\ Mn \cdot 3H_2O$

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*Private communication from unidentified source received from FDA

IV Molecular Weight

Calcium gluconate

430.38

Copper gluconate

453.85

Iron (ferrous) gluconate

446.16

Magnesium gluconate

No molecular weight was encountered in the available literature.

Manganese gluconate

481.27

Sodium gluconate

218.13

Zinc gluconate

No molecular weight was encountered in the available literature.

V. Specifications (47, 48 16,)*

A. Chemical

Calcium gluconate

C 33.49%
H 5.16%
Ca 9.31%
O 52.05%

Copper gluconate

C 31.76%
H 4.89%
Cu 14.00%
O 49.36%

Iron (ferrous) gluconate

C 32.30%
H 4.97%
Fe 12.52%
O 50.21%

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*Private communication from unidentified source received from FDA.

Magnesium gluconate

No chemical specifications were encountered in the available literature.

Manganese gluconate

C	32.1%
H	4.9%
Mn	11.5%
O	48.0%

Sodium gluconate

C	33.04%
H	5.08%
Na	10.54%
O	51.34%

Zinc gluconate

C	27.7%
H	5.6%
Zn	13.7%
O	53.0%

B. Food Grade

Calcium gluconate

Assay. Not less than 98.0 percent and not more than the equivalent of 102.0 percent of $C_{12}H_{22}CaO_{14}$ after drying.

Limits of Impurities

Arsenic (as As). Not more than 3 parts per million (0.0003 percent).
Heavy metals (as Pb). Not more than 20 parts per million (0.002 percent).
Lead. Not more than 10 parts per million (0.001 percent).
Loss on drying. Not more than 3 percent.
Sucrose and reducing sugars. Passes test.

Copper gluconate

Assay. Not less than 98.0 percent and not more than the equivalent of 102.0 percent of $C_{12}H_{22}CuO_{14}$.

Limits of Impurities

Arsenic (as As). Not more than 3 parts per million (0.0003 percent).
Lead. Not more than 10 parts per million (0.001 percent).
Reducing substances. Not more than 1 percent.

Magnesium gluconate

No chemical specifications were encountered in the available literature.

Manganese gluconate

C	32.1%
H	4.9%
Mn	11.5%
O	48.0%

Sodium gluconate

C	33.04%
H	5.08%
Na	10.54%
O	51.34%

Zinc gluconate

C	27.7%
H	5.6%
Zn	13.7%
O	53.0%

B. Food Grade

Calcium gluconate

Assay. Not less than 98.0 percent and not more than the equivalent of 102.0 percent of $C_{12}H_{22}CaO_{14}$ after drying.

Limits of Impurities

Arsenic (as As). Not more than 3 parts per million (0.0003 percent).
Heavy metals (as Pb). Not more than 20 parts per million (0.002 percent).
Lead. Not more than 10 parts per million (0.001 percent).
Loss on drying. Not more than 3 percent.
Sucrose and reducing sugars. Passes test.

Copper gluconate

Assay. Not less than 98.0 percent and not more than the equivalent of 102.0 percent of $C_{12}H_{22}CuO_{14}$.

Limits of Impurities

Arsenic (as As). Not more than 3 parts per million (0.0003 percent).
Lead. Not more than 10 parts per million (0.001 percent).
Reducing substances. Not more than 1 percent.

Iron (ferrous) gluconate

Assay. Not less than 95.0 percent of $C_{12}H_{22}FeO_{14}$, calculated on the dried basis.

Loss on drying. Between 6.5 and 10 percent.

Limits of Impurities

Arsenic (as As). Not more than 3 parts per million (0.0003 percent).
Chloride. Not more than 700 parts per million (0.07 percent).
Ferric iron. Not more than 2 percent.
Lead. Not more than 10 parts per million (0.001 percent).
Mercury. Not more than 3 parts per million (0.0003 percent).
Oxalic acid. Passes test.
Reducing sugars. Passes test.
Sulfate. Not more than 0.1 percent.

Magnesium gluconate

Assay	98% - 102%	M 5.0
Reducing Substances	Maximum 0.15%	R 8.1
Heavy Metals	Maximum 20 ppm	H 2.3
Oxalates	Negative to test	O 5.2
Chlorides	Maximum 500 ppm	C 8.1
Sulfates	Maximum 500 ppm	S 2.52
pH (10% Solution)	7.0 - 8.5	P 24.0
Solubility (15 gm/100 gal H_2O)	Clear and free of foreign matter.	

Manganese gluconate

Assay. Not less than 98.0 percent of $C_{12}H_{22}MnO_{14}.2H_2O$.

Limits of Impurities

Arsenic (as As). Not more than 3 parts per million (0.0003 percent).
Heavy metals (as Pb). Not more than 40 parts per million (0.004 percent).
Lead. Not more than 10 parts per million (0.001 percent).
Reducing substances. Not more than 0.5 percent.

Sodium gluconate

SPECIFICATIONS

Assay. Not less than 98.0 percent of $C_6H_{11}NaO_7$.

Limits of Impurities

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

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

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

Reducing substances. Not more than 0.5 percent.

Zinc gluconate

No specifications were encountered in the available literature.

C. Official Compendia

Food Chemical Codex

VI. Description (47, 48)*(44a)

A General characteristics

Calcium gluconate

White, crystalline granules or powder. It is odorless, tasteless, and stable in air. Its solutions are neutral to litmus.

Copper gluconate

A fine, light blue powder, or crystals. Odorless astringent taste.

Iron (ferrous) gluconate

Fine yellowish gray or pale greenish powder or granules having a slight odor resembling that of burned sugar. Pure monohydrate is reported as colorless.

Magnesium gluconate

Magnesium gluconate is a white powder that is odorless and nearly tasteless.

Manganese gluconate

A slightly pink colored powder.

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*Private communication from unidentified source received from FDA.

Sodium gluconate

A white to tan, granular to fine, crystalline powder.

Zinc gluconate

No general characteristics were encountered in the available literature.

B. Physical Properties

Calcium gluconate

Metal Chelate	Log K (=pK)	μ	t. °C
$Ca(GH_4)^+$	1.21.	0.2	—
	1.22	0.16	25.0
	2.16		—

One gram dissolves slowly in about 30 ml of water at 25° and in alcohol and in many other organic solvents.

Copper gluconate

Solubility in water at 25° =30 g/100 ml; slightly soluble in alcohol practically insoluble in most other organic solvent.

Metal Chelate	Log K (=pK)	μ	t. °C
$Cu_2(GH_2)_4(OH)^{-6}$	38.9	0.45	25.0

Iron (ferrous) gluconate

One gram dissolves in about 10 ml of water with slight heating. It is practically insoluble in alcohol. A 1 in 20 solution is acid to litmus. (a) D=+3.5° in H_2O.

Metal Chelate	Log K (=pK)	μ	t. °C
$Fe(GH_4)^+$	1.0	—	25.0

Magnesium gluconate

Metal Chelate	Log K (=pK)	μ	t. °C
$Mg(GH_4)^+$	0.07	0.2	—

Manganese gluconate

It is very soluble in hot water and is very slightly soluble in alcohol.

Sodium gluconate

It is very soluble in water and is sparingly soluble in alcohol. It is insoluble in ether.

Zinc gluconate

Metal Chelate	LogK (=pK)	μ	t. °C
$Zn(GH_4)^+$	1.70	0.2	—

C. Stability in Containers

Calcium gluconate

Store in tight container.

Copper gluconate

Store in well closed containers

Iron (ferrous) gluconate

Store in tight containers; keep from air.

Magnesium gluconate

Store in well closed containers.

Manganese gluconate

No stability or packaging information was encountered in the available literature.

Sodium gluconate

Store in well closed containers.

Zinc gluconate

No stability or packaging information was encountered in the available literature.

VII. Analytical Methods

Sodium gluconate

Title: Pasexon

Principle Determination Step: Polarimetry

Principle Separation Technique: Water Solution

Principle Analytical Reagent: Ammonium Molybdate A. R.

Moiety Measured: Unspecified

Metallogluconates

Title: Some applications of a dual channel AA spectrophotometer (6a)

Principle Determination Step: Atomic absorption

Principle Separation Technique: Decomposition of organic moiety

Principle Analytical Reagent: None

Moiety Measured: Metaliom

Sensitivity: <1 ppm to> 11,000 ppm

Biological Data

I. Acute Toxicity

Animal	Route	Material	Parameter	Value mg/kg	Reference
Mice	oral	ferrous gluconate	Est. LD_{50}	6,600	43
Mice	oral	ferrous gluconate	LD_{50}	2,450	40
Mice	oral	ferrous gluconate	LD_{50}	3,700 ± 145	44
Mice	i.v.	ferrous gluconate	LD_{50}	98 ± 6.8	44
Mice	i.v.	ferrous gluconate	LD_{50}	199	46
Mice	i.p.	ferrous gluconate	LD_{50}	160 (94-272)	46
Mice	i.p.	ferrous gluconate	LD_{50}	3,950	46
Guinea Pig	oral	ferrous gluconate	Est. LD_{50}	2.100	43
Rats	oral	ferrous gluconate	LD_{50}	4,500 ± 400	44
Rats	i.g.	ferrous gluconate	LD_{50}	7,460 (6,844-8,131)	46
Rabbit	oral	ferrous gluconate	Es Est. LD_{50}	3,500	43
Dogs	i.v.	ferrous gluconate	LD_{50}	7,400	46
Mice	i.g	calcium gluconate	LD_{50}	950 ± 83	22a
Dog	intra-cisterna magna	calcium gluconate	LD	3.76	33
Dog	intra-cisterna magna	calcium gluconate	LD	2.11	33
Dog	" "	calcium gluconate	LD	7.30	33

Animal	Route	Material	Parameter	Value mg/kg	Reference
Rabbit	i.v. (24 hrs.)	calcium gluconate	LD_{50}	60	14
Mice	i.v.	calcium kinate	LD_{50}	1,050 ± 57	22a
Rabbit	i.v.	sodium gluconate	LD_{min}	6,694	9
Rat	s.c.	magnesium gluconate	LD	94-106	34
Guinea Pig	e.p.	magnesium gluconate	LD	16.5-18.8	34
Rabbit	i.v.	magnesium	LD	94-106	34

Twenty-four hour LD_{50} values for ferrous gluconate administered to mice and rats approximate the seven day values reported above from reference (44).

CALCIUM GLUCONATE

Mice were injected intravenously with graded dosage levels of calcium kinate gluconate, calcium gluconate, or calcium chloride in order to compare their acute toxicities. The 24-hour and 7-day i.v. LD_{50}'s were the same; the LD_{50} for calcium kinate gluconate was 1050 $\pm$ 57 mg/kg, for calcium gluconate 950 $\pm$ 83 mg/kg, and for calcium chloride 215 $\pm$ 14 mg/kg (22a).

Dogs were injected with a preparation containing either calcium kinate gluconate or calcium gluconate, administered at a rate of 3 mg of calcium/kg/minute, to study acute intravenous tolerance. One week after these injections, a cross over experiment was done in which each dog was injected with the alternate solution. The maximum calcium tolerance was determined as the moment vomiting occurred. The calcium kinate gluconate was better tolerated than the calcium gluconate in terms of total calcium since vomiting was observed after the administration of 19.7 $\pm$ 26 mg calcium/kg, while with calcium gluconate, vomiting was observed at 13.2 $\pm$ 1.7 mg calcium/kg (22a).

Six dogs per dose level, were injected intravenously with 10 mg of calcium gluconate or 2 mg of calcium/kg of calcium kinate gluconate three times weekly for 6 months, were normal in appearance, behavior, and body weight gain throughout the study (22a).

Rhesus monkeys and dogs were given three times on alternate days 10 mg of calcium/kg as calcium kinate gluconate or calcium gluconate, or 7.5 mg of calcium/kg as calcium kinate gluconate or calcium gluconate

intravenously, to study the effects on hematologic values. The results showed that the total red and white blood cell counts, differential counts, hematocrit and hemoglobin concentrations were within normal limits and comparable to the controls. The clotting times in the dogs injected with the calcium solutions at 10 mg/kg were decreased compared to the controls, but returned to normal 4 days after the last injection (22a).

The comparative rate of availability of calcium ions in calcium kinate gluconate, calcium gluconate, and calcium chloride preparations was determined by the inhibitory effect of calcium ion on the toxicity of magnesium ion. Mice were injected intravenously with solutions containing a constant 5:6 ratio of calcium ions to magnesium ions. The death rate was reduced sharply when any one of the calcium salts studied was added at 40 mg calcium/kg to the injections of magnesium, and the preparations studied were equally effective in inhibiting magnesium toxicity (22a).

A comparison was made of the effects of calcium kinate gluconate and calcium gluconate on the heart and blood pressure of dogs. The animals were injected intravenously in doses ranging from 1.35 mg to 7.5 mg calcium/kg at a rate of 7.5 mg calcium/kg/minute. Blood pressures were recorded prior to the injections and at 10, 20, 30, 60, 90, 120, 180, and 240 minutes post-dose. A cross over experiment was done on the same day so that each dog received both solutions. The results show that at 7.5 mg of calcium/kg of calcium kinate gluconate or calcium gluconate, no significant changes in the electrocardiogram, heart rates or blood pressure of the dogs were observed (22a).

Albino rabbits were used to study the intramuscular tolerance of calcium kinate gluconate and calcium gluconate. Calcium kinate gluconate was administered in doses ranging from 5 to 50 mg, while calcium gluconate was administered in a dose of 10 mg. All doses were administered at a volume of 1 ml to the rabbits on the first, 6th and 7th days. On the 8th day, the animals were sacrificed, and the injection sites were excised and examined. The results showed that there was no adverse effect in any rabbits injected with calcium kinate gluconate or calcium gluconate and that 10 mg of calcium/dose was well tolerated, showing minimal tissue damage (22a).

The effects of subcutaneously injected calcium gluconate were studied in mature fasted male rabbits. 5 ml of blood were drawn from the lateral ear vein immediately before injection and at 3 intervals from 1 1/2 to 6 hours after medication. The injection of calcium gluconate produced a rapid increase in serum calcium, but there was a slow return toward baseline values at 6 hours. In all cases, there was an inverse relationship between serum calcium and magnesium concentrations (22).

After oral or intravenous administration of calcium gluconate, determination of the hydrogen ion concentration in the urine and flowing rabbit blood showed that calcium gluconate lowered the hydrogen ion concentration of the blood but did not affect the urine due to the neutralizing effect of the gluconic acid components. Orally-administered calcium gluconate reduced the hydrogen ion concentration of both the blood and urine because the gluconic acid component was degraded by

intestinal bacteria to organic acid, while orally administered sodium gluconate reduced the hydrogen ion concentration only in the urine. It was found that the degradation of calcium gluconate by intestinal bacteria leads to lactic acid, formic acid, and butyric acid and differs from the bacterial degradation of sodium in that sodium gluconate degradation contains the above and acetic acid (4).

A study of the toxicity and rate of disappearance of intracisternally-injected calcium salts in the dog showed that calcium gluconate containing 0.25 mg or less of calcium/kg of body wieght causes no pronounced toxic reactions. Larger doses caused severe respiratory depression, and 0.40 mg of calcium/kg of body weight was lethal. There was no difference in the rate of disappearance of intracisternally-injected calcium chloride, calcium gluconate or calcium lactate from the cerebral spinal fluid (33).

30 ml (approximately 35 to 40 mg) of a 10% calcium gluconate solution and, later, 1.5 g of calcium lactate in 30 ml of water were injected intravenously in dogs weighing approximately 8 kg to study the comparative pharmacologic effects. A second dog was given the same doses of the compounds in reverse order. The blood pressure and pulse rate were increased significantly by both calcium salts. Half an hour after the injection of calcium lactate, the blood pressure had almost returned to normal limits, but with calcium gluconate, the hemodynamic effect persisted 1 1/2 hours after the administration. With the lactate salt, a very prompt decrease in the pulse rate was obtained, but the effect wore off rapidly. The

effect of calcium gluconate produced a reduced pulse rate which persisted much longer. The investigators note that the therapeutic index of calcium gluconate is not great. Intravascular clotting is the greatest danger following intravenous calcium therapy in that it gives no warning, and the effects can be fatal (31a).

Three clinically normal human subjects were used to study the urinary output of calcium after oral administration of calcium lactate and calcium gluconate. Initially the subjects were given 20 g of calcium gluconate and 10 g of calcium lactate, but the subjective and objective symptoms (abdominal stress, vomiting, and diarrhea) were so violent that the respective doses were halved. Calcium caused a very definite diuretic effect, and the excretion rate of calcium in the urine was between 2 and 5 mg/hour reaching a peak in 4 hours (31b)

Adult human subjects, with idiopathic cardiomyopathy and congestive heart failure, 44 to 56-years-old and weighing approximately 70 kg, were used to study the effects of magnesium sulfate, calcium gluconate, potassium chloride and ammonium chloride on the urinary excretion of magnesium. Urine specimens were collected during a 6- to 10-day control period. On day one of the experimental period 12 ml of 50% magnesium sulfate was given intramuscularly. On the third day of the experimental period, 30 ml of 10% KCL were given orally in three divided doses at 10, 11, and 12 a.m. 40 ml of 10% calcium gluconate (in 500 ml of 5% glucose) were given by continuous infusion between 10 a.m. and 3 p.m. of the 5th day. The intravenous administration of calcium gluconate significantly increased the urinary excretion rate of calcium in all subjects with the increments

greater and more prolonged in the 3 patients with congestive heart failure. Though less marked, the rate of magnesium excretion was similar to that of calcium, and excretion rate of potassium was increased in both patients with congestive heart failure but not in the one control subject (31).

Two cases are reported in which infants born with severe tetany were treated with intramuscular injections of calcium gluconate. The calcium salts were precipitated not only at the sight of injection but also at remote points of the body; reabsorption eventually occurred without known permanent damage. The authors feel that this precipitation could possibly develop as well after intravenous or oral administration of calcium; therefore, there is uncertainty as to whether this is the safest method of treating tetany in newborns (45).

A dog's jejunum was isolated and exposed in order to study the in vivo effects of the i.v. injection of a 5% solution of calcium gluconate. Calcium gluconate stimulated the small intestine more than did calcium chloride and did not affect the respiratory or circulatory systems to any noticeable extent (27b).

COPPER GLUCONATE

Rabbits weighing 2 to 3 kg were given a single intravenous dose of 10, 12, or 15 mg each of new copper compounds to study induced ovulation by sex center activation. At a dose of 10 mg of copper, none of the animals showed induced ovulation, but when the dose was raised to 12 mg, ovulation was induced in 1 of 2 rabbits, and 15 mg of copper gluconate produced ovulation in 8 of 10 rabbits. Copper gluconate has been used for the treatment of patients suffering from anovulation, and no subjective side effects have been observed when the total doses were 100 to 200 mg. Copper gluconate was shown to be the least toxic among copper compounds studied (14).

Female Sprague-Dawley rats with an average body weight of 37 g were depleted of copper for 17 days with a copper-deficient diet. They were then fed a fodder diet containing 50 micromols of copper sulfate + 25 mg of gluconic acid, or 50 micromols of copper sulfate + 250 mg of gluconic acid for a 2 week period. These diets had no effect on copper diffusion in liver tissue (13).

10 to 50 ml doses of copper gluconate (the equivalent of 0.3 to 1.6 mg/kg of animal weight) were injected into the jugular vein of heifers. After 12 to 95 hours, or after 18 to 48 days, the animals were sacrificed and a determination was made of the number of ovulated follicles, zygotes, blastocysts, and embryos to determine the effects of copper gluconate on stimulation of the ovulatory process. In this

study, the optimal dose of copper gluconate, equal to 40 to 50 ml, accelerated the processes of ovulation, the state of estrus, and the stages of development of the follicles in the ovaries. The administration of copper gluconate brought about a premature ovulation and an emergence of incomplete egg cells which, in turn, caused low fertility (11).

For a period of 6 months, copper gluconate was fed to male and female rats at dietary levels of 0.006% and 0.06%. The mean daily consumption of copper gluconate in the test diets approximated 3.46 mg/kg/day for the low level group, and 34.9 mg/kg/day for the high level groups. These dose levels were well tolerated, and no specific adverse effects were noted in food consumption, body weight gain, hemograms, urine analysis, or gross or microscopic examinations of tissues and organs which were obtained at necropsy. Analysis of tissue copper contents of the test animals and controls suggested an elevation in copper content in the kidneys of the test animals at the high dosage level. This high dose level is estimated to be 1,100 times the daily consumption of copper gluconate in marketed products *.

A feeding study in which copper gluconate is administered to male and female beagles at dose levels of 3, 15, and 60 mg/kg/day in the diet is presently in progress. After 6 months of this one-year study, green-colored stools have been observed in all

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*Private communication provided by the FDA.

test animals since the second week of dosing. No adverse effects have been noted in general appearance, behavior, food consumption, or body weight gain, and no changes were noted in hemograms. Clinical chemistry parameters or urine analysis values obtained at 4, 13, or 26 weeks, showed there was a slight increase in serum calcium levels at the end of 6-month intervals in 2 of 6 animals administered 60 mg/kg/day. There were no gross or microscopic pathologic lesions observed at a 6-month minimum sacrifice. Copper gluconate at the level of 60 mg/kg/day is the equivalent of approximately 2,000 times the human exposure level for marketed products, and this dose has been well tolerated *.

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*Private communication provided by the FDA.

IRON GLUCONATE

In a review of the toxicity of iron compounds, the following statement was made in reference to ferrous gluconate: "Toxic symptoms are apparently exceedingly rare beyond occasional nausea, and the like, in susceptible individuals, and even here symptoms are less severe than with other forms of iron. No reports had been found in the literature of poisoning from this salt, and the medical files of a major producer of this preparation contain no privately reported cases of reactions following overdosages in humans...Clinically, at least, this iron salt appears less irritating and less toxic than other common sources of iron" (43).

The acute oral toxicity of ferrous fumerate, ferrous sulfate, ferrous succinate and ferrous gluconate having iron contents of 33.0, 20.0, 24.8, and 11.7, respectively, was determined in male CFW mice weighing 17 to 22 g. The LD_{50} values calculated according to deBeer and expressed in mg of Fe/kg were fumerate-630, succinate-560, gluconate-320, and sulfate-230 (40).

The subacute oral toxicity of 50 and 100 mg Fe/kg of ferrous sulfate, fumerate, gluconate, and succinate was studied for a period of 12 weeks in male and female WHE rats weighing 40 to 100 g. The growth rate data showed that in the male rats, but not in the females, the high dose of all compounds significantly depressed the growth rate. At the low dose level, a non-significant depression was observed in males given fumerate and gluconate. Organ weights of the dose groups did not differ significantly from the controls nor was there any difference in the red or total white cell counts or hemoglobin concentration. Histological examinations

revealed no abnormalities that could be attributed to the drugs (40).

Six adult cats weighing between 1.8 and 3.5 kg were fasted for 18 hours, then orally dosed with gelatin capsules containing 20 or 40 mg of Fe/kg of ferrous gluconate to determine its emetic activity. Both levels of gluconate administered produced emesis (40).

To study the irritant effects on gastric mucosa, 450 mg of Fe/kg of ferrous gluconate, ferrous fumerate, ferrous sulfate, or ferrous succinate were administered orally to adult rabbits. Twelve hours after medication, animals were sacrificed and the stomach and livers removed for histological examination. In the group receiving gluconate, the stomach of one showed iron encrustation of the mucosa while that of another showed superficial mucosal necrosis and iron in the vessels. The pylorus showed early inflammation, and iron impregnation was apparent in the lamina propria, and hepatitis was found in the liver (40).

For 42 consecutive days, albino weanling WAG rats were administered orally a dose of 0.1 mg of iron (ferrous gluconate) in 0.1 ml/rat to study the hematin activity in iron deficiency. Individual body weights and hemoglobin concentrations were recorded initially and at weekly intervals thereafter. The results showed ferrous gluconate was effective against iron deficiency (40).

Anemic rats 2 to 3 months of age were fed by medicine dropper or injected intramuscularly with a solution prepared so that 0.2 ml contained 1 mg of iron. Parenteral administration of ferrous gluconate immediately produced an increase in red blood cell and hemoglobin values.

The injections were stopped, and the administration of the ferrous gluconate was continued orally. No further increase in red blood cells was obtained (44a).

Eleven-week-old male CB stock mice were injected subcutaneously with 0.1 ml of ferrous sodium gluconate for 3 weeks. The following 14 weeks, 0.05 ml of a solution containing 75 mg of Fe/ml were injected to study the induction of tumors with ferrous sodium gluconate. Injection-sight spindle-cell tumors developed in 5 test animals between the 10th and 15th month. No metastasis was found, but 2 of the tumors were successfully transplanted into 2 mice of the same strain. At the site of injection the flanks were thickened, indurated and the subcutaneous tissues were stained brown and contained large number of macrophages. Fibrous tissue was increased in all animals, but these were the usual changes associated with prolonged parenteral administration of iron. Five untreated mice from the control group developed malignant lymphoma, but no other tumors were seen and observed changes such as fatty degeneration and pulmonary infection were similar to those found among the test animals (2).

A 14-month-old child was admitted to the hospital for treatment of acute iron toxicity from the ingestion of an unknown number of ferrous gluconate tablets. The child vomited, passed bloody stools, and became listless. The stomach was lavaged with tap water, a garage of a 1% solution of sodium bicarbonate + 30 ml of a combination of activated attapulgite and pectin was given as well as an enema. The child was given a dose of

92 mg/kg of desferrioxamine intravenously on 3 occasions. At 12-hour intervals after an initial oral dose of 5 g of desferrioxamine, there was prompt improvement in the child's clinical status as shown by the urinary excretion of iron and serum iron concentration (42).

Thirteen female patients ranging in age from 24 to 49 years and suffering from hypochromic anemia were treated with ferrous gluconate in doses ranging from 0.108 to 0.216 mg of iron daily. In 2 patients, intramuscular administration was used; in 8, administration was oral, and in 3 others both routes of administration were employed. In addition, 2 other patients who had demonstrated marked tolerance to other iron compounds were given the ferrous gluconate. The anemia in all patients responded well to the gluconate therapy. However, in 2 patients the hemoglobin level did not reach 11.6, or 80%, and red blood cells did not show any abnormalities in response to treatment. Symptomatically, 7 patients were apparently cured, as shown by a normal blood count and in 4, profuse menstrual bleeding persisted after a normal blood count was reached. It was noted that 4 patients who showed toxic reactions to other iron compounds were able to take ferrous gluconate without any undue distress, and in the patients receiving ferrous gluconate intramuscularly up to the present, no systemic and only rare and mild local reactions have occurred. However, in view of the efficacy of the oral administration of the ferrous gluconate and its lack of toxicity, there is seldom any reason for its parenteral administration (44b).

A proprietary liquid ferrous gluconate preparation providing a daily intake of available iron of 105 mg/day supplemented with anaurin hydro-

chloride, nicotinamide, riboflavin, and natural Vitamin C was administered to a group of anemic patients. The period of treatment required to raise the hemoglobin value to normal was 17.8 days in these patients. "The liquid ferrous gluconate preparation was far and away the most popular with patients and produced a therapeutic response out of all expectations" (41a).

Twenty-seven women were administered 99 mg of iron as ferrous gluconate, 29 women received 102 mg of iron as ferrous lactate, and 27 women received 101 mg of iron as ferrous sulfate in capsule form daily for 4 weeks to study iron absorption and compare the 3 ferrous salts. Complete fecal collections were made during the 3rd and 4th weeks after medication had been discontinued. The mean daily absorption rate of the subjects given ferrous gluconate was 9 mg, ferrous lactate 13 mg, and ferrous sulfate 11 mg, but these differences were not statistically significant (41).

MAGNESIUM GLUCONATE

1.5 to 2.0 cc of 10% magnesium gluconate solution was administered subcutaneously to rats to determine the effects on basal metabolism rates. The animals were placed in a metabolism apparatus, and readings of O_2 consumption were measured at 1/2 hour intervals for 6 hours. After the magnesium gluconate injection, the basal metabolism rate of the rats was reduced and the reduction reached its low point in the 3rd to 4th half hour, after which the basal metabolism rate returned to normal levels between the 5th and 8th half hour intervals (21).

Following the procedures as described in the previous paragraph, sodium gluconate was also treated, but it was found that the injection of sodium gluconate caused no major changes in basal metabolism rate (21).

In early research on magnesium gluconate, it was reported that for both animals and man, an endodermic, hypodermic perivascular or endomuscular injection of a 10% solution produced no pain or irritation. A subcutaneous injection of 10 cc of a 10% solution was well tolerated and without local or general systemic effect. Orally, magnesium gluconate was tasteless and well tolerated even at high doses. At dose levels of 20 g, 10 g, and 5 g, magnesium gluconate administered orally produced a purgative action in rats, guinea pigs, and rabbits, respectively, but this action was not observed following hypodermic or intravenous injections. When magnesium gluconate was

administered orally, absorption was rapid, and approximately 1/3 of the magnesium administered was recovered in the urine during the first 24 hours. Subcutaneous injections of 3 g/kg to the rabbit produced magnesium necrosis which was easily reversed by intravenous injection of $CACO_2$ (34).

The effect of magnesium gluconate on changes in the lipolytic activity of the arterial wall was studied in albino rats weighing 250 - 270 g. The aortas of the rats were removed, and 35 to 40 mg of the tissues were placed in a test tube with 2 ml of hyperlipemic serum obtained from a dog. (Butter + 100 mg/kg of magnesium gluconate was injected intravenously 5 minutes before taking blood). A control tube was placed parallel to the tube containing the test materials, and the lipolytic activity on the arterial wall was determined according to the differences in fatty acid content of the 2 tubes. The lipolytic activity on the aortal wall was greatly increased by the solution containing the hyperlipemic substrates which contained magnesium gluconate. The investigators concluded that magnesium gluconate, by increasing the lipolysis in the arterial wall, decreases the atherogenic potential of lipids containing saturated fatty acids (32).

Thirty male and female pigeons weighing 260 - 400 g were fed an atherogenic diet for 12 weeks. A second group received the same diet for the same period of time, in addition to daily doses of 100 mg/kg of body weight of magnesium gluconate. Pigeons treated with cholesterol-containing magnesium gluconate had a 28% lower serum cholesterol level

as compared to the control, and this difference was statistically significant at a $p \leq 0.01$ level (37).

SODIUM GLUCONATE

The minimum lethal dose by intravenous administration to mice for sodium gluconate was reported to be 0.03500 g equivalent/kg (9).

Experimentally burned mice were orally or intraperitoneally administered a solution of gluconate or chloride containing 140 meq of sodium at a volume of 18% of their body weight in order to study the effectiveness on burn shock. The solutions were effective by both routes of administration and 3/4 of the chloride could be replaced by gluconate without loss of effectiveness. "From a pharmaceutical standpoint this is important, since a gluconate solution is much more palatable than a chloride solution" (6).

The pharmacological changes caused by 0.5 N sodium gluconate were studied in a series of four experiments. In the first study, one solution containing 109 g in 1,000 ml of water and another containing 218 g in 1,000 1.0 N ml of water were infused in the marginal ear vein of the rabbit at a rate of 0.5 ml/kg of body weight/minute. The minimal lethal dose by intravenous infusion in the rabbit was 7.630 g of sodium gluconate /kg of body weight. Among the animals that survived, the heart beat was not changed as to rhythm, rate, or intensity. Respiratory rate was negligibly reduced, and no pattern was established as to the fluctuation in respiration. In the animals that died, very little change was observed in cardiac activity before death. Respiratory rate was almost always slightly increased, and some animals had muscular contractions to the point that they could not stand; death occurred 15 to 24 hours after the

injection. Histological examination showed only a slight congestion in all organs without any other noteworthy observations.

In the second study, the action of sodium gluconate on isolated heart from 80-g toads was studied. The concentration of the solutions used ranged upward from .0001g/mol/liter. The very dilute solutions had a slight excitatory effect on the activity of the heart, causing an increase in amplitude and neglible increase in frequency. To obtain a clear depressive action on the heart, a concentration of 2.18 g in 100 ml must be used.

In the next study, very dilute solutions of sodium gluconate in Ringer's solution (2.18 in 10 million), had a vasodilating action on the circulation in the hind section of toads. The vasodilation increased with increased concentration of the solution and reached a peak when the concentration was 2.18 g in 100 ml.

The effects of the infusion of a normal solution of sodium gluconate on arterial pressure and respiration in the rabbit revealed that the respriatory activity was generally increased, and this period of excitation was followed by a depressive period which led to paralysis of respiratory function. The blood pressure measurements showed that there was a slight initial increase by moderate dose of the drug, followed by a progressive reduction to 0 mm Hg. When breathing ceased, the blood pressure underwent a further reduction while the heart continued to beat for a short period (3).

To study the potential thrombolytic effect of sodium gluconate, 6 cats, in which a clot had been experimentally formed in the artery, were given 600 mg/kg body weight of sodium gluconate intravenously in 25 ml of physiological saline over a 30-minute period. The investigators were unable to find any evidence of a thrombolytic effect of gluconate (8).

ZINC GLUCONATE

Zinc gluconate was intravenously administered to rabbits in doses to 1 mg of zinc/kg to study its effect on blood sugar. After injection, distinct blood sugar increases occurred rarely, but a remarkable observation was that the smallest dose, 0.01 g zinc/kg, caused the most marked blood sugar increase (18).

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** Article to be found in summary

* Article to be found in text

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