SIDS INITIAL ASSESSMENT PROFILE

CAS No.	Ferric chloride: 7705-08-0 Ferric sulfate: 10028-22-5 Ferrous sulfate: 7720-78-7 Ferric chloride hexahydrate: 10025-77-1 Ferric sulfate nonahydrate: 13520-56-4 Ferrous sulfate monohydrate: 17375-41-6 Ferrous sulfate heptahydrate: 7782-63-0 Ferric chloride hydrate, unspecified: 24290-40-2 Ferric sulfate hydrate, unspecified:15244-10-7 Ferrous sulfate hydrate, unspecified: 13463-43-9
Chemical Name	Iron Salts Category
Structural Formula	$FeCl_3$, $Fe_2(SO_4)_3$, $FeSO_4$, $FeCl_3.6H_2O$, $Fe_2(SO_4)_3.9H_2O$, $FeSO_4.H_2O$, $FeSO_4.7H_2O$, $FeCl_3.xH_2O$, $Fe_2(SO_4)_3.xH_2O$, $FeSO_4.xH_2O$

SUMMARY CONCLUSIONS OF THE SIAR

Iron is the fourth most common element in the natural environment, comprising about 5 % of the Earth's crust. It is abundant in minerals, soils, sediments and natural waters. Iron is biologically an essential element for micro-organisms, plants and higher animals. They have adapted to naturally occurring high environmental levels of iron, and have active intake mechanisms for it.

Rationale for iron salts category

Structural similarities of the inorganic iron ions, which will dissociate immediately in aqueous based media to the respective anions and cations, and form common reaction products via environmental and physiological processes. Iron dichloride (CAS No. 7758-94-3) was reviewed at SIAM 19 and the data from the SIAP and Dossier are published on the UNEP website.

Human Health

Toxicokinetics: Iron is an essential element in humans. Iron salts are absorbed from the GI-tract to varying degree. Before absorption ferrous iron is oxidised to ferric form, which is then transferred into the mucosal lining of the small intestine with the aid of various chelates such as ascorbate and citrate. Tannins and plant phytates inhibit the absorption. Diet may have a significant effect on iron absorption. Iron absorption in the rat is higher and the dietary intake is about 100 times greater than that of humans. Percutaneous absorption of iron in non-chelated form has not been reported. No data is available on respiratory iron absorption. Following absorption the majority of iron is bound to transferrin and transported to the bone marrow where it is incorporated into haemoglobin. Any remaining iron is contained within the storage forms, ferritin or haemosiderin, or as myoglobin, with smaller amounts occurring in haem-containing enzymes or in plasma bound to transferrin. About 1-2 mg of iron is lost daily.

Acute toxicity: In rats, the oral LD_{50} was 300-2000 mg/kg (132-881 mgFe/kg) for ferrous chloride. For ferric sulfate, the oral LD_{50} for iron is 500-2000 mg/kg (139 to 558 mg Fe/kg) in females. Ferrous sulfate heptahydrate did not show acute toxicity in rats up to 2000 mg/kg (400 mgFe/kg). The following acute toxic doses of ferrous sulfate have been considered to apply in humans: infants (<6 y) 20 mg/kg (7 mgFe/kg) (for gastrointestinal irritation only), children 200-300 mg/kg (74-111 mgFe/kg), adults 1400 mg/kg (516 mgFe/kg). The dermal LD_{50} for dry ferrous chloride in rats was >2000 mg/kg (881 mgFe/kg). No relevant data were available for inhalation.

Irritation and sensitisation: Ferrous sulfate solids were irritating to skin. Ferrous chloride solid was weakly irritating, ferric sulfate solid and ferrous sulfate solutions were non-irritating in OECD 404. Ferric chloride was found irritating to respiratory tract in rats.

Ferrous chloride was corrosive, ferric chloride was irritating and ferrous sulfate heptahydrate solution was not irritating to the eye. Ferric solutions are acidic, whereas ferrous ones are not until they oxidise to ferric. The pattern of results is therefore somewhat inconsistent.

Although mixed results have been obtained from sensitisation tests, there is no convincing or reliable evidence of iron sensitisation.

Repeated dose toxicity: In a 13-week study with 0.12, 0.25, 0.5, 1.0 and 2.0% w/v ferric chloride in drinking water, a NOAEL of 0.5% approximately 277 mg/kg bw/day in males, and 314 mg/kg bw /day in females was found. Ferrous sulfate heptahydrate was assessed in oral (gavage) toxicity in rats in an OECD combined repeated dose and reproductive/developmental toxicity screening test under GLP at doses of 0, 30, 100, 300, and 1000 mg/kg/day. Based on extramedullary hematopoiesis of the spleen in the males at 300 mg/kg and increased levels of inorganic phosphate in females at 300 mg/kg, the oral NOAEL for repeated dose toxicity was considered to be 100 mg/kg/day, equivalent to 20 mgFe/kg bw/day for both sexes. In an OECD TG422 study, 0, 125, 250 or 500 mg/kg/day ferrous chloride was administered to rats for up to 42 days in males or 42-54 days in females using oral gavage, deaths were noted at 500 mg/kg. The NOAEL was concluded to be 125 mg/kg/day for males and females, equivalent to 55 mg Fe/kg. These results are applicable across the category.

Mutagenicity and Carcinogenicity: Most Ames tests conducted with iron salts are negative. In an *in vitro* mouse lymphoma test ferric chloride produced a positive and dose-related response in presence of S9 with a marked increase of cytotoxicity. Ferrous sulfate heptahydrate produced chromosomal aberrations in CHL/IU cells after short term treatment with and without S9. *In vivo*, iron has not produced positive responses in the five studies available. Overall iron category substances are not mutagenic *in vivo*.

No increase in tumour incidence was reported for rats ingesting ferric chloride in drinking water at received doses of up to 320-340 mg/kg body weight/day (110-117 mg Fe/kg body weight/day) for two years. Epidemiological investigations have not provided evidence of an increased cancer risk in human populations with increased iron intakes arising from food or clinical supplementation. The Scientific Panel on Dietetic Products, Nutrition and Allergies of the European Commission has concluded that some results indicate the possibility of a role of luminal exposure to excessive iron in the development of colon carcinoma, but the evidence is limited and not convincing.

Reproductive toxicity: In an OECD 422 study rats received 0, 125, 250 and 500 mg/kg/day of ferrous chloride by the oral route (gavage) for 42 days in males or 42 - 54 days in females with treatments continuing through a 14 day pre-mating period. A NOAEL of 500 mg/kg body weight/day was obtained, based on no significant difference in mating data and pre-and post-implantation loss rate. In another OECD 422 study rats received ferrous sulfate heptahydrate orally at doses of 0, 30, 100, 300, and 1000 mg/kg/day. The NOEL for reproductive performance from this study was considered to be 1000 mg/kg/day for both parental animals and pups. For developmental effects, the OECD 422 screening study with ferrous chloride found a NOAEL of 500 mg/kg (220 mg/kg iron). The study with ferrous sulfate heptahydrate using the same protocol found a development NOAEL of 1000 mg/kg, (200 mg/kg iron). These results are applicable across the category.

Environment

Environmental fate: Fe (II/III) category salts are non-volatile solid substances which are very soluble in water and have an acidic reaction with water (Fe(III) species being moderately strong acids). Fe(II) species are unstable in oxygenated water with a half-life under favourable conditions of minutes – hours, and oxidises easily to the Fe(III) state. Under conditions of high light intensity Fe (III) can be photo-reduced to Fe (II). Fe (III) species are soluble and stable in aqueous solution only at very low pH conditions. Normally they react with water to form colloidal and insoluble $Fe(OH)_3$ which in typical aquatic environmental condition precipitates to sediments. Other metals and organic matter may be strongly adsorbed to Fe precipitates. Fe may also typically form precipitates with phosphate. Iron ions, especially Fe(II) ions may be also adsorbed to dissolved organic material and some dissolved iron in natural waters may be present as soluble organic-complexes. Physical effects arising from the presence of precipitated or colloidal $Fe(OH)_3$ may be responsible for the effects observed in the tests that are summarised below.

Bioconcentration: Bioconcentration of iron to species is relatively low. Iron is an essential element for most living species and may be actively regulated in organisms.

Ecotoxicity: In general, Fe(II) seems to exhibit higher toxicity to aquatic species compared to Fe(III) ions. However, precipitating and colloidal $Fe(OH)_3$ may have lethal effects through clogging and causing inflammation in respiratory organs of invertebrates and fish. It is difficult to separate these physico-chemical effects from the true ecotoxic effects even in the standard laboratory tests, other than on the reasonable chemical basis of knowledge of the solubility properties.

Acutely toxic levels of the iron salts to aquatic organisms are observed in nominal exposure concentrations in the range equivalent to 1 – 1000 mg/l salt, with the majority of the results being in the 10 – 100 mg/l range. Chronic effects on aquatic organisms are also observed at nominal concentrations in the range 1 – 1000 mg/l for each individual salt with the majority of the results being >10 mg/l. Summary acute results expressed, for consistency of comparison, relative to concentrations of Fe are:

Green algae (*Pseudokirchneriella subcapitata*)	E_rC_{50} (72 h) = 18 mg/l (growth rate)
Invertebrates (*Daphnia magna*, 4 results):	EC_{50} (48 h) = 1 - 10 mg/l
Fish (various fish species):	LC_{50} (96 h) = 0.41 - >28 mg/l
Micro-organisms (*Vibrio fischeri*)	EC_{50} (15 min) = 40 mg/l

It is not possible to differentiate physical and direct toxic effect mechanisms as the cause of effects observed in the tests.

Ferric(III): it is unlikely that ferric iron salts will have direct toxic effects in aquatic environments because the rapid conversion to ferric hydroxide will result in very low concentrations of dissolved iron even under conditions of low pH.

Ferrous(II): it is possible that ferrous iron could have true toxic effects in circumstances where pH is low (<5), oxygen content is low and iron concentration is high (of the order of the apparent $E(L)C_{50}$ values).

Physical effects are a genuine hazard expressed via the concentrations reported above, but these are not an indication of a significant chronic hazard.

Exposure: Environmental exposure assessment takes into account exposure arising from intentional use of the specific iron salts in the Sponsor Country. It is important to note that Fe-ion discharges and environmental impact from other (potentially high) exposure sources like production of ferro metals and titanium dioxide, mining and mineralogy are outside the scope of this exposure assessment.

It is noted also that these Fe-category substances typically contain impurities such as Cd and Zn; however, their normal use does not give rise to concentrations exceeding international standards for surface waters.

In 1999 the annual production of these iron salts was 3,44 million tonnes for the European member companies of Inorganic Coagulants Producers Association (Incopa). The main application (ca. 45 % by volume) of the substances in the iron salt category is water treatment: they are used as flocculating and

precipitating agents in mechanical and biological wastewater treatment plants and paper mills as well as treatment of potable water. It has been estimated that about 30% of world iron coagulants are produced in Europe, about 40% in Asia Pacific and about 20% in North America.

Other applications include use as fertilizers, plant protection products, as raw material in synthesis, etching of copper and stainless steel, corrosion inhibition, colouring agent in cosmetics, laboratory and textiles, cement additive to prevent chromium(VI) dermatitis, and production of pharmaceuticals.

RECOMMENDATION AND RATIONALE FOR THE RECOMMENDATION AND NATURE OF FURTHER WORK RECOMMENDED

Human Health: The chemicals in this category are low priority for further work. They do possess properties indicating a hazard for human health, namely, acute toxicity (ferrous chloride, ferric sulfate), skin irritation (ferrous sulfate), eye irritation (ferric chloride) and eye corrosivity (ferrous chloride). These hazards do not warrant further work as they are related to acute toxicity which may become apparent only at high exposure levels. Based on data presented by the Sponsor country, adequate risk management measures are being applied. Countries may desire to check their own risk management measures to find out whether there is a need for additional measures.

Environment: The members of the category are currently of low priority for further work. The hazard profile of iron salts is dependent on the environmental conditions and the necessary conditions for harmful effects to be expressed are very specific (low pH and low dissolved oxygen) and are, in themselves, intrinsically unfavourable to many aquatic species.