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Office of Emergency and Remedial Response
Washington DC 20460

Office of Research and Development
Office of Health and Environmental Assessment
Environmental Criteria and Assessment Office
Cincinnati OH 45268

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HEALTH EFFECTS ASSESSMENT FOR IRON (AND COMPOUNDS)

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Office of Solid Waste and Emergency Response
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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with iron (and compounds). All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) source has been extensively utilized:

U.S. EPA. 1981. Multimedia Criteria for Iron and Compounds. Environmental Criteria and Assessment Office, Cincinnati, OH. Internal draft.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980). Since cancer is a process that is not characterized by a threshold, any exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Iron deficiency is much more prevalent and has been given much greater attention than iron toxicity. As a result, minimum required levels are well defined (10 mg/day, men; 18 mg/day, women) while essentially no quantitative data are available for maximum tolerable oral exposure.

Limited data are available for inhalation exposures. Occupational experience provides some information. An AIC for inhalation of 0.6 mg/day has been suggested based on the ACGIH (1980) recommended TLV-TWA of 0.8 mg/m^3. Data were insufficient for calculation of a CS from either the oral or the inhalation data.

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Scientists from the following U.S. EPA offices provided review comments for this document series:

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Editorial review for the document series was provided by:

Judith Olsen and Erma Durden
Environmental Criteria and Assessment Office
Cincinnati, OH

Technical support services for the document series was provided by:

Bette Zwayer, Pat Daunt, Karen Mann and Jacky Bohanon
Environmental Criteria and Assessment Office
Cincinnati, OH

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
CAS	Chemical Abstract Service
CS	Composite score
DNA	Deoxyribonucleic acid
EDTA	Ethylenediaminetetraacetic acid
LD_{50}	Dose lethal to 50% of recipients
ppm	Parts per million
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

Iron is a metal belonging to the first transition series of the periodic table. The CAS Registry number for elemental iron is 7439-89-6. The inorganic chemistry of iron is dominated by compounds in the +2 and +3 valence states. The primary examples of iron in the 0 valence state are metal and alloys and the carbonyl compounds. Selected physical properties of a few environmentally significant iron compounds are given in Table 1-1.

The predominant sources of iron in the atmosphere are natural processes including continental dust created by wind erosion of weathering mineral deposits, volcanic gas and dust and forest fires (Lantzy and Mackenzie, 1979). An insignificant amount of iron may enter the atmosphere through aerosol formation from sea surface (Lantzy and Mackenzie, 1979). Anthropogenic sources of atmospheric iron may contribute ~28% of the total atmospheric burden for iron (Lantzy and Mackenzie, 1979). The principal anthropogenic sources of atmospheric iron are industrial emissions and burning of fossil fuels (Lantzy and Mackenzie, 1979). In the atmosphere, iron is likely to be present in the particulate form (U.S. EPA, 1981) or different chemical forms that may undergo chemical or photochemical reactions, frequently with subsequent changes of oxidation states, but these processes may not be directly responsible for the removal of iron from the atmosphere. The processes that may remove iron from the atmosphere are wet and dry deposition (U.S. EPA, 1981). It has been estimated that the residence time of iron in the atmosphere may be 10-20 days (Lantzy and Mackenzie, 1979).

In aquatic media, iron can undergo primarily chemical reactions including precipitation, speciation, oxidation-reduction and chelation; photochemical reactions including photoaquation, photosensitization and

TABLE 1-1

Selected Physical Properties of a Few Iron Compounds[a]

Element/Compound	Formula	Molecular/Atomic Weight	Specific Gravity/ Density	Water Solubility	Vapor Pressure (mm Hg)
Iron	Fe	55.847	7.86	insoluble[b]	1 mm at 1787°C
Iron (III) chloride	$FeCl_3$	162.21	2.898^{25}_{4}	74.4 g/100 mL at 0°C	NA
Iron (II) sulfide	FeS	87.91	4.74	0.62 mg/100 mL at 18°C	NA
Iron (III) oxide	Fe_2O_3	231.54	5.24	insoluble	NA
Iron (0) pentacarbonyl	$Fe(CO)_5$	195.90	1.457 of liquid at 21°C	insoluble	40 mm at 30.3°C[c]
Iron (II) sulfate, heptahydrate	$FeSO_4 7H_2O$	278.09	1.898	15.65 g/100 mL[d]	NA
Iron (II) ferrocyanide	$Fe_4[Fe(CN)_6]_3$	859.25	1.80[c]	insoluble	NA

[a]Source: Weast (1980)

[b]No further data regarding solubility are available from Weast (1980).

[c]These data are taken from NIOSH (1980).

[d]Temperature not specified

NA = Not available

photoredox; microbial interactions resulting in oxidation, reduction and precipitation; and sorptive interactions (U.S. EPA, 1981). Photochemical reactions probably are not significant in most natural bodies of water at increasing water depths because of reflection and scattering of light. The chemical reactions in bodies of water depends on the pH and oxidation reduction potential of the body of water. The microbial reaction will depend primarily on pH and the concentration of microorganisms. Similarly, the sorption process depends on the pH, and concentration and nature of the sorptive species. In most bodies of water, iron is expected to be present largely in the form of suspended particles and sediments, although small amounts of dissolved iron may occur as Fe(II) or Fe(III) ions, and inorganic and organic complexes of both Fe(II) and Fe(III). Small quantities of iron also exist in colloidal form, generally as ferric oxyhydroxides. The residence time of iron in aquatic media has been estimated to be >140 years (U.S. EPA, 1981).

Iron is present primarily in the Fe(III) state in most soils, although Fe(II) may be predominant in oxygen deficient soils (flooded soils and soils rich in organic matter). The principal iron-containing minerals in soils are the ferric oxyhydroxides. The fate of iron compounds in soils is primarily determined by chemical and microbiological reactions in soils and the capacity of soils to sorb iron-organic complexes. These processes have been discussed in detail in a U.S. EPA (1981) report. In most soils, iron is not mobile. Both biological and chemical reactions may cause precipitation of iron in soils; however, small amounts of iron are transported through soil in the form of colloidal ferric oxyhydroxides, and in solution as iron-organic chelates formed under the peptizing action of

dissolved organic compounds. Soil pH is one of the most important regulators of iron mobility, with lower pH favoring mobility. The mobility of iron in soils is such that it is not likely to leach from soil to groundwater under most conditions. Leaching of iron into groundwater, however, may occur from coal mine drainage areas and from waste burial sites (U.S. EPA, 1981). The transport of iron from soils to the atmosphere and surface waters probably occurs through dusts produced by blowing winds and the transport of flooded soil water into receiving surface water, respectively.

2. ABSORPTION FACTORS IN HUMANS AND EXPERIMENTAL ANIMALS

2.1. ORAL

According to Cook and Monsen (1976), iron is absorbed from two dietary sources, heme iron from meats and nonheme iron from grains and vegetables. Nonheme iron is absorbed in the range of 1-10%, depending on the presence of enhancing or inhibiting factors. Absorption of heme iron does not seem to be dependent on enhancing or inhibiting agents, and ranges from 10-25%.

Bjorn-Rasmussen et al. (1974) investigated the absorption of iron in 32 healthy male human subjects whose dietary intake of iron was 17.4 mg/day, [1 mg of iron from heme and the remainder (16.4 mg) from nonheme sources]. The total iron absorbed averaged 1.19 mg/day (~7% of the daily intake). Of this, 31% (0.37 mg) was from the heme iron in the diet, representing 37% efficiency, and 69% (0.82 mg) was from the nonheme iron, representing 5% efficiency.

According to Bothwell and Finch (1962), an approximately linear relationship exists between the amount of iron administered and the amount absorbed in normal human subjects given 50-400 mg of ferrous salts. Bothwell et al. (1979) determined that the availability of the ferrous iron for absorption was greater than the availability of the ferric iron. The presence of excess reducing agents in the intestine may, therefore, influence the availability of dietary iron. As intestinal pH rises above 5, coincident with passage down the intestinal tract, less ferric iron remains solubilized in the ionic form compared with ferrous iron.

Exogenous ligands affect the absorption of nonheme iron. Ascorbic acid, citric acid and cysteine form complexes with iron that facilitate its uptake into mucosal cells. Carbonates, oxalates, phosphates and tannins inhibit

iron absorption by forming insoluble complexes in the gut (U.S. EPA, 1981). EDTA, a common food preservative, can greatly reduce iron absorption (Cook and Monsen, 1976).

Absorption of iron can be divided into two processes, uptake by mucosal cells and transfer from the mucosal cells to the plasma. Wheby et al. (1964) found that uptake is the faster process and that it occurs preferentially in the proximal duodenum and diminishes in the distal region of the small intestine. It is likely that the brush borders of cells in the proximal regions of the intestine may bind iron more specifically than occurs more distally in the gut.

The regulation of iron absorption and transfer to the plasma depends on the level of available stores and the rate of erythropoiesis, the latter being the primary factor that depletes available body stores (Bothwell et al., 1979). Plasma concentrations of ferritin, which have been shown to reflect body stores, are inversely related to iron absorption (Cook et al., 1974). Hemolytic anemia (Bannerman et al., 1964; Chirasiri and Izak, 1966; Erlandson et al., 1962; Robertson et al., 1963) has been shown to stimulate iron absorption, probably by stimulating erythropoiesis regardless of body stores of iron. Hypoxia (Hathorn, 1972; Linder and Munro, 1977) and anemia (Mendel, 1961; Schiffer et al., 1965; Linder and Munro, 1977) enhance iron absorption even when erythropoiesis is inhibited. Humoral factors have been suggested to play a role in regulating iron absorption. Apte and Brown (1969) found a low molecular weight factor in the blood of iron deficient humans and pregnant women that, when administered to rats, enhances iron absorption.

Gastric achlorhydria, frequently associated with iron-deficiency anemia, has been suspected to decrease iron absorption (Grace et al., 1954).

Although hydrochloric acid per se is not required for absorption of iron, at lower gastric pH dissociation of iron compounds with solubilization of ionic iron may be expected to occur. Interaction of the soluble iron ions with ligands present in the chyme (secreted or resulting from food digestion) will prevent precipitation of iron hydroxides at the higher pH of the intestinal tract (Jacobs et al., 1964; Murray and Stein, 1968).

2.2. INHALATION

Pertinent data regarding the absorption of iron (and compounds) could not be located in the available literature. Pulmonary siderosis, the accumulation of iron oxide in the lungs, has been observed in workers exposed to iron oxide. The nodules characteristic of this affliction regress gradually after exposure is discontinued, suggesting that absorption of these particulates from the lung is slow (Morgan and Kerr, 1963; Morgan, 1978).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. In humans, oral exposure to toxic levels of iron or its compounds has the potential for being chronic (Section 3.2.1.). Acute toxicity in humans has been reported by many investigators (U.S. EPA, 1981). In children, as little as 0.3-3 g of iron as ferrous sulfate has been associated with severe toxic effects (Greenblatt et al., 1976); in adults, 2-10 g of ferrous succinate or ferrous sulfate has been associated with severe toxicity and death (Eriksson et al., 1974; Lavender and Bell, 1970). In animals, oral LD_{50} values range from 12 mg/kg for iron carbonyl in rabbits to 4000 mg/kg for ferric dimethyldithiocarbamate in rats (U.S. EPA, 1981). Ferrous sulfate, the iron compound most commonly involved in human toxicity, had oral LD_{50}s of 979-1520 mg/kg in mice, 1200 mg/kg in guinea pigs and 319 mg/kg in rats.

Majumder et al. (1975) administered 1 or 5 mg of iron as ferrous sulphate to male Charles Foster rats or male short-hair guinea pigs for 45 or 10-20 days, respectively. These animals were fed diets of unfortified wheat flour, unfortified rice flour or casein-fortified wheat flour. Vitamin C was added to 50% of the guinea pig diets.

Guinea pigs treated with 5 mg iron/day in diets not fortified with vitamin C suffered severe toxicity and mortality. In rats treated with 5 mg iron/day, reduced growth rate was the only manifestation of toxicity. Neither rats nor guinea pigs treated with 1 mg of iron/day exhibited any signs of toxicity. The length of exposure was too short to be used with confidence in risk assessment.

3.1.2. Inhalation. Inhalation exposure of humans to iron and its compounds is most likely to occur as a result of occupational exposure. Since the likelihood exists that such exposure would be chronic, repeated human expo- sure to iron compounds by inhalation will be discussed in Section 3.2.2.

No subchronic inhalation studies in animals have been located in the available literature. Nettesheim et al. (1975) reported iron accumulation in the lungs of hamsters exposed to 4 mg ferric oxide dust/m^3, 30 hours/week for 1 month.

3.2. CHRONIC

3.2.1. Oral. Chronic toxicity to iron usually results from prolonged accumulation of iron in the tissues (siderosis). Excessive amounts of iron stored in the tissues results in a condition called hemochromatosis, a pathological general tissue fibrosis. Most cases of hemochromatosis probably result from sources of iron intrinsic to the tissues after hemolytic anemias or repeated blood transfusions. Idiopathic or primary hemochromatosis is a genetic disorder of iron metabolism that is characterized by deposition of unusually large amounts of iron in the tissues (Charlton and Bothwell, 1966; Goossens, 1975; Scheinberg, 1973). Absorption of iron from the gut is greatly in excess of body requirements, therefore increasing tissue deposition over several years (Bothwell and Finch, 1962). The liver and pancreas may typically contain stores of iron that are 50-100 times the normal levels. The thyroid, pituitary, heart, spleen and adrenals are other sites of unusually high iron deposition (Sheldon, 1935). Males are 10 times more frequently affected than females; the disease is typically manifested in the fifth or sixth decade of life (Prasad, 1978).

A similar syndrome has been seen among the Bantu people of South Africa, who reportedly ingest large amounts of iron in their home-brewed beer. Their condition may be exacerbated by unusually high intake of alcohol, which reportedly increases iron absorption (Bothwell et al., 1965). No estimates of iron intake were mentioned.

Pertinent data regarding the chronic oral toxicity of iron in animals could not be located in the available literature.

3.2.2. Inhalation. Chronic inhalation exposure of man to iron or its compounds is likely to result from occupational exposure. Iron-ore mining, arc welding, iron grinding and polishing, metal working, pigment manufacture and rubber manufacturing are occupations that predispose workers to inhalation of dust or fumes of iron or its compounds (Hueper, 1966).

Epidemiological studies of mortality among steel workers have not indicated an association with exposure to iron oxide (Lerer et al., 1974; Lloyd and Ciocco, 1969; Lloyd et al., 1970; Redmond et al., 1975). In lung function studies on workers in these occupations, no relationship was found between the incidence of chronic bronchitis and emphysema and exposure to iron oxide dusts (Lowe et al., 1970), although the respirable fraction never exceeded a mean level of 2 mg/m^3.

Pertinent data regarding chronic inhalation exposure of laboratory animals to iron (and compounds) could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. In Sweden, iron or vitamin deficiencies or both have been associated with the occurrence of dead or malformed infants (Kullander and Kallen, 1976). In Scotland, Nelson and Forfar (1971) found associations between congenital malformations and insufficient iron intake in the early

weeks of pregnancy. Most women taking supplemental iron during their pregnancy delivered normal infants. Forfar and Nelson (1973) reported that of the 911 pregnant Scottish women studied, 49% took supplemental ferrous sulphate, 14% took ferrous succinate and 14% took ferrous carbonate. Bishop (1979) recommended that pregnant women should take 30-60 mg supplemental iron/day regardless of their apparent nutritional status.

Tadokoru et al. (1979) found that antianemic "slow iron" given orally to pregnant rats and mice at 120-380 mg/kg/day for 6 days (unspecified) caused no teratogenic or toxic effects. Some embryo mortality was seen at doses of 1200 mg/kg/day.

In a study designed to assess the effects of trisodium nitrilotriacetate with and without ferric chloride on methyl mercury teratogenesis in rats, Nolen et al. (1972) found that ferric chloride (7 mg/kg/day) administered in drinking water on days 6-15 of gestation significantly reduced the incidence of fetal malformation induced by trisodium nitrilotriacetate and methyl mercury. Exposure to ferric chloride alone did not affect fetal development.

3.3.2. Inhalation. Pertinent data regarding teratogenesis associated with inhalation exposure of humans or animals to iron (and compounds) could not be located in the available literature.

4. CARCINOGENICITY

4.1. HUMAN DATA

Esophageal carcinoma has been associated with either iron deficiency or iron overload (MacPhail et al., 1979), although a causal relationship has not been established. MacPhail et al. (1979) found that the hepatic iron content of 85 South African blacks who died from esophageal carcinoma was higher than those of males of the same ages who died of other causes. Alcohol consumption has also been associated with esophageal carcinoma. It was unclear, therefore, whether the esophageal carcinoma observed by MacPhail et al. (1979) was due to excessive iron intake or to the alcohol contained in home-brewed beer, a substantial part of the diet of the Bantu.

One report on inhalation exposure to iron mining dusts described an association with excess deaths from lung cancers (Boyd et al., 1970). More recently, it has been found that the presence of radon gas was a more likely cause of the reported excess of lung cancers (Hueper, 1979).

IARC (1972) briefly summarized the early reports of lung tumors associated with exposure to iron-ore dusts or fumes from hot metals (i.e., from welding operations). In these cases, reports of excess lung tumors from exposure to iron have not been corroborated. Exposure to alcohol, tobacco, silica, soot and fumes of other metals confound the validity of association of lung cancers with iron and its compounds. IARC (1972) concluded that, "exposure to hematite dust may be regarded as increasing the risk of lung cancer in man...it is not known whether the excess risk is due to radioactivity in the air of mines, the inhalation of ferric oxide or silica or to a combination of these or other factors."

4.2. BIOASSAYS

Pertinent data regarding carcinogenicity related to oral exposure to iron (and compounds) could not be located in the available literature.

Iron oxide dust has been used extensively in experimental carcinogenesis as a relatively inert carrier for known carcinogens. Port et al. (1973) demonstrated that 10 intratracheal instillations of 5 mg iron oxide dust (dosing interval not specified) resulted in a complete loss of ciliary cells and hyperplasia of the tracheobronchial epithelium in hamsters. These changes were completely reversible after 7 weeks. It was suggested (Port et al., 1973) that iron oxide causes hyperplasia of the tracheobronchial epithelium, which may promote the induction of cancer by known carcinogens.

According to IARC (1972), Campbell (1940, 1942, 1943) reported a higher frequency of lung tumors in mice exposed by inhalation to ferric oxide steel grindings, to a mixture of aluminum oxide, ferric oxide and silicon dioxide, or to a mixture of the oxides of aluminum, silicon, iron and calcium than in control mice. IARC (1972) suggested that these experiments must be regarded as inconclusive because of the genetic randomness of the mice used and the fact that the differences in the incidence of tumors was small.

A series of 15 once-weekly intratracheal injections of 3 mg of ferric oxide dust in 24 male and 24 female Syrian golden hamsters failed to produce lung tumors (Saffiotti et al., 1968). The animals were observed for life with >50% of the animals surviving for >1 year.

4.3. OTHER RELEVANT DATA

Demerec et al. (1951) reported point mutations in Escherichia coli induced by ferrous or ferric chloride and ferric sulfate at "unusually high" concentrations. In Bacillus subtilis H17 and M45 tests, concentrations of 0.05 M ferrous and ferric chloride, potassium ferro- and ferri-cyanides were

not mutagenic (Nishioka, 1975). Ferric sulfate (0.00001-0.5%) and ferric nitrate (0.00001-0.01%), but not ferric chloride, caused changes in cell nuclei and disturbances in cell division in the roots of the broad bean, Vicia baba (Komczynski et al., 1963).

Extensive studies with ferrous sulfate and ferrous gluconate in Salmonella typhimurium and Saccharomyces cerevisiae have been performed by Litton Bionetics, Inc. (1974, 1975). Ferrous sulfate induced reverse mutations in S. typhimurium strains TA1537 and TA1538, but not in TA1535. Mutagenesis was most pronounced in tests containing microsomal activating systems. Mutagenesis was not reported in S. cerevisiae. More recently, however, Singh (1983) reported a positive gene conversion at trp 5 and a weak reversion at ilv 1 in S. cerevisiae strain D7 by ferrous sulphate but not ferric chloride.

Castro et al. (1979) reported that ferrous sulfate and ferrous chloride inhibited transformation of Syrian hamster embryo cells by a simian adenovirus (SA7). This effect was attributed to a relative increase in viral transformation and to an absolute increase in the number of transformed foci.

Robison et al. (1982) tested the ability of many metal compounds to induce strand breakage, measured as decreased molecular weight of DNA isolated from Chinese hamster ovary cells. Ferrous chloride, the only iron compound tested, produced no significant change in the molecular weight of DNA.

Incubation of isolated rat liver nuclei with either ferrous chloride or ferric chloride resulted in single-strand breaks in DNA (Shires, 1982). The ferrous salt was about twice as active as the ferric salt.

Patton and Allison (1972) reported that nontoxic concentrations of iron dextran were not mutagenic to cultures of human leukocytes.

4.4. WEIGHT OF EVIDENCE

As mentioned in Section 4.1., reports exist associating excessive incidence of lung cancer with hematite dust in underground mining operations. Coincident exposure to tobacco, alcohol, silica, soot and fumes of other metals complicates interpretation of these reports. Inhalation or intratracheal exposure to ferric oxide has not consistently resulted in formation of lung tumors (IARC, 1972).

In mice (Haddow and Horning, 1960; Haddow and Roe, 1964) and rats (Haddow and Horning, 1960; Langvad, 1968; Roe and Carter, 1967; Roe et al., 1964; Golberg et al., 1960; Kren et al., 1968; Braun and Kren, 1968), local injection-site tumors (sarcomas > histiocytomas > fibromas) resulted from subcutaneous or intramuscular injections of iron-dextran. Negative results were obtained by Pai et al. (1967), who administered subcutaneous doses of 0.05, 0.1 or 0.2 mℓ iron-dextran (concentration not reported) to groups of 10-18 female mice, once weekly for 10 weeks. Observations were performed for 7 months after the first treatment.

Local tumors in mice were observed after 30 weekly subcutaneous injections of iron-dextran (Fielding, 1962) and after 13 weekly subcutaneous injections of saccharated iron oxide (Haddow and Horning, 1960), but not after 30 weekly subcutaneous injections of iron-sorbitol-citric acid complex.

Taken collectively, these studies suggest that injection of some iron-carbohydrate complexes may cause local injection-site tumors in animals. Since the introduction of iron-dextran to clinical practice in the 1950s, only one case of cancer in humans, an injection-site sarcoma, has been reported (Robinson et al., 1960). It is not possible to determine whether the association in this single case is causal and no long-term observations have been made on humans receiving this drug.

Applying the criteria for evaluating the overall weight of evidence of carcinogenicity to humans proposed by the Carcinogen Assessment Group of the U.S. EPA (Federal Register, 1984), iron and its compounds, including ferric dextran, are most appropriately classified in Group C - Possible Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

Based primarily on the suggestions of Drinker et al. (1935), who reviewed the health effects of workers exposed to iron oxide, and Weber (1955), who suggested that siderosis occurred in workers exposed to ~15 mg iron as oxide/m^3, the ACGIH (1980) recommended a TWA-TLV of 5 mg iron/m^3 and a STEL of 10 mg iron/m^3 for ferric oxide. On the recommendation of Brief et al. (1967), who recommended an "action point" of 0.1 ppm for occupational exposure, the TWA-TLV for iron from iron pentacarbonyl was recommended to be 0.1 ppm (~0.8 mg/m^3). A STEL of 0.2 ppm (~1.6 mg/m^3) was recommended. To protect from respiratory and skin irritation, a TWA-TLV of 1 mg/m^3 was suggested for soluble iron salts. A STEL of 2 mg/m^3 was suggested. The OSHA standard for iron oxide fume is 10 mg/m^3 (Code of Federal Regulations, 1981).

In drinking water, the current quality criterion is 0.3 mg iron/ℓ (NAS, 1974), based primarily on a study by Cohen et al. (1960), that indicated that 20% of those tested were able to distinguish between distilled water and a solution of 0.3 mg iron/ℓ as ferrous sulfate.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

6.1.1. Oral. In humans, severe acute toxicity has occurred with ingestion of 300-3000 mg of iron by children (Greenblatt et al., 1976) or 2000-10,000 mg of iron by adults (Eriksson et al., 1974; Lavender and Bell, 1970). No subchronic oral exposure studies of iron (and compounds) suitable for use in risk assessment were located in the available literature. The scanty oral and inhalation toxicity data was evaluated for iron and its compounds and it was concluded that data were insufficient for derivation of a CS. Although minimal subchronic oral data in animals were available, the fact that iron accumulation occurs indefinitely and may result in toxicity later in life precludes the use of these short-term studies to derive a CS.

6.1.2. Inhalation. Nettesheim et al. (1975) reported iron accumulation in the lungs of hamsters exposed to 4 mg ferric oxide dust/m^3, 30 hours/week for 1 month. Unfortunately, reported exposure and effect data were insufficient to use this study in risk assessment. No other studies of subchronic inhalation exposure to iron (and compounds) have been located in the available literature. Therefore, no AIS for inhalation exposure has been calculated.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

6.2.1. Oral. Chronic toxicity from oral intake of iron by humans is rare. Section 3.2.1. mentions hemochromatosis, a primary genetic disorder that results in unusual uptake of dietary iron and its distribution to and storage in various tissues of the body. Among the Bantu people of South Africa, a hemochromatosis-like syndrome has been identified and associated with unusually high dietary intakes of both iron and alcohol. No studies of chronic toxicity in humans or animals relating effects to dosages that are useful for risk assessment have been located in the available literature.

Iron deficiency is much more common than iron toxicity. NAS (1980) suggested the following Recommended Daily Dietary allowances: infants to 6 months old, 10 mg; 6 months to 6 years, 15 mg; 7 to 10 years, 10 mg; males 11-18, 18 mg; males over 18, 10 mg; females 11-50, 18 mg; over 50, 10 mg. In addition, iron supplements of 30-60 mg/day are recommended for pregnant women. It has also been suggested that daily intakes of 25-75 mg should be well tolerated in healthy adults (NAS, 1980).

Iron deficiency has been given much greater attention than iron toxicity. Reliable quantitative data are not available which could be used to estimate an AIC.

6.2.2. Inhalation. Many occupations predispose workers to inhalation exposure to various compounds of iron (Hueper, 1966). Neither epidemiological studies of mortality among steel workers exposed to iron oxides (Lerer et al., 1974; Lloyd and Ciocco, 1969; Lloyd et al., 1970; Redmond et al., 1975) nor lung function studies of workers exposed to iron oxide dusts (Lowe et al., 1970) indicated excess risks associated with exposure to iron oxides. Additionally, no other reports of toxicity resulting from chronic inhalation exposure of humans or animals to iron (and compounds) have been located in the available literature. Therefore, it seems reasonable to use the TWA-TLV suggested by ACGIH (1980) for the most toxic compound of iron for which a recommendation has been made as a starting point in deriving an inhalation AIC. The ACGIH (1980) has set the TWA-TLV for iron pentacarbonyl at 0.8 mg/m^3. Based on a human exposed to the workroom for 5 days/week and inhaling 10 m^3 of air/workday, an interim ADI can be calculated by applying an uncertainty factor of 10 to protect unusually sensitive population groups. An AIC of 0.6 mg iron/day is calculated.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. Although esophageal cancers have been associated with high intakes of beer containing high levels of iron, alcohol has also been associated with esophageal cancers; hence, these high incidences of esophageal cancers in South African Bantu people are difficult to interpret properly. No other reports of cancers in humans or animals associated with oral exposure to iron (and compounds) have been located in the available literature; hence, no q_1* for oral exposure can be calculated.

6.3.2. Inhalation. Boyd et al. (1970) found an association between excess deaths from lung cancer and exposure to iron mining dusts; however, Hueper (1979) found that the presence of radon gas in these underground mines was a more likely cause of the lung cancers. Port et al. (1973) demonstrated that intratracheal administration of iron oxide dust caused hyperplasia of the tracheobronchial epithelium in hamsters. Campbell (1940, 1942, 1943) reported a higher incidence of lung tumors in mice exposed to ferric oxide steel grinding, a mixture of aluminum oxide, ferric oxide and silicon dioxide, than in control mice; however, a series of 15 once-weekly intratracheal injections of 3 mg of ferric oxide dust in 24 male and 24 female Syrian golden hamsters failed to produce lung tumors. Over 50% of the animals survived for >1 year (Saffiotti et al., 1968). IARC (1972) suggested that these experiments should be regarded as inconclusive because of the genetic randomness of the mice used and the fact that the incidence of tumors was small. Therefore, no q_1* for inhalation exposure can be calculated.

7. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. p. 231-233.

Apte, S.V. and E.B. Brown. 1969. Effects of plasma from pregnant women on iron absorption by the rat. Gastroenterology. 57: 126-131. (Cited in U.S. EPA, 1981)

Bannerman, R.M., S.T. Callendee, R.M. Hardisty and R.S. Smith. 1964. Iron absorption in thalassemia. Br. J. Haematol. 10: 490-495. (Cited in U.S. EPA, 1981)

Bishop, C. 1979. Nonprescription drugs: A guide to the pregnant patient. Part 6. Can. Pharmacol. J. 113: 8-14. (Cited in U.S. EPA, 1981)

Bjorn-Rasmussen, E., L. Hallberg, B. Isaksson and B. Arvidsson. 1974. Food iron absorption in man: Applications of the two-pool extrinsic tag method to measure heme and nonheme iron absorption from the whole diet. J. Clin. Invest. 53: 247-255. (Cited in U.S. EPA, 1981)

Bothwell, T.H. and C.A. Finch. 1962. Pathologic and clinical aspects of iron overload. In: Iron Metabolism. Little, Brown and Co., Boston, MA. p. 364, 440. (Cited in U.S. EPA, 1981)

Bothwell, T.H., R.W. Charlton and H.C. Seftel. 1965. Oral iron overload. S. Afr. Med. J. 39: 892-900. (Cited in U.S. EPA, 1981)

Bothwell, T.H., R.W. Charlton, J.D. Cook and C.A. Finch. 1979. Iron nutrition, Chapter 1. In: Iron Metabolism in Man. Blackwell Science Publishers, Oxford, London and Edinburgh. p. 7, 44, 245, 284, 311, 327. (Cited in U.S. EPA, 1981)

Boyd, J.T., R. Doll, J.S. Faulds and J. Leiper. 1970. Cancer of the lung in iron ore (haematite) miners. Br. J. Ind. Med. 27: 97-105. (Cited in U.S. EPA, 1981)

Braun, A. and V. Kren. 1968. Attempt to induce tumours by subcutaneous and intraperitoneal administration of ferridextran ("Spofa"). Neoplasma (Bratisl.). 15: 21. (Cited in IARC, 1973)

Brief, R.S., R.S. Ajemian and R.G. Conger. 1967. No title provided. J. Am. Ind. Hyg. Assoc. 28: 21-30. (Cited in ACGIH, 1980)

Campbell, J.A. 1940. Effects of precipitated silica and of iron oxide on the incidence of primary lung tumours in mice. Br. Med. J. 2: 275. (Cited in IARC, 1972)

Campbell, J.A. 1942. Lung tumours in mice: Incidence as affected by inhalation of certain carcinogenic agents and some dusts. Br. J. Med. 1: 217. (Cited in IARC, 1972)

Campbell, J.A. 1943. Lung tumours in mice and man. Br. Med. J. 1: 179. (Cited in IARC, 1972)

Castro, B.C., J. Meyers and J.A. DiPaolo. 1979. Enhancement of viral transformation for evaluation of the carcinogenic or mutagenic potential of inorganic metal salts. Cancer Res. 39: 193-198. (Cited in U.S. EPA, 1981)

Charlton, R.W. and T.H. Bothwell. 1966. Hemochromatosis: Dietary and genetic aspects. Prog. Hematol. 5: 298-323. (Cited in U.S. EPA, 1981)

Chirasiri, L. and G. Izak. 1966. The effect of acute haemorrhage and acute haemolysis on the intestinal iron absorption in the rat. Br. J. Haematol. 12: 611-622. (Cited in U.S. EPA, 1981)

Code of Federal Regulations. 1981. OSHA Safety and Health Standards. 29 CFR 1910.1000.

Cohen, J.M., L.J. Kamphake, E.K. Harris and R.L. Woodward. 1960. Taste threshold concentrations of metals in drinking water. J. Am. Water Works Assoc. 52: 660-670. (Cited in U.S. EPA, 1981)

Cook, J.D. and E.R. Monsen. 1976. Food iron absorption in man. II. The effect of EDTA on absorption of dietary nonheme iron. Am. J. Clin. Nutr. 29: 614-620. (Cited in U.S. EPA, 1981)

Cook, J.D., D.A. Lipschitz, L.E.M. Miles and C.A. Finch. 1974. Serum ferritin as a measure of iron stores in normal subjects. Am. J. Clin. Nutr. 27: 681-687. (Cited in U.S. EPA, 1981)

Demerec, M., G. Bertani and J. Flint. 1951. A survey of chemicals for mutagenic action on E. coli. Am. Natur. 85: 119-136. (Cited in U.S. EPA, 1981)

Drinker, P., H. Warren and R. Page. 1935. No title provided. J. Ind. Hyg. 17: 133. (Cited in ACGIH, 1980)

Eriksson, F., S.V. Johansson, H. Mellstedt, O. Stranberg and P.O. Wester. 1974. Iron intoxication in two adult patients. Acta Med. Scand. 196: 231-236. (Cited in U.S. EPA, 1981)

Erlandson, M.E., B. Walden, G. Steen, M.W. Hilgartner, J. Wehman and C.H. Smith. 1962. Studies on congenital hemolytic syndromes. IV. Gastrointestinal absorption of iron. Blood. 19: 359-378. (Cited in U.S. EPA, 1981)

Federal Register. 1984. Environmental Protection Agency. Proposed guidelines for carcinogenic risk assessment. 49 FR 46294-46299.

Fielding, J. 1962. Sarcoma induction by iron-carbohydrate complexes. Br. Med. J. i: 1800-1803. (Cited in IARC, 1973)

Forfar, J.O. and M.M. Nelson. 1973. Epidemiology of drugs taken by pregnant women: Drugs that may affect the fetus adversely. Clin. Pharmacol. Therap. 14: 632-642. (Cited in U.S. EPA, 1981)

Golberg, L., L.E. Martin and J.P. Smith. 1960. Iron overloading phenomena in animals. Toxicol. Appl. Pharmacol. 2: 125-145. (Cited in IARC, 1973)

Goossens, J.P. 1975. Idiopathic haemochromatosis: Juvenile and familial type-endocrine aspects. Neth. J. Med. 18: 161-169. (Cited in U.S. EPA, 1981)

Grace, W.J., R.K. Doig and H.G. Wolff. 1954. Absorption of iron from the gastrointestinal tract. J. Clin. Nutr. 2: 162-167. (Cited in U.S. EPA, 1981)

Greenblatt, D.J., M.D. Allen and J. Koch-Weser. 1976. Accidental iron poisoning in childhood: Six cases including one fatality. Clin. Pediatr. 15: 835-838. (Cited in U.S. EPA, 1981)

Haddow, A. and E.S. Horning. 1960. On the carcinogenicity of an iron-dextran complex. J. Natl. Cancer Inst. 24: 109-127. (Cited in IARC, 1973)

Haddow, A. and F.J.C. Roe. 1964. Iron-dextran and sarcomata. Br. Med. J. ii: 121. (Cited in IARC, 1973)

Hathorn, M.K.S. 1972. The influence of hypoxia on iron absorption in the rat. Gastroenterology. 60: 76-81. (Cited in U.S. EPA, 1981)

Hueper, W.C. 1966. Occupational and environmental cancers of the respiratory system. Springer-Verlag, Berlin. p. 93-96. (Cited in U.S. EPA, 1981)

Hueper, W.C. 1979. Some comments on the history and experimental explorations of metal carcinogens and cancers. J. Natl. Cancer Inst. 62: 723-725. (Cited in U.S. EPA, 1981)

IARC (International Agency for Research on Cancer). 1972. Haematite and iron oxide. In: Some Inorganic and Organometallic Compounds. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. WHO, IARC, Lyon, France. Vol. 1, p. 80.

IARC (International Agency for Research on Cancer). 1973. Iron carbohydrate complexes. In: Some Inorganic and Organometallic Compounds. IARC Monographs on the Evaluation of the Carcinogenic Risk of Chemicals to Man. WHO, IARC, Lyon, France. Vol. 2, p. 161-178.

Jacobs, P., T. Bothwell and R.W. Charlton. 1964. Role of hydrochloric acid in iron absorption. J. Appl. Physiol. 19: 187-188. (Cited in U.S. EPA, 1981)

Komczynski, L., H. Nowak and L. Rejniak. 1963. Effect of cobalt, nickel and iron on mitosis in the roots of the broad bean (Vicia faha). Nature. 198: 1016-1017. (Cited in U.S. EPA, 1981)

Kren, V., A. Braun and D. Krenova. 1968. The transplantability of the tumour induced in rats by Ferridextran Spofa. Neoplasma (Bratisl.). 15: 29. (Cited in IARC, 1973)

Kullander, S. and B. Kallen. 1976. A prospective study of drugs and pregnancy: Miscellaneous drugs. Acta Obstet. Gynerol. Scand. 55: 287-295. (Cited in U.S. EPA, 1981)

Langvad, E. 1968. Iron-dextran induction of distant tumours in mice. Int. J. Cancer. 3: 415. (Cited in IARC, 1973)

Lantzy, R.J. and F.T. Mackenzie. 1979. Atmospheric trace metals: Global cycles and assessment of man's impact. Geochim. Cosmochim. Acta. 43: 511-525.

Lavender, S. and J.A. Bell. 1970. Iron intoxication in an adult. So. Br. Med. J. 1: 406. (Cited in U.S. EPA, 1981)

Lerer, T.J., C.K. Redmond, P.P. Breslin, L. Salvin and H.W. Rush. 1974. Long-term mortality study of steelworkers. VII. Mortality patterns among crane operators. J. Occup. Med. 16: 608-614. (Cited in U.S. EPA, 1981)

Linder, M.C. and H.N. Munro. 1977. The mechanism of iron absorption and its regulation. Fed. Proc. 36: 2017-2023. (Cited in U.S. EPA, 1981)

Litton Bionetics, Inc. 1974. Mutagenic evaluation of compound FDA 71-06, ferrous sulfate. NTIS PB 245-435. (Cited in U.S. EPA, 1981)

Litton Bionetics, Inc. 1975. Mutagenic evaluation of compound FDA 71-63, ferrous glucconate. NTIS PB 245-477. (Cited in U.S. EPA, 1981)

Lloyd, J.W. and A. Ciocco. 1969. Long-term mortality study of steelworkers. J. Occup. Med. 11: 299-310. (Cited in U.S. EPA, 1981)

Lloyd, J.W., F.E. Lundin, C.R. Redmond and P.B. Geiser. 1970. Long-term mortality study of steelworkers. I. Methodology. J. Occup. Med. 12(5): 151-157. (Cited in U.S. EPA, 1981)

Lowe, C.R., H. Campbell and T. Khosla. 1970. Bronchitis in two integrated steel works. III. Respiratory symptoms and ventilatory capacity related to atmospheric pollution. Br. J. Ind. Med. 27: 121-129. (Cited in U.S. EPA, 1981)

MacPhail, A.P., J.D. Torrance, T.H. Bothwell and C. Isaacson. 1979. Changing patterns of dietary iron overload in black South Africans. Am. J. Clin. Nutr. 32: 1272-1278. (Cited in U.S. EPA, 1981)

Majumder, A.K., B.K. Nandi, N. Subramanian and I.B. Chatterjee. 1975. Nutrient interrelationship of ascorbic acid and iron in rats and guinea pigs fed cereal diets. J. Nutr. 105(2): 240-244.

Mendel, G.A. 1961. Studies on iron absorption. I. The relationship between the rate of erythropoiesis, hypoxia, and iron absorption. Blood. 18: 727-736. (Cited in U.S. EPA, 1981)

Morgan, W.K.C. 1978. Magnetite pneumoconiosis. J. Occup. Med. 20: 762-763. (Cited in U.S. EPA, 1981)

Morgan, W.K.C. and H.D. Kerr. 1963. Pathologic and physiologic studies of welders' siderosis. Ann. Int. Med. 58: 293-304. (Cited in U.S. EPA, 1981)

Murray, M.J. and N. Stein. 1968. A gastric factor promoting iron absorption. Lancet. 1: 614-616. (Cited in U.S. EPA, 1981)

NAS (National Academy of Sciences). 1974. Water Quality Criteria, 1972, a Report of the Committee on Water Quality Criteria. U.S. EPA, Washington, DC. (Cited in U.S. EPA, 1981)

NAS (National Academy of Sciences). 1980. Recommended Dietary Allowances. 9th ed. National Academy Press.

Nelson, M.M. and J.O. Forfar. 1971. Associations between drugs administered during pregnancy and congenital abnormalities of the fetus. Br. J. Med. 1: 523-527. (Cited in U.S. EPA, 1981)

Nettesheim, P., D.A. Creasia and T.J. Mitchell. 1975. Carcinogenic and cocarcinogenic effects of inhaled synthetic smog and ferric oxide particles. J. Natl. Cancer Inst. 55: 159-165. (Cited in U.S. EPA, 1981)

NIOSH (National Institute for Occupational Safety and Health). 1980. Information Profiles on Potential Occupational Hazards: Iron and Compounds. NIOSH Contract No. 210-79-0030. PHS, CDC, Rockville, MD.

Nishioka, H. 1975. Mutagenic activities of metal compounds in bacteria. Mutat. Res. 31: 185-189. (Cited in U.S. EPA, 1981)

Nolen, G.A., R.L. Bohne and E.V. Buehler. 1972. Effects of trisodium nitrilotriacetate, trisodium citrate, and a trisodium nitrilotriacetate ferric chloride mixture on cadmium and methyl mercury toxicity and teratogenesis in rats. Toxicol. Appl. Pharmacol. 23: 238-250. CA 77: 148150j. (Cited in U.S. EPA, 1981)

Pai, S.R., S.V. Gothoskar and K.J. Ranadive. 1967. Testing of iron complexes. Br. J. Cancer. 21: 448. (Cited in IARC, 1973)

Patton, G. and A. Allison. 1972. Chromosome damage in human cell cultures induced by metal salts. Mutat. Res. 16: 332-336. (Cited in U.S. EPA, 1981)

Port, C.D., M.C. Henry, D.G. Kaufman, C.G. Harris and K.V. Ketels. 1973. Acute changes in the surface morphology of hamster tracheocarbronchial epithelium following benzo[a]pyrene and ferric oxide administration. Cancer Res. 33: 2498-2506. (Cited in U.S. EPA, 1981)

Prasad, A.S. 1978. Iron, Chapter 5. Trace Elements and Iron in Human Metabolism. Plenum Book Co., NY. p. 77-155. (Cited in U.S. EPA, 1981)

Redmond, C.K., J. Gustin and E. Kamon. 1975. Long-term mortality experience of steelworkers. VIII. Mortality patterns of open hearth steelworkers (A preliminary report). J. Occup. Med. 17: 40-43. (Cited in U.S. EPA, 1981)

Robertson, E.F., G.M. Maxwell and R.B. Elliott. 1963. Studies in thalassaemia major. Med. J. Aust. 2: 705-709. (Cited in U.S. EPA, 1981)

Robinson, C.E.G., D.N. Bell and J.H. Sturdy. 1960. Possible association of malignant neoplasm with iron-dextran injection. A case report. Br. Med. J. ii: 648. (Cited in IARC, 1973)

Robison, S.H., O. Cantoni and M. Costa. 1982. Strand breakage and decreased molecular weight of DNA induced by specific metal compounds. Carcinogenesis (London). 3(6): 657-662.

Roe, F.J.C. and R.L. Carter. 1967. Iron-dextran carcinogenesis in rats. Influence of dose on the number and types of neoplasm induced. Int. J. Cancer. 2: 370. (Cited in IARC, 1973)

Roe, F.J.C., A. Haddow, C.E. Dukes and B.C.B. Mitchley. 1964. Iron-dextran carcinogenesis in rats. Effect of distributing injected material between one, two, four or six sites. Br. J. Cancer. 18: 801-808. (Cited in IARC, 1973)

Saffiotti, U., F. Cefis and L.H. Kolb. 1968. A method for the experimental induction of bronchogenic carcinoma. Cancer Res. 28: 104-124. (Cited in IARC, 1972)

Scheinberg, I.H. 1973. The genetics of hemochromatosis. Arch. Intern. Med. 132: 126-128. (Cited in U.S. EPA, 1981)

Schiffer, L.M., D.C. Price and E.P. Cronkite. 1965. Iron absorption and anemia. J. Lab. Clin. Med. 65: 316-321. (Cited in U.S. EPA, 1981)

Sheldon, J.H. 1935. Haemochromatosis. Oxford University Press, London. 382 p. (Cited in U.S. EPA, 1981)

Shires, T.K. 1982. Iron-induced DNA damage and synthesis in isolated rat liver nuclei. Biochem. J. 205(2): 321-329.

Singh, I. 1983. Induction of reverse mutation and mitotic gene conversion by some metal compounds in Saccharomyces cerevisiae. Mutat. Res. 117(1-2): 149-152.

Tadokoru, T., et al. 1979. Teratogenicity studies of slow-iron in mice and rats. Oyo Yakuri. 17: 483. CA 91: 134052f. (Cited in U.S. EPA, 1981)

U.S. EPA. 1980. Guidelines and Methodology Used in the Preparation of Health Effects Assessment Chapters of the Consent Decree Water Quality Criteria. Federal Register. 45:79347-79357.

U.S. EPA. 1981. Multimedia Criteria for Iron and Compounds. Environmental Criteria and Assessment Office, Cincinnati, OH. Internal draft.

U.S. EPA. 1983. Methodology and Guidelines for Reportable Quantity Determinations Based on Chronic Toxicity Data. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the Office of Solid Waste and Emergency Response, Washington, D.C.

Weast, R., Ed. 1980. CRC Handbook of Chemistry and Physics, 61st ed. CRC Press, Boca Raton, FL. p. B-107 to B-109, D-200.

Weber, H. 1955. No title provided. Am. Ind. Hyg. Assoc. J. 16: 38. (Cited in ACGIH, 1980)

Wheby, M.S., L.R.G. Jones and W.H. Crosby. 1964. Studies on iron absorption. Intestinal regulatory mechanism. J. Clin. Invest. 43: 1433-1442. CA 61: 7466b. (Cited in U.S. EPA, 1981)

APPENDIX

Summary Table for Iron (and Compounds)

	Species	Experimental Dose/Exposure	Effect	Acceptable Intake (AIS or AIC)	Reference
Inhalation					
AIS				ND	
AIC	human	TWA-TLV: 0.8 mg/m³	none	0.6 mg/day	ACGIH, 1980
Oral					
AIS				ND*	
AIC				ND*	

*An RDA has been established but this estimate reflects minimum required intake not acceptable intake.

ND = Not derived