Iron salts, water-soluble

Health-based Reassessment of Administrative Occupational Exposure Limits

Committee on Updating of Occupational Exposure Limits,
a committee of the Health Council of the Netherlands

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1 Introduction

The present document contains the assessment of the health hazard of water-soluble iron salts by the Committee on Updating of Occupational Exposure Limits, a committee of the Health Council of the Netherlands. The first draft of this document was prepared by AAE Wibowo, Ph.D. (Coronel Institute, Academic Medical Centre, Amsterdam, the Netherlands).

The evaluation of the toxicity of water-soluble iron salts has been based on the reviews by Elinder (Eli86) and by the American Conference of Governmental Occupational Hygienists (ACGIH) (ACG96). Where relevant, the original publications were reviewed and evaluated as will be indicated in the text. In addition, literature was retrieved from the databases Medline, Chemical Abstracts, Embase (starting from 1966, 1970 and 1988, respectively), and HSELINE, NIOSHTIC, CISDOC, and MHIDAS (backwards from 1997) and Poltox (Toxline, Cambr Sc Abstr, FSTA) (backwards from 1994), using the following key words: ferric chloride, ferric nitrate, ferric sulfate, ferrous chloride, ferrous sulfate, 7705-08-0, 10421-48-4, 10028-22-5, 7758-94-3, and 7720-78-7. The final search was carried out in November 1997.

In December 1998, the President of the Health Council released a draft of the document for public review. No comments were received.

An additional literature search in September 2003 did not result in information changing the committee's conclusions.

2 Identity

name		ferric chloride	ferric nitrate	ferric sulphate	ferrous chloride	ferrous sulphate
molecular formula	:	$FeCl_3$	$Fe(NO_3)_3$	$Fe_2(SO_4)_3$	$FeCl_2$	$FeSO_4$
CAS number	:	7705-08-0	10421-48-4	10028-22-5	7758-94-3	7720-78-7

3   Physical and chemical properties

	$FeCl_3$	$Fe(NO_3)_3$	$Fe_2(SO_4)_3$	$FeCl_2$	$FeSO_4$
molecular weight	162.21	241.87	399.88	127.76	151.91
boiling point[a]	315ºC (dec)	<100ºC (dec)	-	1023ºC	-
melting point	306ºC	47ºC	-	674ºC	-
flash point	-	-	-	-	-
vapour pressure	-	-	-	-	-
solubility	soluble	soluble	soluble	soluble	soluble
log $P_{octanol/water}$[b]	0.16	-0.83	-	-0.15	-0.37
conversion factors	not applicable				

[a]   dec = decomposes.
[b]   All estimated values.

Data from ACG96, http://esc.syrres.com.

The appearances and odours vary depending on the specific soluble iron salts. Ferric chloride is a black-brown solid; ferric nitrate is a pale violet, green, or white, odourless solid in a lumpy crystalline form; ferric sulphate is a greyish-white or yellow solid in a powder or lumpy crystalline form; ferrous chloride is a pale greenish, salt-like crystal or powder; and ferrous sulphate is a greenish or yellow solid in fine or lumpy crystalline form (ACG96).

4   Uses

Ferric chloride is used to treat sewage and industrial waste. It is also used in engraving, textiles, and photography, as a disinfectant, and as a food additive. Ferric nitrate is used in textile dyeing, tanning, and weighting silk. Ferric sulphate is used in pigments, textile dyeing, water treatment, and metal pickling. Ferrous chloride is used in textile dyeing, metallurgy, the pharmaceutical industry, and sewage treatment. Ferrous sulphate is used as a fertiliser, as a food or feed additive, and in herbicides, process engraving, dyeing, and water treatment. Ferrous salts (including the most widely used ferrous sulphate USP) are used in treatment of iron-deficient anaemia (ACG96). It has been reported that iron sulphate is added to cement (in Scandinavian countries) to induce precipitation of three-valent chromium, hereby diminishing the incidence of contact dermatitis in sensitive subjects (Bru90a, Fre79).

| 5 | **Biotransformation and kinetics** |

The comitttee did not find data on the absorption of iron in the respiratory tract. It may be surmised that water-soluble iron salts are better absorbed than water-insoluble iron compounds. In both humans and animals, iron absorption from the digestive tract is adjusted to a fine homeostasis with low iron stores resulting in increased absorption and, alternately, sufficient body stores of iron decreasing absorption (Eli86). Iron is an essential element in humans. About 2 to 15% of the iron ingested via food is absorbed.

Normally, the human body contains about 3 to 5 g of iron. Two-thirds of this amount is found in the blood bound to haemoglobin. Less than 10% of the body iron is found in myoglobin and iron-requiring enzymes. Of the remaining amounts of iron, about 20 to 30% of the body pool is bound to iron-storage proteins: ferritin and haemosiderin. These iron-storage proteins are mainly found in liver, bone marrow, and spleen (Eli86).

The total elimination of iron from the body, under normal conditions, is limited to 0.6-1.0 mg/day. Disregarding the non-absorbed iron, about 0.2-0.5 mg/day of iron is eliminated via the faeces. The mean urinary excretion of iron has been reported to be about 0.1-0.3 mg/day. The biological half-time of iron in humans is estimated to be 10 to 20 years (Eli86).

| 6 | **Effects and mechanism of action** |

Human data

The committee did not find epidemiological data on humans exposed by inhalation to water-soluble iron salts. A few cases of acute intoxication induced by excessive accidental ingestion of iron compounds have been reported. These mostly concern children with fatal endings after taking estimated doses of up to 15 g of ferrous sulphate (DeC77, Kel68).

For some years, ferrous sulphate has been added to cement manufactured in the Scandinavian countries to prevent sensitisation to and elicitation by chromate in cement (Bru90a, Fre79). Bruze et al. investigated whether cement with or without ferrous sulphate differed in capacity to elicit allergic patch-test reactions in 8 chromate-sensitive subjects. The results showed that no patch-test reactions were obtained from a water extract of cement with ferrous iron when appropriately buffered (Bru90b).

Kleinman et al. performed a human volunteer study to investigate the effects on pulmonary function and respiratory symptoms of 2-hour inhalation of ferric sulphate aerosols. The subjects, 18- to 55-year old, alternately rested and exercised on a bicycle ergometer for 15-minute periods during the experiment. The number of volunteers was 38, of which 20 subjects with normal pulmonary function and no history of lung diseases and 18 subjects diagnosed as asthmatics. The nominal concentration was 0.075 mg/m^3 ferric sulphate (equivalent to 0.02 mg Fe/m^3), and the mass median aerodynamic diameter of the aerosols was 2 μm with a geometric standard deviation of 3 μm. Each subject underwent exposures on 2 separate days: a sham exposure to highly purified air at one day and an exposure to the test atmosphere at the other day. The 2 days were separated by a 3-week period. Each subject was treated as his or her own control in the subsequent statistical analysis of the data. The results of the experiment showed that, on the average, the 2 groups of subjects did not exhibit significant changes in total respiratory system resistance, forced expiratory flow/volume performance, and single breath nitrogen washout parameters. None of the subjects reported more than slight changes in symptoms during exposure. Five individuals (one normal and 4 asthmatics) showed small but significant decrements in pulmonary function. However, 9 subjects (6 normal and 3 asthmatics) tended to improve after exposure (Kle81). From this study, the committee concludes that the no-observed-adverse-effect level (NOAEL) in humans for (instant) effects on the respiratory tract would probably be higher than 0.02 mg Fe/m^3 of respirable aerosols for a 2-hour exposure period.

Animal data

Acute toxicity

Acute lethal toxicity data for water-soluble iron salts are presented in Table 1.

Table 1 Acute lethal toxicity data of water-soluble iron salts.

compound	species	route	LD$_{50}$ (mg/kg bw)	reference
FeCl$_3$	mouse	oral	400	ACG96
	mouse	oral	1500	Hop55
	rabbit	oral	1200	Hop55
	guinea pig	oral	600	Hop55
	mouse	intraperitoneal	68	ACG96
FeCl$_3$.6H$_2$O	mouse	intraperitoneal	260	ACG96
Fe(NO$_3$)$_3$.9H$_2$O	rat	oral	3250	Smy69
FeCl$_2$	rat	oral	600	Hop55

	rabbit	oral	1000	Hop55
$FeSO_4$	rat	oral	3100	Bom00
	rat	oral	2625	Wea61
	rat[a]	oral	5500	Whi02
	mouse	oral	1025	Wea61
	mouse	intraperitoneal	137	Wea61
	mouse	intravenous	112	Wea61
	dog	intravenous	79	Wea61
$FeSO_4.7H_2O$	mouse	oral	4500	Hop55
	rabbit	oral	3000	Hop55
	guinea pig	oral	1500	Hop55
	dog	oral	800	Hop55

[a]   'Young' male animals (age not specified).

For ferrous sulphate, the oral rat LD_{50} of 3100 mg/kg bw (see Table 1) was determined following administration of doses of 1000, 2000, 2500, 3100, and 5000 mg/kg bw (n=5/sex/group). Symptoms were seen 1 hour after administration and included poor general condition, sedation, growth retardation, and piloerection. Deaths occurred from days 1 to 3, necropsy revealing loss of gastric mucosal relief and reddened stomach and intestines (partly filled with grey-black liquid). Surviving animals were free by day 10 and did not show gross lesions at necropsy (Bom00).

Repeated-dose toxicity

The effects of subacute ambient exposure to ferric chloride aerosols on the lungs of male rabbits were studied by Johansson et al. Groups of 8 rabbits were exposed to 0, 1.4, or 3.1 mg Fe/m^3, 6 hours/day, 5 days/week, for 2 months. The mass median aerodynamic diameter of the aerosols was about 1 μm. After exposure, the rabbits were killed. The upper left lung lobe was used for light microscopy. The lower lobes were examined by electron microscopy, and the remainder was used for phospholipid analysis. The results showed that the high-concentration group had significantly higher lung weights that were not observed for the low-concentration group. The lungs of the high-concentration group showed large nodules of densely packed granular macrophages with brown appearance. Sometimes, accumulations of such granular macrophages were found in terminal bronchioles as well. Foci of interstitial inflammatory reaction, involving mostly lymphocytes, were seen in the high-concentration group. Accumulations of normal as well as granular macrophages were observed in the

alveoli of rabbits of both exposed groups. The control rabbits showed essentially normal lung tissue. The volume density of the alveolar type II cells was significantly higher in the high-concentration group compared to that of the controls. Further studies were performed on the alveolar macrophages obtained by lavage. The overall impression was that 96% of the macrophages from the controls appeared normal, while one or several changes, e.g., cells with surface-lacking protrusions and macrophages with a large number of surfactant-like inclusions, were found in about 18 and 48% of the low- and high-concentration group, respectively. There was a tendency toward higher oxidative metabolic activity in the macrophages from the high-concentration group. The concentration of total phospholipids was significantly increased in the high-concentration group. There was no significant difference between the groups concerning the concentration of phosphatidylcholines in the lung or the percentage of 1,2-depalmytoilphosphatidylcholines in the phosphatidylcholines (Joh92). From this study, the committee concludes that the lowest-observed-adverse-effect level (LOAEL) is 1.4 mg Fe/m^3, as respirable aerosols/particles, for effects on the lungs of rabbits after subacute inhalation exposure.

In order to determine appropriate dose levels for a carcinogenicity study, Sato et al. administered ferric chloride to rats (Fischer 344; n=10/sex/group) at amounts of 0, 0.12, 0.25, 0.5, 1.0, or 2.0% in the drinking water, for 13 weeks. Rats were observed daily for clinical signs and mortality, and body weights were recorded weekly. At the end of the study, surviving animals were killed for haematological, blood chemistry, gross and microscopic examinations. No mortality occurred; no information on clinical signs was presented. Water consumption was significantly decreased in animals given doses of 0.5% or more. No data on food consumption were given. At study termination, body weight gain decreases of at least 10% compared with controls were observed in male and female animals given 1.0 and 2.0%. In male treated groups, there were dose-related increases in serum iron and a significant increase in red blood cell counts when compared to controls. Microscopic examination showed pigment deposition in several organs/tissues at doses of 0.25% or more (Sat92).

Carcinogenicity

In the carcinogenicity study, Sato et al. treated male and female rats (F344; n=50/sex/group) with ferric chloride solutions of 0, 0.25, and 0.5% in the drinking water, for 2 years, resulting in mean daily doses of 170 and 320 mg/kg bw for males and of 188 and 336 mg/kg bw for females. Clinical signs and mortality were recorded daily and body weights weekly during the first 13 weeks and once

every 4 weeks thereafter. All rats were subjected to a full post-mortem examination and investigated macroscopically and microscopically for the occurrence of neoplastic and non-neoplastic lesions. Sato et al. did not present findings on signs of toxicity. Apart from a statistically significant increase in high-dose males, no differences were seen in final survival rates and mean survival time between exposed and control groups. In all exposed groups, there were statistically significant, dose-related decreases in final body weights and mean daily water intake when compared to controls. Comparison with control groups showed that ferric-chloride treatment did not induce statistically significant increases in the overall tumour incidence or in the incidence of any specific tumour. All tumours observed in this study were similar to those that are known to occur spontaneously in this strain of rats. Although various types of non-neoplastic lesions were observed in each group, there were no specific lesions that could be attributed to treatment to ferric chloride. Although observed in the 13-week study at drinking water doses as low as 0.25% (see above), iron deposition was not increased in any dose/tissue of the high dose compared with the control group at study termination. Sato et al. considered that in this study the level of iron overload was too low to increase lipid peroxidation, although this was not assessed quantitatively (Sat92). From this study, the committee could not establish a NOAEL for chronic oral exposure to ferric chloride, since administration of daily doses of 170-188 mg/kg bw, the lowest levels tested, caused decreased body weights in male and female rats. The committee concludes that ferric chloride was not carcinogenic in rats at doses as high as 320-336 mg/kg bw/day, the highest levels tested. Since no overt signs of toxicity were observed at these levels, the committee cannot draw a definite conclusion on the carcinogenicity of ferric chloride.

Mutagenicity and genotoxicity

- *In vitro* tests:
  - gene mutation assays. Brusick reported in an abstract that ferrous sulphate induced reverse mutations in *S. typhimurium* strains TA1537 and TA1538, but not in TA1535. The mutagenic response was most pronounced in suspension assays in the presence of metabolic activating systems from mouse, rat, guinea pig, monkey, and human liver, while variable and weak response were seen in assays without activating systens (Bru76). Ishidate et al. reported that ferrous sulphate was negative in a bacterial mutation assay using *S. typhimurium* strains TA92, TA94, TA98, TA100, TA1535, and TA 1537 tested with and without induced rat liver

S9 mix at doses up to 10,000 µg/plate (Ish84). Shimizu et al. found that ferric chloride at concentrations of 5 to 5000 µg/plate did not induce mutations when tested with or without induced rat liver S9 mix in *S. typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 and *E. coli* strain WP2 *uvrA* (Shi85). Ferric chloride and ferrous sulphate were both negative when tested with and without metabolic activating systems from induced rat and hamster livers in *S. typhimurium* strains TA97a, TA98, TA100, TA102, TA1535, TA1537, and TA1538 (Dun99). However, Pagano and Zeiger found that ferrous sulphate induced mutations in *S. typhimurium* TA97 when pre-incubations were done in deionised water or HEPES/saline buffer, but not when phosphate buffer was used (Pag92).

In yeast, ferrous sulphate induced reverse mutations and mitotic gene conversions at *trp 5* and *ilv 1* loci in *S. cerevisiae* strain D7. Ferric chloride was negative in this test (Sin83).

McGregor et al. reported that ferric chloride was negative in the L5178Y TK$^{+/-}$ mouse lymphoma cell forward mutation assay. Four experiments were conducted, 2 in each activation condition. In none of the experiments, there was a mutagenic response without precipitation of ferric chloride, precipitation occurring at a concentration of 150 µg/mL (McG88). However, in a separate test, Dunkel et al. concluded that ferric chloride was positive in this test. A dose-related mutagenic response was found in the presence of an induced rat liver S9 mix, with a marked increase in cytotoxicity (concentration range tested: 0.2-1.2 µg Fe/mL) while no increase in the number of mutants was seen in the absence of metabolic activation (concentration range: 309-1030 µg/mL). Ferrous sulphate induced a weakly positive response in the absence and a dose-related increase in mutant frequency (and a marked increased cytotoxicity) in the presence of a S9 mix (concentration ranges: 20.1-201 and 0.8-2.1 µg/mL, respectively) (Dun99).

Ogawa et al. reported that ferrous chloride and ferric chloride were negative in the *D. melanogaster* wing spot test (Oga94). Ferrous sulphate was listed among compounds that did not give a mutagenic response in the *Drosophila* sex-linked recessive lethal assay (Lee83)

- cytogenicity assays. Ferrous sulphate (heptahydrate) and ferric chloride (hexahydrate), tested at a single dose of 32 µg/mL (i.e., the concentration causing 50% growth inhibition of tissue-culture cells), did not cause a statistically significant increase in the frequency of sister-chromatid exchanges in Don Chinese hamster cells (Ohn82).

Ferrous sulphate was concluded to be positive in a chromosomal aberration assay in a Chinese hamster lung fibroblast cell line, inducing increases in the percentage of polyploid cells and of cells with structural aberrations (including gaps) at doses of up to 2.5 mg/L (Ish84).

- other tests. In tests indicative for DNA damage, negative results were obtained for ferric chloride, ferric nitrate, and ferric sulphate in the SOS-chromotest using *E. coli* strains PQ37 and PQ35 (Oli87) and for ferric and ferrous chloride in the rec assay using *B. subtilis* strains H17 and M45 (Nis75).

   Robinson et al. did not find considerable changes in the alkaline sucrose profile of Chinese hamster ovary cells treated with a concentration of ferrous chloride of 10 μM (the only concentration tested) for 4 hours, from which they concluded that no DNA strand breaks had been induced (Rob82). Using Syrian hamster embryo cells, ferrous sulphate caused increases in the level of DNA damage (OH8dG) and in the incidence of DNA strand breaks (comet assay). Co-treatment with antioxidants prevented these events, indicating the involvement of reactive oxygen species (hydroxy radicals; oxidative stress) (Par02).

- *In vivo* tests:
   Bianchini et al. studied the cytotoxicity and genotoxicity (micronuclei induction) of ferrous sulphate and ferric chloride in the gastrointestinal tract after single oral (gavage) or intrarectal administration of doses of 0, 10, 32.5, and 65 mg/kg bw to female C57BL/6J mice (n=4-10/group). In fasting animals, ferric chloride induced a dose-related increase in the frequency of (not further specified) nuclear aberrations in the stomach, whereas ferrous sulphate was not active. In normally fed animals, no increase in the frequency of nuclear aberrations was observed. The effects of the compounds on the duodenum were minimal. In fasting animals, a dose-related increase in the frequency of nuclear aberrations was found in the colon, with no difference between ferrous and ferric compounds. After intrarectal administration, an increased incidence of nuclear aberrations was induced especially by ferric chloride. The frequency of micronuclei was not increased in the stomach, duodenum, or colon (Bia88).

- Other tests:
   Casto et al. reported that ferrous chloride and ferrous sulphate at 0.9 to 5.0 mM enhanced the transformation of Syrian hamster embryo (SHE) cells by a simian adeno virus, causing a 2- to 3-fold increase in the absolute number of

SA7 foci per dish (Cas79). In agreement with these results, Park et al. found ferrous sulphate to induce morphological transformation in SHE cells. This was prevented by concomitant treatment with antioxidants indicating the involvement of reactive oxygen species (hydroxy radicals; oxidative stress) (Par02).

Immunotoxicity

Ikarashi et al. studied possible immunotoxicity of some metal salts using the local lymph node assay (LLNA) on female BALB/c mice. The ability to induce lymph node cell proliferation was compared among the metals. This assay is known as a predictive test to detect contact allergens. The animals (n=3) received 25 μL of test solution on the dorsum of each ear repeatedly for 3 consecutive days. Four days following the initial application, the mice were killed and the draining lymph nodes were excised and pooled per animal. Iron salt (ferrous sulphate) failed to induce lymph node proliferation in this assay, in contrast to nickel, cobalt, chromium, and copper salts (Ika92a). In another experiment, the same authors performed LLNA in mice, guinea pigs, and rats. Iron salt (ferrous chloride) failed to induce changes in rats; the experiment was not performed in the other species. From these experiments, the authors concluded that water-soluble iron salts did not cause allergic contact dermatitis (Ika92b).

Ban et al. reported that ferrous sulphate and ferric citrate had an immunosuppressive effect in an *in vitro* model for the evaluation of the humoral immune response of mice spleen cells to sheep red blood cells (SRBC), the response being indicated by the number of antibody-forming cells (AFC) per million nucleated cells (Ban95).

Reproduction toxicity

The committee did not find data from experimental animal reproduction toxicity studies on water-soluble iron compounds.

In which can be considered being a screening test, no toxicity or teratogenicity was observed in developing chick embryos when concentrations of ferrous sulphate up to 2.5 mg/egg were injected into the eggs (Ver80).

7   Existing guidelines

The current administrative occupational exposure limit (MAC) for water-soluble iron salts in the Netherlands is 1 mg/m^3, 8-hour TWA.

Existing occupational exposure limits for water-soluble iron salts in some European countries and in the USA are summarised in the annex.

8   Assessment of health hazard

The target organs after exposure by inhalation to water-soluble iron salts are the lungs. A human volunteer study has shown that no (instant) effects on lung functions were found when healthy as well as asthmatic subjects were exposed to a respirable aerosol of ferric sulphate of 0.02 mg Fe/m^3 for 2 hours (Kle81). This means that the NOAEL would probably be higher than this level.

A subacute inhalation experiment in rabbits exposed to ferric chloride indicated that the LOAEL for effects on the macrophages of the lungs is 1.4 mg Fe/m^3, as respirable aerosols (Joh92).

The committee takes the rabbit study with an LOAEL of 1.4 mg Fe/m^3 as a starting point in deriving a health-based recommended occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, an overall assessment factor of 12 is established. This factor covers the following aspects: the absence of a NOAEL, inter- and intraspecies variation, the relatively short duration of exposure, and the type of critical effect. Thus, applying this factor of 12 and the preferred value approach, the committee recommends a health-based occupational exposure limit of 0.1 mg Fe/m^3 for respirable particles of water-soluble iron salts.

The committee underlines that the recommendation is based on a study where local effects after exposure to water-soluble *ferric* salts have been found. Therefore, the recommended OEL is not applicable for water-soluble *ferrous* salts.

The committee considers the toxicological database on water-soluble *ferrous* salts too poor to justify recommendation of a health-based occupational exposure limit. The committee concludes that there is insufficient information to comment on the level of the present MAC value.

The committee recommends a health-based occupational exposure limit for respirable particles of water-soluble *ferric* salts of 0.1 mg Fe/m^3, as an 8-hour time-weighted average (TWA).

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Annex

Occupational exposure limits for water-soluble iron salts in various countries.

country - organisation	occupational exposure limit[a]		time-weighted average	type of exposure limit	note[b]	reference[c]
	ppm	mg/m^3				
the Netherlands - Ministry of Social Affairs and Employment	-	1	8 h	administrative		SZW03
Germany - AGS	-	-				TRG00
- DFG MAK-Kommission	-	-				DFG03
Great Britain - HSE	-	1	8 h	OES		HSE02
	-	2	15 min			
Sweden	-	-				Swe00
Denmark	-	1				Arb02
USA - ACGIH	-	1	8 h	TLV		ACG03b
- OSHA	-	-				ACG03a
- NIOSH	-	1	10 h	REL		ACG03a
European Union - SCOEL	-	-				EC03

[a] In all cases as Fe.
[b] S=skin notation; which means that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.
[c] Reference to the most recent official publication of occupational exposure limits.