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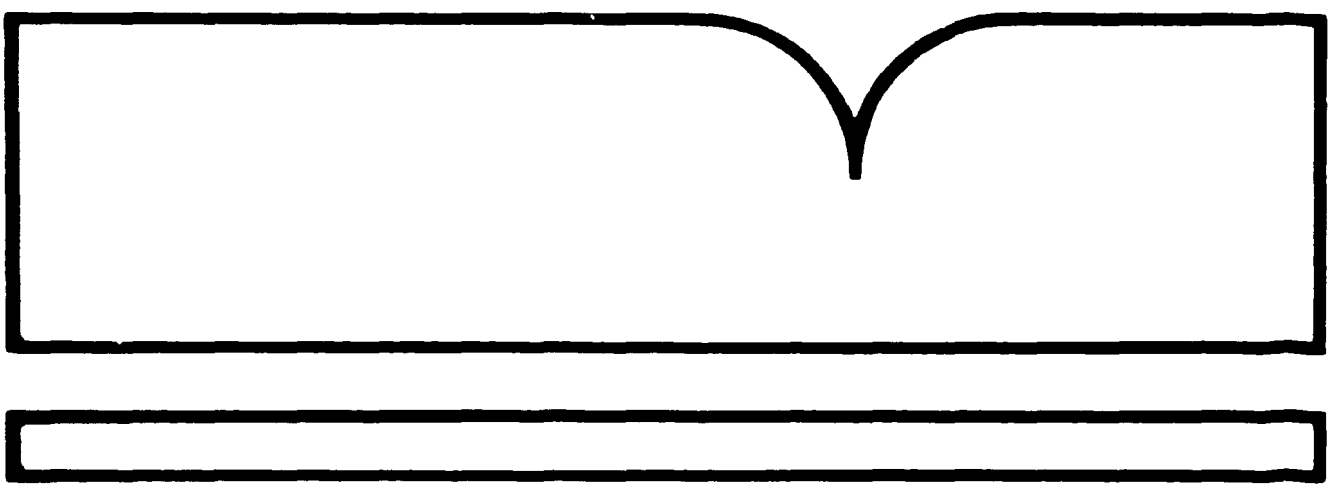
Information Profiles on Potential Occupational Hazards Metallocenes. Second Draft

Syracuse Research Corp., NY

Prepared for

National Inst. for Occupational Safety and Health, Rockville, MD

Nov 81



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16. Abstract (Limit: 200 words)

Information on potential occupational hazards from metallocenes was reviewed. Topics discussed included chemical and physical properties, chemical structure, production volumes, uses and manufacturing process. A list of manufacturers was developed. More detailed profiles were presented for ferrocene (102545), acetyl-ferrocene (1271552) and ethyl-ferrocene (1273898). Ferrocene has been used as a smoke suppressant for rigid polyurethane and rigid PVC, an additive in fuel oils, an antiknock agent, a catalyst, and an ingredient in coatings for missiles and satellites. High temperature lubricants and intermediates for high temperature polymer formation also use ferrocene. Studies indicated that ferrocene is slightly to moderately toxic in animals with rodent oral median lethal doses (LD50s) greater than 1000mg/kg being reported. Cirrhosis of the liver and testicular hypoplasia in dogs were reported to be caused by subchronic oral exposures. Acetyl-ferrocene appeared to be more toxic than ferrocene in the only study performed thus far. Data on carcinogenicity, mutagenicity and teratogenicity of acetyl-ferrocene were not available. No information on the biological effects of ethyl-ferrocene was presented.

17. Document Analysis a. Descriptors

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SECOND DRAFT

Information Profiles on Potential Occupational Hazards: Metallocenes

Center for Chemical Hazard Assessment
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Contract No. 210-79-0030

November 1981

Prepared for:

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I. SCOPE OF DOCUMENT AND SUMMARY OF MAJOR FINDINGS

A. CLASS IDENTIFICATION

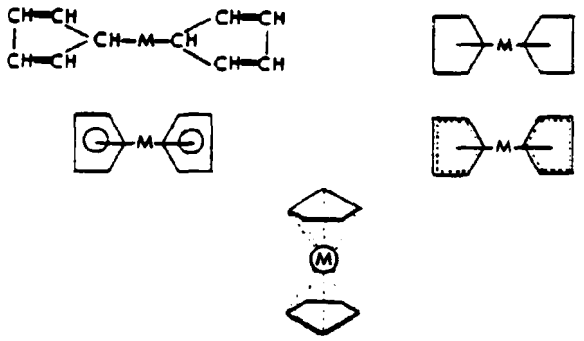
Metallocenes are organometallic coordination compounds obtained as cyclopentadienyl derivatives of a transition metal or metal halide. The metal is bonded to the cyclopentadienyl ring by electrons moving in orbitals that extend above and below the plane of the ring (π bond). There are three types of metallocenes (Hawley, 1977; Johnson, 1973):

(a) Dicyclopentadienyl metals with the general formula $(C_5H_5)_2M$, where M is a transition metal,

(b) Dicyclopentadienyl metal halides with the general formula $(C_5H_5)_2MX_{1-3}$, where X is a halide, and

(c) Monocyclopentadienyl metal compounds of the formula $C_5H_5MR_{1-3}$, where R is CO, NO, a halide, an alkyl, etc.

Structural formulas assigned to the metallocenes by workers in the field are varied and include the following (Johnson, 1973):



Because of their structures, the terms "sandwich compounds" and "half sandwich compounds" have been applied to the metallocenes.

B. CHEMICALS TO BE ADDRESSED

Individual profiles have been prepared for ferrocene and two of its derivatives, acetyl ferrocene and ethyl ferrocene. These are the only metallocenes which were identified to have an annual production in excess of 1000 pounds.

C. SUMMARY OF BIOLOGICAL ACTIVITY

With the exception of a single subchronic study of acetyl ferrocene, toxicological information is available only for ferrocene; however, this information is limited and incomplete. Ferrocene is slightly to moderately toxic in animals (rodent oral LD50s have generally been reported to be greater than 1000 mg/kg), and subchronic oral exposure has caused cirrhosis of the liver and testicular hypoplasia in dogs. The toxicity of ferrocene in humans has not been evaluated.

The single study of acetyl ferrocene indicates that this compound is more toxic than ferrocene when administered via oral or subcutaneous routes.

II. DATA FOR COMMERCIALLY IMPORTANT CHEMICALS NOT INDIVIDUALLY PROFILED

Other metallocene compounds that are listed in the U.S. EPA TSCA list, are apparently produced in small quantities and have potential commercial applications, they are listed in Tables 1, 2, 3, and 4. Table 1 presents synonyms, CAS numbers, RTECS numbers, and chemical structures; Table 2 lists chemical and physical properties; Table 3 describes production volumes, uses, and manufacturing processes; and Table 4 lists the manufacturers.

Table 1. Metallocenes

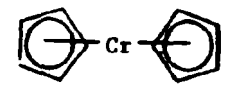
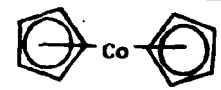
Compound and Synonyms	CAS Number	RTECS Number	Chemical Structure
Chromocene Chromium dicyclopentadienyl Di-2,4-cyclopentadienylchrome	1271-24-5	---	
Cobaltocene Dicyclopentadienylcobalt	1277-43-6	GG0350000	
Ferrocene, butyl- Butyl ferrocene	31904-29-7	---	C_5H_5-Fe-C_5H_4-C_4H9
Ferrocene, 1,1'-dibutyl- 1,1'-Dibutylferrocene	1274-08-4	---	C_4H_9-C_5H_4-Fe-C_5H_4-C_4H_9
Ferrocene, benzoyl- Benzoyl ferrocene Phenyl ferrocenyl ketone	1272-44-2	---	C_5H_5-Fe-C_5H_4-COC_6H_5
Ferrocene,(dimethylamino)methyl- (Dimethylaminomethyl) ferrocene	1271-86-9	---	$(CH_3)_2NCH_2C_5H_4$-Fe-C_5H_5
Ferrocene, formyl- Formyl ferrocene	12093-10-6	---	C_5H_5-Fe-C_5H_4-OCH

Table 1. Metallocenes (Cont'd)

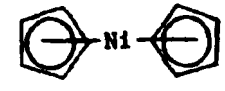
Compound and Synonyms	CAS Number	RTECS Number	Chemical Structure
Ferrocene, pentyl- Pentyl ferrocene Amyl ferrocene	1274-00-6 (normal) 1277-58-3 (test)	---	C_5H_5-Fe-C_5H_4-C_5H_{11}
Hafniumocene dichloride Bis(cyclopentadienyl)hafnium dichloride	12116-66-4	---	$(C_5H_5)_2HfCl_2$
Nickelocene Dicyclopentadienyl nickel Nickel biscyclopentadiene	1271-28-9	QR6500000	
Titanocene dichloride Titanium ferrocene Dicyclopentadienyltitanium dichloride Titanium, dichlorobis (eta, 5-2,4-cyclopentadien-1-yl)-	1271-19-8	XR2050000	$(C_5H_5)_2TiCl_2$
Zirconocene dichloride Dicyclopentadienylzirconium dichloride	1291-32-3	ZH7525000	$(C_5H_5)_2ZrCl_2$

Table 2. Metallocenes: Chemical and Physical Properties

Compound	Description	Boiling Point (°C)	Melting Point (°C)	Vapor Pressure	Water Solubility[a]	Specific Gravity	Molecular Weight
Chromocene	Scarlet crystals	---	170-173	---	---	---	182.19
Cobaltocene	Purple crystals	---	172-173	---	decomp.	---	189.13
Ferrocene, butyl-	Orange crystals	---	---	---	---	---	242.15
Ferrocene, 1,1'-dibutyl-	Orange crystals	---	---	---	---	---	298.25
Ferrocene, benzoyl-	Dark red crystals	---	107-108	---	---	---	290.15
Ferrocene, (dimethylamino)methyl-	Amber liquid	124-128 (2.5 mm Hg)	>112	---	---	1.28	243.13
Ferrocene, formyl-	---	---	---	---	---	---	214.04
Ferrocene, pentyl-(tert)	Liquid	80-90 (0.05 mm Hg)	---	---	---	1.170	256.17
Hafniumocene dichloride	Off-white crystals	---	---	---	---	---	379.59
Nickelocene	Dark green crystals	---	171-173	---	insol.	---	188.91
Titanocene dichloride	Red crystals	---	287-289	---	sp. sol.	---	249.00
Zirconocene dichloride	White crystals	---	248	---	---	---	292.32

[a]decomp. = decomposes; insol. = insoluble; sp. sol. = sparingly soluble

Table 3. Production Volumes, Uses, and Manufacturing Processes of Some Metallocenes

Compound	Production	Uses	Manufacturing Processes
Chromocene	1977: > 0-1000 lb (U.S. EPA, 1980)	Catalysts; polymers; ultraviolet absorbers (various patent literature).	(1) From cyclopentadiene sodium and a chromium salt. (2) From cyclopentadiene potassium and $Cr(SCN)_2(NH_3)_4$. (3) $Cr(CO)_6 + 2C_5H_6 \rightleftharpoons Cr(C_5H_5)_2 + 6CO + H_2$ (Wiese, 1965)
Cobaltocene	Not available	Polymerization inhibitor of olefins up to 200°C; Diels-Alder reaction; catalyst; paint drier; oxygen stripping agent (Hawley, 1977). Supplied in aromatic solvents in bottles and steel drums (Hawley, 1977).	Same as above but with cobalt compounds instead of chromium; also $2C_5H_6 + CoCl_2 \longrightarrow (C_5H_5)_2Co + 2HCl$ (Wiese, 1965)
Ferrocene, butyl-	Not available	Intermediate (various patent literature)	Not available
Ferrocene, 1,1'dibutyl-	Not available	Intermediate (various patent literature)	Not available
Ferrocene, benzoyl-	1977: under 1000 lbs (U.S. EPA, 1980)	Intermediate (Hawley, 1977)	Not available
Ferrocene, (dimethylamino)methyl-	1977: under 1000 lbs (U.S. EPA, 1980)	Intermediate (various patent literature)	Not available
Ferrocene, formyl-	Not available	Intermediate (various patent literature)	Not available
Ferrocene, pentyl-	1977: under 1000 lbs (U.S. EPA, 1980)	Intermediate (various patent literature)	Not available
Hafniumocene dichloride	1977: under 1000 lbs (U.S. EPA, 1980)	Not available	Not available
Nickelocene	Not available	Catalyst; antiknock agent for fuels; complexing agent (Hawley, 1977). Supplied in an inert atmosphere in bottles and steel containers (Hawley, 1977).	Same general methods as cobaltocene.
Titanocene dichloride	1977: 0 to 1000 lb (U.S. EPA, 1980)	Catalysts (Wiese, 1965).	From C_5H_5MgBr, cyclopentadiene sodium, or cyclopentadiene with titanium chlorides (Wiese, 1965).
Zirconocene dichloride	1977: 0 to 1000 lb (U.S. EPA, 1980)	Rubber accelerator; component of a catalyst system for polymerization of vinyl monomers; curing agent for water-repellent silicone materials; agent for plating with zirconium (Hawley, 1977).	From C_5H_5MgBr and zirconium chloride (Wiese, 1965).

Table 4. Metallocenes: Manufacturers (U.S. EPA, 1980; SRI International, 1980; Chem. Sources - USA, 1980)

Compound	Manufacturers
Chromocene	Union Carbide (Bound Brook, NJ) Boulder Scientific (Boulder, CO)
Cobaltocene	Not available
Nickelocene	Pressure Chemical Co. (Pittsburg, PA)
Titanocene dichloride	Boulder Scientific (Boulder, CO)
Zirconocene dichloride	Boulder Scientific (Boulder, CO) Arapahoe Chemical (Boulder, CO)
Ferrocene, butyl-	Arapahoe Chemical (Boulder, CO)
Ferrocene, 1,1'-dibutyl	Not available
Ferrocene, benzoyl-	Columbia Organics (Columbia, SC)
Ferrocene,(dimethylamino)methyl-	Columbia Organics (Columbia, SC) Pressure Chemical (Pittsburg, PA)
Ferrocene, formyl-	Eastman Kodak (Rochester, NY)
Ferrocene, pentyl-	Columbia Organics (Columbia, SC)
Hafniumocene dichloride	Boulder Scientific (Boulder, CO)

III. INFORMATION PROFILES

A. FERROCENE

1. Chemical Name: Ferrocene

2. Chemical Structure: 

3. Synonyms: bisCyclopentadienyliron
Di-2,4-cyclopentadien-1-yliron
Iron dicyclopentadienyl
Iron bis(cyclopentadiene)
FE55

4. Chemical Abstracts Service (CAS) Number: 102-54-5

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

LK0700000

6. Chemical and Physical Properties:

Description:	orange crystalline solid with a mild turpentine-like odor
Molecular Weight:	186.04
Boiling Point:	249°C
Melting Point:	173°C
Vapor Pressure:	0.03 mm Hg at 40°C
Solubility:	insoluble in water; soluble in alcohol and ether
Specific Gravity:	---
Stability:	moderate fire hazard; incompatible with oxidizing material (especially ammonium perchlorate)

7. Production

Data available from the U.S. EPA (1980) regarding producers of ferrocene and production volumes are presented below:

Anderson Development Co. (Adrian, MI)
Manufacturer
1977 Production of 0 to 1000 lb

Arapahoe Chemicals, Inc. (Boulder, CO)
Manufacturer
Production not available

Henley and Co., Inc. (NYC, NY)
Importer
Production not available

As of 1964, none of the metallocenes (cyclopentadienyl metal compounds) were produced commercially because no large outlet had yet been found for them (Wiese, 1965). Ferrocene is produced on a commercial scale at the present time (Arapohoe, 1980a); however, the actual annual production levels are not available. Based upon uses and various corporate sales data, current annual production of ferrocene may be significantly less than 1 million pounds (SRC estimate).

8. Use

Ferrocene is used as a smoke suppressent for rigid polyurethane and rigid PVC (Arapahoe, 1980a). It is also used as an additive to fuel oils to improve efficiency of combustion and eliminate smoke, as an antiknock agent, as a catalyst, as an ingredient in coatings for missiles and satellites, and high-temperature lubricants, as an intermediate for high-temperature polymers, as an ultraviolet absorber (Hawley, 1977), and in photomasks for integrated circuit manufacture (Lawler, 1977). A variety of patent literature suggests that ferrocene derivatives are useful as hematinic agents.

9. Manufacturers and Distributors

SRI International (1980) lists the following manufacturers:

Pressure Chemical Co.	Pittsburg, PA
Syntex (Arapahoe Chemical)	Boulder, CO

Data available from the U.S. EPA (1980) regarding producers of ferrocene and production volumes are presented in Section 7.

In addition to the manufacturers, the distributors include (Chemical Week: 1981 Buyers' Guide Issue, 1980; Chem. Sources - USA, 1980):

Aldrich Chem.
Apache Chem.
Atomergic Chemetals
Bio-Clinical Lab.
Bodman Chem.
Boulder Sci.
Columbia Organics
Chem. Procurement Lab.
Eastern Guardian Chemical
Eastman Kodak
Fisher Sci.
ICN/K and K
Lachat Chem.
Metron Inc.
Parish Chem.
Pfaltz and Bauer
Polysciences
Pressure Chem.
Reliable Chem.
Sigma Chem.
Spectrum Chemical
Strem Chemical
Tridom Chem.

10. Manufacturing Processes

The exact commercial method of preparing ferrocene is not available; however, ferrocene can be conveniently prepared by a number of methods, all of which involve reacting cyclopentadiene or its derivatives with iron or its salts. Some of these methods are outlined below (Wiese, 1965; Hawley, 1977):

(1) $2C_2H_5MgBr + FeCl_2 \longrightarrow (C_5H_5)_2Fe + MgBr_2 + MgCl_2$

(2) $2C_5H_6 + FeCl_2 \longrightarrow (C_5H_5)_2Fe + 2HCl$

(3) $2C_5H_5Na + FeCl_2 \longrightarrow (C_5H_5)_2Fe + 2NaCl$

(4) treating cyclopentadiene with reduced iron in the presence of certain metal oxides.

In the processes that use iron chloride, the reaction is carried out in an organic solvent or non-aqueous medium. The ferrocene formed precipitates in the solvent media and is collected by filteration, washed to remove impurities, and dried (Johnson, 1973).

Ferrocene is supplied to consumers in glass bottles or fiber drums (Hawley, 1977).

11. Impurities or Additives

Commercially available ferrocene is essentially free of foreign matter; it contains 0.2% max toluene insolubles and 0.4% max nonvolatile matter (Arapahoe, 1979).

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to ferrocene.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to ferrocene were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

Ferrocene has been shown to be moderately to slightly toxic depending on the species and route of administration (Table 5).

Ferrocene has been described as being non-irritating to the rabbit eye or skin (Arapahoe, 1980b).

(2) Subchronic Exposures

Oral administration of 200 mg/kg ferrocene for 2 weeks produced no fatalities in 6 animals (species not specified) (du Pont, 1955).

Gershbein (1980) undertook an oral and subcutaneous study to discern possible stimulatory activity of ferrocene on liver regeneration in partially hepatectomized rats and on liver weight in intact animals. Diets containing 0.10 or 0.30% ferrocene were fed to partially hepatectomized Charles River rats, and 0.20% ferrocene was fed to intact male rats for a period of 10 days. Results showed that there was neither enhancement of liver regeneration in the operated animals nor increased liver weight in the intact animals. Daily subcutaneous injections of ferrocene in peanut oil for a total overall dosage of 240 or 255 mg/kg body weight during 7 days also had no effect, respectively, on liver regeneration in partially hepatectomized rats or liver weight increase in intact rats sacrificed 10 days after intitation of treatment.

Table 5. Acute Toxicity of Ferrocene

Route[a]	Species	Dose (mg/kg)	Response	Reference
oral	rats	1320	LD50	Shell Chemical Co., 1961
oral	rats	1890	LD50	Arapahoe, 1980b
oral	mice	>498 <830	LD50	Madinaveitia, 1965
oral	mice	1550	LD50	Shell Chemical Co., 1961
inhalation	rats	>150 mg/m^3 (≈20 ppm)	LD50	Arapahoe, 1980b
i.p.	rats	500	LD50	Institute of Chemical Biology, 1965
i.p.	mice	335	LD50	Institute of Chemical Biology, 1965
i.p.	mice	500	LD50	Mueller, 1974
i.v.	mice	178	LD50	U.S. Army (no date)

[a] i.p. = intraperitoneal; i.v. = intravenous

Hepatic iron deposition was found histologically to be greater in the hepatectomized rats fed ferrocene than in the intact animals or in the injected animals, but no significant depression of body weight was noted following either the oral doses or injections (Gershbein, 1980).

(3) Chronic Exposures

Mixed-breed dogs (3 males and 3 females) were administered 30, 100, or 300 mg ferrocene/kg body weight daily in gelatin capsules (Yeary, 1969). At 12 weeks, 2 male and 2 female dogs were killed, while the remaining male and female dog of each group received the compound for an additional 4 months. Weight loss was observed in 1 male dog, and another dog showed signs of toxicity and was no longer treated. Signs of toxic effects, noted at the time of autopsy or biopsy, included cirrhotic changes in the liver; an effect on erythrocytes (decrease in packed cell volume, hemoglobin, and erythrocyte count); and testicular hypoplasia. Extensive accumulation of iron occurred in the livers of all dogs; in a single dog of each exposure group maintained for 20 months post-treatment, there was no observed reduction in the iron content. The authors suggested that the aromatic portion of ferrocene, and not the iron overloading of the liver, was the cause of cirrhosis.

(4) Carcinogenicity

A subcutaneous injection of 5 mg ferrocene into 20 mice at weekly intervals for 28 weeks produced no tumors in 17 surviors up to 9 months after the initiation of treatment (Haddon and Horning, 1960). In this study, where the carcinogenicity of an iron dextran complex was assayed, ferrocene was used as one of the control agents.

Ferrocene has been reported to be an equivocal tumorogenic agent in rodents following intermittent intramuscular injection (5175 mg/kg) for a period of two years (Institute of Chemical Biology, 1969).

(5) Mutagenicity

Results of mutagenicity testing of ferrocene in Salmonella typhimurium have been reported to be equivocal (NTP, 1980); strains TA98, TA100, TA1535 and TA1537 were tested with and without metabolic activation.

Ferrocene also has been scheduled for mutagenicity testing in Drosophila by the NTP (NTP, 1980).

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

In a study of mixed-breed dogs, Yeary (1969) reported testicular hypoplasia after subchronic oral treatment with ferrocene (see sthe Summary of Biological Activity, Section III, C.)

(8) Other Relevant Information

Ferrocene has been evaluated as a hematinic agent in animals. Following oral administration, ferrocene was almost completely absorbed in the rat (Goldberg and Martin, 1964; Madinaveitia, 1965; Dratz et al., 1964), guinea pig, and mouse (Goldberg and Martin, 1964). After absorption, ferrocene first accumulated in the adipose tissue; this was followed by progressive accumulation of the iron in the liver with depletion of the iron in the fat (Dratz et al., 1964; Goldberg and Martin, 1964). The adipose tissue does not appear to be a storage site for ferrocene in the guinea pig or the mouse (Goldberg and Martin, 1964). The iron of ferrocene was excreted in the urine as water-soluble iron in the rat, mouse, pig, and man; only in the guinea pig was it excreted as organic-soluble iron, indicating that ferrocene was metabolized in most species (Goldberg and Martin, 1964). The availability of the iron in ferrocene to the hemopoietic system varied with the species and physiological state of the animal (Dratz et al., 1964; Goldberg and Martin, 1964). The use of

the iron in ferrocene was high in anemic animals, including man (Goldberg and Martin, 1964), and ferrocene could prevent anemia in dogs following repeated venesections of 100 ml of blood a week for 20 weeks (Yeary, 1969).

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

A study of toxicity and metabolic disposition of ferrocene is in progress in the laboratory of Hanzlik et al at the University of Kansas (SSIE Current Research, June 24, 1981).

16. Exposure Standards

The ACGIH (1981) recommends an 8-hour Time-Weighted Average (TWA) Threshold Limit Value (TLV) of 10 mg/m^3 for occupational exposure to Ferrocene. A Short-Term Exposure Limit (STEL) of 20 mg/m^3 is also recommended.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of ferrocene as an occupational hazard was found in the literature searched.

B. FERROCENE, ACETYL-

1. Chemical Name: Ferrocene, acetyl-

2. Chemical Structure: C_5H_5-Fe-$C_5H_4COCH_3$

3. Synonyms: Acetylferrocene
(Acetylcyclopentadienyl)cyclopentadienyliron
Ferrocenyl methyl ketone

4. Chemical Abstract Service (CAS) Number: 1271-55-2

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not Listed

6. Chemical and Physical Properties:

Description:	orange crystalline solid
Molecular Weight:	228.07
Boiling Point:	---
Melting Point:	85-86°C
Vapor Pressure:	---
Solubility:	---
Specific Gravity:	---
Stability:	air-stable; combustible

7. Production

Data available from the U.S. EPA (1980) regarding producers of acetylferrocene and production volumes are presented below:

Columbia Organic Chemicals (Columbia, SC)
Manufacturer
1977 Production: under 1000 lbs.

Arapahoe Chemicals Inc. (Boulder, CO)
Manufacturer
1977 Production: 1-10 thousand lbs.

8. Use

Acetylferrocene is used as a chemical intermediate (Hawley, 1977). Arapahoe Chemical, the primary commerical producer, manufactures it for

captive use (U.S. EPA, 1980). Arapahoe Chemical Manufactures Grignard Reagents for captive use (SRI International, 1980).

9. Manufacturers and Distributors

Acetylferrocene is manufactured by Arapahoe Chemical and Columbia Organic Chemical (U.S. EPA, 1980).

Distributors include (Chem. Sources - USA, 1980):

Aldrich Chem.	Pfaltz and Bauer
Bodman Chem.	Polysciences
Chem. Procurement Lab.	Pressure Chem.
Eastman Kodak	Parish Chem.
Fairfield Chem.	Reliable Chem.
Fisher Sci.	Sigma Chem.
ICN/K and K	Strem Chem.
Marstan Chem.	Tridom Chem.
PRC Research	TransWorld Chem.

10. Manufacturing Processes

Acetylferrocene can be manufactured as follows (Grahman and Whiteman, 1958): ferrocene and acetic anhydride are heated to 65°C, treated with 85% phosphoric acid, maintained to 90°C for 10 minutes, and poured onto crushed ice to give and aqueous mixture which neutralized with sodium carbonate and filtered to yield crude acetylferrocene. Purification is accomplished by sublimation and recrystallization.

11. Impurities or Additives

No information was found in the literature searched.

12. Occuapational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to acetylferrocene.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent empolyee exposure to acetylferrocene were not found in the literature searched.

14. Biological Effects

a. Animal Studies

(1) Acute Exposures

No information was found in the literature searched.

(2) Subchronic Exposures

Gershbein (1980) undertook an oral and subcutaneous study to discern possible stimulatory activity of acetylferrocene on liver regeneration in partially hepatectomized rats and on liver weight in intact animals. Diets containing 0.10% acetylferrocene were fed to 11 partially hepatectomized Charles River rats and 0.15% acetylferrocene was fed to 9 intact male rats for a period of 10 days. Results showed that there was no enhancement of liver regeneration in the operated animals, although wet and dry liver weight to body weight ratios did increase in the intact rats. Twelve of 14 hepatecomized rats fed a 0.02% diet died. Daily subcutaneous injections of ferrocene in peanut oil for a total overall dosage of 12.7 or 11.0 mg/kg during 7 days had no effect on, respectively, liver regeneration in 14 partially hepatectomized rats or liver to body weight ratios in 11 intact rats sacrificed 10 days after initiation of treatment. It should be noted, however, that injection of acetylferrocene into the hepatectomized rats was quite toxic (5 of 14 rats survived). No effect on body weight gain was elicited by either the oral or subcutaneous treatments.

(3) Chronic Exposures

No information was found in the literature searched.

(4) Carcinogenicity

No information was found in the literature searched.

(5) Mutagenicity

No information was found in the literature searched.

(6) Teratogenicity

No information was found in the literature searched.

(7) Reproductive Effects

No information was found in the literature searched.

(8) Other Relevant Information

No information was found in the literature searched.

b. Human Studies

(1) Pharmacokinetics

No information was found in the literature searched.

(2) Health Effects

No information was found in the literature searched.

(3) Target Organ Toxicity

No information was found in the literature searched.

(4) Epidemiology

No information was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of acetylferrocene were found.

16. Exposure Standards

No recommended or promulgated occupational exposure stnadards for acetylferrocene were found.

17. Sources of Additional Relevant Information

No sources oa additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of acetylferrocene as an occupational hazard was found in the literature searched.

C. FERROCENE, ETHYL-

1. Chemical Name: Ferrocene, ethyl-

2. Chemical Structure: C_5H_5-Fe-C_5H_4-CH_2CH_3

3. Synonyms: Ethylferrocene

4. Chemical Abstract Service (CAS) Number: 1273-89-3

5. Registry of Toxic Effects of Chemical Substances (RTECS) Number:

Not listed

6. Chemical and Physical Properties:

Description:	orange solid
Molecular Weight:	214.09
Boiling Point:	---
Melting Point:	---
Vapor Pressure:	---
Solubility:	---
Specific Gravity	---
Stability:	combustible

7. Production

Data available from the U.S. EPA (1980) regarding producers of ethylferrocene and production volumes are presented below:

Arapahoe Chemicals, Inc. (Boulder, CO)
Manufacturer - Not Distributed
1977 Production: 1-10 thousand lbs.

8. Use

Arapahoe Chemical manufacturers Grignard Reagents for captive use (SRI International, 1980).

9. Manufacturers and Distributors

Ethylferrocene is manufactured by Arapahoe Chemical (U.S. EPA, 1980)

10. Manufacturing Processes

No information was found in the literature searched.

11. Impurities or Additives

No information was found in the literature searched.

12. Occupational Exposure

The National Occupational Hazard Survey does not provide an estimate of the number of workers who are potentially exposed to ethylferrocene.

13. Control Technology and Work Practices

Specific factors that may contribute to or prevent employee exposure to ethylferrocene were not found in the literature searched.

14. Biological Effects

No information regarding the biological effects of ethylferrocene was found in the literature searched.

15. Ongoing Studies

No current toxicological or environmental studies of ethylferrocene were found.

16. Exposure Standards

No recommended or promulgated occupational exposure standards for ethylferrocene were found.

17. Sources of Additional Relevant Information

No sources of additional relevant information were identified.

18. Other Pertinent Data

No other information that would aid in the assessment of ethylferrocene as an occupational hazard was found in the literature searched.

APPENDIX A

The following list includes all of the metallocenes considered for possible individual profiles. The metallocenes in this list were taken from the U.S. EPA TSCA list and the U.S. EPA (1980).

	CAS No.
Chromocene	1271-24-5
Cobaltocene	1277-43-6
Ferrocene	102-54-5
Ferrocene, acetyl-	1271-55-2
Ferrocene, benzoyl-	1272-44-2
Ferrocene, butyl-	31904-29-7
Ferrocene, 1,1'-dibutyl-	1274-08-4
Ferrocene, [(dimethylamino)methyl]-	1271-86-9
Ferrocene, ethyl-	1273-89-8
Ferrocene, formyl-	12093-10-6
Ferrocene, pentyl-	1274-00-6
Hafniumocene dichloride	12116-66-4
Nickelocene	1271-28-9
Titanocene dichloride	1271-19-8
Zirconocene dichloride	1291-32-3

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists) (1981). Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1981. Cincinnati, OH: ACGIH, p. 16.

Dratz, A.F.; Coberly, J.C.; and Goldstein, J.H. (1964). An exploratory study of Fe^{59}-labeled ferrocene as a carrier in tracer techniques. J. Nuclear Med. 5:40-47.

du Pont (1955). Dicyclopentadienyl iron, Publication No. 89. E.I. du Pont, Jackson laboratory, May 2, 1955. (Cited in ACGIH, 1977.)

Gershbein, L.L. (1980). Rat liver regeneration in the presence of nonbenzenoid aromatic agents: Ferrocenes and Cycloheptatrienes. Research communications in Clinical Pathology and Pharmacology 27:139-145.

Goldberg, L., and Martin, L.E. (1964). The absorption, distribution, and utilization of iron in fat-soluble form. In: Life Sciences. Elmsford, NY: Pergamon Press, Inc., Vol. 3, pp. 1465-1474.

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

Hawley, G.G. (1977). The Condensed Chemical Dictionary, 9th ed. New York: Van Nostrand Reinhold Co., pp. 216, 217, 946, 866, 609.

Hawley, G.G. (1977). The Condensed Chemical Dictionary, 9th ed. New York: Van Nostrand Reinhold Co., p. 379.

Institute of Chemical Biology (1965). ProgrEss Report for Contract No. PH-43-64-886. Submitted to the Natural Cancer Institute by the Institute of Chemical Biology, University of San Francisco, January, 1965. Cited in NIOSH, 1981.

Institute of Chemical Biology (1969). Progress Report for Contract No. PH-43-64-886. Submitted to the Natural Cancer Institute by the Institute of Chemical Biology, University of San Francisco, August, 1969. Cited in NIOSH, 1981.

Johnson, J.C. (1973). Metallocene Technology. Park Ridge, NJ: Noyes Development Corp., pp. 1-2.

Johnson, J.C. (1973). Metallocene Technology. Park Ridge, NJ: Noyes Development Corp. pp. 13-19.

Lawler, G.M., editor (1977). Chemical Origins and Markets, 5th ed. Menlo Park, CA: Stanford Research Institute, p. 46.

Madinaveitia, J.L. (1965). Ferrocenes as haematinics. Brit. J. Pharmacol. 24:352-359.

Muller, A. (1974). Classification and properties of iron preparations. Arzneim.-Forsch. 24(6):880-883.

NIOSH (National Institute for Occupational Safety and Health) (1981). Registry of Toxic Effects of Chemical Substances. Lewis, R.J., and Tatken, R.L., editors. Taken from: NLM (National Library of Medicine) MEDLARS RTECS on-line. U.S. Dept. of Health and Human Services, Public Health Service, NIOSH.

Shell Chemical Co. (1961). Unpublished Report. Cited in NIOSH, 1981.

SRI International (1980). 1980 Directory of Chemical Producers: United States of America. Menlo Park, CA: SRI International, p. 541.

SSIE (Smithsonian Science Information Exchange) (1981). SSIE Current Research. The Lockheed Dialog Retrieval Service, File 65.

U.S. Army (no date). U.S. Armament Research and Development Command, Chemical Systems Laboratory. NIOSH Exchange Chemicals, NX No. 02382. Cited in NIOSH, 1981.

U.S. EPA (U.S. Environmental Protection Agency) (1980). Computer print-out of nonconfidential production data from TSCA Inventory. U.S. EPA, Office of Pesticides and Toxic Substances, Chemical Information Division, Washington, DC.

Wiese, H.K. (1965). Cyclopentadiene and dicyclopentadiene. In: Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed. Standen, A., editor. New York: John Wiley and Sons, Inc., Vol. 6, pp. 697-699.

Wiese, H.K. (1965). Cyclopentadiene and dicyclopentadiene. In: Kirk-Othmer Encyclopedia of Chemical Technology, 2nd ed. Standen, A., editor. New York: John Wiley and Sons, Inc., Vol. 6, pp. 696-700.

Yeary, R.A. (1969). Chronic toxicity of dicyclopentadienyliron (ferrocene) in dogs. Toxicol. Appl. Pharmacol. 15:666-676.