EVALUATION OF THE HEALTH ASPECTS OF IRON AND IRON SALTS AS FOOD INGREDIENTS

1980

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

Contract No. FDA-223-75-2004
EVALUATION OF THE HEALTH ASPECTS OF IRON AND IRRON SALTS AS FOOD INGREDIENTS

1980

Prepared for

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

Contract No. FDA 223-75-2004

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
<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>I. Introduction</td>
<td>1</td>
</tr>
<tr>
<td>II. Background information</td>
<td>3</td>
</tr>
<tr>
<td>III. Consumer exposure data</td>
<td>11</td>
</tr>
<tr>
<td>IV. Biological studies</td>
<td>19</td>
</tr>
<tr>
<td>V. Opinion</td>
<td>49</td>
</tr>
<tr>
<td>VI. References cited</td>
<td>52</td>
</tr>
<tr>
<td>VII. Scientists contributing to this report</td>
<td>69</td>
</tr>
</tbody>
</table>
I. INTRODUCTION

This report concerns the health aspects of using elemental iron and iron 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; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff. In addition, announcement was made in the Federal Register on August 28, 1979 (44 FR 50414) 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 using iron or iron salts as food ingredients or, in lieu of an oral presentation, to submit a written statement. In response to requests for opportunity to make oral presentations, a hearing was held on November 19, 1979. Names of those who made presentations at the hearing and those who submitted written statements are given on page 71.

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) [21 CFR 170.30] recognizes further that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

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,

*Reference 1 (PB-221 236) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
the 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 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 Committee, there are insufficient data upon which to base a conclusion. The Committee is aware that these 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 elemental iron and iron 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

Iron is the fourth most abundant element in the earth's crust, exceeded only by oxygen, silicon, and aluminum (3). It is essential for a number of biological processes and is present in all living matter (4). In water and soil, it is usually in the form of ferrous and ferric oxides and hydroxides (3), but in biological material, the forms are considerably more numerous and varied (5). Thus, the iron in foods may be ingested in its elemental form, as relatively simple inorganic and organic compounds, and as iron complexes, such as heme, in which iron is bound to porphyrin, a tetrapyrrole structure (6).

Iron deficiency is widely viewed as a prime example of nutritional inadequacy (3). The World Health Organization in 1968 (7) characterized nutritional anemia as the most frequent type of malnutrition in the world at that time. However, it has proved difficult to define the term with sufficient precision to obtain a reliable measure of its prevalence. Estimates are usually based on the incidence of hypochromic anemia and the assumption that iron deficiency is its principal cause (8). Even if this assumption should be correct, the estimates would denote only overt and not latent iron deficiencies. Furthermore, there is no unanimity concerning what constitutes normal hematological values. Utilization of different standards would alter the apparent incidence of anemia.

To provide a more precise definition of iron deficiency, investigators have attempted to relate it to the concentration of specific iron substances in the blood and tissue. Moore (8) characterized iron-deficiency anemia as a condition with small, pale erythrocytes, depleted iron stores, plasma iron value below 40 µg per dl, elevated iron-binding capacity, and less than 15 percent saturation of transferrin, an iron-transporting protein. Infants and preschool children appear to be especially vulnerable to iron deficiency if transferrin saturation is used as the criterion (9,10). Owen et al. (9) reported that almost half of 1-year-old children from all income groups had a serum transferrin saturation less than 15 percent. About 10 percent of all children aged 1 to 5 years, and 14 percent of this age group in low income families, had "low" transferrin saturations (10).

The development of a sensitive immunoradiometric assay for the iron-storage molecule, ferritin, has provided an additional promising technique to evaluate the iron stores in the body. Jacobs and Worwood (11) found that the serum ferritin in patients with uncomplicated iron deficiency was less than 12 µg per liter, in contrast with 12 to 250 µg per liter in normal subjects, and as much as 10,000 µg per liter in patients with iron overload. In addition, red-cell protoporphyrin, the noniron portion of heme, has been employed as a screening test for iron deficiency (12).
Nevertheless, as pointed out in a recent review, no single test is without its pitfalls, and even a battery of tests is not infallible in detecting iron deficiency (13).

Inasmuch as iron deficiency occurs in some individuals, and the content, form, and availability of iron in foods vary greatly, it has become customary to fortify certain foods with forms of iron to help ensure nutritional adequacy. FDA regulations impose certain labeling requirements on foods to which sufficient vitamins or minerals have been added to provide 50 percent or more of the U.S. Recommended Daily Allowance in a single serving [21 CFR 101.9] (2). Iron fortification of foods is usually kept below this level to avoid such requirements. Three basic questions must be considered whenever the decision is made to fortify foods with iron: a) the level of iron to be added; b) the vehicle to be used; and c) the form of iron to be added (14). The selection of a suitable vehicle for the addition of iron is important, and will depend largely on the eating habits of a given culture or country. Whatever food is selected should be one that is already widely consumed by the population and will remain stable and palatable after enrichment (14). In the U.S., cereal foods have been selected as the most suitable vehicles for enrichment and the addition of iron is now authorized for a number of such products (Table I). However, in a recent review, Lee and Clydesdale (15) point out that bread and cereal themselves impair the availability of iron, and they conclude that these products are inappropriate vehicles for iron fortification.

Four categories of substances are considered in this report: elemental iron and iron compounds which have been accorded GRAS status and which are published in the Code of Federal Regulations (CFR) (2); prior-sanctioned substances employed in the manufacture of food-packaging materials [21 CFR 181.25]; iron compounds which the FDA has approved as GRAS by letter to inquiring manufacturers, but which are not published in the CFR (16); and iron compounds of potential utility which FDA has requested the Select Committee to evaluate (17).

A. Published GRAS Substances

In selecting the form of iron for enrichment, not only must its chemical and physical properties be examined, but those of the foods to be fortified as well. Solubility, stability, bioavailability, organoleptic qualities, and cost must all be considered. Inasmuch as no one substance has proved to be clearly preeminent as an enrichment agent, the food industry has used, or contemplated the use of, a score of different forms and compounds of iron. Of these, ten have been considered GRAS, either as nutrients and/or dietary supplements or as ingredients of paper and paperboard products used in food packaging. These are listed in the CFR (2) and are indicated together with some of their properties in Table II.
### TABLE I

**Authorized Iron Enrichment for Food Products**

<table>
<thead>
<tr>
<th>Product</th>
<th>Iron enrichment levels mg/kg</th>
<th>Authorization</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bread, rolls, and buns</td>
<td>17.6-27.5*</td>
<td>21 CFR 136.115</td>
</tr>
<tr>
<td>Flour</td>
<td>28.6-36.3*</td>
<td>21 CFR 137.165</td>
</tr>
<tr>
<td>Self-rising flour</td>
<td>28.6-36.3*</td>
<td>21 CFR 137.185</td>
</tr>
<tr>
<td>Corn grits</td>
<td>28.6-57.2**</td>
<td>21 CFR 137.235</td>
</tr>
<tr>
<td>Corn meal</td>
<td>28.6-57.2**</td>
<td>21 CFR 137.260</td>
</tr>
<tr>
<td>Farina</td>
<td>not less than 28.6**</td>
<td>21 CFR 137.305</td>
</tr>
<tr>
<td>Rice</td>
<td>28.6-57.2**</td>
<td>21 CFR 137.350</td>
</tr>
<tr>
<td>Macaroni products</td>
<td>28.6-36.3**</td>
<td>21 CFR 139.115</td>
</tr>
<tr>
<td>Macaroni products with fortified protein</td>
<td>36.3**</td>
<td>21 CFR 139.117</td>
</tr>
<tr>
<td>Non-fat milk macaroni products</td>
<td>28.6-36.3**</td>
<td>21 CFR 139.122</td>
</tr>
<tr>
<td>Vegetable macaroni products</td>
<td>28.6-36.3**</td>
<td>21 CFR 139.135</td>
</tr>
<tr>
<td>Noodle products</td>
<td>28.6-36.3**</td>
<td>21 CFR 139.155</td>
</tr>
<tr>
<td>Vegetable noodle products</td>
<td>28.6-36.3**</td>
<td>21 CFR 139.165</td>
</tr>
</tbody>
</table>

* "... may be supplied by any safe and suitable substance."

** "... may be added only in forms which are harmless and assimilable."
<table>
<thead>
<tr>
<th>Form</th>
<th>Formula</th>
<th>GRAS use</th>
<th>Authorization</th>
<th>Solubility Water</th>
<th>HCl</th>
<th>Limits of impurities (ppm) (Food Chemicals Codex) (18)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iron, Reduced</td>
<td>Fe</td>
<td>a</td>
<td>21 CFR 182.5375</td>
<td>Insol.</td>
<td>Sol.</td>
<td>Arsenic, 8; lead, 25; mercury, 5; fluoride, 3.</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>Fe(C₆H₁₁O₇)₂·2H₂O</td>
<td>a</td>
<td>21 CFR 182.5308</td>
<td>Sol.</td>
<td></td>
<td>Arsenic, 3; lead, 10; mercury, 3. Ferric iron, 2 percent.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrous lactate</td>
<td>Fe(C₃H₅O₃)₂·3H₂O</td>
<td>a</td>
<td>21 CFR 182.5311</td>
<td>Sol.</td>
<td></td>
<td>None given.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b</td>
<td>21 CFR 182.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>FeSO₄·7H₂O</td>
<td>a</td>
<td>21 CFR 182.5315</td>
<td>Sol.</td>
<td></td>
<td>Arsenic, 3; lead, 10; mercury, 3.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>b</td>
<td>21 CFR 182.90</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ferric phosphate</td>
<td>FePO₄·XH₂O</td>
<td>a</td>
<td>21 CFR 182.5301</td>
<td>Insol.</td>
<td>Sol.</td>
<td>Arsenic, 3; lead, 10; mercury, 3.</td>
</tr>
<tr>
<td>Ferric pyrophosphate</td>
<td>Fe₄(P₂O₇)₃·9H₂O</td>
<td>a</td>
<td>21 CFR 182.5304</td>
<td>Insol.</td>
<td>Sol.</td>
<td>Arsenic, 3; lead, 10; mercury, 3.</td>
</tr>
<tr>
<td>Ferric sodium pyrophosphate</td>
<td>Fe₄Na₈(P₂O₇)₅·XH₂O</td>
<td>a</td>
<td>21 CFR 182.5306</td>
<td>Insol.</td>
<td>Sol.</td>
<td>None given.</td>
</tr>
<tr>
<td>Ferric sulfate</td>
<td>Fe₂(SO₄)₃</td>
<td>b</td>
<td>21 CFR 182.90</td>
<td>Slowly</td>
<td>Sol.</td>
<td>None given.</td>
</tr>
</tbody>
</table>

a) Nutrient and/or dietary supplement.
b) Ingredients of paper and paperboard products used in food packaging.
Two entries in Table II require clarification: "Iron, reduced" and "Oxides of iron." "Reduced iron" or "ferrum reductum" is broadly used as a term for all food-grade iron powders. This designation engenders confusion, because reduced iron is a metallurgical term for a specific form of powdered iron (15). The process employed in preparing the elemental iron determines the particle size, surface area, density, amount of impurities, and other factors which in turn profoundly influence the bioavailability of the product from iron-fortified foods. Lee and Clydesdale (15) suggest, and the Select Committee agrees, that "elemental iron" be used to include the various forms of metallic iron; this term will be employed henceforth. Actually, three forms of elemental iron are used in food fortification: reduced iron, electrolytic iron, and carbonyl iron (6).

Reduced iron is prepared by the reduction of ground ferric oxide with hydrogen or carbon monoxide at an elevated temperature. The purity of the product is dictated by the purity of the ferric oxide used. The reduced powder is comminuted, and those particles passing through a 100 mesh sieve (149 μ or less) are used for food fortification. Some of the original ferric oxide may remain in the center of the particles, thus reducing the bioavailability of the powder (6).

Electrolytic iron is produced by plating chemically pure iron onto stainless steel cathodes. The iron deposit is removed from the electrodes, ground, and sieved to food grade specifications. The particles are described as irregular, dendritic or fernlike, shapes which provide greater surface areas than the more symmetrical reduced iron powder (6).

Carbonyl iron is produced by treating scrap or reduced iron with carbon monoxide under heat and pressure. Iron pentacarbonyl [Fe(CO)₅], the product of this treatment, is then decomposed under controlled conditions. Carbon, the major impurity at this stage, is removed by further reduction in wet hydrogen. This process yields iron particles of high purity and small size (0.5 to 10 in diameter) (6).

"Oxides of iron" are GRAS as ingredients of paper and paperboard products used in food packaging. The term presumably refers to ferrous oxide (FeO) and ferric oxide (Fe₂O₃) present independently or as mixtures of uncertain proportions.

B. PRIOR-SANCTIONED SUBSTANCES

Iron caprylate, linoleate, naphthenate, and tallate were sanctioned for use in the manufacture of food-packaging materials before the 1958 enactment of the food additives amendment to the Federal Food, Drug and Cosmetic Act. The CFR (2) indicates that
these substances are not considered "food additives" within the meaning of the Act "... provided that they are of good commercial grade, are suitable for association with food, and are used in accordance with good manufacturing practice" [21 CFR 181.22].

These four iron preparations are included among the commercial products known as metallic driers (19). They hasten the drying of oleoresinous coating materials which are used to line the inner surfaces of food-containing cans. Each preparation represents a mixture rather than a single compound; its composition will depend upon the nature and amount of organic acids in the parent oil. Commercial preparations contain both ferrous and ferric salts, with a total iron content of about 6 or 7 percent (20). No specifications for food grade quality are included in the Food Chemicals Codex (18).

Iron caprylate is better known as iron octanoate. Metallic salts of normal octanoic acid (caprylic acid) are relatively insoluble in oil, so that the octanoates used commercially are usually the more soluble salts of a branched-chain isomer, 2-ethylhexanoic acid (21).

Iron linoleate is usually prepared from linseed oil or the fatty acids of linseed oil. It contains not only iron linoleate, but iron salts of the other fatty acids present (21).

Iron naphthenate refers to the iron salts of various mixed acids occurring in naphthalene-base crude petroleums. Naphthenic acid is a complex mixture of cyclic compounds with aliphatic side chains. Driers are usually prepared from acid fractions with molecular weights between 220 and 230 (21).

Iron tallate. Commercial tall oil is a by-product derived from the waste liquors of pine wood pulp mills. It consists of a mixture of fatty and cyclic acids. Oleic and linoleic acids comprise the bulk of the fatty acids although some linolenic and stearic acids are also present (22). Metallic driers, including iron tallate, are prepared from this mixture.

C. Unpublished GRAS Compounds

In addition to the iron forms discussed above which have been accorded GRAS or prior-sanctioned status in the CFR, seven other compounds have been authorized by FDA as unpublished GRAS substances (16). Of this group, only ferrous fumarate (18) and ferric ammonium citrate (23) are listed in the Food Chemicals Codex with specifications defined for food grade materials.

Ferrous carbonate (FeCO₃) is insoluble in water, but soluble in dilute acids. It is also GRAS as a trace mineral added to animal feeds [21 CFR 528.80] (24).
Ferrous citrate (FeC₆H₅O₇•H₂O) is insoluble in water, alcohol, and acetone; soluble in dilute acid (25).

Ferrous fumarate (FeC₄H₆O₄) is only slightly water-soluble. The limits of impurities for the food grade compound (in ppm) are: arsenic, 3; lead, 10; and mercury, 3. When used as a special dietary and nutritional additive [21 CFR 172.350] (2) it must contain a minimum of 31.3 percent total iron, of which not more than 2 percent can be in the ferric state.

Ferric ammonium citrate is a complex salt of ammonia, iron, and citric acid of undetermined structure. The food grade preparation must contain 16.5 to 18.5 percent iron and not more than 3 ppm arsenic, 10 ppm lead, 1 ppm mercury, and 0.3 percent sulfate. It is very soluble in water but insoluble in alcohol. It is GRAS as a trace mineral added to animal feeds [21 CFR 582.80] (24) and is a regulated additive to human foods as an anticaking agent [21 CFR 172.430] (2). According to industry representatives, ferric ammonium citrate is one of the few soluble iron compounds which can be added to dairy products without inducing off-flavors (26).

Ferric chloride (FeCl₃) is very hygroscopic and water-soluble. It readily forms a hexahydrate (25). It is also GRAS as a trace mineral added to animal feeds [21 CFR 582.80] (24). It is an authorized component of adhesives [21 CFR 175.105] (2) and of paper and paperboard contacting aqueous and fatty foods [21 CFR 176.170] (2).

Ferric citrate (FeC₆H₅O₇•5H₂O) is slowly soluble in cold water, readily soluble in hot water, and practically insoluble in alcohol (25).

Ferric oxide (Fe₂O₃) is insoluble in water, but soluble in acid (25).

Iron peptonate is a compound of ferric oxide and peptone of undetermined structure. It contains 16 to 18 percent iron in nonionic form. It is made water-soluble by the addition of sodium citrate (25).

D. Additional Iron Compounds

The FDA, in response to interest expressed by the food industry, has asked the Select Committee to include the following iron compounds in its GRAS safety review (17). The inclusion in this report does not imply the award of GRAS status by the FDA. Food grade specifications have not been established for any of these compounds.

Sodium ferric ethylenediamine tetraacetate (sodium iron EDTA, ferric versenate, sodium iron edetate, ferric sodium ede-
tate) is prepared from disodium EDTA and ferric nitrate (25). It is readily soluble in water and in alkaline media, but insoluble in acid (27). Disodium EDTA is an authorized preservative in various foods and multivitamin preparations, at concentrations of 36 to 500 ppm [21 CFR 172.135] (2). It would be expected to chelate some of the iron present in these preparations to form the ferric EDTA complex.

Ferrous ascorbate has been prepared by treating ferrous hydroxide with ascorbic acid to yield a blue-violet product containing 16 percent iron (28). In most studies to be discussed later, synthetic ferrous ascorbate is not used, but the formation of the compound is assumed when ascorbic acid and ferrous iron (usually ferrous sulfate) are mixed in solution in a 2 to 1 molar ratio or when an excess of ascorbic acid is employed.

Iron polyvinylpyrrolidone. Iron polyvinylpyrrolidone has been identified as a mixture of reduced iron or an iron salt with polyvinylpyrrolidone (PVP) in unspecified proportions; complex formation of iron with PVP presumably does not occur (29). Primary functions of PVP are as a binder and dispersant in tablets. PVP itself, with an average molecular weight of 40,000 is an authorized food additive: as a clarifying agent for beer, vinegar, and wine; as a tableting adjuvant for flavor concentrates, nonnutritive sweeteners, and vitamin and mineral concentrates; and as a stabilizer, bodying agent, and dispersant in concentrated liquid nonnutritive sweeteners [21 CFR 173.55] (2). It forms stable, water-soluble complexes with various ions (30).

Sodium ferricitropyrophosphate (soluble ferric pyrophosphate) is a mixture of salts of uncertain composition produced by combining sodium pyrophosphate with ferric citrate (26).
III. CONSUMER EXPOSURE DATA

The total dietary iron consumed by various groups of individuals in the United States has been studied extensively. The Select Committee believes the best available data to be those from the 1971-1974 Health and Nutrition Examination Survey (HANES) (31, 32). This was the first survey to supply measures of nutritional status for a scientifically designed sample, representative of the civilian, noninstitutionalized population of the United States. Over 20,000 persons were examined to provide weighted samples according to sex, age (1 to 74 years), race, and income levels. The food intake was estimated from a 1-day dietary recall. Iron intake was somewhat (but not strikingly) higher among the more affluent consumers. The mean daily intake for all persons with incomes above the poverty level was 12.1 mg contrasted with 10.7 mg for those below this level. The respective medians were 10.8 and 9.4 mg. A somewhat comparable racial difference was evident. The mean intake for white subjects was 12.1 and for black subjects, 10.8 mg daily (medians 10.7 and 9.6 mg, respectively). Age and sexual differences were more marked, as shown in Table III. The daily iron intake by both sexes increased through adolescence, reached a plateau during the early adult years, and gradually declined after middle age. A somewhat different pattern emerged when iron intake was related to caloric consumption. The iron content per 1000 kcal intake remained virtually constant in both boys and girls through their childhood and teens, but then increased steadily with increasing years.

As indicated in Table IV, the 95th percentile intake of iron by males ranged from 15 to 32, and for females, from 13 to 20 mg per day.

The National Research Council (NRC) (33) surveyed food processors to determine the extent of iron addition to food in 1970, the forms of iron employed, and the recipient products. The findings are summarized in Table V. Based on these data, together with estimates by the Department of Agriculture on the size of portions normally consumed, and data from the Market Research Corporation of America on the frequency with which foods in various categories are consumed, the NRC subcommittee calculated possible average daily intakes of the different forms of iron added to foods. In each case it was assumed that only the form of iron under consideration was added to food and that it was added to all foods in a given category at the level shown in Table V. The intakes calculated in this manner are not additive for the various iron compounds. Moreover, these intakes are likely to be high since these compounds have not been added to all foods in a given category. For individuals over two years of age, these possible average daily intakes were 16.5 mg of ferric phosphate, 4.6 mg of ferric pyrophosphate, less than 0.1 mg of ferrous gluconate, 111.2 mg of ferrous sulfate, 7.7 mg of "reduced iron", and 15.7 mg of sodium.
<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Median intake (mg/day)</th>
<th>Mean Intake (mg/day)</th>
<th>Mean Intake (mg/1000 kcal)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Male</td>
<td>Female</td>
<td>Male</td>
</tr>
<tr>
<td>1</td>
<td>6.29</td>
<td>5.51</td>
<td>7.50</td>
</tr>
<tr>
<td>2-3</td>
<td>7.24</td>
<td>6.56</td>
<td>8.25</td>
</tr>
<tr>
<td>4-5</td>
<td>8.37</td>
<td>7.85</td>
<td>9.40</td>
</tr>
<tr>
<td>6-7</td>
<td>10.19</td>
<td>8.35</td>
<td>11.16</td>
</tr>
<tr>
<td>8-9</td>
<td>10.32</td>
<td>9.30</td>
<td>11.27</td>
</tr>
<tr>
<td>10-11</td>
<td>11.72</td>
<td>9.55</td>
<td>12.66</td>
</tr>
<tr>
<td>12-14</td>
<td>12.09</td>
<td>9.68</td>
<td>13.58</td>
</tr>
<tr>
<td>15-17</td>
<td>14.76</td>
<td>8.50</td>
<td>16.30</td>
</tr>
<tr>
<td>18-19</td>
<td>14.68</td>
<td>8.84</td>
<td>16.44</td>
</tr>
<tr>
<td>20-24</td>
<td>15.28</td>
<td>8.88</td>
<td>16.54</td>
</tr>
<tr>
<td>25-34</td>
<td>15.40</td>
<td>9.32</td>
<td>16.67</td>
</tr>
<tr>
<td>35-44</td>
<td>14.69</td>
<td>9.44</td>
<td>15.89</td>
</tr>
<tr>
<td>55-64</td>
<td>12.56</td>
<td>8.94</td>
<td>13.66</td>
</tr>
<tr>
<td>65-74</td>
<td>11.02</td>
<td>8.22</td>
<td>12.13</td>
</tr>
</tbody>
</table>
### TABLE IV

Percentile Distribution of Dietary Iron Intake in mg (32)

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mean</th>
<th>5th</th>
<th>10th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>90th</th>
<th>95th</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>7.50</td>
<td>2.79</td>
<td>3.22</td>
<td>4.48</td>
<td>6.29</td>
<td>8.46</td>
<td>11.00</td>
<td>15.01</td>
</tr>
<tr>
<td>2-3</td>
<td>8.25</td>
<td>3.32</td>
<td>4.32</td>
<td>5.51</td>
<td>7.24</td>
<td>9.80</td>
<td>12.67</td>
<td>16.05</td>
</tr>
<tr>
<td>4-5</td>
<td>9.40</td>
<td>4.32</td>
<td>5.21</td>
<td>6.43</td>
<td>8.37</td>
<td>10.95</td>
<td>14.62</td>
<td>17.92</td>
</tr>
<tr>
<td>6-7</td>
<td>11.16</td>
<td>4.47</td>
<td>5.87</td>
<td>7.66</td>
<td>10.19</td>
<td>13.37</td>
<td>17.89</td>
<td>22.51</td>
</tr>
<tr>
<td>8-9</td>
<td>11.27</td>
<td>5.16</td>
<td>6.54</td>
<td>8.29</td>
<td>10.32</td>
<td>13.03</td>
<td>17.13</td>
<td>20.76</td>
</tr>
<tr>
<td>15-17</td>
<td>16.30</td>
<td>5.98</td>
<td>7.44</td>
<td>10.11</td>
<td>14.76</td>
<td>20.58</td>
<td>26.29</td>
<td>29.93</td>
</tr>
<tr>
<td>20-24</td>
<td>16.54</td>
<td>6.25</td>
<td>8.21</td>
<td>11.20</td>
<td>15.28</td>
<td>20.73</td>
<td>26.70</td>
<td>30.15</td>
</tr>
<tr>
<td>35-44</td>
<td>15.89</td>
<td>6.86</td>
<td>8.53</td>
<td>11.01</td>
<td>14.69</td>
<td>19.26</td>
<td>24.76</td>
<td>28.68</td>
</tr>
<tr>
<td>45-54</td>
<td>14.62</td>
<td>6.36</td>
<td>7.94</td>
<td>10.54</td>
<td>13.71</td>
<td>17.51</td>
<td>22.50</td>
<td>25.55</td>
</tr>
<tr>
<td>55-64</td>
<td>13.66</td>
<td>5.91</td>
<td>7.27</td>
<td>9.22</td>
<td>12.56</td>
<td>16.48</td>
<td>21.69</td>
<td>25.31</td>
</tr>
<tr>
<td>65-74</td>
<td>12.13</td>
<td>5.06</td>
<td>6.23</td>
<td>8.51</td>
<td>11.02</td>
<td>14.54</td>
<td>19.03</td>
<td>22.86</td>
</tr>
<tr>
<td>1-74</td>
<td>14.15</td>
<td>5.31</td>
<td>6.61</td>
<td>9.29</td>
<td>12.74</td>
<td>17.68</td>
<td>23.19</td>
<td>27.20</td>
</tr>
</tbody>
</table>

Female

<table>
<thead>
<tr>
<th>Age (years)</th>
<th>Mean</th>
<th>5th</th>
<th>10th</th>
<th>25th</th>
<th>50th</th>
<th>75th</th>
<th>90th</th>
<th>95th</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>7.20</td>
<td>2.61</td>
<td>3.18</td>
<td>4.17</td>
<td>5.51</td>
<td>7.46</td>
<td>11.71</td>
<td>19.32</td>
</tr>
<tr>
<td>2-3</td>
<td>7.17</td>
<td>2.75</td>
<td>3.49</td>
<td>4.64</td>
<td>6.56</td>
<td>8.77</td>
<td>11.39</td>
<td>13.31</td>
</tr>
<tr>
<td>4-5</td>
<td>8.43</td>
<td>3.73</td>
<td>4.41</td>
<td>6.00</td>
<td>7.81</td>
<td>10.16</td>
<td>12.81</td>
<td>14.96</td>
</tr>
<tr>
<td>6-7</td>
<td>9.55</td>
<td>4.67</td>
<td>5.05</td>
<td>6.51</td>
<td>8.35</td>
<td>11.48</td>
<td>15.38</td>
<td>18.25</td>
</tr>
<tr>
<td>8-9</td>
<td>9.76</td>
<td>4.53</td>
<td>5.67</td>
<td>7.08</td>
<td>9.30</td>
<td>11.72</td>
<td>15.10</td>
<td>17.03</td>
</tr>
<tr>
<td>12-14</td>
<td>10.42</td>
<td>4.41</td>
<td>5.34</td>
<td>7.23</td>
<td>9.68</td>
<td>12.72</td>
<td>16.76</td>
<td>20.19</td>
</tr>
<tr>
<td>15-17</td>
<td>9.48</td>
<td>3.54</td>
<td>4.45</td>
<td>5.84</td>
<td>8.50</td>
<td>12.19</td>
<td>15.80</td>
<td>19.61</td>
</tr>
<tr>
<td>18-19</td>
<td>10.04</td>
<td>3.98</td>
<td>5.18</td>
<td>6.83</td>
<td>8.84</td>
<td>12.33</td>
<td>16.95</td>
<td>19.41</td>
</tr>
<tr>
<td>20-24</td>
<td>10.01</td>
<td>3.69</td>
<td>4.59</td>
<td>6.52</td>
<td>8.88</td>
<td>12.35</td>
<td>16.39</td>
<td>19.28</td>
</tr>
<tr>
<td>25-34</td>
<td>10.33</td>
<td>3.83</td>
<td>5.00</td>
<td>6.96</td>
<td>9.32</td>
<td>12.69</td>
<td>16.52</td>
<td>19.78</td>
</tr>
<tr>
<td>45-54</td>
<td>10.55</td>
<td>4.60</td>
<td>5.45</td>
<td>7.07</td>
<td>9.71</td>
<td>12.89</td>
<td>16.97</td>
<td>19.63</td>
</tr>
<tr>
<td>55-64</td>
<td>9.82</td>
<td>4.11</td>
<td>4.78</td>
<td>6.76</td>
<td>8.94</td>
<td>11.89</td>
<td>15.59</td>
<td>18.59</td>
</tr>
<tr>
<td>65-74</td>
<td>9.21</td>
<td>3.87</td>
<td>4.71</td>
<td>6.36</td>
<td>8.22</td>
<td>11.20</td>
<td>14.80</td>
<td>17.66</td>
</tr>
<tr>
<td>1-74</td>
<td>9.88</td>
<td>3.92</td>
<td>4.82</td>
<td>6.60</td>
<td>8.94</td>
<td>12.09</td>
<td>15.95</td>
<td>19.13</td>
</tr>
</tbody>
</table>

---
### TABLE V

Level of Addition (Weighted Means) of Iron and Iron Salts to Various Food Categories, 1970 (33)

<table>
<thead>
<tr>
<th>Food Category</th>
<th>Ferric ammonium citrate</th>
<th>Ferric chloride</th>
<th>Ferric phosphate</th>
<th>Ferric pyrophosphate</th>
<th>Ferric sodium pyrophosphate</th>
<th>Ferrous gluconate</th>
<th>Ferrous sulfate</th>
<th>Iron, reduced</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Mg per kg (ppm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baked goods, baking mixes</td>
<td>69</td>
<td>210</td>
<td>44</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Breakfast cereals</td>
<td>639&lt;sup&gt;3&lt;/sup&gt;</td>
<td>500</td>
<td>1487&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
<td></td>
<td>116</td>
<td>175&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Grain products such as pastas or rice dishes</td>
<td>76&lt;sup&gt;3&lt;/sup&gt;</td>
<td>195</td>
<td>21</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Milk products</td>
<td>47</td>
<td>61&lt;sup&gt;3&lt;/sup&gt;</td>
<td>27</td>
<td></td>
<td></td>
<td>53</td>
<td>11</td>
<td></td>
</tr>
<tr>
<td>Meat products</td>
<td></td>
<td>286</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Poultry products</td>
<td></td>
<td>16</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fish products</td>
<td>90</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Condiments, relishes, salt substitutes</td>
<td>10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>20</td>
</tr>
<tr>
<td>Sweet sauces, toppings, syrups</td>
<td></td>
<td>600</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>1630&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Gelatins, puddings, fillings</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>150</td>
<td></td>
</tr>
<tr>
<td>Snack foods</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Beverages, nonalcoholic</td>
<td>16</td>
<td>160</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>2750&lt;sup&gt;3&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Beverages, alcoholic</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Reconstituted vegetable proteins</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>Gravies, sauces</td>
<td>109</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dairy products analogs</td>
<td>191</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Instant coffee and tea</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>10</td>
<td>130</td>
</tr>
<tr>
<td>Baby formulas</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>53</td>
<td>1000</td>
</tr>
<tr>
<td>Baby cereals</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Blanks in the table mean that the substance is not added to the foods indicated.

*Not in original National Academy of Sciences survey. Manufacturers volunteered tabulated data.

<sup>1</sup> Indicates four or more manufacturers reported addition. All other entries represent weighted averages from three or fewer manufacturers.

<sup>2</sup> A fortified fruit beverage. This value appears extremely high to the Select Committee.
ferric pyrophosphate. Most of these values seem to be unrealistically high estimates of the amounts actually added to food. The NRC subcommittee has recognized that such calculations often yield gross overestimations of actual intake and has urged caution in their acceptance (33). Consequently, the Select Committee has availed itself of other data to estimate per capita intakes which it believes reflect more accurately the actual intakes of iron added to food.

Total amounts of the various forms of iron added to foods in the U.S. in 1970 and 1975 were obtained by the NRC from surveys of the food processors (33,34). As shown in Table VI the estimated per capita consumption of iron from all added sources was 6.8 mg per day in 1970 and 8.3 mg in 1975. Even this value is likely to be an overestimate because of wastage. Comparison of the 1970 and 1975 data reveals a striking trend towards the use of elemental iron as the fortifying agent. During this period, the amount of added elemental iron almost doubled, while that of ferrous sulfate, ferric phosphate, and ferric sodium pyrophosphate decreased by over 10, 40, and 90 percent, respectively.

Somewhat lower values for the amount of total added iron can be derived from the data of the U.S. Department of Agriculture published in 1965 (Table VII) (36). Most of the iron used to enrich the diet is found in grain products, which contribute about 25 percent of the total daily intake. Since the total daily intake is approximately 15 mg by men and 9 to 10 mg by women (Table III), the average amount from grain products alone would be about 4 and 2.5 mg, respectively. In the 90th percentile groups (Table IV), the daily intake from grain products could be about 6 mg for men and 4 mg for women. Since these values represent the total iron content of the grain, both naturally occurring and added, the added iron must be somewhat less. Thus, the per capita daily consumption of iron added to foods is unlikely to be more than 5 mg, supplied mainly in the form of elemental iron.

In this report, the Select Committee considers only iron added to foods and not that ingested in the form of vitamin and iron dietary supplements. It recognizes that for some individuals, the intake from these sources may exceed that obtained from food.

In 1971, FDA proposed an increase in the level of iron in enriched wheat flour and related products (37). The regulation would have increased the iron content of enriched flour from 13.0-16.5 mg to 40 mg per pound, and that of enriched bread, buns, and rolls from 8.0-12.5 mg to 25 mg per pound. These increases in the iron fortification were proposed to prevent or reduce the incidence of iron deficiency in the United States. The possibility of "overloading" certain individuals with iron, as well as other considerations, persuaded the FDA in 1977 to withdraw the proposal and to continue the existing level of iron enrichment (38).
TABLE VI

Estimated Addition of Elemental Iron and Certain Iron Salts (34)

<table>
<thead>
<tr>
<th>Substance</th>
<th>Total quantity added* (kg)</th>
<th>Per capita daily intake iron (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferric phosphate</td>
<td>490,000</td>
<td>290,000</td>
</tr>
<tr>
<td>Ferric pyrophosphate</td>
<td>1,100</td>
<td></td>
</tr>
<tr>
<td>Ferric sodium pyrophosphate</td>
<td>300,000</td>
<td>17,000</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>1,700</td>
<td></td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>310,000</td>
<td>270,000</td>
</tr>
<tr>
<td>&quot;Iron reduced&quot;</td>
<td>260,000</td>
<td>510,000</td>
</tr>
<tr>
<td>Ferric ammonium citrate</td>
<td></td>
<td>13,600^</td>
</tr>
<tr>
<td>TOTAL</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Recalculated to 100 percent from survey data that the NRC subcommittee estimated to represent about 60 percent of actual usage.


1974 estimate (35).
TABLE VII
Contribution of Different Foods in the U.S. Diet to
Iron Intake of Normal Adults (20-34 yr)

<table>
<thead>
<tr>
<th>Food categories</th>
<th>Percentage of total iron intake</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Males</td>
</tr>
<tr>
<td>Meat, poultry, fish</td>
<td>46.3</td>
</tr>
<tr>
<td>Grain products</td>
<td>23.3</td>
</tr>
<tr>
<td>Eggs</td>
<td>6.7</td>
</tr>
<tr>
<td>Other vegetables, fruit</td>
<td>6.6</td>
</tr>
<tr>
<td>Legumes, nuts</td>
<td>4.5</td>
</tr>
<tr>
<td>Potatoes</td>
<td>3.7</td>
</tr>
<tr>
<td>Beverages other than milk</td>
<td>2.5</td>
</tr>
<tr>
<td>and fruit juices</td>
<td></td>
</tr>
<tr>
<td>Sugars, sweets</td>
<td>2.1</td>
</tr>
<tr>
<td>Tomatoes, citrus fruit</td>
<td>1.5</td>
</tr>
<tr>
<td>Dark green, deep yellow</td>
<td></td>
</tr>
<tr>
<td>vegetables</td>
<td>1.0</td>
</tr>
<tr>
<td>Milk, milk products</td>
<td>1.0</td>
</tr>
<tr>
<td>Fats, oils</td>
<td>0.7</td>
</tr>
</tbody>
</table>

*Adapted from table 16, ref. 36.
Usage data are sparse or unavailable for most of the iron preparations considered as possible food additives. Data for a few are shown in Table V. In addition, ferrous citrate is reportedly used at a level of 16.9 mg per liter in a special dietary beverage and at an unknown level in milk (35). Ferrous fumarate has been used to enrich a corn-soy-milk mixture, a food product included in the U.S. overseas food assistance program, at a level of 180 mg iron per kg dry product (39). It has also been reported in enriched cereals and beverages (0.08 percent) (35). Ferric oxide is used only in pet foods (40).

The Select Committee has no data on the use as additives of the various other iron compounds considered in this report.
IV. BIOLOGICAL STUDIES

Absorption, transport, and excretion

Iron, in contrast with most other metals, is regulated in the body primarily by absorption rather than by excretion. It has long been known that little iron is excreted in the urine even when large doses are ingested. This fact led McCance and Widdowson (41) in 1937 to conclude that iron in the body must be regulated by controlled absorption. A number of comprehensive reviews on iron absorption since that time have amply confirmed the critical importance of the gastrointestinal tract in controlling the total body iron (42-44). Absorption is strongly influenced by the status of iron stores and the erythropoietic activity in the body. Extrinsic factors such as the form of ingested iron, the nature of accompanying food, the composition of intestinal secretions, the products of digestion, and the pH of the intestinal contents can all affect the absorption of iron.

Since the normal diet contains several times the amount of iron needed to maintain iron balance, it is obvious that availability of iron, rather than its total intake is the limiting factor in achieving adequate absorption. It is generally agreed that iron of animal origin with the exception of eggs, is more readily available to man than the iron in plants (45,46). Heme, the principal source of iron in animal tissues and organs, is directly and rapidly absorbed, whereas nonheme iron is more slowly and less completely absorbed. The difference in bioavailability of plant and animal iron is so great that heme iron is generally considered independently of nonheme iron in iron balance studies. Björn-Rasmussen et al. (47) fed 32 young men meals containing both heme and nonheme (plant) iron appropriately labeled. They found that the absorption of heme iron averaged 37 percent but absorption of nonheme iron only 5 percent. Layrisse and Martínez-Torres (48) obtained similar results with subjects fed a diet of meat, beans, maize, and rice. In this instance, absorption of heme iron was 27 percent while that of nonheme iron was 6 percent. One factor probably contributing to the superior bioavailability of heme iron is its protection from agents which may react with nonheme iron compounds to reduce their absorption (49).

Although there are individual differences among the various iron compounds, ferrous salts are generally more readily absorbed in man than ferric salts. This has been observed both clinically (50) and experimentally (51). Brise and Hallberg (51) used two isotopes to study the absorption of 14 different iron salts. The absorption of ferrous sulfate was used as a basis for comparison. The relative absorptions of the different compounds are shown in Table VIII. A partial explanation for the more rapid absorption of the ferrous salts may be the greater solubility of ferrous than ferric hydroxide in the alkaline milieu of the duodenum (8). Insoluble salts, such as the various iron phosphates,
TABLE VIII

Absorption of Labeled Iron Salts

<table>
<thead>
<tr>
<th>Salt</th>
<th>Absorption ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ferrous succinate</td>
<td>1.22</td>
</tr>
<tr>
<td>Ferrous lactate</td>
<td>1.06</td>
</tr>
<tr>
<td>Ferrous glycine sulfate</td>
<td>1.02</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>1.01</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>1.00</td>
</tr>
<tr>
<td>Ferrous glutamate</td>
<td>0.96</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>0.89</td>
</tr>
<tr>
<td>Ferrous citrate</td>
<td>0.74</td>
</tr>
<tr>
<td>Ferrous tartrate</td>
<td>0.64</td>
</tr>
<tr>
<td>Ferrous pyrophosphate</td>
<td>0.59</td>
</tr>
<tr>
<td>Ferric choline isocitrate</td>
<td>0.43</td>
</tr>
<tr>
<td>Ferric sulfate</td>
<td>0.36</td>
</tr>
<tr>
<td>Ferric citrate</td>
<td>0.31</td>
</tr>
<tr>
<td>Ferric versenate (ferric EDTA)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

*Adapted from (51).  
*Compared with absorption of ferrous sulfate.
are poorly available (52). The presence of precipitating agents, certain chelators, and lowered gastric acidity also significantly reduce iron absorption (51). Gastrectomy (53) and achlorhydria (54) markedly impair iron absorption.

The absorption of iron is significantly less when given after a meal than when administered to a fasting subject. Brise (55) found that the absorption of iron (as ferrous sulfate) after a light meal was only 56 percent of that by the same subject in a fasting state. Phytates, which occur mainly in cereal foods, are often claimed to inhibit iron absorption by the formation of insoluble iron phytate during the process of digestion. However, the findings with phytate are difficult to interpret, since they depend somewhat upon the nature of the other food constituents. Phytates in some foods are bound to proteins or other plant constituents and have little effect on iron. Thus, Sharpe et al. (56) found no correlation between the natural phytate content of oats and the bioavailability of iron. However, when sodium phytate was added to milk, the availability of iron to human subjects was sharply reduced. Iron utilization is also reduced when the amount of wheat bran in the diet is increased (57). This reduction has been attributed to the phytate content of the bran although phytin-free fiber also reduces iron utilization (58).

Both heme and ascorbic acid are known to enhance the absorption of iron. When beef, a rich source of heme, was substituted for an equivalent amount of egg albumin, the absorption of nonheme iron from a test meal increased more than five-fold (59). Similarly, the addition of relatively small amounts of ascorbic acid has been reported to increase the absorption of iron from maize porridge (60). When papaya containing 66 mg of ascorbic acid was consumed with 100 g of maize, five times as much iron was absorbed than from maize alone (61). Ascorbic acid is thought to act both by reducing some of the ferric iron to the ferrous state, and by forming simple chelates with the remainder. Both actions increase the solubility of iron in the intestine.

The formation of iron chelates is an important factor in the regulation and facilitation of iron absorption (43). Iron forms complexes with a large number of organic compounds which keep the iron available for absorption by preventing the formation of poorly soluble hydroxides and phosphates. The stability of these iron complexes or chelates varies widely, depending upon the size, the nature of the ligand, and other factors. Chelates with low stability will release their iron to receptor sites in the intestinal mucosa, whereas highly stable chelates will prevent this release. Chelate stability is generally expressed as a stability constant K. Forth (62) states that chelates with K values below 12-13 will release their iron to mucosal receptors. Most iron chelates considered in this report have K values well below this threshold (63).
Of perhaps even greater importance than extrinsic factors in modifying the absorption of iron, is a systemic regulatory mechanism dependent upon the iron status of the individual. This mechanism is poorly understood. It does stimulate iron absorption during iron deficiency, during active erythropoiesis, and during the latter half of pregnancy. Conversely, it tends to decrease the absorption of iron when erythropoiesis is depressed or when an iron overload develops (8). Monsen et al. (64) have estimated that an individual with low iron stores absorbs approximately 20 percent of nonhem e iron from a high availability meal. This was defined as meals containing more than 90 g lean meat, poultry, or fish; 30 to 90 g of these foods plus 25 to 75 mg ascorbic acid; or a non-meat, non-fish meal with more than 75 mg ascorbic acid. When consuming such meals, persons with adequate iron stores absorb about 7 to 8 percent, and individuals with high iron stores absorb only about 4 percent of the dietary nonheme iron.

The detailed mechanism of iron absorption is still somewhat controversial. It is generally agreed that iron is bound by receptors in the brush border of mucosal cells in the upper small intestine; transferred across the membrane by an unknown, but presumably energy-dependent process; transported to the basal surface of the epithelium by a carrier; and finally delivered to the iron-transporting protein, transferrin, in the plasma (3). As already indicated, the iron status of the individual, his erythropoietic rate, and other factors regulate the amount of iron transported across the intestinal mucosa. Transferrin transports iron to the bone marrow, liver, or other tissues where it can be utilized for the synthesis of hemoglobin, cytochromes, ferritin, and other iron-containing compounds (65). Ferritin is an iron-storage molecule with a large iron-binding capacity. It exists as a ferric oxide complex and a protein shell (apoferitin). When saturated, each molecule can contain up to 4500 iron atoms, although it usually contains less than 3000 (66). Ferritin provides a mobile reserve of iron to meet the varying needs of the body. Large amounts are found in the liver, spleen, and hematopoietic organs, and lesser amounts in other tissues which have no apparent iron-storage function (67,68). Serum ferritin has been used as an index of total body iron (11,12) because it mirrors closely the quantity of iron stored in the tissues (69).

Another substance which functions as an iron-storage compound is hemosiderin. Its structure is ill-defined, being a relatively amorphous compound, containing up to 35 percent iron. Hemosiderin exists in the tissues as a brown, granular, readily stainable pigment; its iron is mainly ferric hydroxide (70). It has been suggested, on the basis of similar physical characteristics, that hemosiderin is formed from the denaturation and proteolytic cleavage of ferritin (71). Up to certain levels, both ferritin and hemosiderin are deposited in liver and spleen in roughly equal amounts. Morgan and Walters (72) concluded from
human necropsy material that hemosiderin begins to predominate when total iron storage requirements exceed approximately 1 mg per g of liver or spleen.

Iron is an important but complex determinant in the susceptibility of animals to infection. On the one hand, iron deficiency impairs host defense mechanisms and reduces the animals' resistance to microbial attack (73). On the other hand, iron is essential for microbial growth; its availability to the invading microorganisms is reduced when blood levels are low (74).

The bulk of excreted iron is found in the feces, which includes not only the unabsorbed portion from ingested food but also small amounts from biliary excretion, desquamation from epithelial surfaces, and gastrointestinal blood loss. These losses amount to approximately 1 mg per day or less (75). Virtually none is lost through the urine. Green et al. (76) reported that the daily excretion of an 80 kg male subject was approximately 0.1 mg. Menstrual loss is highly variable but averages about 15 to 20 mg monthly (75,77). Because of the great differences in physiological availability of iron compounds in food, an overall absorption rate of 10 percent has been adopted in estimating the Recommended Dietary Allowance (RDA) (78). Thus, in order to provide the necessary retention of 1 mg iron per day in men and in postmenopausal women, the RDA has been set at 10 mg. For women of childbearing age, the RDA is increased to 18 mg to allow for the extra demands imposed by menstruation, pregnancy, and lactation. For infants, the recommended allowance is 1.5 mg per kg body weight. During pregnancy, daily supplements of 30 to 60 mg of iron are recommended.

**Acute toxicity**

Oral administration of large doses of soluble iron compounds to fasting experimental animals may cause irritation and ulceration of the gastrointestinal mucosa. Doses in the lethal range produce marked erosion and mucosal sloughing if death is delayed for 24 to 48 hours (79).

The acute toxicities of various iron salts for laboratory animals are summarized in Table IX. It is evident that wide variations in toxicity have been reported among different iron salts and animal species. Thus, 150 (82) to 305 mg (81) iron per kg body weight has been reported as the LD50 for mice given ferrous sulfate by mouth, but 3800 mg per kg is the comparable oral dose with ferrous carbonate (83). Species differences also appear to be great. The LD50 for ferrous fumarate was reported to be 516 mg iron per kg in the mouse but more than 2300 mg per kg in the rat (81). Dogs given lethal amounts of iron consistently displayed reduced cardiac output, increased peripheral resistance, decreased plasma volume, hemoconcentration, decreased blood volume, and
<table>
<thead>
<tr>
<th>Compound</th>
<th>Species</th>
<th>LD$_{50}$ mg Fe/kg</th>
<th>Ref.</th>
</tr>
</thead>
<tbody>
<tr>
<td>&quot;Reduced iron&quot;</td>
<td>Rat</td>
<td>98600</td>
<td>84</td>
</tr>
<tr>
<td>Ferrous carbonate</td>
<td>Guinea pig</td>
<td>2000</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td>2220</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>3800</td>
<td>83</td>
</tr>
<tr>
<td>Ferrous fumarate</td>
<td>Mouse</td>
<td>630</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>516</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>&gt;2329</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>580</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>1100</td>
<td>83</td>
</tr>
<tr>
<td>Ferrous gluconate</td>
<td>Mouse</td>
<td>320</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>457</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>865</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Guinea pig</td>
<td>350</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td>580</td>
<td>83</td>
</tr>
<tr>
<td>Ferrous sulfate</td>
<td>Mouse</td>
<td>230</td>
<td>80</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>150</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>305</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>780</td>
<td>81</td>
</tr>
<tr>
<td></td>
<td>Guinea pig</td>
<td>350</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td>600</td>
<td>83</td>
</tr>
<tr>
<td>Ferric ammonium citrate</td>
<td>Rabbit</td>
<td>560</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Guinea pig</td>
<td>350</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>1000</td>
<td>83</td>
</tr>
<tr>
<td>Ferric chloride</td>
<td>Mouse</td>
<td>440</td>
<td>82</td>
</tr>
<tr>
<td></td>
<td>Mouse</td>
<td>500</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Guinea pig</td>
<td>200</td>
<td>83</td>
</tr>
<tr>
<td></td>
<td>Rabbit</td>
<td>400</td>
<td>83</td>
</tr>
<tr>
<td>&quot;Iron oxide&quot;</td>
<td>Mouse</td>
<td>&gt;15000</td>
<td>85</td>
</tr>
<tr>
<td></td>
<td>Rat</td>
<td>&gt;15000</td>
<td>85</td>
</tr>
</tbody>
</table>
lowered blood pressure. Metabolic acidosis and the accumulation of organic acids were also evident before circulatory collapse (86).

An estimated 2000 human cases of iron poisoning occur annually with approximately 12 deaths (3). Most cases occur among children, especially those in the 1 to 2 year age group, who poison themselves accidentally with oral iron preparations prescribed for adults (87). In a review of 1645 cases in which children had ingested toxic agents, Greengard and McEnery (88) reported that ferrous sulfate was responsible for 6.2 percent of the incidents. In adults, cases of acute toxicity have been observed almost exclusively among individuals with suicidal intentions (3). Crotty (87) estimated the average lethal dose for an adult male to be 200 to 250 mg per kg body weight (about 14 g of elemental iron) or approximately 1000 times the Recommended Dietary Allowance.

Large doses of iron salts cause severe gastroenteritis with hematemesis, abdominal pain, diarrhea, tachycardia, rapid respiration, depression, lassitude, and shock (89). Hemorrhagic necrosis and sloughing of the gastric mucosal areas with extension into the submucosa are commonly observed. The necrotic surfaces are covered with an iron-containing pigment. Similar, but less severe, changes are noted in the small intestine, with the most striking damage in the proximal portions. Metabolic acidosis is common in these cases.

Acute toxicity resulting from consumption of iron-fortified foods has not been reported. The Select Committee considers that studies of acute toxicity of the various iron forms are of limited usefulness in evaluating the safety of iron and iron salts as food ingredients.

**Subchronic and chronic toxicity**

Subchronic and chronic toxicities of iron are characterized by disorders associated with excessive iron loading or storage in the body. The storage iron is predominantly in the form of insoluble hemosiderin, and an increase of iron storage is called hemosiderosis or simply siderosis. Under certain conditions, organs may contain grossly excessive amounts of storage iron and show evidence of damage. Such a condition is termed hemochromatosis. As Jacobs (75) has commented, our present ignorance of iron disorders is compounded by the semantic confusion resulting from the indiscriminate use of hemochromatosis and hemosiderosis as synonyms for iron loading.

In this report, the term **hemosiderosis** is applied to conditions of increased iron stores confined mainly to the cells of the reticuloendothelial system and without obvious malfunction or disease which can be attributed to the presence of the iron. The
term hemochromatosis is applied when the organs containing excessive amounts of storage iron show evidence of damage, usually fibrosis. It is distinguished from hemosiderosis by well characterized clinical signs and symptoms, even though the total amount of iron in the body may be comparable in the two conditions.

Generalized hemosiderosis may result from chronic ingestion of large amounts of bioavailable iron, from repeated transfusions, and from certain microcytic hypochromic anemias, such as thalassemia major (90). Substantial iron overload resulting from dietary intake is rare. The most striking example of such a dietary overload is the hemosiderosis which occurs among members of the Bantu tribe in South Africa who consume large amounts of a beverage prepared in iron drums and pots. The resulting brew is of low pH and contains 40 to 80 mg iron per liter (91). The iron in the beverage is well absorbed, presumably in the form of small soluble complexes produced during fermentation (92). The average iron intake of adult Bantu men was estimated to be about 100 mg per day and even greater intakes are possible among heavy drinkers (93). In the siderotic Bantu, hemosiderin is deposited in the liver parenchymal and Kupffer cells and in the spleen and bone marrow (94). Significant involvement of parenchymal tissues in organs other than the liver is uncommon, even in the presence of marked siderosis. The pattern of both organ and cellular deposition of iron appears to differ from that found in hemochromatosis.

Hemochromatosis is generally regarded as a disease entity characterized by extensive iron deposits in the liver, skin, heart, pancreas, and spleen. Its etiology remains controversial. The typical patient with hemochromatosis will show portal cirrhosis, bronze pigmentation, diabetes mellitus, endocrinopathy, arthropathy, and cardiac insufficiency (8). The normal control of iron absorption is faulty in these individuals but the basic metabolic defect has not yet been identified. The dominant view regards hemochromatosis as a rare inborn error of metabolism, and considerable evidence supports this contention. One or more abnormalities in iron metabolism have been repeatedly recognized in 25 to 75 percent of first-degree relatives of patients with this condition. Siblings are often affected and in a few cases, overt disease has been detected in successive generations (95). MacDonald (96), however, has argued that hemochromatosis is always secondary to dietary, toxic, or other factors responsible for increased retention of iron.

The frequency of hemochromatosis has been estimated at 1 in 20,000 hospital admissions and at 1 in 7000 hospital deaths (97). However, this apparent low frequency has been questioned by some investigators, who believe it to be a gross underestimation of the true frequency, inasmuch as diagnosis has usually been restricted to the end stage of the disease (95,98).
Crosby (29,98) has been critical of the iron fortification program in the United States; he believes it may contribute to the development of hemochromatosis among susceptible individuals. This concern prompted Olsson and coworkers (99,100) to search for cases in Sweden, which has fortified foods with iron for more than 30 years. The average iron intake in Sweden is considerably higher than in the United States (19 mg versus 12 mg per day); 42 percent of the Swedish intake comes from food fortification (101). Olsson et al. (99) studied the iron status of virtually all (347 of 363) persons between 30 and 39 years of age in a small rural district in Sweden. All persons with elevated serum iron levels (above 300 μg per dl) were subjected to further tests to evaluate possible iron overload. Nine men (of 197), but no women, had persistently high serum iron levels. Four of these demonstrated increased iron stores, as indicated by high transferrin iron saturation (over 70 percent), increased iron excretion induced by deferoxamine injection, and liver parenchymal iron. Phlebotomy revealed excessive mobilizable iron stores in one man. Although the investigators characterized their findings as "preclinical hemochromatosis," each of the four men was in good health, with no clinical signs of the disorder. Liver function and glucose tolerance tests were normal in all cases. None had laboratory signs of organ damage attributable to iron.

In a more recent report, Olsson (100) extended to 17, his series of patients with suspected hemochromatosis. This group consisted of 14 men and 3 women between the ages of 36 to 78 years, who had been treated in a regional hospital serving approximately 133,000 inhabitants. Two of the patients had been identified as possible hemochromatotics from their clinical signs and symptoms, three from clinical and laboratory investigations of their relatives, and the remainder from routine laboratory tests or from liver biopsies performed to clarify suspected hepatic disorders. Transferrin iron saturation, serum ferritin, urinary iron excretion after deferoxamine injection, and liver iron were elevated in all cases. Cirrhosis or significant fibrosis was reported in 11, and elevated serum transaminase in 14 of the patients. Abnormal glucose tolerance curves were present in 10 cases, but only three patients required insulin treatment. Abnormal pigmentation was noted in several of the patients, but this was seldom marked. Joint pains were reported by seven patients. Phlebotomies were performed on 12 of the patients. Only two of the 17 patients exhibited all of the typical signs and symptoms normally associated with hemochromatosis.

Olsson (100) commented that the incidence of hemochromatosis in the region of his investigation appeared to be about ten times that of another Swedish region (Uppsala). He offered no explanation for this marked geographic variation.

The most reliable method for assessing body iron stores is the chemical estimation in various tissues, especially the liver. Sheldon (102) reported the mean concentration of liver
nonheme iron in patients with hemochromatosis to be 3.6 percent dry weight (range 1.0 to 7.6 percent). The median hepatic concentrations found in 422 adult Swedish men was about 0.05 percent (91). The median values for Czechoslovakian males was about 0.10 and that for American males, about 0.08 percent. In a study of 3983 liver specimens from 18 different countries, only three were found to contain iron in concentrations approaching 1 percent, the lower limit of that found in hemochromatosis (103).

Attempts to produce hemochromatosis experimentally have been largely unsuccessful. Various iron preparations have been administered in large amounts to rabbits, dogs, mice, rats, guinea pigs, and chickens (104). They have been given orally with normal and deficient diets, and in single or multiple doses intravenously, subcutaneously, intraperitoneally, and intramuscularly. Heavy deposits of iron in many tissues have been induced both after oral and parenteral administration, but the associated fibrosis of the liver, spleen, and pancreas, characteristic of human hemochromatosis, has not been observed.

The only study known to the Select Committee in which liver injury in animals has been reported to resemble human hemochromatosis, is that of Lisboa (105). This investigator administered a total of 3.5 to 5.8 g iron per kg body weight to dogs intravenously and/or intramuscularly by repeated injections of iron dextran or iron sorbitol. Of 19 dogs, six survived the experimental period of 35 to 47 months, and five developed cirrhosis. Liver histology showed disorganization of lobular architecture, with nodular regeneration, slight fibrosis, and mild inconsistent mononuclear infiltration. Massive deposits of iron were found in the parenchyma. There were no signs of diabetes.

On the other hand, Brown and coworkers (106) also repeatedly injected iron (as saccharated iron oxide) intravenously into dogs over a period of 6 to 10 weeks, until a total of 0.5 to 1.0 g per kg had been administered. The animals were sacrificed 81 and 84 months after the start of the experiment. Large amounts of iron were found in the liver, spleen, bone marrow, and lymph nodes, but liver function tests and histologic sections at biopsy or necropsy failed to reveal any evidence of cirrhosis. There was no diabetes or pancreatic fibrosis. Blindness developed about 3 years after the start of the experiment, with lesions resembling those of retinitis pigmentosa. [Lisboa (105) found no sign of this condition in his animals]. In a subsequent experiment, Brown et al. (107) injected dogs intravenously, intraperitoneally, or intramuscularly with 125 to 250 mg iron (as iron dextran or saccharated iron oxide) daily or twice weekly until the death of the animals. Death occurred in 5 to 10 months after total injections of 2.5 to 3.3 g iron per kg body weight. After about 4 months, when more than 2 g iron had been injected, the animals showed a decreased serum albumin, anorexia, apathy, and weight loss. One dog developed ascites and anasarca. Except for scattered, small
areas of focal necrosis and massive reticuloendothelial iron depo-
sits, the livers of these dogs did not appear seriously damaged.
There was no fibrous tissue response to the iron deposits, and no
evidence of hemochromatosis, cirrhosis, or diabetes.

Feeding studies in animals also have failed to produce
changes resembling hemochromatosis. Rather (108) fed rats a diet
containing 6 percent ferric citrate (about 1 g iron per kg per
day) for 6 to 18 months. At necropsy, livers were engorged with
hemosiderin, chiefly in the parenchymal and Kupffer cells, with
large deposits also in the spleen, abdominal lymph nodes, pan-
creas, kidneys, and adrenals. However, cirrhosis was not observed
in any of the experimental animals. Similarly, Finch et al. (109)
fed mice a diet containing 2 percent ferric citrate (about 500 mg
iron per kg per day) for 24 days. The liver iron increased twenty-
fold during this period and represented 74 percent of the total
body iron, in contrast to 17 percent in the control animals. No
other change was reported. Adult mongrel dogs fed about 200 mg
iron per kg daily as ferric citrate for 2 to 6 months developed
marked hepatic parenchymal hemosiderosis but no cirrhosis or
fibrosis. Kinney et al. (110) fed adult male rats a corn grit
diet supplemented with 2 percent ferric citrate which provided
about 300 mg iron per kg daily. After 27 to 33 days, the liver
iron of the experimental rats was 3.6 times that of controls and
after 56 to 61 days it was 16.3 times. The histological picture
was that of progressive hemosiderosis of the hepatic parenchyma
and of the reticuloendothelial system.

Biological effects of individual iron forms

A. Elemental iron powders

Included under this heading are iron particles produced
by the reduction of iron oxide, by electrolysis, or by decomposi-
tion of iron pentacarbonyl. As pointed out earlier, all these
forms of elemental iron have often been erroneously subsumed with-
in the terms "reduced iron" or "ferrum reductum." However, the
bioavailability of each depends upon its particle size, surface
area, and purity; these properties vary with the method of pre-
paration.

Elemental iron has certain disadvantages as a fortifying
agent for flour. Its high density compared with flour makes it
difficult to maintain stable blends of uniform iron content, and
its dark color may be objectionable in some products such as
pasta. Nevertheless, the chemical inertness and low cost of this
form have made it an important agent in fortifying flour and other
products requiring extended periods of storage. Waddell (6) esti-
mated that approximately 30 percent of all iron added to grain pro-
ducts in 1970 was elemental iron; a recent survey by NRC (34)
suggests that the percentage may be even higher today. This survey revealed that in 1975, almost 80 percent of the total fortification of foods with iron was with elemental iron.

Berg and van Pelt (111) state that electrolytic iron of "small particle size" is currently used by all manufacturers of infant cereals. The Select Committee has no data on the relative use of the different forms of elemental iron for other food fortification.

The effectiveness of "reduced iron" in repleting hemoglobin of anemic rats or chicks was studied in a collaborative experiment among eight American and Canadian laboratories (112). Compared with ferrous sulfate, which was assigned a biological value of 100, the "reduced iron" had an average rating of 46, with values in the individual laboratories ranging from 27 to 100. Amine et al. (113), in similar bioassays with anemic rats and chicks, reported bioavailability of reduced iron to be 91.4 percent that of ferrous sulfate.

The importance of particle size in the absorption and utilization of powdered iron was convincingly demonstrated by Motzok et al. (114). They determined the biological values of different-sized particles in repleting the hemoglobin of anemic rats and chicks. The iron particles were 7 to 10 μ, 14 to 19 μ, and 27 to 40 μ in size. The investigators found the biological values compared with ferrous sulfate were 45, 21, and 12 in the rat, and 65, 49, and 41 in the chick, respectively.

In man even higher values for the bioavailability of reduced iron were reported by Cook et al. (115). Iron reduced by hydrogen was milled to particles 5 to 10 μ in size, incorporated into dinner rolls, and consumed by human volunteers. The bioavailability of the reduced iron was 95 percent that of ferrous sulfate in rolls similarly prepared. The major determinant for the bioavailability of elemental iron appeared to be the size of the particles. Sacks and Houchin (116) compared the ability of various elemental iron powders of different particle sizes prepared by different techniques, to repair iron deficiency in rats. They found carbonyl iron to be the most effective of the various forms tested. This form can be obtained in extremely pure form and manufactured to rigid specifications. With particles less than 5 μ in size, carbonyl iron was 66 percent as bioavailable as ferrous sulfate. Electrolytic iron particles were somewhat larger (up to 20 μ) and had a 48 percent bioavailability, while hydrogen-reduced iron with particle sizes up to 149 μ had a bioavailability only 24 percent that of ferrous sulfate.

As shown in Table IX, powdered iron appears to be among the least toxic of the various iron preparations tested. Shanas and Boyd (84) administered "reduced iron" intragastrically to rats. Below doses of 10 g per kg body weight there was no evidence of gastrointestinal irritation. No deaths occurred in
animals receiving less than 50 g per kg and the LD$_{50}$ was 98.6 g per kg body weight. Death was apparently caused by bowel obstruction rather than by cellular damage. At this dosage level death usually occurred within 48 hours. When death was delayed to 60 hours, it resulted primarily from severe gastroenteritis complicated by dehydration, hemoconcentration, and electrolyte imbalance. As previously stated, the Select Committee considers such acute studies of little relevance to the questions of food fortification.

Carbonyl iron has been reported to have a comparably low acute toxicity. Volkheimer et al. (117) fed massive doses (250 g) to fasting dogs without apparent harm. Sacks and Houchins (116) gave 1 to 2 g intragastrically to 100 g rats, and Crosby (118) fed 5 g doses to rats (weight and age not reported). No diarrhea, intestinal lesions, or other ill effects were noted. Crosby (118), serving as his own subject, consumed 5 to 10 g doses without discomfort.

Sacks and Houchins (116) fed 130 mg carbonyl iron per kg body weight daily to rats for 6 months. Upon necropsy, they found no stainable iron in the duodenum, liver, or pancreas. Siderosis was seen in the spleen, but the investigators claimed this to be no more marked than that observed in animals fed a laboratory ration.

B. Ferrous compounds

It has been repeatedly demonstrated that iron in the ferrous state is more readily absorbed from the intestinal tract of man than ferric iron (119-121). The difference can be explained most readily by the formation of undissociated ferric hydroxide at the pH existing in the small intestine when a ferric salt is given. Furthermore, the ferric iron is more apt than the ferrous to form other insoluble or complex compounds which further reduce absorption. Brise and Hallberg (121) concluded that the difference in absorption between ferrous and ferric iron is of such a magnitude that "ferric iron has no place in oral iron therapy." However, in contrast to man's relative inability to absorb ferric iron, rats, dogs, and chicks appear to absorb both ferrous and ferric iron with roughly equal facility. For this reason, Narasinga Rao et al. (122) have criticized the customary use of these animals in studying iron availability from human diets. They recommended the monkey as a more appropriate animal model.

Ferrous ascorbate. Moore et al. (123) in 1939, first reported that ascorbic acid increased the absorption of nonheme iron in food. It has now been confirmed repeatedly that ascorbic acid given in combination with various iron salts, both ferrous and ferric, will significantly enhance the absorption of iron from the diet (60,124-126). The enhancing property of ascorbic acid is believed to result from its dual action of reducing the ferric
iron and of forming soluble chelates (3). The soluble iron-ascorbate chelate maintains solubility in the neutral or alkaline milieu of the duodenum and also prevents the formation of insoluble ligands such as oxalates, carbonates, and phytates which would precipitate iron (127). It has a low stability constant (63) which suggests that the chelate would readily release its iron to the mucosal receptors.

As little as 60 mg ascorbic acid added to a meal of rice more than tripled the absorption of iron (128). Cook and Monsen (129) tested the effect of various doses of ascorbic acid on the absorption of iron from a semisynthetic diet containing no meat. They found the absorption to be directly proportional to the amount of added ascorbic acid over the range of 25 to 1000 mg. At these extremes, iron absorption was increased 1.65 and 9.57 times, respectively, that of the unsupplemented diet. The investigators concluded that individuals who routinely ingest large amounts of ascorbic acid may increase their iron absorption several-fold, thus posing a potential problem among persons with faulty iron-regulatory mechanisms.

Møller (28) reported that iron given as synthetic ferrous ascorbate was much more readily absorbed in pigs of different ages than when fed as ferric ammonium citrate, iron fructose, or iron dextran. The Select Committee is aware of no other report in which the synthetic form has been employed. As stated earlier (p. 10), stoichiometric or excess quantities of ascorbic acid are usually added to an iron salt and the resulting preparation considered to be ferrous ascorbate. Mikhaylova (130) found that a ferrous ascorbate "preparation" was more effective than hydrogen-reduced iron, ferrous carbonate, or ferrous malate in raising the serum level of iron in patients with iron-deficiency anemia. Administration of 1 g ferrous ascorbate increased the serum iron from 28 μg to 200 μg per 100 ml serum within 3 hours. The serum level remained elevated in some patients 24 hours after ingestion of ferrous ascorbate, an effect not observed with any other iron preparation tested. Beresford et al. (131) administered a solution of labeled ferrous sulfate together with ascorbic acid via nasogastric tube to 19 infants and young children. The authors designated the resulting preparation as ferrous ascorbate. The average absorption of the labeled iron in children with normal temperatures was 41.2 percent of the administered dose but only 15.1 percent during their febrile states.

Twenty stock mice were injected subcutaneously with 0.2 ml of "ferrous ascorbate" containing 0.3 mg iron at weekly intervals for 43 weeks without developing tumors at any site (132).

Ferrous carbonate. Ferrous carbonate was the earliest preparation used in the treatment of iron-deficiency anemias. It was first adopted by the French physician Pierre Blaud in 1831 to treat "chlorosis" and for decades, ferrous carbonate in the form
of "Blaud's Pills" or "Blaud's Mass" was the accepted hematinic (133). A mixture of 15 percent ferrous carbonate with sucrose (ferrous carbonate saccharate) forms a more soluble preparation and has also been used as a hematinic.

When given orally to dogs, the acute toxicity of ferrous carbonate was reported to be less than that of ferrous sulfate, gluconate, or succinate (79) and has therefore been suggested as an alternative to more commonly used therapeutic agents. D'Arcy and Howard (134) administered as much as 1.0 g iron per kg body weight as ferrous carbonate to dogs for 14 days, with no toxic signs, or evidence of damage to the stomach or intestine at necropsy. Ferrous sulfate and gluconate caused vomiting, diarrhea, or gastrointestinal damage at iron intakes of one-fourth or less of this amount. The low toxicity of this compound probably results from its relative insolubility in the gastrointestinal tract (83). Its low solubility probably also explains its poor bioavailability. Fritz et al. (135) found it to be 0 to 6 percent as effective as ferrous sulfate in repleting hemoglobin in anemic chicks and rats.

Ferrous citrate. Little information is available on this compound. Citrate is produced in normal metabolic processes and no hazard is suspected when it is ingested in moderate amounts (136). Ferrous citrate is absorbed moderately well, but more poorly than some of the other ferrous compounds investigated. Brise and Hallberg (51) compared its absorption with other iron compounds in man. In five normal subjects, the absorption of iron from ferrous citrate was 56 to 91 percent (average 74 percent) that of ferrous sulfate. It has a low stability constant (63) which suggests that its iron should be relinquished to the mucosal receptors. Seven other ferrous salts were more readily absorbed than citrate, and only tartrate and pyrophosphate among the ferrous salts tested showed poorer absorption. Theuer et al. (137), however, reported that ferrous citrate provided the greatest iron availability of eight salts tested when added to liquid infant formulas. Anemic rats were fed supplements of a lyophilized, milk-based infant formula containing 0.25 mg iron as ferrous citrate daily. The hemoglobin increase in these rats was greater than that attained from any other iron supplement, including ferrous sulfate.

The amount of ferrous citrate used as a dietary supplement in foods is not known and the Select Committee is not aware of current use in infant formulas. It is reportedly used in a special dietary beverage at a level of 16.9 mg per liter, and in an extremely small percentage of the milk sold by dairies (35). The International Nutritional Anemia Consultative Group, on the basis of bioavailability and cost, lists ferrous citrate as a commercially available compound and recommends its use as a fortifying agent in beverages and sugars (14).

Ferrous fumarate. Ferrous fumarate is used extensively as an oral hematinic for adults and infants, but the extent of its
addition to foods is not known. It is an iron supplement to cer-
tain cereals and beverages and to a corn-soy-milk blended food
(35). It has been reported to produce unacceptable flavors in
milk (14), but to be an acceptable additive in cocoa powder (14)
and coffee (138). Ferrous fumarate is relatively soluble and is
readily absorbed from the gastrointestinal tract. It, too, has a
relatively low stability constant (63). Fritz et al. (135) re-
ported that it was as effective as ferrous sulfate in repleting
hemoglobin in rats and chicks made anemic on a low-iron diet.
Similarly, it was absorbed as well as ferrous sulfate by normal
human subjects (51). Its acute toxicity in animals is less than
that of ferrous sulfate and of ferrous gluconate (Table IX); it
causes less gastric irritation in rabbits and vomiting in cats
than these compounds (80).

Clinical studies have confirmed the effectiveness of fer-
rous fumarate as a hematinic (139,140). The incidence of side ef-
fects is approximately that experienced with ferrous sulfate or
ferrous gluconate (141). A total of 118 men and women were given
74 mg iron, three times daily for 14 days, in the form of ferrous
fumarate. Side-effects were reported in 26.4 percent of the cases,
compared with 27.9, 31.5, and 13.9 percent from subjects receiving
ferrous sulfate, ferrous gluconate, and placebo, respectively.
The most common complaint was constipation (10 percent), followed
by diarrhea (6.4 percent) and "heartburn" (5.5 percent). Six (5.5
percent) of the subjects discontinued therapy. Ferrous fumarate
enjoys one advantage in pill form over the other iron salts: it
is stable without a sugar coating, thus reducing the danger of
overdosing in children attracted by the sweet taste of coated
pills (142). It is widely used in pill or liquid form as iron sup-
plements sold over the counter. The Physicians' Desk Reference
(143) lists more than a score of such preparations currently avail-
able.

Ferrous fumarate is one of the compounds recommended by
the International Nutritional Anemia Consultative Group (14) for
use in infant formulas on the basis of its bioavailability and
cost.

Ferrous gluconate. Relatively large amounts of the glu-
conate anion are produced daily by the normal individual, and the
consumption of moderate amounts poses no significant hazard (144).
The solubility and safety of various gluconates have made it a
popular vehicle with which to introduce certain metallic cations
into the body as dietary supplements. Gluconate salts are GRAS
with copper [21 CFR 182.5260], sodium [21 CFR 182.6757], manganese
182.1199], as well as with iron [21 CFR 182.5308] (2). Ferrous
 gluconate is also used as a color additive in ripe olives [21 CFR
73.160] (145).
The bioavailability of ferrous gluconate is high, approaching that of ferrous sulfate (Table VIII) whereas its acute toxicity is significantly less (Table IX). Its low stability constant should allow a rapid release of iron to intestinal receptors (63). When given at levels of 100 mg iron per day to male patients with iron-deficiency anemia it produced an increase in hemoglobin of about 65 percent within 4 weeks (146). Two of 20 patients developed abdominal pains and diarrhea within the first week and one complained of vomiting. Hallberg et al. (141) gave 196 normal subjects 180 mg iron in the form of ferrous gluconate daily for 14 days. Approximately one-quarter of the subjects complained of side effects, the most common of which was constipation. No difference could be detected in the incidence or type of side effects between these subjects and those receiving an equal amount of iron in the form of ferrous sulfate. Hoppe et al. (147) in 1955 reviewed the toxicity of the various iron compounds used therapeutically and concluded that ferrous gluconate appeared to be less toxic and irritating than the other common sources of iron then used in anemia therapy. A number of ferrous gluconate preparations are available without prescription as sources of iron supplementation (143).

When thermally processed and freeze-dried, ferrous gluconate maintained high availability in both soy- and milk-infant formula products (137,148).

Ferrous gluconate was tested for mutagenic activity in a series of in vitro microbial assays with and without metabolic activation by mammalian systems (149). Both the plate and suspension test procedures were employed with Salmonella typhimurium strains TA-1535, -1537, and -1538 and Saccharomyces cerevisiae, strain D4 as the test organisms. Activating preparations were made from lung, liver, and testes of ICR random-bred mice, Sprague-Dawley rats, and Macaca mulatta monkeys. Ferrous gluconate was mutagenic in the activation test systems with TA-1538 and monkey liver tissue using the suspension test procedure. However, in reviewing these data, the investigator (150) subsequently concluded that the results were variable, and no firm conclusion could be drawn. None of the other tests was positive. Ferrous gluconate was nonmutagenic in tests with Drosophila (151).

Haddow and Horning (132) reported that weekly subcutaneous injections of 5 mg ferrous gluconate into 20 stock mice for 13 weeks produced one fibroma at the site of injection, one thecoma, and one thymoma.

Ferrous gluconate was injected into the egg air cell and yolk at preincubation and after 96 hours incubation (152). Air cell treatment at 96 hours produced a significant increase in mortality and abnormalities over the control birds. The abnormalities included anophthalmia, buphthalmia, ablepharia, eyelid dysplasia, cleft palate, and exencephaly.
Ferrous lactate. Ferrous lactate is very soluble, and its iron is readily bioavailable. No stability constant could be found for this compound, but values for other metallic lactate complexes (63) suggest that the iron from ferrous lactate would be readily given up to mucosal receptors. The anion is produced in normal metabolic processes at levels many-fold that employed in usual iron supplementation (153). Brise and Hallberg (51) compared the absorption of various iron salts and found ferrous lactate to be one of the most effective studied. Its average absorption in five human subjects was 106 percent that of ferrous sulfate used as a standard. Theuer et al. (137,148) reported similar results when ferrous lactate was added to milk- or soy-based infant formula products and then heated and freeze-dried. The relative biological value (RBV) based on the hemoglobin repletion test was 104 in the soy isolate base and 118 in the milk base compared with ferrous sulfate. The addition of this salt as a fortifying agent in beverages has been recommended by the International Nutrition Anemia Consultative Group (14), on the basis of its bioavailability and cost.

Weekly subcutaneous injections of 5 mg of ferrous lactate trihydrate (1.0 mg iron) into 20 albino mice were associated with two carcinomas and one fibrosarcoma at the injection sites within the 21 week test period (132).

Altschinger (154) investigated the teratogenic effects of ferrous lactate to the developing chick embryo. Various scattered abnormalities occurred, but serious abnormalities were not significantly greater or different from controls. The investigator concluded that ferrous lactate was nonteratogenic under the test conditions employed.

Ferrous oxide. (See Oxides of iron, p. 44)

Ferrous sulfate. Ferrous sulfate has been the most thoroughly investigated of the iron salts and has become recognized as the standard against which other compounds are evaluated. It appears to be the most acutely toxic of the iron salts summarized in Table IX. However, it is difficult to place these salts in rank order, for, as Hosking (82) has pointed out, the LD₅₀ values may reflect variations in strain specificity or prior treatment of the animals rather than the intrinsic toxicity of the iron salt. Further, as already mentioned, it is the opinion of the Select Committee that acute toxicity has little relevance to the safety of iron fortification of foods.

Rats receiving 100 to 300 mg iron per kg body weight intragastrically as ferrous sulfate survived and showed no gross evidence of liver necrosis (155). Four of six rats receiving 400 mg per kg died within 48 hours, and 39 of 55 rats receiving 500 mg per kg within 12 hours. The latter animals suffered periportal or midzonal liver cell necrosis. The surviving animals developed peripheral vasoconstriction and diarrhea within 1 hour following
iron ingestion. They were listless but exhibited only moderate decreases in blood pressure. Electron microscopic examination of the liver cells revealed stainable iron in swollen or necrotic hepatocytes although these cells appeared normal by light microscopy. The parenchymal cells were irreversibly injured and became greatly swollen prior to necrosis. All animals receiving iron, including those with no other evidence of cell injury, had characteristic granules in the intracristal lumina of liver cell mitochondria. These mitochondrial changes appear to be the first observable effects of acute iron toxicity.

Dogs given 150 to 400 mg iron per kg as ferrous sulfate by gavage or by enema, or 10 mg per kg intravenously, began to hyperventilate within an hour after administration (86). Marked metabolic acidosis developed with blood pH values as low as 6.7 after 6 hours. The severity of the acidosis was roughly proportional to the amount of ferrous sulfate administered. The cardiac output decreased progressively because of diminished venous return, but arteriolar constriction maintained normal blood pressure until final collapse. When animals survived the acute phase of iron intoxication, their blood pH returned to normal within 24 hours. The direct cause of death in most cases was respiratory failure.

Acute toxicity of ferrous sulfate in man is highly variable. As little as 1 g (about 3 mg iron per kg body weight) has proved fatal in an adult (156), whereas recovery has been reported in a 30-month-old child who had ingested 15 g (about 250 mg iron per kg body weight) (157). The extensive experience with therapeutic doses of ferrous sulfate and other iron salts in the treatment of iron deficiency in all age groups indicates a low toxicity. Thus, adults in many cases have taken 300 mg ferrous sulfate three times daily for years without apparent ill effect (156). Murphy (158) reported a woman who had taken over 4.5 kg of ferrous sulfate over a 19-year period with no clinical or biochemical evidence of hemochromatosis or other pathology. For most of this period, she had taken three 200 mg tablets of ferrous sulfate daily and for approximately 12 months had taken six tablets daily. Her serum iron, total iron-binding capacity, and liver function tests were within normal limits. Liver biopsy was not performed. Wallerstein and Robbins (159) reported hemochromatosis in a patient with chronic hemolytic anemia who had ingested about 500 g iron in the form of ferrous sulfate over a period of 12 years.

Ferrous sulfate was found not to be teratogenic to the developing chick embryo (160). The administration of up to 200 mg per kg of ferrous sulfate orally to pregnant rats or of 160 mg per kg to pregnant mice for 10 consecutive days had no clearly discernible effect on nidation or on maternal or fetal survival (161). The number of abnormalities seen in either soft or skeletal tissues did not differ from controls.
Ferrous sulfate was tested for mutagenic activity with *S. cerevisiae*, strain D4, and *S. typhimurium*, strains TA-1535, -1537, and -1538, with and without activation (162). Mutagenicity was evaluated by both plate and suspension assay procedures. According to the investigators, the results from the Salmonella suspension assay "strongly suggest" some mutagenic activity after metabolic activation. No mutagenicity was observed using the plate assay procedure with or without metabolic activation. Results with the yeast indicator organisms showed no mutagenic activity. Ferrous sulfate showed no mutagenic activity when tested in *Drosophila* (151).

No tumors were reported among 10 mice (strains A and FAIC) receiving single intradermal injections of 0.05 ml of 0.05 M ferrous sulfate (about 0.15 mg iron) (163). Weekly subcutaneous injection of 2.5 mg of ferrous sulfate (0.5 mg iron) into 20 stock mice for 16 weeks produced one fibroma at the injection site (132).

Ferrous sulfate promotes the oxidation of fat, producing undesirable effects on color, flavor, and aroma during storage of fat-containing products (164). To prevent the induction of rancidity in enriched flour, an encapsulated ferrous sulfate has been developed, which significantly lengthens the storage life (15). It has the added advantage of possessing a density similar to flour, thus eliminating the settling problem encountered with elemental iron.

As mentioned earlier, ferrous sulfate is the standard against which other iron compounds are compared for bioavailability and has been so recommended by the Association of Official Analytical Chemists (165). Although its RBV thus becomes 100 by definition, this does not imply that it is completely utilized. Actually, the absorption in man may vary widely, from less than 1 to more than 50 percent, depending on the individual and on various other factors (121).

C. Ferric compounds

Reference has already been made to the greater bioavailability of iron in ferrous than in ferric compounds. This has been demonstrated both in laboratory and clinical studies. Clinical investigators report that patients with hypochromic anemia generally require about five times as much ferric iron as ferrous iron to achieve maximal hemoglobin production (119). The difference in effectiveness is attributed in large part to the lesser solubility of ferric compounds in the intestine. However, Viteri et al. (166) claim that aqueous solutions of ferrous salts are rapidly oxidized to the ferric state unless strict reducing conditions are maintained. In any event, ferric compounds remain a major source of food fortification, although they appear to be
relinquishing their preeminence in favor of elemental iron. In 1970, according to the NRC survey (33), more than twice as much ferric phosphate and ferric sodium pyrophosphate were used to fortify foods as elemental iron. By 1975 (34), this ratio had been reversed, because of a marked increase in the use of elemental iron and a precipitous decline in that of ferric sodium pyrophosphate (Table VI).

**Ferric ammonium citrate.** Ferric ammonium citrate is an unpublished GRAS substance of uncertain structure. It is prepared by adding ferric hydroxide to an aqueous solution of citric acid and ammonia, neutralizing the mixture and then drying. It has enjoyed some popularity as a medicament, for it is relatively well utilized by the body and lacks the objectionable astringent properties found in other ferric salts (147). Heath (167) used it successfully to treat "hypochromic anemia." He recommended that patients be given 2 g per day (0.4 g iron) initially, with gradual increases to 6 g daily (1.2 g iron). Patients were successfully treated on this regimen for many months. He claimed this dosage schedule could be tolerated with ease by the majority of the patients. Only occasional cramps or diarrhea developed and these symptoms disappeared during the course of the treatment.

The acute toxicity of ferric ammonium citrate is low, with oral LD₅₀ values ranging from 1.75 (guinea pig) to 5.0 (mouse) g per kg body weight (83). One fatality has been reported in a woman who consumed 15 g of this compound (with an unknown quantity of whiskey). She died three days later with toxic hepatitis (147). In another case, a 58-year-old woman received 10 g ferric ammonium citrate per day for 23 days and 12.5 g on the 24th day. On the 25th day, the patient lost consciousness, but recovered when the medication was discontinued.

Its use in food is minor and was estimated at 1400 kg in 1974 (35). The reported levels of this usage were 10 mg per liter in milk and frozen dairy products and 15 mg per kg in cheese (35). It was stated that in recent years, as much as 150 million liters of milk nationwide had been fortified with ferric ammonium citrate (26) although accurate figures are not available.

The availability of iron in ferric ammonium citrate compares favorably with that of ferrous sulfate when fed to animals. Fritz et al. (135) reported its RBV as 98 to 115 as measured by hemoglobin repletion in anemic chicks and rats. Hinton and Moran (168) reported it to be as effective as ferrous sulfate when baked in bread, in the regeneration of hemoglobin in anemic rats. However, in severely anemic patients, the iron was poorly available when baked in bread (169). Similarly, when used to fortify chapatti made from wheat flour, only 2 to 4 percent of the iron was absorbed (170).

**Ferric chloride.** The NRC survey of food processors (33) indicates that ferric chloride was not widely used as a food addi-
tive. It was reportedly added only to nonalcoholic beverages and at levels less than 0.01 percent. It is authorized as a component of paper and paperboard in contact with aqueous and fatty foods [21 CFR 176.170] and with dry foods [21 CFR 176.180] (2).

Its acute toxicity in animals appears to be comparable with that of ferrous sulfate, based on their respective iron contents (Table IX). Hoppe et al. (147), in their extensive review of the acute toxicity of iron compounds, reported five cases in which a tincture of ferric chloride had been taken. The ingestion of 45 ml (about 6 g of the salt) proved fatal to a male adult, but as much as twice this amount had been taken by the other four patients without fatality.

Ferric chloride is readily soluble and efficiently absorbed. Blumberg and Arnold (171) compared the bioavailability of ferric chloride and ferrous sulfate in enriched breads. When fed at two levels, both preparations were equally effective in producing hemoglobin regeneration in anemic rats. The iron from each of these compounds was four to five times as available as the iron in ferric phosphate.

Pirzio-Biroli et al. (172) administered labeled ferric chloride to subjects during a standard meal. They reported an absorption of 5 percent in normal and 22 percent in iron-deficient subjects. Layrisse and Martínez-Torres (48) obtained similar results when ferric chloride was incorporated in pancakes made from maize. The average absorption in 8 normal subjects was 4.2 percent. When heme (veal muscle) was added to the diet, iron absorption increased to 7.5 percent.

Ammerman et al. (173) fed radioactive iron in the form of ferric oxide, ferric chloride, ferrous carbonate, or ferrous sulfate to calves and lambs. The availability of iron from ferric chloride, as measured by the levels of $^{59}$Fe in the serum and red blood cells did not differ significantly from that of ferrous sulfate. A more recent study (135), however, indicates that although the bioavailability of iron in ferric chloride is reasonably good, it is significantly less than that of ferrous sulfate.

Ferric citrate. Ferric citrate is unpublished GRAS, and is generally referred to as iron citrate. No data are available on the use of this compound as a fortifying agent in foods. The citrate ion is widely distributed in plants and animals and is a naturally occurring component of the diet. Relatively large amounts are produced and oxidized by normal metabolic processes in man (136). The iron from ferric citrate is more readily available than from most of the ferric compounds. Its bioavailability in anemic chicks and rats averaged 73 percent that of ferrous sulfate (135).
Rather (108), in an attempt to induce hemochromatosis, fed large amounts of ferric citrate to rats for most of their normal life spans. Diets containing 16 and 4 percent protein and 6 percent ferric citrate were fed to 90-day-old male Addis rats for up to 521 days. The daily intake of ferric citrate was approximately 6 g per kg body weight or about 1 g per kg of elemental iron daily. The iron content of the liver per 100 g dry weight increased from 38.5 to 1070 mg in the rats on the high protein diet (average duration 352 days) and from 73.9 to 1775 mg per 100 g dry weight among those on the low protein diet (average duration 434 days). Despite extensive hemosiderin deposits in the liver and pancreas of both groups, equivalent to those observed in hemochromatosis, no fibrosis of either organ was observed.

Twenty stock mice were injected subcutaneously with 5 mg ferric citrate (about 40 mg iron per kg body weight) weekly for 33 weeks. Thirteen mice survived the experimental period. No tumors were reported (132).

Ferric oxide. (See Oxides of iron, p. 44)

Ferric phosphate (ferric orthophosphate). Ferric phosphate has been one of the major sources of iron for the fortification of breakfast cereals and flour, because its relative chemical inertness and inconspicuous white color minimize changes in the appearance and taste of the fortified product. These properties have made ferric phosphate attractive to the food processors. However, as illustrated in Table VI, the use of ferric phosphate is declining, having dropped by 40 percent between 1970 and 1975. This decline has been attributed to the high cost and low RBV of this compound (15).

The low absorption of ferric phosphate has been demonstrated repeatedly. Pla and Fritz (112), employing their hemoglobin repletion assay in rats and chicks, reported ferric phosphate to be only 12 percent as effective as ferrous sulfate. It fared even more poorly when the increase in plasma iron in man was used as an index of absorption. With this criterion, ferric phosphate was only 7 percent as effective as ferrous sulfate. When baked in dinner rolls, less then 1 percent of the iron in ferric phosphate was available, contrasting with 8.6 percent of reduced iron and 5.7 percent of ferrous sulfate (115).

Hodson (174) suggests that storage of foods fortified with ferric phosphate may convert the iron to the ferrous state and improve its absorbability. He analyzed canned liquid dietary foods to which ferric phosphate had been added and found up to 90 percent of the iron to be in the ferrous form after 5 to 6 months' storage. However, the product had also been fortified with ascorbic acid, and the cans had limited headspace, conditions favorable to a reducing environment. The storage conditions and thermal processing procedures were not described.
Food grade ferric phosphate was tested for mutagenicity against *S. cerevisiae*, strain D4 and *S. typhimurium*, strains TA-1535, -1537, and -1538. The tests were conducted with and without addition of metabolic activation preparations derived from lung, liver, and testes of ICR random-bred mice, Sprague-Dawley rats, and *M. mulatta* monkeys. None of the tests revealed mutagenic activity.

**Ferric pyrophosphate.** Ferric pyrophosphate is very insoluble in water and is generally added to fat-containing foods, where more soluble sources of iron might induce rancidity. Its use, however, is quite limited, and estimates indicate that only about one metric ton was used by American food processors in 1970 (33). A 1975 survey failed to reveal any use (34) (Table VI).

The relative biological value (RBV) of ferric pyrophosphate was only 7 percent that of ferrous sulfate, as determined by the chick hemoglobin repletion assay. However, when the diet was subjected to heat and pressure processing (1055 g per cm² and 121°C for 15 minutes), the RBV increased to 90 percent and did not differ significantly from that of ferrous sulfate. Theuer et al. (137, 148) also found ferric pyrophosphate to be an excellent iron source when infant formulas containing this salt were subjected to commercial sterilization processes.

No acute or chronic toxicity data for ferric pyrophosphate, either with animals or man, are available to the Select Committee. This compound has been tested for mutagenic activity in a series of *in vitro* microbial assays with and without metabolic activation. The organisms employed were *S. typhimurium*, strains TA-1535, -1537, and -1538, and *S. cerevisiae*, strain D4. Activating preparations were made from lung, liver, and testes of ICR random-bred mice, Sprague-Dawley rats, and *M. mulatta* monkeys. Ferric pyrophosphate induced no mutagenic activity in these tests (177). It showed little toxicity to the developing chick embryo when administered via the air sac before incubation at levels up to 200 mg per kg (10 mg per egg). Air cell treatment after a 96-hour incubation gave a calculated LD₅₀ of 43 mg per kg (2.2 mg per egg). The observed abnormalities did not differ in kind or number from controls (178).

**Ferric sodium pyrophosphate.** Ferric sodium pyrophosphate shares with ferric phosphate the light color and the chemical inertness desired by industry as an iron fortifying agent for grain products. In 1970 (33) (Table VI), it comprised about 16 percent of all iron products used for fortification and, together with ferric phosphate, was the major iron source for the enrichment of cereals, rice, macaroni, and similar products (6). A 1975 survey (34), however, revealed a drop of approximately 95 percent in the use of ferric sodium pyrophosphate as a fortifying agent. It is more costly and less biologically available than ferric phosphate, which probably contributed to its reduced use (15). The
iron provided by this compound in 1970 was estimated to be about 0.7 mg per person per day, but this value had dropped to less than 0.05 mg in 1975.

The bioavailability of ferric sodium pyrophosphate has been determined by various techniques and has been shown to be poor. Pla and Fritz (112) found its iron availability to be only 13 percent that of ferrous sulfate as determined by the hemoglobin repletion method in rats and chicks. When measured by an increase of plasma iron in man, it was rated as 7 with ferrous sulfate as 100. When baked in dinner rolls, less than 1 percent was absorbed (115). It was only 15 percent as efficient as ferrous sulfate when fed to anemic rats in iron-fortified cereal-milk diets (179). Kios et al. (180) confirmed the poor absorption from infant cereal and stated it was an undependable source of iron to meet the nutritional needs of the infant. However, sterilization of infant formulas (137,148) and heat and pressure processing of diets (176) have been reported to convert ferric sodium pyrophosphate from a poor to a relatively good supplemental iron source. The reason for this increase is not known. Wood et al. (176) speculated that processing may enhance the formation of soluble chelates which are more readily absorbed than the inorganic salt.

At a concentration of 1.25 percent, ferric sodium pyrophosphate was tested for mutagenicity in several in vitro microbial assays, with and without metabolic activation (181). The organisms employed were S. typhimurium, strains TA-1535, -1537, and -1538, and S. cerevisiae, strain D4. Activating preparations were made from lung, liver, and testes of ICR random-bred mice, Sprague-Dawley rats, and M. mulatta monkeys. No mutagenic activity was observed in these tests.

Intraperitoneal injection of 1600 mg per kg ferric sodium pyrophosphate (about 300 mg iron) into pregnant rats and mice (182) for 10 consecutive days, had no discernable effect on nidation, on maternal or fetal survival, or on fetal abnormalities.

Ferric sulfate. Ferric sulfate is GRAS for use in paper and paperboard food packaging materials. No data are available to the Select Committee on the amounts used for this purpose. Ferric sulfate is slowly soluble in water. Brise and Hallberg (51) reported its absorption in man to be 36 percent that of ferrous sulfate while Fritz et al. (135) found it to be 83 percent as effective in hemoglobin repletion in chicks and rats.

Viteri et al. (166) state that ferrous sulfate, added to solutions as an enrichment agent, is actually ingested in most cases as ferric sulfate. According to these investigators, 80 percent of the ferrous iron is rapidly oxidized in aqueous solutions to the ferric state unless strict reducing conditions are maintained. They compared the absorption of iron from ferric sulfate with that from sodium ferric EDTA and from hemoglobin. When 5 mg
labeled iron in these forms were given to children (mostly iron-deficient) with a milk-rice-sugar formula, 34.5 percent of hemo-globin iron, 8.6 percent of sodium ferric EDTA iron, and only 3.3 percent of ferric sulfate iron were absorbed. Normal and iron-deficient men also showed a similar pattern of absorption. Addition of ascorbic acid and of sodium ferric EDTA enhanced the absorption of iron from ferric sulfate.

Oxides of iron. Ferrous and ferric oxides are categorized as "oxides of iron" [21 CFR 182.90] (2) which accords them GRAS status as substances migrating to foods from paper and paperboard products used in food packaging. Ferric oxide, in addition, has been given unpublished GRAS status as a dietary supplement (16). "Synthetic iron oxide" is also authorized as a color additive in pet food, not to exceed 0.25 percent by weight of food [21 CFR 73.200] (145). Ferrous oxide is practically insoluble in water but readily soluble in acids. It is readily oxidized to the ferric state in the presence of air. No biological data are available to the Select Committee for this compound.

Ferric oxide is poorly absorbed from the gastrointestinal tract. Doty et al. (183) introduced [59Fe] ferric oxide into the stomach of rats by gavage. Four hours after administration, 99.3 percent of the labeled material could be recovered, indicating an absorption of less than 1 percent. Tests for bioavailability reflect this poor solubility. Fritz et al. (135) reported a bioavailability in anemic chicks and rats of 0 to 6 percent for ferric oxide compared with that of ferrous sulfate. Of the 19 iron preparations tested for their ability to regenerate hemoglobin in anemic animals, only ferric oxide and ferrous carbonate showed relative biological values below 10 percent.

No tumors were produced when dialyzed 5 percent colloidal ferric oxide was injected subcutaneously into 20 CBA mice in doses of 0.2 ml weekly for 16 weeks (132). Single intraperitoneal injections of 0.5 ml of ferric oxide suspension (concentration not reported) into 15 albino mice also failed to produce tumors during an observation period of 5 months (184).

Epidemiologic evidence suggests that exposure to hematite dust (mainly ferric oxide) increases the risk of lung cancer in man, but the role of ferric oxide in its development is still uncertain (185). Ferric oxide given intratracheally or by inhalation has not been found carcinogenic in hamster, mouse, or guinea pig (185). Stenback et al. (186), however, claimed that ferric oxide given intratracheally increased the carcinogenic potential of subcutaneously injected dimethylnitrosamine (DMN) on respiratory tissues. With DMN alone, 12 of 24 Syrian golden hamsters developed tumors, none of which was in the respiratory system. With DMN injection followed by repeated endotracheal instillations of ferric oxide, 14 of 30 animals showed tumors, including four in the respiratory system.
Sodium ferricitropsyrophosphate. This is a mixed salt of uncertain composition produced by combining sodium pyrophosphate with ferric citrate. According to industry representatives (26) it is soluble and leaves no off-flavor, properties which make it a useful source of iron in the fortification of milk. Between 1955 and 1967, it was used in the preparation of multivitamin and mineral concentrates for the dairy industry. There is no evidence that it is now used for this purpose.

No data are available on its biological or toxicological properties.

D. Iron complexes

Iron caprylate. The Select Committee was unable to obtain any production data on iron caprylate or on the other iron compounds used to hasten the drying of films which coat the inner surfaces of food-containing cans. The film coating a no. 303 can (capacity about 0.5 kg) weighs approximately 170 mg, of which 10 percent is dryer (20). The dryer in turn contains 6 to 7 percent iron, or about 0.1 mg iron per can for a total of 0.2 mg iron per kg of contents. It is not known how much would migrate into the food, but the amount is believed to be very small.

Caprylic acid is a naturally occurring constituent of many foods, readily metabolized and utilized by man (187). Few biological data are available for 2-ethyl hexanoic acid, whose iron salt would also be found in the film coating. It has been reported that the minimal lethal dose of this compound by mouth for rats was 1600 mg per kg body weight (188).

Iron linoleate. The possible exposure to iron from iron linoleate would be roughly the same as that discussed for iron caprylate; namely, a maximum of 0.2 mg per kg canned contents. Linoleic acid and the other fatty acids in linseed oil, which might form iron salts, are naturally occurring food components readily metabolized and utilized by man (189).

Iron naphthenate. This term encompasses a mixture of iron salts and acids of variable composition. The Select Committee is unaware of biological studies on naphthenic acids or on iron naphthenates. The possible migration into foods might be similar to that described above for the other iron salts in can coatings.

Iron peptonate. This complex is unpublished GRAS as a dietary supplement (16). There is no evidence that it has any current usage. The Grocery Manufacturers of America surveyed its membership in 1976 and reported that none of the firms queried was using iron peptonate for iron supplementation (40). No information on its biological effects is available to the Select Committee.
Iron polyvinylpyrrolidone. As indicated earlier (p. 10) iron or iron salts with polyvinylpyrrolidone (PVP) are used as mixtures of variable proportions, authorized as tableting adjuvants or stabilizers in various mineral and vitamin concentrates [21 CFR 75.355] (2). The Select Committee is not aware of the use of any chemically defined iron-PVP complex as an iron fortifying agent in foods, nor of the biological properties of such a complex.

Iron tallate. The fatty acid fractions of tall oil comprise about half the total acid content and consist mainly of oleic and linoleic acids. Both are naturally occurring constituents of many edible oils, and are consumed without ill effect in relatively large amounts. Acute toxicity tests of the resin fraction have given LD$_{50}$ values of 4.6 g per kg for mice and guinea pigs and 7.6 g per kg for rats. Tall oil resins have been fed at levels of 50 mg per kg per day to rats and 40 mg per kg per day to beagle dogs for 2 years with no significant differences from controls in their hematology, urinalyses, and liver and kidney function tests (190).

Sodium ferric EDTA. Ethylene diamine tetraacetic acid (EDTA) forms water-soluble chelates with many metallic ions, including iron, and this property has been widely exploited. Its disodium salt is used to solubilize trace minerals in animal feeds [21 CFR 573.360] (24) and to stabilize iron salts in liquid multi-vitamin preparations [21 CFR 172.135] (2). It is also used as a preservative or to promote color retention in a variety of food products in concentrations of 36 to 500 ppm [21 CFR 172.135].

Ferric EDTA is a very stable complex (63) with a stability constant well above the threshold for ready release of iron to mucosal receptors (62). Helbock and Saltman (191) present evidence that the iron chelate is transported intact across the intestinal mucosa. In the plasma, the iron is relinquished very slowly to plasma transferrin (192), so that most of the chelate is eliminated in the urine.

This compound has been shown to be an effective source of iron for animals (193) and for iron-deficient patients (194). Anderson et al. (193) fed cereal-milk diets supplemented with 100 mg iron per 100 g diet in the form of sodium ferric EDTA to 5-day-old Pitman-Moore miniature pigs for 28 days. Efficient utilization of iron from this source was observed. It was significantly greater than that obtained with equivalent amounts of catalytically reduced iron or sodium iron pyrophosphate. Iron absorption from the EDTA complex was 90 percent that of ferrous sulfate.

Will and Vilter (195) administered sodium ferric EDTA containing 100 mg iron three times daily to three anemic patients for 35 to 59 days. The total doses of elemental iron administered were 10.5 to 17.7 g. The hematologic response was comparable to that from equivalent doses of ferrous sulfate.
Brise and Hallberg (51) found the absorption of iron from sodium ferric EDTA to be the least of 14 iron salts tested and only 20 percent that of ferrous sulfate. This finding may be misleading, for the investigators added 10 mg ascorbic acid to the ferrous sulfate solution to prevent oxidation of the ferrous ion. Since ascorbic acid promotes iron absorption, the net result of such differential treatment would be to decrease the percentage absorption of sodium ferric EDTA compared with ferrous sulfate.

Cook and Monsen (196) reported that the absorption of iron from test meals was reduced by 28 percent at a 1:1 molar ratio of EDTA with iron and by half at a 2:1 molar ratio. The authors estimated that American diets may contain 50 to 100 mg EDTA daily, amounts shown by this study to impair significantly the absorption of nonheme iron.

Layrisse and Martínez-Torres (194) on the other hand, claim that sodium ferric EDTA possesses certain advantages over other iron salts, including ferrous sulfate. They reported that iron absorption in human subjects from maize or milk enriched with this compound was consistently greater than from ferrous sulfate enrichment. Iron absorption from sodium ferric EDTA or from ferrous sulfate-fortified sugar was comparable, but the chelated form was considered preferable since it precipitated more slowly from tannin-containing beverages, thus allowing better absorption of the iron.

A recent study (197) from the same laboratory suggested that ferric EDTA was a more reliable salt than ferrous sulfate as an enrichment agent in foods. These investigators added either ferric EDTA or ferrous sulfate to six different foods (sugar, cane syrup, milk, sweet manioc, wheat, or maize) and determined the iron absorption in man. The mean iron absorption from ferrous sulfate ranged from 2.0 percent from maize to 30.0 percent from refined sugar. On the other hand, no significant difference could be detected in the iron absorption from these foods enriched with ferric EDTA (range 8.2 to 13.1 percent); these results indicate that ferric EDTA is less affected than ferrous sulfate by substances in foods which inhibit iron absorption.

Viteri et al. (166) have also demonstrated excellent bioavailability of iron from sodium ferric EDTA when given to infants and adults. They, too, claim this chelated form is superior to ferrous sulfate as a source of available iron. Referring to unpublished studies in their laboratory, they reported preliminary findings which showed that infants absorbed labeled iron in milk fortified with sodium ferric EDTA 2.5 times better than iron from ferrous sulfate. They suggested that one reason for the greater availability of iron in this form than from most iron salts may be due to the solubility of the iron EDTA complex at the pH characteristic of the duodenum and upper jejunum. The affinity of EDTA for iron is very strong at these pHs and tends to protect it from forming insoluble and unabsorbable complexes. No adverse effects
were reported in any of these studies from the administration of sodium ferric EDTA.

Ascorbic acid and EDTA appear to display opposing effects on the absorption of iron. Ferrous sulfate labeled with $^{59}$Fe was placed in an isolated rat intestinal loop together with various amounts of ascorbic acid and/or EDTA. Iron absorption was significantly higher in the presence of ascorbic acid. When both compounds were added, EDTA was capable of negating the enhancing effects of ascorbic acid even at molar ratios of ascorbate:EDTA as high as 4:1 (198).

The variable results obtained with the iron EDTA complex are confusing, and suggest that the experimental conditions or the presence or absence of other substances are critical in evaluating its effectiveness as an iron source.
V. OPINION

The body content of iron in the normal individual is regulated primarily by absorptive processes. Relatively small amounts of iron are absorbed when body stores of iron are high, and relatively large amounts when body stores are low. This regulation of iron absorption is faulty in individuals with the metabolic disorder, hemochromatosis.

Although hemochromatosis is generally considered a rare, genetically transmitted disorder, several investigators believe that a latent form of hemochromatosis may be much more common. In Sweden, where food fortification with iron is at a higher level than in the United States, and where medicinal iron supplements are widely consumed, investigators reported several cases of hemochromatosis and iron overload in a sparsely populated district. The significance of these findings with respect to the general population of Sweden, or to other populations, is not yet clear. However, these findings suggest that it is possible that a significant number of apparently normal and unidentified individuals might be at risk of developing liver damage from intakes of iron which are innocuous and, in fact, probably beneficial for the population at large.

It should be noted that in the United States (and probably in other industrialized countries), individuals ingesting large amounts of iron may achieve these intakes through regular consumption of iron supplements. For these individuals, food fortification contributes a relatively small fraction of total intake. The question of total intake of iron by the U.S. population and its relation to chronic iron toxicity merit further study. Monitoring of the population with respect to iron nutritional status is essential. The estimated per capita intake of 5 mg per day obtained from food fortification comprises more than one-third the total iron intake for much of the population.

Iron deficiency is a leading nutritional problem in the United States. Intakes of iron are below recommended levels for a large fraction of the population. Hence, it is evident that an increase in iron fortification of selected foods could be an important public health measure.

The form of iron utilized to fortify foods should be of adequate bioavailability. Iron forms evaluated in this report which appear to be adequately bioavailable are elemental iron (reduced, electrolytic, carbonyl), ferrous ascorbate, ferrous citrate, ferrous fumarate, ferrous gluconate, ferrous lactate, ferrous sulfate, ferric ammonium citrate, ferric chloride, and ferric citrate. In contrast, the bioavailability of ferrous carbonate, ferrous oxide, ferric oxide, ferric phosphate, ferric pyrophosphate, or ferric sodium pyrophosphate is relatively low compared
with ferrous sulfate. Insufficient data are available to judge the relative bioavailability of the other iron preparations considered in this report.

Experimental data are sparse for most of the forms of iron considered in this report. Animal studies have been largely confined to determination of the acute toxicity and bioavailability of specific iron forms. Such studies have limited relevance in evaluating the possible hazards of the addition of iron to foods. Few reports are available on the effects of long-term feeding experiments. An extensive literature exists on the use of certain forms given as hematinics, but the reports are largely anecdotal and their interpretation is of questionable value. Certain compounds have been employed extensively for many years both as additions to food and in the treatment of iron deficiency with no reported adverse effects. In view of the need for, and wide use of, iron compounds, it would appear prudent to place this historical and anecdotal experience on a scientifically rigorous basis in the reasonably near future. The Select Committee emphasizes the need for well-controlled chronic feeding studies with most of the individual compounds, before confident appraisal can be made of their relative merits or hazards.

In the light of the above considerations, the Select Committee concludes that:

There is no evidence in the available information on reduced, electrolytic, and carbonyl iron, ferrous ascorbate, ferrous carbonate, ferrous citrate, ferrous fumarate, ferrous gluconate, ferrous lactate, ferrous sulfate, ferric ammonium citrate, ferric citrate, ferric phosphate, or ferric pyrophosphate that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used at levels now current and in the manner now practiced or, if deemed necessary at somewhat higher levels to meet nutritional needs. However, it is not possible to determine without additional data whether a major increase in consumption would constitute a dietary hazard.

Serious deficiencies exist in the experimental data or clinical experience with a number of iron compounds employed or suggested as iron fortifying agents for foods.

The Select Committee concludes that:

In view of the deficiency of relevant biological studies, it has insufficient data upon which to base an evaluation of ferric oxide, iron peptonate, iron polyvinylpyrrolidone, sodium ferric EDTA, sodium ferricitropyro-
phosphate, or ferric sodium pyrophosphate when it is used as a food ingredient.

Several iron compounds are used in the preparation of paper and paperboard materials contacting foods or as ingredients used to hasten the drying of films used in coating the inner surface of food cans. Neither the amounts used for these purposes nor the extent to which they might migrate to foods are known to the Select Committee. However, the extent of their migration to food is believed to be very slight.

The Select Committee concludes that:

There is no evidence in the available information on elemental iron, ferrous sulfate, ferric chloride, ferric oxide, ferric sulfate, iron caprylate, iron linoleate, iron tallate, or the oxides of iron that demonstrates, or suggests reasonable grounds to suspect, a hazard to the public when they are used as ingredients of paper and paperboard materials or in films coating the inner surface of cans in the manner now practiced or that might reasonably be expected in the future.

No information is available on the metabolism or toxicity of the various substances included under the term iron naphthenate.

The Select Committee concludes that:

In view of the deficiency of relevant biological studies, it has insufficient data upon which to base an evaluation of iron naphthenate when it is used as an ingredient of films which coat the inner surface of cans containing food.
VI. REFERENCES CITED


- 59 -


- 66 -


VII. SCIENTISTS CONTRIBUTING TO THIS REPORT

1. Members of the Select Committee on GRAS Substances:

*Joseph F. Borzelleca, Ph.D., Professor of Pharmacology, Medical College of Virginia, Health Sciences Division, Virginia Commonwealth University, Richmond, Virginia.

Harry G. Day, Sc.D., Professor Emeritus of Chemistry, Indiana University, Bloomington, Indiana.

Samuel J. Fomon, M.D., Professor of Pediatrics, College of Medicine, University of Iowa, Iowa City, Iowa.

Bert N. Le Du, Jr., M.D., Ph.D., Professor and Chairman, Department of Pharmacology, University of Michigan Medical School, Ann Arbor, Michigan.

John R. McCoy, V.M.D., Professor of Comparative Pathology, New Jersey College of Medicine and Dentistry, Rutgers Medical School, New Brunswick, New Jersey.

*Sanford A. Miller, Ph.D., Professor of Nutritional Biochemistry, Massachusetts Institute of Technology, Cambridge, Massachusetts.

Gabriel L. Plaa, Ph.D., Professor and Chairman, Department of Pharmacology, University of Montreal Faculty of Medicine, Montreal, Canada.

Michael B. Shinkin, M.D., Professor of Community Medicine and Oncology, School of Medicine, University of California, San Diego, La Jolla, California.

Ralph G.H. Siu, Ph.D., Consultant, Washington, D.C.

Marion E. Swendseid, Ph.D., Professor of Nutrition, University of California School of Public Health, Los Angeles, California.

John L. Wood, Ph.D., Distinguished Service Professor, Department of Biochemistry, University of Tennessee Medical Units, Memphis, Tennessee.

George W. Irving, Jr., Ph.D., (Chairman), Life Sciences Research Office, Federation of American Societies for Experimental Biology, Bethesda, Maryland.

*Did not participate in the final opinion reached in this report.
2. LSRO staff:

Kenneth D. Fisher, Ph.D., Director
Frederic R. Senti, Ph.D., Associate Director
C. Jelleff Carr, Ph.D., Director Emeritus
Richard G. Allison, Ph.D., Staff Scientist
Sue Ann Anderson, Ph.D., Staff Scientist
Herman I. Chinn, Ph.D., Senior Staff Scientist
Andrew F. Freeman, Senior Staff Scientist
John M. Talbot, M.D., Senior Medical Consultant
Michael J. Wade, Ph.D., Staff Scientist

Report submitted by:

March 26, 1980
Date

George W. Irving, Jr., Chairman
Select Committee on GRAS Substances
PUBLIC HEARING ON IRON AND IRON SALTS

HELD NOVEMBER 19, 1979*

An oral presentation at the hearing was made by L. Blecher, GAF Corporation, 140 West 51st Street, New York, New York.

Written statements in lieu of oral presentations were submitted by the following:

1. H.P. Sarett, Mead Johnson Nutritional Division, Evansville, Indiana.


3. W.H. Crosby, Scripps Clinic and Research Foundation, 10666 North Torrey Pines Road, La Jolla, California.


A written statement was submitted after the hearing by R. Ullman of Bass, Ullman and Lustigman, 747 Third Avenue, New York, New York, Attorneys for National Nutritional Foods Association.

A letter submitting copies of articles in the published literature on iron and iron salts was received from H.L. Schlesinger, Gallard-Schlesinger, Chemical Manufacturing Corporation, 584 Mineola Avenue, Carle Place, New York.
