Justification Document for the Selection of a CoRAP Substance

- Update -

Substance Name (Public Name):	Cerium Dioxide
Chemical Group:	-
EC Number:	215-150-4
CAS Number:	1306-38-3
Submitted by:	Germany
Date:	17/03/2015 21/03/2017 (Updated version)

Note

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

Contents

1 IDENTITY OF THE SUBSTANCE

1.1 Other identifiers of the substance

Table 1: Substance identity

EC name:	Cerium dioxide
IUPAC name:	Cerium dioxide
Index number in Annex VI of the CLP Regulation	-
Molecular formula:	CeO_2
Molecular weight or molecular weight range:	172.14 g/mol
Synonyms/Trade names:	

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

Structural formula:

CeO_2

1.2 Similar substances/grouping possibilities

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2 CLASSIFICATION AND LABELLING

2.1 Harmonised Classification in Annex VI of the CLP

Not listed in Annex VI.

2.2 Self classification

- In the registration

No self classification (both nano and bulk form)

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

STOT RE 2:	H373 (inhal.)/H373
Acute Tox. 4:	H302/H302
Acute Tox. 3:	H331/H315, H335, H319
Acute Tox. 1:	H330/H330
Skin Irrit. 2:	H315/H315
Eye Irrit. 2:	H319/H319
STOT SE 3	H335 (resp. syst.)/H335
Aquatic Chronic 4	H413

Note: It is unclear, if notifications also include nanoforms of the substance

2.3 Proposal for Harmonised Classification in Annex VI of the CLP

No CLH proposal has been submitted (ECHA dissemination site last accessed on 20 September 2016.

3 INFORMATION ON AGGREGATED TONNAGE AND USES

From ECHA 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
☒ 1000+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential

The tonnage for CeO_2 is 1000+ t/a according to the ECHA dissemination site.

For the nanoform the lead dossier estimated a quantity of 20 t in 2010.
Individual registration dossiers did not identify quantities or uses for the nanoform.

☒ Industrial use	☒ Professional use	☒ Consumer use	☐ Closed System

The Commission Staff working paper "Types and uses of nanomaterials, including safety aspects" {COM(2012) 572 final} (http://ec.europa.eu/nanotechnology/pdf/second_regulatory_review_on_nanomaterials_-_staff_working_paper_accompanying_com%282012%29_572.pdf) states:

"According to SRI, the global market for nanoform cerium oxide is around 10 thousand tonnes.
Nanostructured CeO2-x films are used in applications in optical, electro-optical, microelectronic and optoelectronic devices. Nanoform ceria is used inter alia as a polishing material for glass surfaces and silicon wafers, to finish photomasks and disk drives, as an anticorrosion material, e.g. in exterior architectural paint, steel and other metal plates, and in fuel cells. Another major application is as a catalytic diesel fuel additive, decreasing toxic diesel emissions and increasing fuel efficiency.
Workplace exposure can occur at production, use, when machining materials and from waste and depends on the work procedure and applied risk management measures. Except in applications as a fuel additive, exposure to humans and the environment at the use stage is estimated to be rather low. There are ongoing discussions whether release at the waste stage could lead to exposure to significant amounts of nanoparticles."

A review by Cassee et al. (Critical Reviews in Toxicology, 2011; 41(3): 213–229) identified the following applications:

"Cerium is most heavily used in the form of mischmetal for metallurgical purposes. Further, it is used either in the pure form or in a concentrate as a polishing agent for glass mirrors, plate glass, television tubes, ophthalmic lenses, electronic silica wafers, precision optics and fuel cells. CeO2 is employed in coatings due to its UV properties and hardness and has potential biomedical applications. […]
CeO_2 nanoparticles have a variety of applications similar to those previously described for microscale CeO_2 as well as emission reduction technology and therapeutics. Due to the fact that CeO_2 absorbs ultraviolet radiation strongly, it is considered to be used in sunscreens since it is also transparent for visible light. Globally CeO_2 nanoparticles have been commercially employed as a diesel fuel additive since 1999."

According to the French notification system, the tonnage in 2013 was in the range of 100-1000 (Éléments issus des déclarations des substances à l'état nanoparticulaire. RAPPORT d'étude Novembre 2013; https://www.r-nano.fr/). The French register mentions a number of diverse industrial applications for the nanoform which are also listed in the CSR for the bulk form. In addition, the use as filler, mastic, plaster and plasticine are mentioned (most likely for professional worker uses).
Documented uses are predominantly in industrial settings. Only one professional worker and consumer use as wood paint is mentioned.

4 OTHER COMPLETED/ONGOING REGULATORY PROCESSES THAT MAY AFFECT SUITABILITY FOR SUBSTANCE EVALUATION

☐ Compliance check, Final decision	☐ Dangerous substances Directive 67/548/EEC
☐ Testing proposal	☐ Existing Substances Regulation 793/93/EEC
☐ Annex VI (CLP)	☐ Plant Protection Products Regulation 91/414/EEC
☐ Annex XV (SVHC)	☐ Biocidal Products Directive 98/8/EEC ; Biocidal Product Regulation (Regulation (EU) 528/2012)
☐ Annex XIV (Authorisation)	☐ Other (provide further details below)
☐ Annex XVII (Restriction)	

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[1]	
☐ 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)

In the following, issues related the bulk form are also addressed, although the primary scope of the screening is the nanoform of CeO_2.

Human Health

Bulk form:

1. A TG 413 inhalation study reported effects of hyperplasia of alveolar epithelia and lymphoid tissue that give a concern on potential persistence, proliferative changes and/or chronic disease. The overload concept was stressed but pulmonary overload and disturbance of alveolar clearance as well as recovery (in the absence of a post-exposure period) was not shown. The need for a chronic inhalation study (TG 452), a carcinogenicity study (TG 451), or a combined chronic/carcinogenicity study (TG 453) is to be assessed taking the information on potential exposure due to the widespread use an high tonnage into account.
2. The provided studies on reproductive toxicity are non-compliant for this tonnage band. Annex IX studies (TG 414 and 443) are lacking.
3. The appropriateness of the DNEL based on a generic dust limit value for granular biopersistent particles has to be assessed for the specific nanosubstance.
4. The oxidative/anti-oxidative properties of CeO_2 and their toxicological impact need further clarification.

Nanoform:

1. It is acknowledged that the lead dossier differentiates bulk and nanoform study records. However, only two toxicological endpoints were addressed by nanospecific studies:
   a) Skin irritation (negative)
   b) Genetic toxicity in vitro (Ames test, negative).
   Note: A positive combined comet/micronucleus study was listed under specific investigation which gives rise to a concern with regard to mutagenicity.
2. In particular, no nanospecific information is supplied regarding inhalation repeated dose toxicity. There is a general concern for particulate nanomaterials that pulmonary inflammation and hyperplasia can be induced at considerably lower airborne mass concentrations compared to the bulk material.

[1] 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

3. No specific information is supplied in terms of behaviour and fate of the fairly stable CeO_2 nanoparticles in the body, including their barrier penetration potential and their cellular uptake, respectively. A potential concern for systemic availability and bioaccumulation at distant organs over time cannot be ruled out.
4. The ROS generation potential of nano-CeO_2 following exposure is unclear but putatively much higher compared to that of the bulk material because of the relatively larger surface area. This, together with small size raises a specific concern for increased tissue damage and genotoxicity.
5. It is expected that in many areas of application the nanoform of the substance will successively replace the bulk form and new uses for the nanoform will be identified, thus also considerably increasing the tonnage for the nanomaterial. This would add to cumulative exposure which presently stems primarily from diesel fuels as well as industrial and professional worker settings. Innovative simplified syntheses of the nanomaterial certainly favors this development (e. g. Ikeda-Ohno, A., Hennig, C., Weiss, S., Yaita, T. and Bernhard, G. (2013), Hydrolysis of Tetravalent Cerium for a Simple Route to Nanocrystalline Cerium Dioxide: An In Situ Spectroscopic Study of Nanocrystal Evolution. Chem. Eur. J., 19: 7348–7360.)

Though the Commission Staff Working Paper assumes low human exposure, it stresses that this depends on implementation of appropriate risk management measures. The appropriateness of measures should be verified when the missing information for the toxicological evaluation of the nanoform and the concerns for pulmonary inflammation/hyperplasia for the inhalation route are clarified.

Environment

The substance has a wide dispersive use with the potential of release to the environment.

Based on the intrinsic characteristics and properties of nanomaterials compared to bulk materials the concern raises that deviant effects on environmental organisms, bioavailability, and exposure occur. There is an uncertainty whether corresponding existing information requirements are appropriate to sufficiently assess potential hazards and risk of the nanoform(s) of CeO_2.

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)

Human health

The lead dossier addressed only few toxicological endpoints. Accordingly there are major data gaps, also with respect to standard information requirements for the bulk substance. Clarification if further information is needed based on the inhalation toxicity of the bulk material, the potentially higher toxicity of the nanoform in comparison to the bulk material and considering the potential exposure from the widespread uses of the nanoform.

The most important exposure route for a nanoparticular toxicity is the inhalation route. Accordingly, a 90 day inhalation study (TG 413) may have the highest priority. It shall be considered whether the study should include experimental kinetic parameters that address overload, agglomeration, translocation, distribution and bioaccumulation, both locally and at distant organs. A sufficiently long post-exposure period has to be taken into account to record recovery, persistence or proliferative effects.

As known from other comparative RDT inhalation studies with biopersistent particles, the nanoform has a higher toxic potency in the lung than the bulk form of the same substance, based on mass concentration. Accordingly, a much lower LOAEC, relevant for classification, is not unlikely.

Secondly, genotoxic studies with the nanomaterial are required, both in vitro (using mammalian putative target cells) and in vivo. These studies should consider the particle uptake and availability at target organs, respectively, as well as oxidative genotoxic damage.

Data on exposure of nanoparticles from the production process and products are required to be able to reasonably estimate a nanospecific RCR for the substance.

During the substance evaluation on the nanosubstance, new relevant inhalation kinetic and toxicity information from the literature specifically addressing the nanoform that is or will become available has to be considered, e.g.:

1. Aalapati S, Ganapathy S, Manapuram S, Anumolu G, Prakya BM. (2014). Toxicity and bio-accumulation of inhaled cerium oxide nanoparticles in CD1 mice. Nanotoxicology, 8, 786-98
2. Demokritou P, Gass S, Pyrgiotakis G, Cohen JM, Goldsmith W, McKinney W, Frazer D, Ma JY, Schwegler-Berry D, Brain JD, Castranova V. (2013). An in vivo and in vitro toxicological characterization of realistic nanoscale CeO2 inhalation exposures. Nanotoxicology, 7, 1338-50
3. Geraets L, Oomen AG, Schroeter JD, Coleman VA, Cassee FR. (2012). Tissue distribution of inhaled micro- and nano-sized cerium oxide particles in rats: results from a 28-day exposure study. Toxicol Sci, 127, 463-73
4. Gosens I, Mathijssen LE, Bokkers BG, Muijser H, Cassee FR. (2014). Comparative hazard identification of nano- and micro-sized cerium oxide particles based on 28-day inhalation studies in rats. Nanotoxicology, 8, 643-53

Furthermore, a nano-CeO_2 dossier submitted to the WPMN/OECD within the Sponsorship Programme for the Testing of Manufactured Nanomaterials will become publicly available soon (http://www.oecd.org/science/nanosafety/).

Environment

The information on PC properties, environmental fate and behavior as well as environmental fate is limited within the dossier. Further information on particle characteristic (e.g. primary particle size, shape, coating) and their impact on environmental effects of the different registered grades will be necessary; Further information on soil, sediment, terrestrial environment effects, long term effects, bioaccumulation, fate and behavior, and release over the life cycle might be necessary to assess the nanoforms of the substance. The rationale for waiving and read across needs to be reconsidered.

5.5 Potential follow-up and link to risk management

☒ Harmonised C&L	☐ Restriction	☐ Authorisation	☐ Other (provide further details)
Depending on the outcome of the evaluation, harmonized classification and labelling might be a possible follow-up.			