GreenScreen™ Assessment for Diiron Trioxide (CAS# 1309-37-1)

GreenScreen™ Version 1.2 Criteria, Information Sources and Specified Lists - Draft Assessment
Note: Validation Has Not Been Performed on this Green Screen Assessment

Chemical Name: **Diiron Trioxide (Fe2O3)**

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Date: August 8, 2012
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Organization: SciVera LLC
Date: August 8, 2012

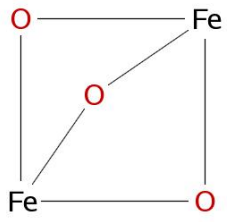
Confirm application of the *de minimus* rule[1]: (if no, what *de minimus* did you use?) Yes

Chemical Name (CAS #): Diiron Trioxide (CAS# 1309-37-1)

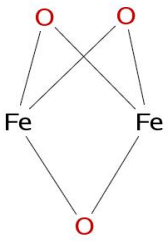
Also Called: Ferric Oxide, Hematite, C. I. Pigment 101, Red Iron Oxide, Iron(III)oxide, C.I. 77491, Red Iron Oxide 190, Iron Oxide (Fe2O3), Bayferrox 130, Blood stone

Chemical Surrogates, analogs or moieties used in this assessment (CASs #): Triiron tetraoxide (Fe3O4, CAS# 1317-61-9)

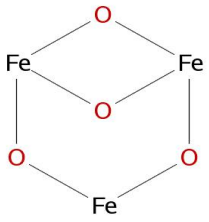
Chemical Structure(s):
*Note: Include chemical structure(s) of all surrogates, analogs (and /or moieties) used in the assessment.



Fe2O3



Fe2O3



Fe3O4

Notes related to production specific attributes[2]: Diiron Trioxide is either mined or produced synthetically through the oxidation of iron or thermal decomposition of iron salts. (7

[1] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm.

[2] Note any composition or hazard attributes of the chemical product relevant to how it is manufactured. For example, certain synthetic pathways or processes result in typical contaminants, by-products or transformation products. Explain any differences between the manufactured chemical product and the GreenScreen assessment of the generic chemical by CAS #.

For Inorganic Chemicals and relevant particulate organics (*if not relevant, list NA*)
Define Properties:

1. Particle size (e.g. silica of respirable size): Red-brown, odorless, inorganic solid/powder. Typical particle size ranges from 0.3-0.9 microns. (1) Pigment shades will vary depending on particle size, shape and whether the diiron trioxide is naturally or synthetically derived. (2)
2. Structure (e.g. amorphous vs. crystalline): The most common and naturally occurring form of diiron trioxide (alpha- Fe2O3) has a rhombohedral crystalline structure. Mol wt – 159.69g/mol. (6)
3. Mobility (e.g. Water solubility, volatility): Diiron trioxide has very low water solubility, determined according to OECD Guideline 105. With a loading of 10 g/l Fe2O3 to water at pH8 the dissolved iron was determined to be < 1µg/l. (3a). Diiron trioxide is non-volatile with a melting point of 1569^{o} C. (4)
4. Bioavailability: Diiron trioxide is a stable, insoluble metal oxide. On ingestion, Fe2O3 would likely ionize to Fe^{+3}/Fe^{+2} due to the acidic environment in the stomach. This would then result in circulating plasma iron being readily bound to transferrin and incorporated into the reticuloendothelial system, involved with recycling iron from dead red cells and reused for new hemoglobin production. (5) Inhaled particles of diiron trioxide would most likely be phagocytized with eventual excretion. Dermal absorption of Fe2O3 is unlikely through intact skin.

Identify Applications/Functional Uses:
(e.g. Cleaning product, TV casing)

1. Diiron trixode is as a colorant/ pigment in the following applications:
   - Adhesives and sealants
   - Coatings and paint
   - Inks and toners
   - Leather tanning, dyeing
   - Lubricants, greases
   - Paper and board dyeing
   - Plastics
   - Textile dyes
2. Feedstock for the production of steel, iron and other alloys

Green Screen Rating[3]: Diiron Trioxide is assigned a Benchmark Score of 2. This substance is classified as having Moderate potential for Carcinogenicity, Moderate potential for Systemic Toxicity and Moderate Skin and Eye Irritation potential. Data gaps exist for Endocrine Disruption and Neurotoxicity. Data gaps also existed for Reproductive and Developmental Toxicity, Respiratory Sensitization, and Bioaccumulation, however, expert judgment could be used to assess these endpoints. If the data gaps were filled with High scores (Endocrine Disruption and Neurotoxicity), diiron trioxide would be classified as a Benchmark 1 chemical.

Green Screen Hazard Ratings: Diiron Trioxide																			
Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeated*	single	repeated*										
M	L	*L*	*L*	DG	L	M	M	DG	DG	L	*L*	M	M	L	L	H*	*M*	L	L

[3] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.
* - denotes that this is an inorganic chemical

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL) in *italics* reflect estimated values and lower confidence. Hazard levels in **BOLD** font reflect values based on test data (See Guidance).

Transformation Products and Ratings:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[4]

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	On CPA Red List[5]?	Green Screen Rating[6]
Pigment/Colorant	Manufacture, Use, End of life	Biotransformation	Fe^{+3}/ Fe^{+2}	7439-89-6	No	

Introduction

Diiron Trioxide (Fe2O3) is a naturally occurring metal oxide also known as hematite. Iron is an essential element, and diiron trioxide is widespread in nature. It can be obtained in various polymorphs, the most common being alpha and gamma. It is stable and insoluble in water.

It is commonly used as a pigment or colorant in paints, coatings, inks and plastics and is a feedstock for the steel and iron industries. It can be mined and produced naturally or manufactured by synthetic means through oxidation of iron or thermal decomposition of iron salts (7). Natural iron oxides may contain contaminants, reducing their tinting strength compared to the synthetic materials. Non-coloring contaminants are commonly natural extenders used in industry as industrial fillers, including clays, talc and calcium carbonate (2). Therefore, it is important to understand the supplier and source (natural or synthetic) of the specific diiron trioxide being used to determine the potential relevance of any contaminants or additives in the material.

Fe2O3 has been relatively well characterized through testing in standard toxicology test methods. Additionally, data on iron(II,III)oxide (Fe3O4), which also occurs naturally as magnetite, was used as a surrogate substance.

The primary hazards associated with Fe2O3 occur through inhalation exposure to dusts or fumes and irritation from eye or skin contact. Reports of metal fume fever in workers, resulting in reversible flu-like symptoms from exposure to iron oxide fumes, have been reported (8a). Intratracheal instillation in hamsters of 5 mg iron oxide, once/week for 15 weeks resulted in ambiguous results for carcinogenicity, including hyperplastic lesions in the respiratory tract (3b). Another study in hamsters following intratracheal instillation of 3 mgFe2O3 once weekly for 18 weeks, resulted in slight alveolar/bronchial hyperplasia and pigment deposition in the lungs (3c). These effects in experimental animals are most likely due to particulate loading and the subsequent biological irritation/inflammation response and not specific to the toxicity of Fe2O3. Skin and eye irritation has been reported in humans (8b,c), however results in animal studies have indicated that iron oxide is non-irritating (3y, z, aa). It is unlikely that Fe2O3 would be absorbed through intact skin.

Epidemiology studies of potential carcinogenicity of workers exposed to iron oxide have resulted in mixed results – some reporting an increase in lung cancers (9), while others have been negative (10). The current recommended

[4] A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.
[5] The CPA "Red List" refers to chemicals 1. flagged as Benchmark 1 using the GreenScreen™ List Translator or 2. flagged as Benchmark 1 or 2 using the GreenScreen™ List Translator and further assessed and assigned as Benchmark 1. The most recent version of the GreenScreen™ List Translator should be used.
[6] The way you conduct assessments for transformation products depends on the Benchmark Score of the parent chemical (See Guidance).

Time-Weighted Average for occupational exposures to diiron trioxide is 5mg/m3 due to concern for pneumoconiosis (9).

Fe2O3 has been reviewed by the US FDA and is listed as "Generally Regarded as Safe" (GRAS) (11).

Fe2O3 has low aquatic toxicity. It is, however, persistent in the environment since it is an inorganic, stable metal oxide.

Hazard Classification Summary Section:
Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M or L): M
Diiron Trioxide was assigned a score of **Moderate** due to some observance of tumors following long-term exposure in experimental animals as well as mixed results in epidemiology studies of workers exposed to iron oxide.

Authoritative and Screening Lists:

- Diiron trioxide was not listed on relevant authoritative or screening lists.

Results:

- 2-yr intratracheal application; rats were dosed every other week at 10 mg/kg for 13 appl., then 20 mg/kg for 6 appl., then 40 mg/kg|total dose 1530 mg/kg bw, doses of 10 to 40 mg/kg bw. - substance-related effects in lungs (foreign body deposit, metaplasia); no significant increase in carcinogenicity. Not co-carcinogenic. (3d)
- Application of ferric oxide intratracheally or by inhalation, in mice, hamsters or guinea-pigs resulted in no conclusive carcinogenic effect. (12)
- Intraperitoneal administration, at doses of 200 mg/kg/dose (total dose 600 mg/kg), 3 injections; every 8 weeks, for 790-914 days, in Sprague-Dawley rats was negative for carcinogenicity. (3e)
- Hamsters (35 f + 35 m) received a course of 15 weekly intratracheal instillations of 3mg/kg Fe2O3/week. At the end of the treatment period (week 15) 3 males and 3 females were sacrificed for pathological examination. The experiment was terminated after 78 weeks. No effect on survival or body weights, no tumors of the respiratory tract, no other tumors after instillation of ferric oxide alone. (3f)
- Four groups of 33 to 36 female Wistar rats were treated 1x or 4x by intraperitoneal injection. Three groups of controls were treated with saline (3x or 50x 1 ml; 4x 2ml). Animals were observed for their lifetime. Gross necropsy of the abdominal cavity and histopathology of tumors and gross lesions were negative for carcinogenicity. (3g)
- Male Syrian Hamsters (50) were treated by intratrachea instillation for 15 weeks with 5mg/animal/week and killed 5 weeks later and evaluated for histopathologic effects. Survival rate was unchanged, however ambiguous results for carcinogenicity were reported, including hyperplastic lesions in the respiratory tract. (3b)
- Syrian hamsters (50 f + 50 m) received intratracheally once weekly 3 mg Fe2O3 in 0.2 ml for 18 weeks - slight alveolar/ bronchial hyperplasia was present in all groups to some degree, lungs showed pigment deposition, 2 male animals showed adenomas and 1 female a plasmacytoma of the lung, 1 male had a carcinoma of the main bronchi. (3c)
- Exposure to ferric oxide dust (40 mg/m³), inhalation was continued for life in male Syrian hamsters. No effect on mortality or growth, no tumors in lungs, tracheas and nasal cavities of 132 evaluated animals. Ferric oxide enhanced diethylnitrosamine tumorigenicity in the lung slightly. With the combination of ferric oxide and synthetic smog no tumors were induced. (3h)
- Female Wistar rats were treated intratracheally 15 times with 10 mg haematite - 34 rats examined (only lungs were examined), 18 rats showed tumors (1 adenoma, 4 adenocacinomas, 7 benign cystic keratinizing squamous cell tumors, 6 squamous cell carcinomas). (3i)

- In a human exposure study, an increase in lung cancer incidence among foundry workers exposed to iron oxide was reported. (9)
- Epidemiology study of a cohort comprised of 16,742 males and 959 females. Among males, the observed mortality was lower than expected for lung cancer when compared to the local population (233 deaths, SMR 0.89, 95%CI 0.78-1.01) and higher than expected when compared to the French population (SMR 1.30, 95%CI 1.15-1.48). No lung cancer excess was observed for exposure to iron oxides (RR 0.80, 95%CI 0.55-1.17) and there was no dose-response relationship with intensity, duration of exposure, and cumulative index. (10)

Mutagenicity/Genotoxicity (M) Score (H, M or L): L
Diiron Trioxide was assigned a score of **Low** for mutagenicity based on the weight of negative evidence in experimental studies, both on diiron oxide (Fe2O3) itself and triiron tetraoxide (Fe3O4).

Authoritative and Screening Lists:

- Diiron trioxide was listed on relevant authoritative or screening lists.

Results:

- Bacterial reverse mutation assay (e.g. Ames test) with S. typhimurium TA 97 and TA 102 – with and without metabolic activation. Test concentrations - 0-0.01-0.05-0.1-0.5-1 mg/plate. Negative. (3j)
- Cytotoxicity and neoplastic transformation - BALB/3T3/A31-1-1 mammalian cell line. Hematite was neither cytotoxic nor did it induce neoplastic transformation. (3k)
- 12 Male OFA Sprague-Dawley rats in 4 groups of 3. Animals were anesthesized by i.p, injection and treatment was performed by intratracheal instillation of a suspension of iron oxide, benzopyrene or a mixture of both. The control group was treated with the vehicle (saline) only. Iron oxide and BaP : 3.75 mg/kg or the sum of these. 24 hours after treatment animals were killed, cells isolated (alveolar macrophages, lung cells, peripheral lymphocytes, hepatocytes) and assessed by alkaline single cell electrophoresis (Comet Assay; 100 cells per slide). No increase in DNA damage in Fe2O3 treated cells. (3l)
- in vitro mammalian chromosome aberration test following OECD Guideline 473 (In vitro Mammalian Chromosome Aberration Test) using Chinese hamster lung fibroblasts (V79) with and without metabolic activation (S9 mix). Test concentrations of 0, 6.25, 12.5 and 25 µg/ml. None of the cultures treated with Bayferrox 306 (Fe3O4) in the absence and in the presence of S9 mix showed biologically relevant or statistically significant increased numbers of aberrant metaphases. (3m)
- Bacterial reverse mutation assay (e.g. Ames test), S. typhimurium TA 1535, TA 1537, TA 98 and TA 100, with and without metabolic activation (S9). Test concentrations of 8 - 40 - 200 - 1000 - 5000 µg/plate. Negative results. (3n)
- Gene mutation in mammalian cells (HPRT test), using OECD Guideline 476 (In vitro Mammalian Cell Gene Mutation Test). Test concentrations of 6. 9. 12, 18, 24, 36 µg/ml in DMSO, using Chinese hamster lung fibroblasts (V79) with and without metabolic activation. Without and with S9 mix there was no biologically relevant increase in mutant frequency above that of the negative controls. (3o)

Reproductive Toxicity (R) Score (H, M, or L): *L*
Diiron Trioxide was assigned a score of *Low* for Reproductive Toxicity based on expert judgment due to a lack of experimental studies. Expert judgment used to assess this chemical classifies it as having *Low* potential for Reproductive toxicity based on the chemical's physical state/properties and general evidence, including poor absorption through dermal or inhalation exposures. Additionally, on ingestion, diiron trioxide would likely ionize to Fe+3/Fe+2 and be incorporated into the reticuloendothelial system, with incorporation into hemoglobin with binding and storage by ferritin and hemosiderin. This chemical has been reviewed by the US FDA and is listed as GRAS (11), and although many substances on this list have not been thoroughly tested, diiron trioxide has historically been widely used with no reported adverse effects on reproduction.

Authoritative and Screening Lists:

- Diiron trioxide is listed on the US FDA Generally Regarded as Safe (GRAS) list. (11)
- Diiron trioxide was not listed on other relevant authoritative or screening lists.

Results:

- No experimental data was available for this endpoint, however, other repeat-dose studies both via oral or inhalation exposures, indicated that Fe2O3 is poorly absorbed. (3u, 8a)
- On ingestion, Fe2O3 would likely ionize to Fe^{+3}/Fe^{+2} due to the acidic environment in the stomach. This would then result in circulating plasma iron being readily bound to transferrin and incorporated into the reticuloendothelial system, involved with recycling iron from dead red cells and reused for new hemoglobin production. (5) Inhaled particles of diiron trioxide would most likely be phagocytized with eventual excretion. Dermal absorption of Fe2O3 is unlikely through intact skin.
- Both ferritin and hemosiderin act as storage sites for excess intracellular iron and are protective in that they maintain the intracellular iron in bound form. (14)

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M or L): *L*

Diiron Trioxide was assigned a score of *Low* for Developmental Toxicity including Developmental Neurotoxicity based on expert judgment due to a lack of experimental studies. Expert judgment used to assess this chemical classifies this substance as having *Low* potential for Developmental Toxicity including Developmental Neurotoxicity based on the chemical's physical state/properties and general evidence, including poor absorption through dermal or inhalation exposures. Additionally, on ingestion, diiron trioxide would likely ionize to Fe+3/Fe+2 and be incorporated into the reticuloendothelial system, with incorporation into hemoglobin, with binding and storage by ferritin and hemosiderin. This chemical has been reviewed by the US FDA and is listed as GRAS (11), and although many substances on this list have not been thoroughly tested, diiron trioxide has historically been widely used with no reported adverse effects on development.

Authoritative and Screening Lists:

- Diiron trioxide is listed on the US FDA Generally Regarded as Safe (GRAS) list. (11)
- Diiron trioxide was not listed on other relevant authoritative or screening lists.

Results:

- No experimental data was available for this endpoint, however, other repeat-dose studies both via oral or inhalation exposures, indicated that Fe2O3 is poorly absorbed. (3u, 8a)
- On ingestion, Fe2O3 would likely ionize to Fe^{+3}/Fe^{+2} due to the acidic environment in the stomach. This would then result in circulating plasma iron being readily bound to transferrin and incorporated into the reticuloendothelial system, involved with recycling iron from dead red cells and reused for new hemoglobin production. (5) Inhaled particles of diiron trioxide would most likely be phagocytized with eventual excretion. Dermal absorption of Fe2O3 is unlikely through intact skin.
- Both ferritin and hemosiderin act as storage sites for excess intracellular iron and are protective in that they maintain the intracellular iron in bound form. (14)

Endocrine Activity (E) Score (H, M or L): DG

Diiron trioxide was assigned a score of **DG** for endocrine activity based on a lack of experimental data for this endpoint.

Authoritative and Screening Lists:

- Diiron trioxide was not listed on relevant authoritative or screening lists.

Group II and II* Human Health Effects (Group II and II* Human)

Note: Group II and Group II* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.

Acute Mammalian Toxicity (AT) Group II Score (vH, H, M or L): L

Diiron Trioxide was assigned a score of **Low** for acute mammalian toxicity based on oral LD50 studies. Acute inhalation and dermal toxicity data were lacking, however, based on diiron trioxide's insolubility and poor absorption, it is estimated that there would be a low potential for acute toxicity via these routes as well.

Authoritative and Screening Lists:

- Diiron trioxide was not listed on relevant authoritative or screening lists.

Results:

- Oral LD50 study in male and female Wistar rats (EU Method B.1 (Acute Toxicity (Oral) Cited as Directive 84/449/EEC, B.1); a single dose of 5000mg/kg body weight of a mixture of Fe2O3 (73.2%), Al2O3 (19.5%)and Mn2O3 (3.0%) administered by oral gavage in water resulted in no mortality or signs of toxicity after observation for 14 days. LD50>5000 mg/kg for mixture, equivalent to >3660 mg/kg Fe2O3. (3p)
- Single oral dose by gavage of Fe3O2 in water at 10,000 mg/kg body weight to male Wistar rats resulted in no signs of toxicity or increased mortality. LD50>10,000 mg/kg. (3q)

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST) Group II Score (single dose: vH, H, M or L); M

Diiron Trioxide as assigned a score of **Moderate** for systemic toxicity/ organ effects including immunotoxicity based on experimental data and reports in workers.

Authoritative and Screening Lists:

- Japan GHS – Category 3 (respiratory tract irritation) – May cause respiratory irritation or cause drowsiness and dizziness (respiratory tract irritation) (17)

Results:

- Saline suspensions of Fe2O3 were intratracheally injected at the 3 dose levels of 10, 33 and 100 µg per mouse. Control mice received saline. There were 24 mice in each dose group (including controls), and each study was replicated 3 times. Exposed and control mice were simultaneously challenged with aerosols of viable Group C Streptococcus sp. After the challenge, deaths were recorded daily over a 14 day observation period. Mortality was significantly increased in exposed animals however no dose/effect relationship was reported. (3r)
- Mice were exposed for 3 hours to a Fe2O3 aerosol. Exposures ranged from 50-400 mg/m³. To evaluate PAM (pulmonar aveolar macrophage) function, Fe2O3 exposed, sham-exposed and control animals received an aerosolized challenge of radiolabelled S.aereus one hour following Fe2O3 exposure. Intrapulmonary bacterial inactivation values 4 hours following the bacterial challenge revealed a dose-dependent depression in bactericidal activity of Fe2O3, however this impairment was partially reversible. (3s)
- Metal fume fever has been reported in workers exposed to iron oxide fumes. This is a flu-like illness with reversible symptoms of metallic taste, aches, chills and fever, chest tightness and cough. (8a)

Group II* Score (repeated dose: H, M, L): M

Diiron Trioxide was assigned a score of **Moderate** for systemic toxicity/organ effects based on repeated exposure based on results in experimental animals. This score is based primarily on the pneumonia and ademtous hyperplasia reported in hamsters, in that the other studies using Fe2O3 were negative. The 90-day study with a

structurally similar compound, Fe3O4, reported increased lung and LALN weights at 0.166mg/l for female rats (a High score) and 0.052 mg/l in male rats (a Moderate score). Since the most severe effect occurred in only one sex/species, the overall weight of evidence justifies the Moderate score. Although Japan GHS classification results in a High score, this is not supported by other country-specific GHS classifications/scores.

Authoritative and Screening Lists:

- Japan GHS – Category 1 (respiratory organs) – Causes damage to organs (respiratory organs) through prolonged or repeated exposure (17)

Results:

- OECD Guideline 412 (Repeated Dose Inhalation Toxicity: 28/14-Day), via inhalation with exposure at mean actual concentrations of 0, 185.2, 195.7 and 210.2 mg/m3 Fe2O3 in air for 6 hours per day, 5 days/week for a total of 2 weeks in male Wistrar rats. The exposure was not associated with any specific clinical signs and no consistent changes in body weights were observed; no NOAEC was defined. Iron oxide related findings could not be detected in the extrapulmonary organs (kidneys, testes, liver) both at the end of exposure and after 2 weeks of recovery. Solubilized Fe was detected within/around the alveolar macrophages, but not in the interstitium and hepatic tissue. Histopathological evaluations of the lungs demonstrated an effect-pattern consistent with that of poorly soluble particles. (3t)
- Daily dietary exposure of 700, 1100, 1610 and 2060 mg/kg Fe2O3 for 21 days in male rats. No increase of liver non-hemoglobin iron content. (8d)
- Hamsters were dosed via intratracheal instillation once per week to 5mg iron oxide for 15 weeks and observed for 5 weeks post exposure. No effect on survival or weight gain but pneumonia and adenomatous hyperplasia were observed. (8e)
- Male and female Wistar rats exposed subchronically (OECD Guideline 413 (Subchronic Inhalation Toxicity: 90-Day) to three different concentrations of Fe3O4 (4.7, 16.6, 52.1 mg/m³) revealed findings clearly consistent with and typical for a poorly soluble particle. The retention kinetics of inhaled Fe3O4 particles revealed neither analytical nor toxicological evidence that free, biosoluble iron was liberated from the inhaled dust to any appreciable extend. Also in this study no evidence of extrapulmonary toxicity existed. The results of this study support the view, that the NOAEL of Fe3O4 is 4.7 mg/m³ (0.0047mg/L). The lung and LALN (lung associated lymph nodes) weights were increased at 52.1 mg/m³ in males and at 16.6 mg/m³ in females. (3u)

Neurotoxicity (N)
Group II Score (single dose: vH, H, M or L): DG
Diiron Trioxide was assigned a score of **DG** for neurotoxicity based on single exposure due to a lack of experimental data for this endpoint.

Authoritative and Screening Lists:

- Diiron trioxide was not listed on relevant authoritative or screening lists.

Group II* Score (repeated dose: H, M, L): DG
Diiron Trioxide was assigned a score of **DG** for neurotoxicity based on repeated exposure due to a lack of experimental data for this endpoint.

Authoritative and Screening Lists:

- Diiron trioxide was not listed on relevant authoritative or screening lists.

Skin Sensitization (SnS) Group II* Score (H, M or L): L
Diiron Trioxide was assigned a score of **Low** for skin sensitization based on experimental data and human studies.

Authoritative and Screening Lists:

- Diiron trioxide was not listed on relevant authoritative or screening lists

Results:

- Maurer Optimization test in guinea pigs - 10 intradermal injections of a 0.1 % Fe2O3 and Fe2O2.H2O in 3 weeks. In the second and third week Freund's adjuvant was used as vehicle. Thereafter a 2-week rest period was followed by intradermal challenge, which was followed again by epidermal challenge 10 days later. Evaluation parameters were skin fold thickness, erythema. The results were reported as ambiguous. (3v)
- 623 patients were patch tested with a series of metal compounds. Positives were retested with several soluble iron salts and iron oxide (Fe2O3). Exposure was performed using Finn chambers. Readings were taken after 2 and 3-4 days and scored according to recommendations of ICDRG. Iron oxide was not sensitizing. (3w)
- 190 subjects (126 enameller and 64 decorators) from 5 factories were examined for dermatitis and skin sensitization. Patch tests with 2% Fe2O3 in petrolatum (occlusive; 48 h) were conducted. 7/190 workers reacted positive to red iron oxide. No additional test information was provided. (3x)

Respiratory Sensitization (SnR) Group II* Score (H, M or L): *L*
Diiron Trioxide was assigned a score of *Low* for respiratory sensitization based on expert judgment. This was due to diiron trioxide having *Low* hazard potential for respiratory sensitization based on its inorganic, insoluble solid physical state, negative dermal sensitization potential, and other general evidence including no indication of respiratory sensitization from its history of use.

Authoritative and Screening Lists:

- Diiron trioxide was not listed on relevant authoritative or screening lists.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M or L): M
Diiron Trioxide was assigned a score of **Moderate** for skin irritation/corrosivity based on limited data in experimental animals and on results reported in humans. The Japan GHS classification would score as High, however, since no other country-specific GHS classifications support this, the Moderate overall score is appropriate.

Authoritative and Screening Lists:

- Japan GHS - Category 2 – Causes skin irritation (17)

Results:

- In vivo OECD Guideline 404 (Acute Dermal Irritation / Corrosion) study in New Zealand white rabbits using 500 mg of Bayferrox VP AC 5046 (73.2% Fe2O3, 19.5% Al2O3, 3% Mn2O3), semiocculuded for 4 hr and observed for 24, 48 and 72 hrs resulted in no erythema, edema or irritation. (3y)
- Reported as moderately irritating in humans, may cause burns to skin and eyes. (8b)

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M or L): M
Diiron Trioxide was assigned a score of **Moderate** for eye irritation/corrosivity. This was based on a report in humans, although reports in experimental animals reported the substance to be non-irritating.

Authoritative and Screening Lists:

- Japan GHS – Category 1 – Causes serious eye damage (based on human report listed below) (17)

Results:

- New Jersey Dept of Health reported risk of serious damage/ corrosivity to eyes, along with prolonged or repeated contact resulting in permanent iron staining of eyes. (8c)
- OECD Guideline 405 (Acute Eye Irritation / Corrosion) study in rabbits exposed to 100 mg Bayeferrox VP AC 5122 M (Fe2O3 83.5 %, FeO 12%, Co 4.5%). Observations made at 1, 24, 48, 72 hrs and at the end of the observation period (168 hr). Non-irritating. (3z)

- OECD Guideline 405 (Acute Eye Irritation / Corrosion) study in New Zealand White rabbits exposed to 30 mg Bayferrox VP AC 5046 (73.2% Fe2O3, 19.5% Al2O3, 3% Mn2O3). Observations made at 1, 24, 48, 72 hrs, 7 and 14 days. Non-irritating. (3aa)

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M or L): L
Diiron Trioxide was assigned a score of **Low** for acute aquatic toxicity based on relevant experimental data and Canadian DSL classification of "not inherently toxic to aquatic organisms". Although the mayfly study reported the LC50 to be >40mg/l (Moderate score), this was the highest dose tested with no additional data on mortality or effects reported. The other studies used very high doses with clearly documented negative results, which therefore resulted in the overall Low score for acute aquatic toxicity.

Authoritative and Screening Lists:

- Diiron trioxide is classified as "not inherently toxic to aquatic organisms" by the Canadian Domestic Substances List (CEPA 1999) (15)

Results:

- A static, 96 hr LC50 test was conducted using 1 kg of Bayferrox 130 red mixed with 10 l of water, shaken for 24 h and filtered through a paper filter. The eluate was used in dilutions 1:10 (10 g/L), 1:5 (20 g/L), 1:2 (50 g/L) and undiluted (100 g/L). 4 concentrations of Fe2O3 were tested: 100000, 50000, 20000, and 10000 mg/l. The test concentrations were achieved by dilution. Within 96 hours no effect (LC0) on Brachydanio rerio was observed up to a concentration of >= 50000 mg/l, and a 96-hour LC90 of approximately 100000 mg/l was obtained. (3bb)
- OECD Guideline 202 (Daphnia sp. Acute Immobilization Test) was conducted using a suspension of Fe2O3 in water. The observed 48-hour EC50 on Daphnia magna was >100 mg/l. (3cc)
- ISO 8192 (Test for Inhibition of Oxygen Consumption by Activated Sludge) - a 3-hour EC50 of > 10000 mg/l for Iron(III)oxide was obtained on activated sludge of a predominantly domestic sewage. (3ee)
- Larvae of the mayfly were exposed to up to 40mg/l diiron trioxide for 3, 6, 24 or 48 hrs in static freshwater. The LC50 was reported to be >40 mg/l. (3dd)

Chronic Aquatic Toxicity (CA) Score (vH, H, M or L): L
Diiron Trioxide was assigned a score of **Low** for chronic aquatic toxicity based on relevant experimental data, acute aquatic toxicity information and Canadian DSL classification of "not inherently toxic to aquatic organisms".

Authoritative and Screening Lists:

- Diiron trioxide is classified as "not inherently toxic to aquatic organisms" by the Canadian Domestic Substances List (CEPA 1999) (15)

Results:

- The 48 hr LC0 in fresh water fish was reported to be >1000mg/L (8f)
- This substance has not been classified under CLP, however the ECHA Dossier references EU – H 411, "Toxic to aquatic life with long-lasting effects" if zinc oxide is present at 0.2% or greater. (3ff)

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): H
Diiron Trioxide was assigned a score of **High** for persistence in the environment based on the fact that it is a naturally occurring metal oxide that is insoluble in water.

Authoritative and Screening Lists:

- Diiron trioxide is classified as Persistent by the Canadian Environmental Protection Act, 1999 (CEPA 1999) (15)

Results:

- Diiron trioxide is a naturally occurring metal compound that is persistent in the environment.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *M*
Diiron Trioxide was assigned a score of *Moderate* for bioaccumulation based on extrapolation from mammalian data listed below and expert judgment. Bioaccumulation hazard potential for this substance cannot be derived or assessed with any certainty for the aquatic environment as no experimental data exist of its chemical properties and organism attributes (Kow, lipid content) that could serve as first-order approximations of Bioaccumulation potential and their use as inputs to simplified, fugacity-based models, and no direct measurement of metal concentrations in the organism or experimentally-determined parameters for use as input to bioaccumulation models. Inorganic compounds are not suitable for data modeling.

Authoritative and Screening Lists:

- Diiron trioxide was not listed on relevant authoritative or screening lists.

Results:

- No data on environmental bioaccumulation or diiron trioxide are available.
- Biological half-life was 33 days in rat lung after iron particles are inhaled and deposited in lung. (16)
- In humans, the yearly lung clearance of deposited iron dust was estimated to be in the order of 20-40% of the deposited amount. (16)

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M or L): L
Diiron Trioxide was assigned a score of **Low** for reactivity based on its physical properties.

Authoritative and Screening Lists:

- Diiron trioxide was not listed on relevant authoritative or screening lists.

Results:

- Diiron trioxide is a stable metal complex.
- An HMIS rating for Fe2O3 is "1" for Reactivity (materials that are normally stable but can become unstable (self-react) at high temperatures and pressures). (13)

Flammability (F) Score (vH, H, M or L): L
Diiron Trioxide was assigned a score of **Low** for flammability based on its physical properties.

Authoritative and Screening Lists:

- Diiron trioxide was not listed on relevant authoritative or screening lists.

Results:

- Diiron trioxide is non-flammable.
- An HMIS rating for Fe2O3 is "1" for flammability (materials that must be preheated before ignition will occur). (13)

References

1) Cathay Pigments, Technical Data, Synthetic Red Iron Oxides, 2003. Available at http://www.cathaypigments.cn/english/images/technical/coating_grade_pdf/TDS-RED-Micronized.pdf (accessed April 2012)

2) Hoover Color Corporation – FAQ. Available at www.hoovercolor.com/about/faq/ (accessed April 2012)

3) ECHA, 2011. European Chemicals Agency (ECHA) Information on Registered Substances. Available at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances#search (accessed April 2012). The following citations are specifically referenced for diiron trioxide (CAS# 1309-37-1):
   a. Exp Key Water Solubility.001
   b. Exp Supporting Carcinogenicity.015
   c. Exp Supporting Carcinogenicity.022
   d. Exp Key Carcinogenicity.001
   e. Exp Key Carcinogenicity.002
   f. Exp Supporting Carcinogenicity.015
   g. Exp Supporting Carcinogenicity.008
   h. Exp Supporting Carcinogenicity.012
   i. Exp Supporting Carcinogenicity.017
   j. Exp Supporting Genetic Toxicity in vitro.001
   k. Exp Supporting Genetic Toxicity in vitro.002
   l. Key Genetic Toxicity in vivo.001
   m. Read Across Cat Key Genetic Toxicity in vitro.009
   n. Read Across Cat key Genetic Toxicity in vitro.007
   o. Read Across Cat Key Genetic Toxicity in vitro.008
   p. Exp Key Acute Toxicity: oral.002
   q. Exp Key Acute Toxicity: oral.001
   r. Exp Supporting Immunotoxicity.002
   s. Exp Supporting Immunotoxicity.001
   t. Exp Key Repeated dose toxicity: inhalation.001
   u. Read across Cat Key Repeated dose toxicity: inhalation.005
   v. Exp Key Skin sensitization.001
   w. Exp Supporting Skin sensitization.002
   x. Exp Supporting Skin sensitization.003
   y. Exp Key Skin Irritation/corrosion.001
   z. Exp Key Eye irritation.002
   aa. Exp Key Eye irritation.003
   bb. Exp Key Short-term toxicity to fish.001
   cc. Exp Key Short-term toxicity to aquatic invertebrates.001
   dd. Exp Supporting Short-term toxicity to aquatic invertebrates.006
   ee. Exp Key toxicity to microorganisms.001
   ff. Classification and Labeling – GHS, Remarks

4) Lide, D.R. CRC Handbook of Chemistry and Physics 88TH Edition 2007-2008. CRC Press, Taylor & Francis, Boca Raton, FL 2007, p. 4-69

5) Transferrin and Iron Transport Physiology, 2001. Available at www.sickle.bwh.harvard.edu/iron_transport.html (accessed April 2012)

6) Heslop, R.B. and Robinson, P.L., Inorganic Chemistry, A Guide to Advanced Study, 3rd Edition, 1967, Elsevier Publishing Co, Amsterdam, London, New York.

7) Iron Oxide Powders from Reade. Available at http://www.reade.com/products/35-oxides-metallic-powders/272-iron-oxide-powders-feo-fe203-fe304-feo-oh-ferrous-ferric-hematite-red-iron-oxide-magnetite-black-iron-oxide (accessed April 2012)

8) IUCLID Dataset on Diiron Trioxide, CAS# 1309-37-1, 2000. European Commission – European Chemicals Bureau. Available at http://esis.jrc.ec.europa.eu/doc/existing-chemicals/IUCLID/data_sheets/1309371.pdf (accessed April 2012)
   a. NIOSH (1983). Health hazard evaluation reportNo. HETA 83-040-1356|Drive train industries Inc. Casper Wyoming, Aug.)
   b. Dept of Transportation, Emergency Response Guidebook, 1984 p.5300.3, Washington, D.C, Govt Printing Office
   c. New Jersey Dept of Health, CN 368, Trenton, NJ, 1984
   d. Van Wyk, C.P. & Robbins, D.J.: South African Med J. 48, 505-509 (1974) (ref. 27)
   e. Shefner, A.A. et al,: Proc. Int. Sympos. 2, 994-1-11, (1980) (ref. 31)
   f. Bayer AG data (ref. 19)

9) American Conference of Governmental Industrial Hygienists, Inc., Documentation of the Threshold Limit Values and Biological Exposure Indices, 6th ed., Vols I, II, III. Cincinnati, OH: ACGIH, 1991, p. 804.

10) Bourgkard E, Wild P, Courcot B, Diss M, Ettlinger J, Goutet P, Hemon D, Marquis N, Mur JM, Rigal C, Rohn-Janssens MP, Moulin JJ, 2008, Lung cancer mortality and iron oxide exposure in a French steel-producing factory, Occup Environ Med published online doi:10.1136/oem.2007.038299, 2008-09-18)

11) U.S. FDA Generally Regarded as Safe (GRAS) List. **21 CFR Part 182** Substances Generally Recognized as Safe. Available at http://www.fda.gov/Food/FoodIngredientsPackaging/GenerallyRecognizedasSafeGRAS/default.htm (accessed April 2012)

12) International Agency for Research on Cancer (IARC) – Summary and Evaluations, Supplement 7 (1987), p. 216.

13) Powder Technology, Inc, PTI, Material Safety Data Sheet, November 14, 2007. Available at http://www.powdertechnologyinc.com/secondary/msds.php (accessed April 2012).

14) Gurzau, Eugen S., Neagu, Cornelia, and Gurzau, Anca Elena, Essential Metals – case study on iron. Ecotoxicology and Environmental Safety, 56 (2003) 190-200.

15) Canadian Environmental Protection Act, 1999 (CEPA 1999), Ecological Categorization of the Substances on the Domestic Substances List (DSL). Available at http://www.ec.gc.ca/substances/ese/eng/dsl/cat_index.cfm (accessed April 2012)

16) Friberg, L., Nordberg, G.F., Kessler, E. and Vouk, V.B. (eds). Handbook of the Toxicology of Metals. 2nd ed. Vols I, II.: Amsterdam: Elsevier Science Publishers B.V., 1986., p. V2 283

17) Japan GHS, chemical classifications. Available at http://www.safe.nite.go.jp/english/ghs_index.html#results (accessed August 2012)

1) Appendix X[7]

Modeling Results

Attach: Inorganic compounds, such as diirion trioxide, are not recommended for modeling by these programs

- **EPISuite Results for Chemical Name (CAS #)**
- **ECOSAR Results for Chemical Name (CAS #)**
- **Other**

[7] Attach separate Appendix for each set of modeling results