EVALUATION OF THE HEALTH ASPECTS OF MANGANOUS SALTS
AS FOOD INGREDIENTS

1979

Prepared for
Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C.

Contract No. FDA 223-75-2004
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Life Sciences Research Office
Federation of American Societies
for Experimental Biology
9650 Rockville Pike
Bethesda, Maryland 20014
NOTICE

This report is one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior sanctioned food substances as food ingredients, being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or nongovernmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available to the public for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

Kenneth D. Fisher, Ph.D., Director
Life Sciences Research Office
FASEB

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I. INTRODUCTION

This report concerns the health aspects of using manganous salts as food ingredients. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1973.* To assure completeness and currency as of the date of this report this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; recent literature searches by the Toxicology Information Response Center, Oak Ridge, Tennessee; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRD staff. In addition, announcement was made in the Federal Register on April 21, 1978 (43 FR 17055) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the health aspects of using manganous salts as food ingredients. Three requests were received. The Select Committee held a hearing on November 6, 1978. Those who requested opportunity to present data, information, and views are identified on page 33. The material presented at the hearing has been considered by the Select Committee in reaching its final conclusions.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarketing clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (2) [21 CFR 170.3 and 170.30] that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. These sections of the Code also indicate that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA (2) recognizes further [21 CFR 170.30] that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

*The document (PB-228 553/4) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions. In reaching its conclusions on safety the Select Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. While the Select Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Select Committee, there are insufficient data upon which to base a conclusion. The Select Committee is aware that its conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on manganous salts and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of these substances under the Federal Food, Drug, and Cosmetic Act.
II. BACKGROUND INFORMATION

Manganese, an essential nutrient, occurs in many foods of plant and animal origin. The naturally occurring manganese levels vary from about 20 ppm in nuts, cereals, dried fruits and non-leafy vegetables to less than 1 ppm in animal products (3).

The Code of Federal Regulations (2) lists the following manganous salts as GRAS for use as nutrients and/or dietary supplements in foods for human consumption: chloride, citrate, gluconate, glycerophosphate, hypophosphite, sulfate, and oxide [21 CFR 182.5446, 182.5449, 182.5552, 182.5555, 182.5558, 182.5561, and 182.5564, respectively]. The Code also lists the following manganese salts as GRAS for use as nutrients and/or dietary supplements in animal feeds: chloride, citrate, gluconate, glycerophosphate, hypophosphite, sulfate, and oxide [21 CFR 582.5446, 582.5449, 582.5452, 582.5455, 582.5458, 582.5461, and 582.5464, respectively]. This report does not concern these feed uses. Manganous glycerophosphate and hypophosphite are included in Select Committee reports on the safety evaluation of glycerophosphates and hypophosphites (4,5).

The responses to a questionnaire survey of the food industry conducted by a subcommittee of the National Research Council (6) indicated that, of the GRAS manganous salts, manganous chloride and manganous sulfate are evidently the only ones currently used as ingredients in foods for human use. However, since manganous citrate, gluconate, and oxide are GRAS substances, all pertinent data on these salts were evaluated.

Table I lists certain physical and chemical characteristics and food grade specifications for some GRAS manganese salts. Manganous oxide is insoluble in hot water but soluble in acid, and manganous citrate is very slightly soluble in cold water (7). However, no food grade specifications were available for manganous citrate and manganous oxide.
### TABLE I

Characteristics and Specifications of Food Grade Manganous Salts (8)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Form, color, odor, taste</th>
<th>Solubility</th>
<th>Assay</th>
<th>Food grade specifications</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Limitations of impurities</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Heavy metals</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Arsenic ppm</td>
</tr>
<tr>
<td>Manganous chloride tetrahydrate</td>
<td>pink translucent crystals</td>
<td>very soluble in water</td>
<td>&lt;98 percent MnCl₂·4H₂O</td>
<td>3</td>
</tr>
<tr>
<td>Manganous sulfate</td>
<td>pink granular odorless powder</td>
<td>very soluble in water; insoluble in alcohol</td>
<td>&lt;98 percent MnSO₄·H₂O</td>
<td>3</td>
</tr>
<tr>
<td>Manganous gluconate</td>
<td>slightly pink powder</td>
<td>very soluble in water; slightly soluble in alcohol</td>
<td>&lt;98 percent C₁₂H₂₂MnO₁₄·2H₂O</td>
<td>3</td>
</tr>
<tr>
<td>Manganous glycerophosphate</td>
<td>white or pink-white odorless, tasteless powder</td>
<td>slightly soluble in water; insoluble in alcohol</td>
<td>&lt;98 percent C₃H₇MnO₆P·x H₂O (after drying)</td>
<td>3</td>
</tr>
<tr>
<td>Manganous hypophosphite</td>
<td>pink granular or crystalline odorless, nearly tasteless powder; air stable</td>
<td>soluble in water; insoluble in alcohol</td>
<td>&lt;97 percent Mn(PH₂O₂)₂·x H₂O (after drying)</td>
<td>3</td>
</tr>
</tbody>
</table>

*Other impurities: <5 ppm iron and 50 ppm sulfate*
III. CONSUMER EXPOSURE DATA

A National Research Council (NRC) subcommittee surveyed manufacturers in 1970 concerning the level of addition of GRAS substances to foods and estimated the possible average daily intake of these substances for several age groups (6). Based upon information supplied by those manufacturers who reported adding the GRAS substance to at least one food in a category, weighted means were calculated for the usual and maximal addition of the substances to foods in a category. Weighted means for the usual levels of addition of manganese salts are given in Table II.

**TABLE II**

<table>
<thead>
<tr>
<th>Food Category</th>
<th>Manganese chloride Weighted mean percent</th>
<th>Manganese sulfate Weighted mean percent</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baked goods, baking mixes</td>
<td>0.027</td>
<td></td>
</tr>
<tr>
<td>Milk, milk products</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Meat products</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Poultry products</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Fish products</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Snack foods</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td>0.006</td>
<td></td>
</tr>
<tr>
<td>Baby formulas</td>
<td>0.03</td>
<td>0.002</td>
</tr>
</tbody>
</table>

*Blanks in the table mean that the substance is not added to the foods indicated. Level of addition of manganous chloride and manganous sulfate is the weighted mean of the levels reported by manufacturers as their usual addition to one or more products in a food category. For discussion of weighted mean see Section X and Exhibit 50 of reference 6.

The concentration listed for baked goods, baking mixes presumably refers to dry mixes rather than to the product as consumed. Similarly, the concentration of manganous chloride in infant formulas appears to be in error. The Select Committee, from a review of the Physicians' Desk Reference (9), is aware of only one infant formula fortified with more than 1 mg of manganese (equivalent to 2.3 mg of manganous chloride or 2.7 mg of manganous sulfate) per quart (0.946 l). One soy-based infant
formula is fortified with 2.5 mg of manganese per quart but this formula is estimated to account for less than 2 percent of all commercially prepared formulas (10). Other manufacturers employ manganous sulfate, usually 2.7 mg per quart (9). The Physicians' Desk Reference (9) indicates that one manufacturer, whose sales account for nearly 50 percent of total infant formula sales, fortifies with manganous chloride. The level of fortification is 36 to 40 μg per quart (11).

The NRC subcommittee also estimated the possible average daily intakes of the chloride and sulfate salts for four age groups from Market Research Corporation of America data on the mean frequency of eating food by food category, U.S. Department of Agriculture data on mean portion size of foods in these categories, and the assumption that all food products within a category contained the substances at the level shown in Table II. The NRC subcommittee has recognized that in most cases its calculations of possible intakes are overstated, often by considerable margins. Because of factors detailed in Section XI of the subcommittee's survey report, estimated total dietary intakes are likely to be much higher than would be the intakes achieved through consumption of a diet consisting totally of processed foods to which the substances had been added at maximum levels. In the case of manganous sulfate, the NRC subcommittee estimated the average daily intake for individuals over two years of age to be 38 mg.

However, as may be seen from Table III, other data accumulated by the NRC subcommittee suggest that the total quantity of manganous sulfate added to foods in 1970 was 2600 kg and 7700 kg in 1975. Assuming a U.S. population of 205 million in 1970 and 215 million in 1975, this amounts to per capita usage of 0.03 and 0.10 mg daily, respectively, values that the Select Committee considers more likely to be correct than the value of 38 mg based on data in Table II. This estimate of an approximate daily intake of 0.03 to 0.1 mg of manganous sulfate (providing 0.01 to 0.03 mg of manganese) added to foods may be compared with the average daily adult intakes of manganese from the amounts occurring naturally in foods -- estimated to range from about 2 to 3 mg (3).

A separate estimate of usage of manganous chloride is possible on the assumption that nearly the entire addition of manganous chloride to foods pertains to infant formulas and that nearly all of this is added by one manufacturer at concentrations of 36 to 40 μg per quart. Assuming that there were approximately 3.5 million infants less than one year of age in the U.S. in 1970, that on any specified day 32 percent of these infants received commercially prepared formulas (10), that approximately half of this consumption is accounted for by formulas produced by the manufacturer who used manganous chloride, and that the average daily
intake of formula is two-thirds of a quart, the total national consumption would amount to about 5.48 kg of manganous chloride. The estimate seems in reasonable agreement with the 8 kg estimate present in Table III.

TABLE III

<table>
<thead>
<tr>
<th>Substance</th>
<th>Relative quantities added(^a)</th>
<th>Total quantities added in 1970(^b)</th>
<th>Per capita daily &quot;intake&quot;(^c)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manganous chloride</td>
<td>0.3</td>
<td>8</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Manganous sulfate</td>
<td>1.4</td>
<td>2600(^d)</td>
<td>0.03</td>
</tr>
</tbody>
</table>

\(^a\) Based only on the reports from those respondents to the National Research Council (NRC) survey who submitted information for both 1960 and 1970.

\(^b\) Total usage is based on the sum of kilograms used in foods as supplied by NRC and Flavor and Extract Manufacturers' Association (FEMA) recalculated to 100 percent from survey data that the NRC subcommittee estimated to represent about 60 percent of the actual usage.

\(^c\) Based on total consumption 1970 and a U.S. population of 205 million.

\(^d\) In a NRC resurvey (116) 8 companies reported that 7700 kg were used in 1975. This may be compared to 1600 kg reported by 12 companies in 1970.

It is also possible to provide an estimate of the largest amount of manganese added to food that might be consumed by an infant. As already mentioned, one infant formula that does not have wide usage is fortified with 2.5 mg of manganese per quart. The 90th percentile for energy intake of infants between two and three months of age is estimated to be 795 kcal per day (10). An infant suspected of milk allergy might consume this entire energy intake from formula, consuming 1187 ml of formula with a consequent intake of added manganese of 3.1 mg. Assuming body weight of 5.4 kg, the intake of added manganese amounts to approximately 0.6 mg per kg per day. An intake as great as this is likely to be achieved by relatively few infants.
IV. BIOLOGICAL STUDIES

Absorption

In general, manganous salts are poorly absorbed from the gastrointestinal tract (12), and the mechanism of manganese absorption is not well understood. Differences in absorbability among various compounds of manganese are suggested by the different blood levels attained when various forms of the salt are fed (13,14). For example, manganese appears more rapidly in the blood if fed in the form of chelates rather than in the form of inorganic salts. There is evidence to suggest that manganese absorption is by an active process in the duodenum (15), based on studies in which the uptake of $^{52}$Mn through inverted duodenal sacs was inhibited under anaerobic conditions. As reported by Underwood (3), studies of Sanssom et al. (16) indicated that manganous ions absorbed into the portal circulation may remain free or rapidly bind to $\alpha_2$-macroglobulin before passing through the liver, where they are almost completely removed. However, some of the manganous ions may pass into the systemic circulation, become oxidized to the manganic form and bound to transferrin.

Manganese levels in the tissues are also influenced by excretion. Greenberg et al. (17) showed that in rats, orally administered manganese (form of manganese and dose not specified) is poorly absorbed from the alimentary canal; that manganese is excreted almost totally with the feces; and that the bile plays an important role in the intestinal excretion of manganese. More recent experiments with several species including man show that manganese is excreted by several routes including biliary and at all levels of the small intestine, and that these together form a relatively efficient homeostatic mechanism for controlling manganese levels in the tissues (18-20). There is a linear relationship between dietary manganese and excretion rate, and this mechanism responds rapidly to changes in manganese intake. For example, in mice, a tenfold increase in dietary manganese intake reduced excretion time of a tracer dose of $^{54}$Mn by approximately one-half (20). Tissue turnover also appears to be dependent upon dietary intake. In addition to the biliary route, manganese can also be excreted by the pancreas (19), and directly through the duodenal and jejunal walls (18). Evidently these pathways become significant only when the hepatic pathways are overloaded, and they represent alternate means of regulating tissue manganese levels (21).

Dietary calcium and phosphorus modify manganese metabolism. Lassiter and his colleagues (22) found that feeding a 0.1 percent calcium diet (about 75 mg per kg per day) to rats increased fecal excretion of parenterally administered radioactive manganese (dose and form of manganese not specified) when compared to 0.6 percent calcium (about 450 mg per kg per day). Dietary levels
of phosphorus had no significant effect on retention of $^{54}$Mn given intraperitoneally; however, phosphorus at 0.9 percent in the diet resulted in significant retention of orally administered manganese compared with 0.4 percent phosphorus. Bourne (23) reported that, in cattle, high levels of calcium and phosphorus in the diet interfere with absorption of manganese, thus increasing the dietary manganese requirement. However, as reported by Watson (24), when rats were fed a diet containing 1.73 percent manganese, fecal excretion of calcium and phosphorus increased, and a similar effect was noted in cattle when manganese constituted 1000 and 2000 ppm of the diet.

**Metabolism**

The distribution of manganese in various tissues has been studied in rabbits (25,26), monkeys (27), and humans (28), as well as other species. In general, the results indicate that the tissue level of manganese is dependent upon level of exposure, particularly at high doses, e.g. more than 0.5 g per kg body weight. Manganese appears to concentrate not only in bile, but also in tissues rich in mitochondria such as liver, pancreas and kidney. For instance, normal human livers contain 6-8 ppm manganese (dry basis); livers of sheep, cattle and laying hens, about 8-10 ppm, while levels in skeletal muscle are among the lowest (3). A total dietary intake of 50 ppm manganese is recommended for growth of chicks and for normal egg production and hatchability. Within the cell, manganese is apparently preferentially associated with the mitochondria (29,30). However, the mitochondrial pool appears to be in equilibrium with the circulating pool (31). Manganese plays a key role in several metabolic systems particularly through its action as a cofactor or as a prosthetic group in several enzymes.

The disappearance of manganese from the blood occurs in three phases (32). The first and most rapid is identical with the clearance rate of other small ions and thus follows the kinetics of normal transcapillary movement. The second can be identified as the movement into the cellular mitochondria, and the third, which is the slowest, is associated with the passage into the cell nuclei. The rapidity with which the liver mitochondrial pool comes into equilibrium with the blood pool suggests that this represents a dynamic, mobile pool of tissue manganese. It is the pool that varies with changing dietary intake.

A role for adrenal regulation of the specific intracellular manganese pathway has been suggested (33,34). In mice, administration of high doses of cortisol acetate or prednisolone acetate resulted in marked reduction of manganese in the liver tissue fractions and an increase in the carcasses (skin, muscle, skeleton, heart, lungs, brain). Adrenalectomy produced an increase in concentration in the liver but only when high doses of manganese were used. The exact role of this type of endocrine regulation is not well understood and may represent an indirect rather than a direct regulatory mechanism.
In animals, manganese has been shown to be involved in a number of metabolic activities. In manganese deficiency, bone growth is impaired by an effect on matrix formation rather than an effect on the calcification process (3). This matrix effect was caused by a defect in the synthesis of mucopolysaccharides resulting from a specific need for manganese in two enzyme systems, the polymerase system responsible for the formation of the polymer from uridine diphosphate-glucuronic acid and the galactotransferase system responsible for the incorporation of galactose into the mucopolysaccharide (35,36). Manganese deficiencies have produced hypoplasia of the pancreas as well as a diabetes-like glucose tolerance curve (37,38). Moreover, administration of manganese has been reported to have a hypoglycemic effect in diabetics (39). Although not well understood, the mechanism of these effects has been attributed to its role as a component of the metalloprotein enzyme, pyruvate carboxylase (40) and its function in trans-carboxylation reactions (41).

Manganese has also been implicated in lipid metabolism. Amdur et al. (42) reported reduction in liver and bone fat upon supplementation of manganese-deficient diets with manganese. Voynar and Galakhova (43) also reported a reduction of fatty infiltration of the liver in carbon tetrachloride-poisoned animals that were subsequently treated with subcutaneous injections of manganous chloride solution. In rabbits on a high-cholesterol diet, daily oral doses of 6 mg manganous chloride lowered serum neutral fats and β-lipoproteins and increased α-lipoproteins (44). It has been suggested that this lipotropic action of manganese may be due to its role as a necessary cofactor for mevalonic kinase (45).

Manganese has been shown to be involved with the arginase system in the liver (46,47), so that increasing manganese intake causes an increase in its activity. Mosendz and Silakova (48) demonstrated increases in tissue ammonia level, particularly in the liver, when single doses of 75 mg per kg manganous chloride were given intratracheally to rats. The authors noted that this may be a significant factor in manganese poisoning.

In addition, manganese is involved in the metabolism of the central nervous system. For example, it has been implicated as an acetylcholinesterase inhibitor and monoamine oxidase activator (49). Conrad and Baxter (50) also found in rats given 300 mg per kg of manganous chloride subcutaneously, an increased uptake of radioactive calcium by the myocardium as well as a simultaneous rise in the Q-T interval.

Increased absorption of manganese from the gut has been observed in the presence of iron deficiency (51–53). In iron-deficient rats given 10 mg per kg manganous chloride orally for 15 days, Chandra and Tandon (54) found accumulation of manganese in liver and kidneys to be 2.5 and 2 times control values, respectively, and also found high concentrations in the testes of experimental animals.
Male weanling rats were given supplements of manganous chloride at the level of 4 percent of the diet (about 4 g per kg body weight at the start and 2 g per kg at the end of the experiment) in experiments lasting up to 120 days (55). In addition, between days 42 and 86, they received a total of 4.5 mg manganous chloride per animal intraperitoneally three times weekly and, between days 86 and 120, surviving animals received a total of 25.5 mg intraperitoneally. Gubler et al. reported a mild microcytic hypochromic anemia, a decrease in iron stores, and an increase in circulating copper in the rats that received such levels of manganous chloride. Similar effects have been found in rabbits and pigs (56) and lambs (57) in which a depression of hemoglobin synthesis was reported when large amounts of manganous sulfate were included in the diet.

Guinea pigs receiving daily oral doses of 10 mg per kg manganous chloride for 30 days showed loss of mucin and pepsinogen granules, reduced ATPase and glucose-6-phosphatase activities, and patchy epithelial necrosis of the gastric mucosa and similar ATPase and glucose-6-phosphatase changes and necrosis of the intestinal villi while acid phosphatase activity was increased in these tissues (58).

**Acute toxicity**

Divalent manganese is among the least toxic of the trace elements (3). Acute systemic intoxication is unlikely after ingestion of manganese salts because of poor absorption from the gastrointestinal tract (12). No acute oral toxicity data for animals are available. Data on acute parenteral lethal doses of manganous chloride, citrate, oxide, and sulfate are summarized in Table IV. Handovsky et al. (59) concluded that very high blood manganese levels must be attained to be lethal while lower concentrations can cause liver damage, and that the citrate salt given subcutaneously was more toxic than the chloride salt.

No acute toxicity data on manganous oxide since those reported in 1883 by Kobert (14) have come to the attention of the Select Committee, and the only additional reference on the biologic effects of manganous oxide (66) involved parenteral administration of high doses.

Toxicity evaluation of added food ingredients in animal feeds is not customarily based upon lethality, but upon such signs as depression of appetite and growth rate (67). According to Underwood (3), in mammals and birds, manganese is among the least toxic microelements. Dietary intakes of 1000 to 2000 ppm do not affect growth in rats, and 1000 ppm produce no adverse effects in hens; however, 4800 ppm are toxic to chicks. Depression of appetite and growth occurs in young pigs fed 500 ppm manganese, and similar effects result in calves from supple-
<table>
<thead>
<tr>
<th>Substance</th>
<th>Animal</th>
<th>Route</th>
<th>LD&lt;sub&gt;100&lt;/sub&gt;</th>
<th>LD&lt;sub&gt;50&lt;/sub&gt;</th>
<th>LDLo&lt;sup&gt;d&lt;/sup&gt;</th>
<th>Maximum no adverse effect</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Manganese chloride</td>
<td>mouse, guinea pig, mouse</td>
<td>s.c.</td>
<td>50</td>
<td>121</td>
<td>60</td>
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<tr>
<td></td>
<td>mouse</td>
<td>i.p.</td>
<td></td>
<td></td>
<td>60</td>
<td></td>
<td>60</td>
</tr>
<tr>
<td></td>
<td>mouse</td>
<td>s.c.</td>
<td></td>
<td>210</td>
<td>60</td>
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<td>rat</td>
<td>s.c.</td>
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<td>61</td>
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<td></td>
<td>rat</td>
<td>i.m.</td>
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<td>62</td>
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<td>s.c.</td>
<td>400</td>
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<td>61</td>
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<td></td>
<td>hamster</td>
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<td>700</td>
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<td></td>
<td>rabbit</td>
<td>par.</td>
<td>18</td>
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<td>61</td>
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<tr>
<td></td>
<td>rabbit</td>
<td>i.v.</td>
<td>18(as Mn)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>2.5</td>
<td>63</td>
<td></td>
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<tr>
<td></td>
<td>rabbit</td>
<td>i.v.</td>
<td>21.4(as Mn)&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12.6</td>
<td>64</td>
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<tr>
<td></td>
<td>dog</td>
<td>par.</td>
<td>56</td>
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<tr>
<td></td>
<td>dog</td>
<td>i.v.</td>
<td>56(as Mn)&lt;sup&gt;b&lt;/sup&gt;</td>
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<tr>
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<td>mouse</td>
<td>i.p.</td>
<td>190</td>
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<td></td>
<td>rat</td>
<td>s.c.</td>
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<td>50</td>
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<tr>
<td>Manganese citrate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>mouse, guinea pig, rabbit</td>
<td>s.c.</td>
<td>50</td>
<td>225</td>
<td>59</td>
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<td>i.m.</td>
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<tr>
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<td>guinea pig</td>
<td>s.c.</td>
<td>28–30</td>
<td>14</td>
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<td></td>
<td>rabbit</td>
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<td>12–13</td>
<td>14</td>
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<tr>
<td></td>
<td>cat</td>
<td>s.c.</td>
<td>6–8(48 h)</td>
<td>14</td>
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<td>6–8(48 h)</td>
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<td></td>
<td>534</td>
<td>60</td>
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<sup>a</sup>Degree of hydration not indicated.
<sup>b</sup>Combined with unspecified amount of Na<sub>2</sub>S<sub>2</sub>O<sub>3</sub>.
<sup>c</sup>Rabbit

The author described his test substance as a soluble complex of manganous oxide and citric acid; however, he reported his results in terms of manganous oxide.
mentation of low-manganese diets with 2460 to 4920 ppm manganous sulfate; however, calves tolerate without apparent effects on appetite and growth, dietary supplements of 820 ppm manganese. A dietary intake of 400 ppm manganese may depress growth rates in growing sheep (3).

Several authors have reported the suitability of manganous oxide as a source of manganese for poultry as well as ruminants and other farm animals (24,68,69), and, according to industry sources (70), perhaps 90 percent of the manganese used to meet the dietary requirements of livestock and poultry is in the form of manganous oxide.

While the manganous ion is considered relatively nontoxic (3), exposure to manganic oxides, such as occurs in mining and industry, can be hazardous (31,71,72). The fact that manganous oxide in the presence of alkali and air will easily oxidize to higher oxides under laboratory conditions has been noted (73). However, feed grade manganous oxide manufactured in the United States by a patented process involving reduction of manganese dioxide ore at a temperature about 1300°F., is said to resist oxidation under ambient or near-ambient conditions provided that it has been cooled to at least 300°F. before exposure to the open atmosphere (74,75).

In addition, when two commercial manganous oxide products were exposed for about 30 days to simulated storage at 50°C., under dry or intermittently humid conditions, the 62 percent product (which is used in poultry and livestock feeds) showed an increase in available oxygen of 1.7 percent (equivalent to approximately 5 percent manganese dioxide), and the high-purity product (nearly 100 percent MnO, not used in feeds) showed no increase in the dry test. The 62 percent and the high-purity products showed 2.3 and 4.0 percent increases, respectively, in available oxygen (equivalent to approximately 7 and 10 percent manganese dioxide) in the variable humidity test (76). In these tests, an increase in available oxygen resulted from reoxidation of the manganous oxide to an oxidation state higher than +2. The foregoing were considered maximum reoxidation values under the test conditions, and it was concluded that extending the simulated storage period probably would not increase the reoxidation. Industry sources point out that the manganous oxide product used in animal feeds contains a maximum of 5 percent manganese dioxide, but usually less than 2 percent (67).

Short-term studies

In rats, daily subcutaneous doses of 10 and 20 mg per kg of manganous chloride for four weeks had no effect on growth, but 30 and 40 mg per kg produced growth inhibition and some deaths (65). The LD$_{50}$ for these treatments was reported to be 50 mg per kg while the LD$_{100}$ was 60 mg per kg.
Because of the metabolic importance of manganese, it is not surprising that the pathogenesis of manganese toxicity should include functional manifestations in several metabolic systems. Thus the widespread observation of central nervous system dysfunction with manganese poisoning can be traced to the inhibition of acetylcholinesterase or stimulation of monoamine oxidase associated with manganese activity (49). Tal and Guggenheim (77) reported that doses of manganous sulfate up to 25 mg per kg of diet fed to mice for six weeks resulted in defective bone calcification.

In several experiments involving short-term feeding or parenteral administration of high levels of manganese, histologic signs of liver damage were observed: in rats given 3 mg manganous chloride (about 12 mg per kg body weight) parenterally every other day for up to 86 days and in rats fed a diet supplemented with 300 to 400 mg per day (estimated to be 1.4 g per kg body weight per day) for up to 70 days (78); in hamsters given 45 mg manganous sulfate per kg per day for 10 days (79); in guinea pigs given 3 mg manganous chloride (about 10.7 mg per kg body weight) subcutaneously on alternate days for 70 days; and in rabbits given single doses of 10 to 60 mg (about 5 to 30 mg per kg body weight) and multiple doses of 3 to 5 mg (about 2.1 to 3.5 mg per kg body weight) of manganous chloride subcutaneously for 70 days (78).

The livers of the rabbits, rats, and guinea pigs exhibited peripheral lobular parenchymal fatty degeneration and congestion, round cell infiltration, and fibrous tissue proliferation of the portal tracts and formation of new bile capillaries surrounded by freshly-formed fibrous tissue (78). In the hamsters, the liver damage took the form of parenchymal cell fatty infiltration and necrosis in the periportal spaces along the periphery of the hepatic lobules, then spreading toward the lobule centers accompanied by infiltration of polymorphonuclear leukocytes. Periportal connective tissue proliferation and cystic duct proliferation were reported in hamsters surviving 15 or more days; however, frank cirrhosis was not reported in hamsters surviving 30 days or longer (79).

Rabbits given subcutaneous doses of manganous chloride two or three times weekly for 12 to 48 weeks (total doses varied from 62 mg to 1 g per animal) had focal necrosis of the liver, pulmonary hemorrhages, and amyloid degeneration of the kidneys. However, no untoward effects were found in five rabbits fed manganous chloride daily for 11 to 41 weeks (total amounts consumed varied from 1 to 47 g per animals) (80).

Witzleben and his associates (81) injected rats intravenously with aqueous solutions of manganous sulfate (estimated to be 100 mg to 200 mg per kg body weight) and studied bilirubin clearance and histopathologic effects in the liver. They observed hepatocellular necrosis accompanied by marked swelling of the
mitochondria and accumulation of lipid in hepatocytes and an associated severe cholestasis. They suggested that manganese overload is a model of intrahepatic cholestasis at the level of the hepatocyte. In studies of bilirubin and manganese as cholestatic agents, Witzleben and Boyce (82) noted that the amount of manganese in the bile is not critical in manganese-bilirubin cholestasis; that the critical cholestatic events occur within the hepatocyte, and that the biliary excretion of manganese is obligate.

Liver sclerosis starting in the connective tissue surrounding the bile duct and a "cholangitis-like cirrhosis" were reported in dogs given 2 mg per kg manganese chloride intramuscularly on alternate days for up to 16 weeks (83). Monkeys given increasing doses from 5 to 25 mg of manganese chloride intraperitoneally on alternate days for 18 months also showed scattered areas of liver necrosis with hemorrhages and fibrosis (27). Body weights of the monkeys were not reported.

Another consistent observation is associated with central nervous system dysfunction. Chandra and Srivastava (84) gave male rats daily injections of manganese chloride intraperitoneally for 180 days at 8 mg per kg body weight. At 90 days no pathology was noted, while at 120 days changes were observed which became more apparent at 180 days. These included fairly large numbers of degenerated neurons in the cerebral and cerebellar cortex. Two rabbits given 75 mg (about 37 mg per kg body weight) of manganese sulfate in drinking water daily for several months had transient paralysis and anesthesia of the hind paws and weight loss (85). Although the insensitivity to pin prick in the hind paws lasted "a long time," the paralysis disappeared after about two months despite continuous administration of manganese sulfate at 75 mg per day. In a more extensive study, monkeys given increasing doses (up to 25 mg) of manganese chloride intraperitoneally every day for 18 months starting at 4 mg per animal, showed extensive neurological changes including degeneration of neurons in the putamen, caudate nuclei and globus pallidus and demyelinization of some interconnecting fibers and gliosis (27). The monkeys developed choreic or choreo-athetoid movements followed by states of rigidity, disturbances of motility, and finally, fine tremors of the forepaws and eventually contractures of the forepaws with extended terminal phalanges.

In one human experience in which several cases of poisoning occurred as a result of drinking well water contaminated with manganese leached from buried dry-cell batteries, similar behavioral and neurological changes were observed (86). Destruction of neurons of the globus pallidus was reported in one of the fatal cases. The authors did not include an estimate of the amounts of manganese ingested by the victims.

It is not surprising that large doses of manganese can cause hematopoietic changes. Rats fed manganese sulfate for four
weeks in a complicated schedule received a dietary concentration of 1.2 percent to 2.4 percent (approximately 2.4 to 4.8 g per kg body weight) (87). They demonstrated decreased food intake, decreased weight gain, decreased food efficiency, and depigmentation of the incisors, as well as decreased hemoglobin and increased erythrocyte count. Subcutaneous administration of single doses of 50 to 300 mg per kg manganous chloride to rats also produced acute changes in hepatic and splenic iron levels resulting in hypochromic anemia (88). Manganese (compound not specified) was also shown to inhibit hemoglobin regeneration in anemic rabbits when fed at levels up to 5000 ppm (estimated to be approximately 150 mg per kg per day) in the diet for six weeks (56). The same authors also found that the inhibition of hemoglobin formation found in rabbits could be duplicated in baby pigs. These effects could be prevented by increasing the iron level of the diet.

Rats injected subcutaneously with 100 mg per kg manganous oxide or manganese dioxide suspended in normal saline on alternate days for a total of 18 injections showed weight loss, adynamia, paralysis of the hind legs in some animals, and at autopsy, hypertrophy of the adrenal cortex and depletion of adrenal cortical ketosteroids (66). The changes were described as more pronounced with manganese dioxide than with manganous oxide although the amount of manganese administered in the two oxides was identical. The authors suggested that, rather than a direct effect on tissue function, the observed changes were secondary to impairment of neurohumoral functions caused by lesions in the central nervous system.

In studies of rats and rabbits given manganous chloride or sulfate or manganese dioxide parenterally, testicular accumulation of manganese occurred associated with enzymatic, morphologic, and functional changes including, in some instances, destruction of seminiferous tubules and sterility (89-92). Doses varied from 3.5 to 8 mg per kg body weight except for rabbits given single intratracheal doses of 250 mg per kg of manganese dioxide of particle size >5μ (92).

Various manganese salts have been used to treat a variety of human disorders including anemia and several infectious diseases (93). In addition, they have been used for rheumatic endocarditis (94), as a hypoglycemic agent (95), and in infectious polyarthritis (96). Except for the fact that manganese is an essential trace element, manganese salts have limited applicability in modern western medical practice.

Long-term studies

In a two-year study, rats were fed diets supplemented with 3.6 percent manganous chloride (equivalent to approximately 5.6 manganous chloride per kg body weight at the start and 1.1 g per kg at the end of the experiment). Although a slight reduction in
weight gain was noted, no other toxic manifestations were reported. No histopathologic examinations were done on these animals. In addition, the diets were high in calcium and phosphorus, thus potentially reducing manganese absorption (97).

There is extensive literature on chronic manganese toxicity in man which has been reviewed thoroughly (31,71,72). This condition is seen almost exclusively in miners exposed to manganic oxide dusts and is characterized by a severe psychotic disorder called "manganic madness." Generally there are marked behavioral and neurological manifestations, and accompanying changes in hematopoiesis and possibly in reproductive function. Tissue levels of manganese are extremely high and the manifestations of the disease may go on for several years after exposure is stopped.

**Special studies**

Chick embryos were exposed to five dose levels of aqueous solutions of manganous sulfate in four sets of conditions: 0.5 to 10 mg per egg (10 to 200 mg per kg, embryo) injected into the air cell at zero h; 0.025 to 0.625 mg per egg (0.5 to 12.5 mg per kg, embryo) into the air cell at 96 h; 0.5 to 10 mg per egg (10 to 200 mg per kg, embryo) into the yolk at zero h; and 0.25 to 5 mg per egg (5 to 100 mg per kg, embryo) at 96 h. No teratogenicity was observed under the test conditions employed (98).

Another laboratory reported high levels of chick embryo mortality from doses of 100 to 500 mg manganous sulfate per kg egg, injected into the air cell at zero h and into the yolk at 0 and 96 h, and from doses as low as 10 mg per kg injected into air cell at 96 h (99). However, the incidence of structural abnormalities in the treated embryos was not significantly different from that observed after injection of the solvent (sterile distilled water) alone.

In an abstract published in 1972, it was reported that the offspring of rats that were given oral and parenteral manganous chloride or potassium permanganate in doses of 0.1 to 0.5 LD₅₀ doses for six months showed decreased postnatal survival, depressed hypophysseal gonadotropic activity, hypogonadism, shortened period of sexual activity, altered sex ratios, and inactivity of cholinesterase and transaminase (100). Attempts to obtain experimental details of this study have been unsuccessful.

Manganous chloride and manganous sulfate have been reported to be mutagenic in vitro in several systems including reversal of streptomycin dependence to independence in Escherichia coli (101, 102) and induction of heritable respiratory deficiency in nondividing tetraploid Saccharomyces (103). Typical concentration of manganous chloride solution was 0.04 percent (101) and of manganous sulfate, 4 mg per liter of medium (103). However, these effects
could be modified within a wide range by a number of associated factors including media, aeration, and growth stage. In addition, the mutagenic properties of manganous chloride were shown to be influenced by the presence of other components in the media (102). In a dominant lethal assay, mice given single intraperitoneal injections of manganous chloride at levels of 20 and 100 mg per kg showed no mutagenic effects when compared with controls (104).

In other studies, manganous sulfate was reported to be non-mutagenic in host-mediated assays and chromosome translocation tests in mice; in dominant lethal tests in rats, and in in vitro microbial assays using *Saccharomyces cerevisiae* D3 and *Salmonella typhimurium* strains TA 1535, 1536, 1537, and 1538 (105). No teratological effects were observed in the offspring after daily oral intubation of up to 125 mg manganous sulfate per kg body weight for 10 days to pregnant mice; up to 78.3 mg per kg for 10 days to pregnant rats; up to 136 mg per kg for 5 days to pregnant hamsters; and up to 112 mg per kg for 13 days to pregnant rabbits (106-109).

Hypoplastic dental enamel has been found in rats given single subcutaneous injections of 400 mg per kg of manganous chloride and in guinea pigs given 150 to 490 mg per kg subcutaneously, but not in hamsters given similar doses (61).

Comens (110) reported that 5 mg per day manganous citrate fed to 10-day-old cockerels prevented hydralazine-induced perosis (syndrome includes malformation of tibiometatarsal joints, deformed tibias, and dislocation of gastrocnemius tendons); that hydralazine-induced convulsions in rats were prevented by injections of manganous glycerophosphate (doses and route not specified); and that parenteral manganous citrate (doses and route not specified) prevented development of glomerular wire loops in hydralazine-fed dogs.

Manganous salts have received limited attention in carcinogenesis evaluations. No long-term feeding studies were identified (111). When given by parenteral injection, manganous chloride was reported to accelerate the appearance of lymphosarcomas in DBA mice (112), and manganous sulfate increased the number of pulmonary adenomas in strain A mice (113). The relevance of these findings to human health in terms of the use of manganous salts as food ingredients is not clear.

Despite the nearly complete lack of scientific reports on the biologic effects of manganous citrate and gluconate, the relatively low toxicity of the manganous ion and the innocuous nature of citrates (114) and gluconates (115) when used as food ingredients suggest that no health hazard would result from similar uses of manganous citrate and gluconate.
V. OPINION

The conclusions in the opinion are limited to the use of manganous salts in foods for human consumption and do not concern the use of manganese in animal feeds.

The available information indicates that a wide margin exists between present intake levels of manganese as manganous salts and those levels that have been reported to produce harmful effects. Manganese is an essential nutrient that is required for the optimal functioning of several metabolic systems largely through its role as a prosthetic group or as an essential cofactor. Divalent manganese is among the least toxic of the trace elements. As was indicated in the review of the experiments involving manganous chloride and manganous sulfate, the oral toxicity of manganese is low largely because of restricted absorption and the existence of a relatively efficient mechanism regulating intestinal excretion.

Manganese interacts metabolically with several other minerals including calcium, phosphorus, iron, and copper. Under most dietary conditions, however, it is unlikely that the ratio of manganese to these elements is distorted enough to produce an adverse effect.

The only manganese salts known by the Select Committee to be in use as ingredients of foods for human consumption are the chloride and the sulfate. Despite the nearly complete lack of scientific reports on the biologic effects of manganous citrate and gluconate, the relatively low toxicity of the manganous ion and the innocuous nature of citrates and gluconates when used as food ingredients suggest that no health hazard would result from similar uses of manganous citrate and gluconate.

While there is good evidence of the short-term tolerance of manganous oxide as an added feed ingredient for poultry and livestock, no acute oral toxicity studies or long-term feeding studies of manganous oxide have been reported. In addition, the Select Committee has no information on the amounts of manganous oxide, if any, that may be used in foods for human consumption in this country.

The Select Committee has weighed the foregoing data and concludes that:

There is no evidence in the available information on manganous citrate, chloride, gluconate, and sulfate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels that are now current or that might reasonably be expected in the future.
In view of the deficiency of relevant biological studies and information on consumer exposure, the Select Committee has insufficient data upon which to base an evaluation of manganous oxide when it is used in food for human consumption.
VI. REFERENCES CITED


- 26 -
74. DeCraene, D.F. 1978. Testimony presented before the Select Committee on GRAS Substances at a public hearing on manganous salts, November 6, Bethesda, Md. Chemetals Corporation, Baltimore, Md.


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Report submitted by:

September 12, 1979

George W. Irving, Jr., Chairman
Select Committee on GRAS Substances
PUBLIC HEARING ON MANGANOUS SALTS, HELD NOVEMBER 6, 1978*

Three requests for a hearing were received and the following individuals made presentations:

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