Justification Document for the Selection of a CoRAP Substance

Substance Name (public name):	Chromium (III) oxide
EC Number:	215-160-9
CAS Number:	1308-38-9
Authority:	French CA
Date:	20/03/2018

Cover Note

This document has been prepared by the evaluating Member State given in the CoRAP update.

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1 IDENTITY OF THE SUBSTANCE

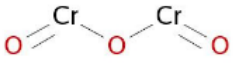
1.1 Other identifiers of the substance

Table: Other Substance identifiers

EC name (public):	Chromium (III) oxide
IUPAC name (public):	Chromium (III) oxide
Index number in Annex VI of the CLP Regulation:	-
Molecular formula:	Cr2O3
Molecular weight or molecular weight range:	151.99 g/mol
Synonyms:	Chromic oxide, Chromium(III) sesquioxide, dichromium trioxide, oxo-(oxochromiooxy)chromium

Type of substance ☒ Mono-constituent ☐ Multi-constituent ☐ UVCB

Structural formula:



1.2 Similar substances/grouping possibilities

Has read-across been used by the registrant for the concern related endpoints?

☒ Yes ☐ No

Is the substance a member of a category? ☒ Yes ☐ No

No information were available in the CSR regarding the other chromium substances used for the read across (no CAS number, structural formula or physico-chemical parameters to allow a comparison). There is a lack of justification for the use of the read-across.

IUPAC Name (oxidation state)	CAS No.	EC No.	Comments
Chromium chloride hexahydrate	–	-	
Chromium hydroxide	1308-41-1	215-158-8	Registered 10-100 t/y
Chromium hydroxide sulfate	10101-53-8	612-056-9	-
Chromium picolinate	14639-25-9	604-524-6	Annex III – Suspected mutagen (*in vivo* micronucleus test outcome equivocal according to ISSMIC)
Chromium propionate		919-722-0	-
Chromium chloride			No more information (hydrated or not)

2 OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

Table: Completed or ongoing processes

RMOA	☐ Risk Management Option Analysis (RMOA)	
REACH Processes	Evaluation	☐ Compliance check, Final decision
		☐ Testing proposal
		☐ CoRAP and Substance Evaluation
	Authorisation	☐ Candidate List
		☐ Annex XIV
	Restric-tion	☐ Annex XVII[1]
Harmonised C&L	☐ Annex VI (CLP) (see section 3.1)	
Processes under other EU legislat	☐ Plant Protection Products Regulation Regulation (EC) No 1107/2009	

[1] Please specify the relevant entry.

	☐ Biocidal Product Regulation Regulation (EU) 528/2012 and amendments
Previous legislation	☐ Dangerous substances Directive Directive 67/548/EEC (NONS)
	☐ Existing Substances Regulation Regulation 793/93/EEC (RAR/RRS)
(UNEP) Stockholm convention (POPs Protocol)	☐ Assessment
	☐ In relevant Annex
Other processes / EU legislation	☐ Other (provide further details below)
Further details	

3 HAZARD INFORMATION (INCLUDING CLASSIFICATION)

3.1 Classification

3.1.1 Harmonised Classification in Annex VI of the CLP

No harmonised classification

3.1.2 Self classification

- In the registration:

  No proposal.

- The following hazard classes are in addition notified among the aggregated self classifications in the C&L Inventory:

Skin Sens. 1	H317
Eye Irrit. 2	H319
Acute Tox. 4	H302
Repr. 1B	H360
Resp. Sens. 1	H334

Skin Irrit. 2	H315
Carc. 1A	H350
Muta. 1B	H340
STOT RE 1	H372
STOT RE 2	H373
STOT SE 3	H335
Aquatic Acute 1	H400
Aquatic Chronic 1	H410
Aquatic Chronic 3	H412
Aquatic Chronic 4	H413

3.1.3 Proposal for Harmonised Classification in Annex VI of the CLP

3.2 Summary of hazard information

Human health

Skin sensitization

Chromium (III) oxide is not a skin sensitizer according to a Buehler test provided by the registrant. However it has to be noted that this test was conducted on Chromium hydroxide trisulfate. Therefore, the relevance of the read across has to be assessed. Additionally, a report from ATSDR stated that the Chromium (III) oxide may be a skin sensitizer.

CMR properties

In a cellular system, water-soluble chromium (III) compounds (ie salts), such as chromium chloride and chromium nitrate have been shown to induce genotoxic effects. In general, data reported in the CSR concerning *in vitro* genotoxicity studies performed with insoluble Chromium (III) oxide (Chromoxid extra green, when specified) were generally negative in bacteria. However,i*n vitro* genotoxicity studies performed on mammalian cells gave mixed results. Results therefore suggest that the inability of Cr (III) to cross bacteria wall and maybe cell membrane effectively reduces activity in *in vitro* system. This could indicate that chromium (III) oxide is genotoxic, but its inability to cross the cell membrane effectively reduces activity in cellular systems.

Although chromium(III) may interact with deoxyribonucleic acid (DNA), the data on *in vitro* and *in vivo* genotoxicity studies provide no evidence on the mutagenicity of trivalent chromium.

In vivo studies in D. melanogaster exposed to chromium chloride gave negative result of gene mutation (Amrani et al. 1999). There were no DNA crosslinks, DNA-protein crosslinks, DNA strain breaks observed in rat liver and kidney nuclei (intraperitoneal exposure with chromium oxide) (Cupo and Wetterhahn 1985). Micronuclei after chromium picolinate exposure and DNA fragmentation after Niacin-bound chromium exposure were negative in rat (respectively NTP, 2008 and Shara et al. 2005). No micronuclei in erythrocyte were found in mice after chromium picolinate monohydrate exposure (NTP, 2008). No micronuclei in peripheral blood cells nor bone marrow cells were found in mice after chromic potassium sulfate dodecahydrate exposure (De Flora et al. 2006). No micronuclei

in erythrocyte were found in mice after chromium chloride intraperitoneal exposure (Itoh and Shimada 1996).
Studies involving 17 workers exposed to chromium(III) (compared to 13 controls) in tanneries (Hamamy et al. 1987) did not report increases in the number of chromosomal aberrations or sister chromatid exchanges in peripheral lymphocytes of these workers. However, parallel measurements in these tannery workers showed that the average chromium levels in plasma (0.115 µg/L) and urine (0.14 µg/L) did not differ from the nonexposed workers.

On the contrary, DNA damage was also reported in chromium(III) tannery workers (Zhang et al. 2008). Significant associations between DNA damage and blood and urinary chromium levels were observed; blood chromium levels ranged from 13.10 to 68.30 µg/L (median of 22.95 µg/L) and urinary chromium levels ranged from 1.50 to 42.20 µg/L (median of 10.60 µg/L) in the high-exposure group and 4.30–64.3 µg/L (median of 22.95 µg/L) and 1.50–18.00 µg/L (median of 2.25 µg/L), respectively, in the low-exposure group.

Micronuclei and DNA-protein crosslinks were also reported by Medeiros (Medeiros et al., 2003) in Lymphocytes from tanners exposed to chromium (III). Methods are available for the biomonitoring of Cr VI. However, Cr VI will be reduced in the human body, to trivalent chromium in urine; thus when there is co-exposure to chromium III compounds it will be difficult to know what proportion came from the hexavalent and trivalent compounds. In such cases, speciation of the inhalation exposure is important in order to interpret biomonitoring data.

There is contradicting results in humans. However, the data available measure concentrations of chromium in blood and or urine without being able to give the speciation of the Chromium the workers were exposed to. On the other hand, all the animal data ensuring exposure to Chromium (III) and not potentially Chromium (VI) are negative. Therefore, the mutagenic database for Chromium (III) is judged of limited alert. **It would be worth that users of Chrome (III) increase the database by documenting the speciation of the Chromium workers who are exposed together with evaluation of genotoxicity.**

Concerning carcinogenicity, 2 experimental studies are available by oral route. In the first study conducted with chromium (III) oxide via oral route, no effect of treatment was seen even at the highest concentration (2500 mg/kg). In the second study (conducted on chromium picolinate monohydrate via oral), increase in incidence of preputial gland adenomas was observed at 10000 ppm, but not at 50000 ppm. Due to the lack of dose response relationship, these effects were not considered relevant by the registrants. In its report, ATSDR stated that "several animals studies show no adverse effects associated with chronic-duration oral exposure to chromium(III) compounds". One experimental study by inhalation route was also available. No carcinogenic effect was observed in this study. Finally, two reviews are available on humans. Both of them concluded that there is no evidence that an exposure to chromium (III) oxide may result in cancer in humans. IARC concluded on a classification in group 3 "Not classifiable as to its carcinogenicity to humans" for metallic chromium and chromium (III) compounds (1990).

Based on studies available for an assessment of the possible developmental effects of chromium (III) oxide (none performed with chromium (III) oxide, only read across, and only by oral route) no effects were observed. ATSDR confirms that the available evidence does indicate that exposure to chromium(III) consistently produces no adverse developmental effects.

Regarding fertility, one subchronic inhalation study is available. No histological or functional effects on reproductive organs were observed. By oral route, two studies are considered by the registrant. A two generation study conducted on ChromeMate CM-100M (an oxygen coordinated niacin-bound chromium (III)

complex or NBC), in which no effects were observed, and a subchronic study in which all mated females became pregnant. However, it has to be noted that 3 studies on chromium chloride and chromium sulfate showing some effects on fertility (changes in organs weights, decreased spermatogenesis, numbers of implantations…) were disregarded by the registrant, due to deficiencies. ATSDR concluded in its report that conflicting results on reproductive effects of chromium(III) compounds have been reported, and therefore, a concern on fertility effects of chromium (III) oxide remains.

Environment

It has to be noted that there is some difference in water solubility evaluation between the one presented in the CSR which gives a value close to zero, and the water solubility provided in the ECHA dissemination website, with a value of 3.13 µg/L (pH=6) and 2.96 µg/L (pH=8).

PBT assessment data

Annex XIII to the REACH Regulation is generally applicable to any substance containing an organic moiety. Based on the common definition of an organic substance in chemistry, **PBT and vPvB criteria are not applicable to inorganic substances.**

As a metallic element, chromium (III) oxide is considered an inorganic substance. The following comparison to the PBT criteria are for informative purpose only.

As a metallic element, chromium (III) oxide cannot be considered as persistent. Kd for soil is comprised between 298 to 55918 (pH 6.03 - 7.41, in 3 soils, but based on a read accross with chromium (III) chloride), indicating that there is a risk of adsorption in sediment/soil leading to potential accumulation of chromium (III) species in sediment/soil.

Regarding bioaccumulation data provided in the CSR, the BCF value in fish is low, under threshold value leading to classification as bioaccumulative chemical. Nevertheless, literature give values of BCF as high as 2800 for *Mytilus edulis* and values between 12 000-130 000 for phytoplancton treated with chromium (III) species. Based on CSR datas, the chromium (III) oxide is not meeting the B criteria, but there is a concern about the potential bioaccumulation when considering other species than fish (as phytoplankton), with a possible risk of bioaccumulation in environment.

For toxicity, in the CSR, no classification for acute toxicity is proposed due to the presence of a chronic value for toxicity. Nevertheless, due to a LC_{50} 96h fish ≥ 1µg/L, the chromium (III) oxide can be classified as Aquatic Acute Cat. 1 H400.

For chronic toxicity, an algae *Desmodesmus subspicatus* test (TG OECD 201) gives a 72h-NOEC of 4,1 µg/L allowing to propose a classification as Aquatic Chronic Cat 1 H410 (both values are based on the read across proposed in the CSR). We recommand to use preferably this value when realizing the PEC/PNEC calculation.

For the environmental classification, based on the available data, chromium (III) oxide can be classified as Aquatic Acute Cat. 1 H400 and Aquatic Chronic Cat 1 H410.

Endocrine disruption assessment

There is only one indication of potential endocrine disruptive effect of chromium (III) oxide considering one of the substances used in the CSR for the read across.

Choe *et al.* (2003[2]) found that chromium(III) chloride shows high estrogenicity in E-screen Assay (MCF-7 cells at 1µM) and in Estrogen dependent transcriptional expression assay (1-10000nM).

This may be further investigated, especially if the read-across can be considered as relevant.

[2] Choe, Suck-Young, So-Jung Kim, Hae-Gyoung Kim, Ji Ho Lee, Younghee Choi, Hun Lee, and Yangho Kim. 2003. "Evaluation of Estrogenicity of Major Heavy Metals." *Science of The Total Environment* 312 (1–3): 15–21. doi:10.1016/S0048-9697(03)00190-6.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[3]

4.1 Tonnage and registration status

Table: Tonnage and registration status

From ECHA dissemination site *		
☒ Full registration(s) (Art. 10)	☐ Intermediate registration(s) (Art. 17 and/or 18)	
Tonnage band (as per dissemination site)		
☐ 1 – 10 tpa	☐ 10 – 100 tpa	☐ 100 – 1000 tpa
☐ 1000 – 10,000 tpa	☐ 10,000 – 100,000 tpa	☐ 100,000 – 1,000,000 tpa
☐ 1,000,000 – 10,000,000 tpa	☐ 10,000,000 – 100,000,000 tpa	☐ > 100,000,000 tpa
☒ <10 000+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential
42 active registrations in one joint submission		

*****the total tonnage band has been calculated by excluding the intermediate uses, for details see the Manual for Dissemination and Confidentiality under REACH Regulation (section 2.6.11):

https://echa.europa.eu/documents/10162/22308542/manual_dissemination_en.pdf/7e0b87c2-2681-4380-8389-cd655569d9f0

[3] *The dissemination site was accessed November 2017.*

4.2 Overview of uses

Table: Uses

Part 1:

☒ Manufacture	☒ Formulation	☒ Industrial use	☒ Professional use	☒ Consumer use	☒ Article service life	☐ Closed system

Part 2:

	Use(s)
Uses as intermediate	Catalyst Manufacture: SU3 industrial manufacture
Formulation	Catalyst manufacture, metal manufacture, production of chromium containing alloys, pigments,
Uses at industrial sites	Industrial use of chromium III oxide, welding and soldering, coating, metal manufacture, pigment, catalyst
Uses by professional workers	Pigment, cosmetics and artists colours/paints/coating, refcratory and foundry material, products of pigments, small scale laboratory use,
Consumer Uses	Pigment, use of pigment formulations, cosmetics and artists colours/paints/coating,
Article service life	

The substance has been identified because it might be used as substitute to other chromium coumpounds in annex XIV.
In the CSR only the following uses are identified :

- Pigment manufacture,
- Catalyst manufacture,
- Refractory metal

Part 3: There is high potential for exposure of

☒ Humans	☒ Environment

5. JUSTIFICATION FOR THE SELECTION OF THE CANDIDATE CoRAP SUBSTANCE

5.1. Legal basis for the proposal

☒ Article 44(2) (refined prioritisation criteria for substance evaluation)

☐ Article 45(5) (Member State priority)

5.2. Selection criteria met (why the substance qualifies for being in CoRAP)

☒ Fulfils criteria as CMR/ Suspected CMR

☒ Fulfils criteria as Sensitiser/ Suspected sensitiser

☐ Fulfils criteria as potential endocrine disrupter

☐ Fulfils criteria as PBT/vPvB / Suspected PBT/vPvB

☒ Fulfils criteria high (aggregated) tonnage (*tpa > 1000*)

☒ Fulfils exposure criteria

☐ Fulfils MS's (national) priorities

5.3. Initial grounds for concern to be clarified under Substance Evaluation

Hazard based concerns		
CMR ☐ C ☐ M ☐ R	Suspected CMR[1] ☐ C ☐ M ☒ R	☐ Potential endocrine disruptor
☐ Sensitiser	☒ Suspected Sensitiser[4]	
☐ PBT/vPvB	☐ Suspected PBT/vPvB[1]	☐ Other (please specify below)
Exposure/risk based concerns		
☐ Wide dispersive use	☐ Consumer use	☐ Exposure of sensitive populations
☐ Exposure of environment	☐ Exposure of workers	☐ Cumulative exposure
☐ High RCR	☐ High (aggregated) tonnage	☐ Other (please specify below)

[4] CMR/Sensitiser: known carcinogenic and/or mutagenic and/or reprotoxic properties/known sensitising properties (according to CLP harmonized or registrant self-classification or CLP Inventory)
Suspected CMR/Suspected sensitiser: suspected carcinogenic and/or mutagenic and/or reprotoxic properties/suspected sensitising properties (not classified according to CLP harmonized or registrant self-classification)
Suspected PBT: Potentially Persistent, Bioaccumulative and Toxic

Human health

Chromium(VI) compounds rapidly (within seconds to minutes) enter cells by facilitated diffusion, while chromium(III) compounds enter much more slowly (within days) by simple diffusion (Kerger et al. ,1996); therefore, chromium(VI) compounds are of greater concern with regard to health effects.

There is a concern about the potential of chromium (III) oxide to induce skin sensitization. In the CSR, the only study presented by the Registrant is negative (Buehler test), but performed on chromium hydroxide sulfate. However, in its report on chromium compounds, ATSDR stated that "*exposure to chromium compounds may induce allergic sensitization in some individuals. In patients with known chromium-induced allergic dermatitis, positive results have been reported using patch tests with chromium(III) compounds as the challenge agent, suggesting that allergic sensitization to chromium(III) can occur. Studies in animals show that chromium(III) can induce sensitization and that cross-reactivity occurs between chromium(VI) and chromium(III). Sensitization to chromium(III) was observed in guinea pigs treated with a series of intradermal injections of 0.004 mg chromium(III)/kg as chromium trichloride.*"
Taking into account that chromium (VI) is a well-known sensitizer, classified as Skin Sens. 1, H317, it seems important to conduct a full assessment of this endpoint.

The *in vivo* results on mutagenicity with Cr(III) in animals, are negative. However, occupational exposure level (speciation not specified) documented by serum and urine chromium III levels has shown contradicting results regarding the effect of this exposure on genotoxicity. Genotoxicity on workers circulating cells should be further documented to ensure that exposure to Cr(III) (and not Cr(VI)) is hazardless regarding genotoxicity.

There are also serious concerns about the effect of Chromium (III) oxide on fertility. The only two-generation study available in the CSR was conducted on NBC, an organic chromium complex. FR considered this read across not acceptable, the compound used being not similar enough of chromium (III) oxide, at least at structural level (one chromium atom binds to 3 molecules of niacin).
Moreover, the 3 studies disregarded and performed with substances included in the read-across approach showed some effect on fertility parameters, like changes in organs weights, decreased spermatogenesis, numbers of implantations…. The reasons to disregard those studies lacked also some justifications, considering that ATSDR and WHO took into account those studies (2 of them for WHO) in their assessments.
ATSDR concluded about chromium compounds that "*conflicting results on reproductive effects of chromium(III) compounds have been reported. It is unclear if differences in results are related to experimental methods, including exposure media (drinking water versus feed), or to differences in toxicity of the specific chromium(III) compounds evaluated*". FR is of the opinion that a full assessment of this endpoint has to be conducted since a concern was raised, and that a guideline study with chromium (III) oxide would be important to remove any doubts on possible effects of the substance on fertility.

Endocrine disruption assessment

There is only one indication of potential endocrine disruptive effect of chromium (III)

oxide considering one of the substance used in the CSR for the read across. Choe *et al.* (2003[5]) found that chromium(III) chloride shows high estrogenicity in E-screen Assay (MCF-7 cells at 1µM) and in Estrogen dependent transcriptional expression assay (1-10000nM). This may be further investigated, especially if the read-across can be considered as relevant.

5.4. Preliminary indication of information that may need to be requested to clarify the concern

☒ Information on toxicological properties	☐ Information on physico-chemical properties
☐ Information on fate and behaviour	☐ Information on exposure
☐ Information on ecotoxicological properties	☐ Information on uses
☐ Information ED potential	☐ Other (provide further details below)
Regarding human health : – Assess the validity of the read-across – Information to clarify the concern for sensitization may be needed – Information to clarify the concern for fertility and potentially mutagenicity and possible endocrine disruption properties may be needed Environment: BCF data other than those on fish should be used to improve the risk assessment for environment especially for the bioaccumulation in aquatic species. A harmonized classification could be proposed for environment as proposed.	

5.5. Potential follow-up and link to risk management

☒ Harmonised C&L	☐ Restriction	☐ Authorisation	☐ Other (provide further details)
Based on the outcome of the SEv of the substance, a CLH dossier may be proposed for sensitization, reprotoxicity and environment for possible further SVHC identification regarding human health.			

[5] Choe, Suck-Young, So-Jung Kim, Hae-Gyoung Kim, Ji Ho Lee, Younghee Choi, Hun Lee, and Yangho Kim. 2003. "Evaluation of Estrogenicity of Major Heavy Metals." *Science of The Total Environment* 312 (1–3): 15–21. doi:10.1016/S0048-9697(03)00190-6.