
Dicyclopentadienyl iron (ferrocene)

(CAS No: 102-54-5)

Health-based reassessment of Administrative
Occupational Exposure Limit

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 dicyclopentadienyl iron, in this document referred to as ferrocene, 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 MA Maclaine Pont, M.Sc. (Wageningen University, Wageningen, the Netherlands).

Literature was retrieved from the databases Medline, Toxline, and Chemical Abstracts, covering the periods 1966 until May 1999, 1981 until April 1999 and 1937 until April 1999, respectively, and using the following key words: ferrocene, iron dicyclopentadienyl-, and 102-54-5.

In December 1998, the President of the Health Council released a draft of the document for public review. Comments were received by the following individuals and organisations: P Wardenbach, Ph.D. (Bundesanstalt für Arbeitsschutz und Arbeitsmedizin, Dortmund, Germany). These comments were taken into account in deciding on the final version of the document.

An additional literature search in May 2002 did not result in information changing the committee's conclusions.

2 Identity

name	:	dicyclopentadienyl iron
synonyms	:	biscyclopentadienyl iron; di-2,4-cyclopentadien-1-yl iron; iron bis(cyclopentadiene); iron dicyclopentadienyl; ferrocene
molecular formula	:	$C_{10}H_{10}Fe$
structural formula	:	
CAS number	:	102-54-5

Data from How92.

3 Physical and chemical properties

molecular weight	:	186.04
melting point	:	173-174°C
boiling point	:	249°C
flash point	:	-
vapour pressure	:	at 20°C: 0.32 - 1.23 Pa
solubility in water	:	insoluble
log P _{octanol/water}	:	3.28 (estimated)
conversion factors (20°C, 101.3 kPa)	:	1 mg/m ³ = 0.13 ppm 1 ppm = 7.8 mg/m ³

Data from Che98, Lid96, NLM02, Pel81, <http://esc.syrres.com>.

Ferrocene consists of orange-coloured crystals with a camphor-like odour (NLM02). Dust explosion is possible, if the compound is finely dispersed in air. When dry, it can be electrostatically charged. Ferrocene reacts vigorously with oxidants like ammonium chlorate with a chance of fire and explosion (Che98).

4 Uses

Ferrocene is a good combustion catalyst, because of its excellent solubility in hydrocarbons, its high iron content (30%), excellent stability, high vapour pressure, and low toxicity. It is also used as an antiknock additive for gasoline (ACG91).

5 Biotransformation and kinetics

After a single oral dose of ⁵⁹Fe-ferrocene, the compound was well absorbed via the gastrointestinal tract by mice, rats, and guinea pigs. Six hours after the administration, 13% of the label was found in the liver and 6% in the large intestine of rats. Only 40% of the dose was accounted for. One day after the administration, 21% of the label was found in the rat liver, 5 to 9% in the guinea pig liver, and 40% in the mouse liver. For stomach and intestines together, these numbers were 10% (rat), 1.6% (guinea pig), and 5.2% (mouse), respectively. Faecal excretion amounted to 10% (rats), 2.0% (guinea pigs), and 7.7% (mice) after 3 days. Urinary excretion amounted to 11% (rats), 36% (guinea pigs),

1.9% (mice), 0.7% (anaemic pigs), and 30% (man) of the ⁵⁹Fe-label in the first day. The percentage label excreted after 3 days was 17% (rats), 38% (guinea pigs), 5.7% (mice), 10% (anaemic pigs), and 30% (man). When rats, guinea pigs and rabbits were given diets containing ferrocene for up to 24 weeks, the liver iron content rose progressively. The utilisation of ferrocene iron in anaemic rats was 37%, in anaemic pigs 35%, and in man 25% (Gol64).

Groups of male and female Fischer 344 rats were exposed nose-only to ferrocene vapour labelled with ⁵⁹Fe and tritium. The exposure duration was 17 minutes and the average ferrocene concentration was 88 mg/m³. Serial sacrifices were performed up to 117 days following exposure. Internal deposition was 61.4 ± 3.7 µg per rat, corresponding to 36.6 ± 2.2% of the total inhaled vapour. At the earliest sacrifice time, 55% of the internally deposited ferrocene was in the nasopharyngeal region, and 30% was in the bronchopulmonary region. The remaining 15% was associated with the gastrointestinal tract or other organs. Over 75% of the tritium label was excreted within the first day but the ⁵⁹Fe label largely remained in the bronchopulmonary and nasopharyngeal regions over the duration of the experiment. The remaining 10% of the iron was primarily associated with the liver (Dah80).

The olfactory tissue of the rat had 7-fold more ferrocene oxidase activity (this is an isoenzyme of cytochrome P450, which one is not mentioned), than liver on nmol/min per g tissue basis; respiratory tissue had 3-fold more activity (Dah91).

6 Effects and mechanism of action

Human data

The committee did not find data on health effects of exposure of humans to ferrocene.

Animal data

Irritation and sensitisation

The committee did not find data from irritation or sensitisation studies in experimental animals.

Acute toxicity

The following LD₅₀s have been found: rat (oral) 1320 mg/kg bw; mouse (oral) 832 mg/kg bw; mouse (intravenous) 178 mg/kg bw (Lew92).

The main signs of toxicity in rats before they died were: apathy, lachrymation, respiratory dyspnoea, and salivation. Autopsy findings of all animals (mice and rats) were cachexia (a combination of wasting, weakness, and anaemia), wet contents and haemorrhages of the gastrointestinal tract, and yellow subcutaneous and mesenteric fat (Sch92).

Repeated-dose toxicity

Exposure to ferrocene vapour concentrations of 0, 2.5, 5.0, 10, 20, and 40 mg/m³ (i.e., 0, 0.32, 0.65, 1.3, 2.6, and 5.2 ppm), 6 hours/day, 5 days/week, for 2 weeks, did not induce any clinical signs of ferrocene-related toxicity in F344/N rats (n=5/sex/group) and B6C3F₁ mice (n=5/sex/group). The highest exposure level represented the highest concentration of ferrocene vapour that could be generated without producing condensation aerosols. No exposure-related gross lesions were seen in any of the rats or mice at necropsy. Histological examination was done only on the nasal turbinates, lungs, liver, and spleen. The only exposure-related findings were histopathological lesions in the nasal turbinates of both species. These lesions were primarily centered in the olfactory epithelium and were morphologically diagnosed as subacute, necrotising inflammation. Nasal lesions were observed in all ferrocene-exposed animals and differed only in severity, which was dependent on the exposure concentration. The lesions were minimal at the lowest concentration and minimal to mild at 5 and 10 mg ferrocene/m³ (Sun91).

Exposure to vapour concentrations of 0, 3.0, 10, and 30 mg/m³ (i.e., 0, 0.39, 1.3, and 3.9 ppm), 6 hours/day, 5 days/week, for 13 weeks, did not induce any clinical signs of ferrocene-related toxicity in F344/N rats (n=10/sex/group) and B6C3F₁ mice (n=10/sex/group). The mean iron lung burden in rats exposed to 30 mg/m³ for 90 days was 4 times greater than the burden in control rats. The relative liver weight of rats showed a dose-related increase, which was significant (p<0.05) at the highest dose level for the males and at the 2 highest dose levels for the females. The relative liver weight of female mice was decreased at 3.0 mg/m³, but there was no dose-response relationship. On the other hand, the absolute liver weight of female mice showed a dose-related decrease, which was significant at all dose levels (p<0.05). The effects of

ferrocene exposures on organ weights may indicate a secondary response to the loss of appetite from the severe nasal lesions or may indicate that these are target organs for chronic toxicity (particularly the liver), according to the authors. No exposure-related changes in respiratory function, lung biochemistry, bronchoalveolar lavage cytology, total lung collagen clinical chemistry, and haematological parameters were observed. There were neither indications of developing pulmonary fibrosis nor of any haematological toxicity. Exposure-related histological alterations, primarily pigment accumulations, were observed in the nose, larynx, trachea, lung, and liver of both species, and in the kidneys of mice. Lesions were most severe in the nasal olfactory epithelium, where pigment accumulation, necrotising inflammation, metaplasia, and epithelial regeneration occurred. Nasal lesions were observed in all ferrocene-exposed animals and differed only in severity which was dependent on the exposure concentration. The results suggest that the mechanism of ferrocene toxicity may be the intracellular release of ferrous ion through ferrocene metabolism, followed by either iron-catalysed lipid peroxidation of cellular membranes or the iron-catalysed Fenton reaction to form hydroxyl radicals that directly react with other key cellular components, such as protein or DNA (Nik93).

When rats were given oral doses of 50 mg ferrocene daily for 15 days, there was an increase in leukocyte, erythrocyte, and thrombocyte count as well as in haemoglobin content (Pap63). It seems that the effects were reversible within 15 days, but the text is not clear.

Daily oral administration of ferrocene at doses of 30, 100, or 300 mg/kg bw, for 6 months, and 1000 mg/kg bw, for 3 months, produced haemosiderosis with unusually high, dose-related accumulation of iron in the liver of dogs. The doses of 300 and 1000 mg/kg bw resulted in cirrhosis, which was considered by the authors to be an effect of the hydrocarbon moiety (Yea69).

The committee did not find data from carcinogenicity or reproduction toxicity studies.

Mutagenicity and genotoxicity

Ferrocene was negative in:

- a bacterial mutation assay (preincubation), using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537, with and without metabolic activating systems from induced rat and hamster livers (Haw83),

- a bacterial mutation assay (plate incubation), using *S. typhimurium* strains TA97a, TA98, TA100, TA102, TA1535, TA1537, and TA1538, with and without metabolic activating systems from induced rat and hamster livers (Dun99),
- a sex-linked recessive lethal assay in *D. melanogaster* after feeding (Zim85),
- a mouse lymphoma L5178Y TK^{+/−} mutation assay in the presence of a induced rat liver S9 mix (Dun99),
- a chromosome aberration assay in Chinese Hamster ovary (CHO) cells, with and without metabolic activation (Gal85).

Ferrocene was positive in:

- a sex-linked recessive lethal assay in *D. melanogaster* after injection (Zim85),
- a heritable translocation assay in *D. melanogaster* in which reciprocal translocation were induced in the offspring of after injection of the fathers (Zim85),
- a mouse lymphoma L5178Y TK^{+/−} mutation assay in the absence of a induced rat liver S9 mix (Dun99),
- a sister chromatid exchange (SCE) assay in CHO cells, with and without metabolic activation (Gal85).

The committee did not find data from genotoxicity studies in intact mammals.

7 Existing guidelines

The current administrative occupational exposure limit (MAC) in the Netherlands is 10 mg/m³, 8-hour TWA.

Existing occupational exposure limits for ferrocene in some European countries and in the USA are summarised in the annex.

8 Assessment of health hazard

The committee did not find data from studies on the effects of ferrocene in humans or from experimental animal irritation and sensitisation, carcinogenicity, reproduction toxicity, or *in vivo* genotoxicity studies.

In a 13-week inhalation study in which rats and mice were exposed to ferrocene vapour concentrations of 3, 10, and 30 mg/m³ (0.39, 1.3, and 3.9

ppm) (Nik93), the most prominent findings were olfactory epithelial lesions which were seen in all animals and which showed a dose-dependent severity.

Ferrocene did not induce mutations in *S. typhimurium*, *D. melanogaster* after feeding (sex-linked recessive lethal assay), and mouse lymphoma cells (with metabolic activation) or chromosome aberrations in CHO cells, but was positive in a mutation assay in mouse lymphoma cells in the absence of a metabolic activating system, in an SCE assay in CHO cells and, after injection, in a sex-linked recessive lethal assay and a heritable translocation assay in *D. melanogaster*.

The committee considers the lesions in the nasal olfactory epithelium as the critical effect, and takes the LOAEL of 3.0 mg/m³ from the 13-week inhalation study as a starting point in deriving a health-based occupational exposure limit (HBROEL). For the extrapolation to a HBROEL, an overall assessment factor of 24 is established. This factor covers the following aspects: the absence of a no-adverse-effect level (NOAEL), inter- and intraspecies variation, and differences between experimental conditions and the exposure pattern of the worker. Thus, applying this factor of 24 and the preferred value approach, a health-based occupational exposure limit of 0.1 mg/m³ is recommended.

The committee recommends a health-based occupational exposure limit for dicyclopentadienyl iron (ferrocene) of 0.1 mg/m³, as an 8-hour time-weighted average.

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Annex

Occupational exposure limits for ferrocene in various countries.

country -organisation	occupational exposure limit		time-weighted average	type of exposure limit	note ^a	reference ^b
	ppm	mg/m ³				
the Netherlands -Ministry of Social Affairs and Employment	-	10	8 h	administrative		SZW02
Germany -AGS	-	5 ^c	8 h	administrative		TRG00
-DFG MAK-Kommission	-	-				DFG02
Great-Britain -HSE	-	10	8 h	OES		HSE02
	-	20	15 min	STEL		
Sweden	-	-				Arb00b
Denmark	-	-				Arb00a
USA -ACGIH	-	10	8 h	TLV		ACG02b
-OSHA	-	15 ^d , 5 ^e	8 h	PEL		ACG02a
-NIOSH	-	10 ^d , 5 ^e	10 h	REL		ACG02a
European Union -SCOEL	-	-				CEC00

^a S = skin notation; which mean that skin absorption may contribute considerably to body burden; sens = substance can cause sensitisation.

^b Reference to the most recent official publication of occupational exposure limits.

^c As inhalable fraction of the aerosol.

^d As total dust.

^e As respirable fraction.