Justification Document for the Selection of a CoRAP Substance

- Update -

Substance Name (public name):	Chromium (III) oxide
EC Number:	215-160-9
CAS Number:	1308-38-9
Authority:	French CA
Date:	20/03/2018 19/03/2019 (1. update)

Cover Note

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

Table of Contents

1 IDENTITY OF THE SUBSTANCE

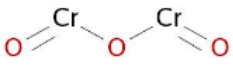
1.1 Other identifiers of the substance

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:	Cr_2O_3
Molecular weight or molecular weight range:	151.99 g/mol
Synonyms:	• Chrome sesquioxide • Chromic oxide • Chromium (III) Oxide • Chromium (III) oxide dihydrate • Chromium (lll) oxide • Chromium III Oxide • CHROMIUM OXIDE • Chromium oxide (Cr2O3) • Chromium(III) oxide • Chromium(III) sesquioxide • Chromium(III)Oxide • Cr2O3 • dichromium trioxide • dichromium(3+) trioxidandiide • oxo(oxochromiooxy)chromium • oxo-(oxochromiooxy)chromium • oxo[(oxochromio)oxy]chromium • Tlenek chromu III • trioxochromium

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.
Toxicokinetic properties are generally linked to the valence of the chromium atom and the nature of the compound, which primarily determines the solubility. Water solubility of trivalent chromium and its salts ranges from low to high, e.g chromium (III) oxide is insoluble in water, and chromic (III) acetate, chromium (III) nitrate and chromium (III) sulfate are soluble in water Chromium(III) chloride-hexahydrate salts is slightly soluble in hot water.

Therefore, the substance put on CoRAP will be evaluated having in mind the available data for CrIII salts in general.

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 (III) chloride or chromium trichloride	10025-73-7	233-038-3	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 legislation	☐ Plant Protection Products Regulation Regulation (EC) No 1107/2009	
	☐ 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	

[1] Please specify the relevant entry.

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 dossiers:

  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
STOT SE 3	H335
Aquatic Acute 1	H400
Aquatic Chronic 1	H410
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 irritation/sensitization

There is no indication of irritation when rabbits are exposed to chromium (III) oxide under an adhesive patch. The substance is not irritating to eyes either.

Chromium (III) oxide is not a skin sensitizer according to a Buehler test provided in the registration dossier. However it has to be noted that this test was conducted with chromium hydroxide trisulfate. Therefore, the relevance of the read across has first to be assessed in order to conclude on the sensitization properties of chrome (III). Additionally, a report from ATSDR (2012)[2] stated that

[2] ATSDR. 2012. Toxicological Profile for Chromium. U.S. Department of Health and Human Services. Agency for Toxic Substances and Disease Registry.

the chromium (III) oxide may be a skin sensitizer as the other trivalent chromium salts. Indeed, 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. In guinea pigs sensitized with chromium (III), cross-sensitivity with chromium (VI) was observed on patch test challenge.

CMR properties

In a cellular system, water-soluble chromium (III) compounds (i.e. salts), such as chromium trichloride 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, *in 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[3]). 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, 2008b[4] and Shara *et al.,* 2005[5]). No micronuclei in erythrocytes were found in mice after chromium picolinate monohydrate exposure (NTP, 2008b). No micronuclei in peripheral blood cells nor bone marrow cells were found in mice after chronic exposure to potassium sulfate dodecahydrate (De Flora *et al*. 2006[6]). No micronuclei in erythrocytes were found in mice after chromium chloride intraperitoneal exposure (Itoh and Shimada 1996[7]).
Studies involving 17 workers exposed to chromium (III) (compared to 13 controls) in tanneries (Hamamy *et al*. 1987[8]) did not report increases in the number of chromosomal aberrations or sister chromatid exchanges in peripheral lymphocytes of these workers. 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.

[3] Amrani S, Rizki M, Creus A, Marcos R. 1999. Genotoxic activity of different chromium compounds in larval cells of *Drosophila melanogaster*, as measured in the wing spot test. *Environmental and Molecular Mutagenesis*, 34:47–51.
[4] NTP. 2008b. NTP technical report on the toxicology and carcinogenesis studies of chromium picolinate monohydrate (CAS No. 27882-76-4)) in F344/N rats and B6C3F1 mice (feed studies). Scheduled peer CHROMIUM 475 review date: February 27-28, 2008. Washington, DC: National Toxicology Program.
[5] Shara M, Yasmin T, Kincaid AE, et al. 2005. Safety and toxicological evaluation of a novel niacin-bound chromium (III) complex. J Inorg Biochem 99(11):2161-2813.
[6] De Flora S, Iltcheva M, Balansky RM. 2006. Oral chromium(VI) does not affect the frequency of micronuclei in hematopoietic cells of adult mice and of transplacentally exposed fetuses. Mutat Res 610:38-47.
[7] Itoh S, Shimada H. 1996. Micronucleus induction by chromium and selenium, and suppression by metallothionein inducer. Mutat Res 367:233-236.
[8] Hamamy HA, Al-Hakkak ZS, Hussain AF. 1987. Chromosome aberrations in workers in a tannery in Iraq. Mutat Res 189:395-398

On the contrary, DNA damage was also reported in chromium(III) tannery workers (Zhang *et al.,* 2008[9]). 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 (tanning place) 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 (finishing place). Short time sampling (15 min) was performed to measure atmospheric concentrations of **total air chromium** (0.054 and 0.016 mg/m^3 in tanning and finishing places resp.). Although it is well know that CrIII is mainly used in tanning industry (chromium suflate as the basic tanning agent), there is a lack of data on atmospheric chromium species measured for both exposure groups. The data observed cannot be attributed to an exposure to Cr(VI) instead of Cr(III).

Micronuclei and DNA-protein crosslinks were also reported by Medeiros (Medeiros *et al.*, 2003a[10]) in Lymphocytes from tanners exposed to chromium (III). The authors performed biological measures of chromium in blood, urine and plasma, they considered that in tanneries, Cr VI contamination is absent or unlikely, they didn't perform atmospheric sampling. 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. Only red blood cell chromium levels are specific to exposure to Cr VI but the technique is invasive and involves a difficult analytical procedure. 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. It is difficult to distinguish between the effects caused by chromium(VI) and those caused by chromium(III) since chromium(VI) is rapidly reduced to chromium(III) after penetration of biological membranes. Whereas chromium(VI) can readily be transported into cells, chromium(III) is much less able to cross cell membranes. The reduction of chromium(VI) to chromium(III) inside of cells may be an important mechanism for the toxicity of chromium compounds. 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) document the speciation of the Chromium workers are exposed to and link this information with the evaluation of genotoxicity. The speciation of metals the workers are exposed to is much more important than total chromium exposure. During substance evaluation, this point will be further investigated to ensure that the data reported above are positive due to exposure to Cr(VI) compounds and not Cr(III). This will also be put in regard with the data for Cr(III).**

Concerning carcinogenicity, 2 experimental studies are available by oral route. In the first study conducted with chromium (III) oxide via oral route, 60 rats/sex/groups were exposed to 0, 600, 1200 and 3000 mg/kg bw /d Cr(III) for two years. No effect of treatment was seen even at the highest concentration (Ivankovoc et al., 1975[11])). In the second study, conducted on chromium picolinate monohydrate according to OECD 453), 50 rats and mice/sex/groups

[9] Zhang M, Chen Z, Chen Q, et al. 2008. Investigating DNA damage in tannery workers occupationally exposed to trivalent chromium using comet assay. Mutat Res 654(1):45-51.
[10] Medeiros MG, Rodrigues AS, Batoreu MC, et al. 2003a. Elevated levels of DNA-protein crosslinks and micronuclei in peripheral lymphocytes of tannery workers exposed to trivalent chromium. Mutagenesis 18(1):19-24.
[11] Ivankovic S, Preussmann R. 1975. Absence of toxic and carcinogenic effects after administration of high doses of chromic oxide pigment in subacute and long-term feeding experiments in rats. Food Cosmet Toxicol 13:347-351

were exposed to 0, 2000, 10000, 50000 ppm. Increase in incidence of preputial gland adenomas was observed at 10000 ppm, but not at 50000 ppm (Stout et al., 2009[12]). 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 performed in rats is available (Derelanko *et al*., 1999[13]). No histological or functional effects on reproductive organs were observed. By oral route, two studies were considered as relevant by the registrants : A two generation study (Deshmukh *et al*., 2009[14]) conducted with ChromeMate CM-100M (an oxygen coordinated niacin-bound chromium (III) complex or NBC) on Sprague–Dawley rats, in which no effects were observed, and a subchronic study in which all mated females became pregnant (Ivankovic et al., 1975). However, it has to be noted that 3 studies showing some effects on fertility were disregarded by the registrant, due to their deficiencies. In the first study (Zahid *et al.,* 1990[15]) also disregarded by WHO, but not by ATSDR, mice exposed for 35 days to 15, 30 or 60 mg chromium (III) kg/day as chromium sulfate in the diet had reduced sperm count, increased number of morphologically abnormal sperms and degeneration of the outer cellular layer of the seminiferous tubules. In the study by Bataineh *et al.* (1997)[16], male Sprague-Dawley rats exposed for 12 weeks to 24 mg Cr(III) kg/day chromium chloride in the drinking water were mated to unexposed females. The untreated females mated to treated males exhibited an increase in the total number of resorptions. Body weight and absolute testes, seminal vesicles and preputial gland weights were significantly decreased in Cr(III) treated males. In the study by Elbetieha et al. (1997)[17], male Swiss mice were exposed to 82 or 204 mg Cr(III) /kg/day chromium chloride in drinking water for 12 weeks. The treated males were mated to unexposed females. The body weights and relative weights of the preputial gland were statistically significantly reduced in treated males, whereas the testis weights were significantly increased. The fertility of males of the high dose group was significantly decreased. In a second experiment, female Swiss mice were exposed to 85 or 212 mg Cr(III) /kg/day chromium chloride in drinking water for 12 weeks. The treated females were mated to untreated males. The relative ovary

[12] Stout MD1, Nyska A, Collins BJ, Witt KL, Kissling GE, Malarkey DE, Hooth MJ. 2009. Chronic toxicity and carcinogenicity studies of chromium picolinate monohydrate administered in feed to F344/N rats and B6C3F1 mice for 2 years. Food Chem Toxicol. 2009 Apr;47(4):729-33.

[13] Derelanko MJ, Rinehart WE, Hilaski RJ, Thompson RB, Löser E. 1999. Thirteen-week subchronic rat inhalation toxicity study with a recovery phase of trivalent chromium compounds, chromic oxide, and basic chromium sulfate. *Toxicological Sciences*, 52:278–288.

[14] Deshmukh NS1, Bagchi M, Lau FC, Bagchi D. 2009. Safety of an oxygen-coordinated niacin-bound chromium(III) complex (NBC): II. Developmental toxicity study in rat . J Inorg Biochem. 2009 Dec;103(12):1755-60.

[15] Zahid ZR, Al-Hakkak ZS, Kadhim AHH, Elias EA, Al-Jumaily IS (1990) Comparative effects of trivalent and hexavalent chromium on spermatogenesis of the mouse. *Toxicology and Environmental Chemistry*, 25:131–136.

[16] Bataineh H, Al-Hamood MH, Elbetieha A, Hani I. 1997. Effect of long-term ingestion of chromium compounds on aggression, sex behavior and fertility in adult male rat. *Drug Chemistry and Toxicology*, 20:133–149

[17] Elbetieha A, Al Hamood MH. 1997. Long-term exposure of male and female mice to trivalent and hexavalent chromium compounds: Effect on fertility. *Toxicology*, 116:39–47

and uterus weights of high dose females were statistically significantly decreased; Impaired fertility (decreased number of implantations and viable fetuses) was observed in treated females in both dose groups. Althought WHO considered that available data suggest a lack of effects on fertility, ATSDR concluded that conflicting results on reproductive effects of chromium (III) compounds have been reported, concluding that a concern on fertility effects of chromium (III) oxide remains. This point will be further investigated during substance evaluation.

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 data, the chromium (III) oxide is not meeting the B criteria as not bioaccumulative in fish.Although there is a concern about the potential bioaccumulation when considering other species than fish (as phytoplankton), the actual criteria do not allow its identification as a bioaccumulative substance.

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. The necessity of drafting a CLH dossier will be evaluated after substance evaluation has been performed.

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[18]) 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.

4 INFORMATION ON (AGGREGATED) TONNAGE AND USES[19]

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

*****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

[18] 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.

[19] *The dissemination site was accessed in August 2018.*

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, refractory 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[20]	
☐ 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)

[20] 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 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 justified enough to be accepted as such, 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 in the registration dossiers and performed with substances included in the read-across approach showed some effect on fertility parameters, like changes in organ weights, decreased spermatogenesis, numbers of implantations…. The reasons to disregard those studies lack also some justifications, considering that ATSDR and WHO took into account those studies (2 of them for WHO) in their assessments.
Althought WHO concluded on a lack of effects of trivalent chromium on fertility, ATSDR concluded 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[21]) 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.			

[21] 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.