Justification for the selection of a substance for CoRAP inclusion

Substance Name (Public Name):	Zinc Oxide
Chemical Group:	
EC Number:	215-222-5
CAS Number:	1314-13-2
Submitted by:	Germany
Date:	17/03/2015

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:	Zinc Oxide
IUPAC name:	oxozinc
Index number in Annex VI of the CLP Regulation	030-013-00-7
Molecular formula:	OZn
Molecular weight or molecular weight range:	81.4084 $g \cdot mol^{-1}$
Synonyms/Trade names:	

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

Note: The scope of this document is limited to the nanoform

Structural formula:

ZnO

2 CLASSIFICATION AND LABELLING

2.1 Harmonised Classification in Annex VI of the CLP

Table 2: Harmonised classification

Index No	International Chemical Identification	EC No	CAS No	Classification		Spec. Conc. Limits, M-factors	Notes
				Hazard Class and Category Code(s)	Hazard statement code(s)		
030-013-00-7	zinc oxide	215-222-5	1314-13-2	Aquatic Acute 1 Aquatic Chronic 1 DSD: N; R50-53	H400 H410		

2.2 Self classification

- In the registration

  The dossier differentiates 3 forms:

  - zinc oxide standard: see above
  - zinc oxide nano: see above
  - zinc oxide lower grade: see above, in addition:

Acute Tox. 4	H302,
Acute Tox. 4	H332
Repr. 1A	H360
STOT RE 2	H373

- The following hazard classes are in addition notified among the aggregated self classifications in the C&L Inventory (The inventory does not reveal which of these notifications applies to the nanoform. Hazard classes denoted with a star may be affected by impurities or additives in the notified material):

Skin Irrit. 2	H315
STOT SE 3	H335 (resp.)
STOT SE 1	H370 (lungs)
Skin Corr. 1B	H314*
Eye Dam. 1	H318*
Carc. 1A	H350*
Muta 2	H341*
Skin Sens. 1	H317*

2.3 Proposal for Harmonised Classification in Annex VI of the CLP

No proposal for harmonised classification is publically available.

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
☐ <1 . . . . . >+ tpa (e.g. 10+ ; 100+ ; 10,000+ tpa)		☐ Confidential

The tonnage for the nanoform is not provided.
According to SRI consulting, the global market size for zinc oxide nanomaterial is estimated to account for about 8,000 t.

Source: Commission Staff Working Paper - Types and uses of nanomaterials, including safety aspects COM(2012) 572 final:
http://ec.europa.eu/health/nanotechnology/docs/swd_2012_288_en.pdf

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

The substance has many different industrial, professional and consumer uses. The latter use encompasses wide dispersive indoor and outdoor uses concerning REACH. It also includes uses covered by other legislations (e.g. cosmetics, biocides). However, there is no allocation for a nanoform to a specific use. This information is very relevant for an adequate exposure assessment and its lack is therefore a major concern. Exposure at workplaces cannot be excluded for zinc oxide.
The Commission Staff Working Paper - Types and uses of nanomaterials, including safety aspects COM(2012) 572 final
(http://ec.europa.eu/health/nanotechnology/docs/swd_2012_288_en.pdf) states
"According to SRI, the global market for nanoform zinc oxide is several thousand tonnes per year. Major uses are as a UV-filter in cosmetics (where it competes with bulk zinc oxide but has the advantage of being transparent), in varnishes (as a UV-filter and self-cleaning agent), ceramics and electronics. Nanoform zinc oxide is also used in rubber, improving toughness, increasing abrasion resistance (e.g. reducing wear loss in tyres) and preventing UV and bacterial degradation. In this way, the life time of rubber products can be prolonged. An emerging use is zinc oxide nanowires for UV nanolasers. Uses are also reported in liquid crystal displays and solar cells.
Workplace exposure can occur at production, use, when machining materials and from waste and depends on the work procedure and applied risk management measures. Exposure to humans and the environment at the use stage varies according to application but can be high in particular in cosmetics. Another source of environmental exposure is wear of tyres. There are ongoing discussions whether release at the waste stage could lead to exposure to significant amounts of nanoparticles."

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)

Note: This justification document focuses on the nanoform and to some of the disseminated dossiers. It could not be clarified which of the dossiers include ZnO nanoforms and may provide any additional information.

Some disseminated dossiers consider ZnO in nanoform but the information provided is insufficient:

1. The material characterization is insufficient, preventing to adequately relate important physicochemical properties to toxicological effects (e.g. particle size information is often missing in toxicological records; reference for the test item to section 1 "General information" is inappropriate because of poor data given there).
2. Dossiers include a number of toxicological endpoint study records that used ZnO in nanoform. No nano-specific information is provided for the following endpoints:
   - Basic toxicokinetics
   - Skin sensitization
   - Repeated dose toxicity (RDT): oral
   - Carcinogenicity
   - Toxicity to Reproduction
3. Endpoint records that included ZnO in nanoform (see below) frequently used a specifically coated nanomaterial ("Z-COTE HP1"), often marked as key studies. However, there is no justification on how representative this nanomaterial is for "zinc oxide nano" referred to for classification (see above).
4. DNELs provided in the dossier do not differentiate between bulk and nanoform. A justification is not provided.
5. The dossiers identify a considerable number of uses including a variety of consumer uses. However, there is no allocation for a nanoform to a specific use.

   To summarize, the information available on material characterization, uses, and toxicology of nanoform ZnO is insufficient to allow an adequate risk assessment.

[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

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)

Information is required that allows a proper differentiation between the bulk form and the nanoform according to uses (to estimate release of and exposure by nanosized particles) and toxicological potency. Most importantly, information is needed that would justify the read-across of one nanoform to another, as some dossiers imply. Accordingly, comparative studies using different nanoforms (both coated and non-coated) may be required with regard to biokinetics and toxicology to relate nano-related properties (including dissolution, agglomeration, translocation, Trojan horse effect, cellular uptake and systemic availability) to adverse effects. If general conclusions are drawn, this should include the putatively most potent nanoform, together with a corresponding justification.

The following issues need particular consideration:

- The endpoints dermal absorption, irritation, sensitisation, subchronic inhalation toxicity, genetic toxicity in vitro and in vivo, as well as developmental toxicity included studies with ZnO nanomaterial. Most of the (key) studies were done with "Z-COTE HP1". The SEv should clarify if this nanoform is sufficiently representative for the hazard characterization of "zinc oxide nano".
- For example, a key 90 d RDT inhalation study (OECD 413) compared the (non-coated) bulk form of ZnO with "Z-COTE HP1" but not with a corresponding non-coated nanoform. In addition, the following issues need to be clarified:
    - Particle size information was not provided despite an MMAD < 3 µm (strong agglomeration?).
    - The derived NOAEC of 1.5 mg/m^3 for local effects is deemed too high, as activation of alveolar macrophages and lung-associated lymph nodes persisted during post-exposure.
    - Systemic toxicity was not reported, though organ weight increases of some distant organs were observed, which were attributed to dissolved zinc ions.
- Effects resulting from dissolution are controversial and require further consideration. For instance, ZnO nanoparticles may release Zn^{2+} ions (which proved highly cytotoxic in a number of in vitro studies) after reaching distant organs. Furthermore, due to delayed pulmonary clearance of nanoparticles compared to bulk particles following lung exposure, continuous release of Zn^{2+} ions may increase the local oxidative stress response (Fukui et al. 2012, Chemico-Biological Interactions 198, 29-37). Dissolution may also play a role following skin administration, e.g. when nanoparticles trapped in hair follicles shed Zn^{2+} ions over time.
- For the above reasons, read-across from zinc salts, as done in the dossier for reproductive toxicity, is very likely not appropriate for the hazard assessment of the nanomaterials, in particular when no biokinetic information (on the most potent form) is provided.

5.5 Potential follow-up and link to risk management

☐ Harmonised C&L	☐ Restriction	☐ Authorisation	☒ Other (provide further details)

Due to insufficient information on the toxicity of the nanoform of the substance a statement on potential follow-up action cannot be currently made.