Justification for the selection of a substance for CoRAP inclusion

Substance Name (Public Name):	Sodium perchlorate
Chemical Group:	
EC Number:	231-511-9
CAS Number:	7601-89-0
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

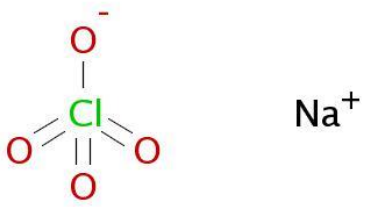
1.1 *Other identifiers of the substance*

Table 1: Substance identity

EC name:	Sodium perchlorate
IUPAC name:	Sodium perchlorate
Index number in Annex VI of the CLP Regulation	017-010-00-6
Molecular formula:	ClHO4.Na
Molecular weight or molecular weight range:	122.4404
Synonyms/Trade names:	Perchlorate de sodium Natriumperchlorat Perchloric acid, sodium salt

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

Structural formula:



1.2 Similar substances/grouping possibilities

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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)		
017-010-00-6	sodium perchlorate	231-511-9	7601-89-0	Ox. Sol. 1 Acute Tox. 4*	H271 H301		

2.2 *Self classification*

- In the registration (derivations from Annex VI entry):

  Acute Tox. 4 H302
  Eye Irrit. 2 H319
  STOT Rep. Exp. 2 H373
  (Affected organs: Thyroid, route of exposure: Oral)

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

  Ox. Liq. 1 H271

2.3 *Proposal for Harmonised Classification in Annex VI of the CLP*

None.

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	
☒ Industrial use	☐ Professional use	☐ Consumer use	☒ Closed System
Sodium perchlorate is u as an intermediate in synthesis and in additive formulations for plastic processing.			

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)	

Directive 2012/18/EU of the European Parliament and of the Council of 4 July 2012 on the control of major-accident hazards involving dangerous substances, amending and subsequently repealing Council Directive 96/82/EC (SEVESO III)
[Annex I - Qualifying quantity (tonnes) of dangerous substances as referred to in Article 3(10) for the application of: Lower-tier requirements: 50 tonnes / Upper-tier requirements: 200 tonnes: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32012L0018&rid=9]

Regulation (EU) No 98/2013 of the European Parliament and of the Council of 15 January 2013 on the marketing and use of explosives precursors (Text with EEA relevance) [Annex I – limit value 40% w/w: http://eur-lex.europa.eu/legal-content/EN/TXT/PDF/?uri=CELEX:32013R0098&from=EN]

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)

Perchlorates are known to competitively inhibit the uptake of iodide into thyroid cells and thus impair the thyroidal hormone synthesis which can lead to reduced levels of serum T3 and T4 in humans and animals. This can lead to the disruption of the thyroid signaling pathway of the endocrine system.[1] Thyroid hormones play a central role in the development of all vertebrate classes, amphibians and some reptiles and birds showing a highly conserved underlying biochemistry across different species. Hence, thyroid disruptors may exert similar adverse effects across at least all vertebrate species.[2] The studies cited above[1,2] and one read-across to the ecotoxicological key study (long term toxicity to fish according to OECD Guideline 215) in the registration dossier of ammonium perchlorate[3] reporting on biomarkers pointing to thyroid disrupting effects of perchlorates (e.g. cell hypertrophy and decreased colloidal immunostaining T4-ring intensity in zebrafish) in wild animals support the concern that sodium perchlorate is an environmentally relevant endocrine disrupting chemical in analogy to ammonium perchlorate. Additionally, the reproduction toxicity study performed with rats referred to in the registration dossier shows a clear antithyroidal effect (on the biomarker level) of perchlorates in the offspring as well as the parental animals. Together with the fact that the thyroid system is highly conserved among vertebrate species these data also support our concern that perchlorates pose a risk to wild vertebrate animals owing to their thyroid endocrine disruption potential.

The key effect of perchlorates in humans is reversible interference with the normal thyroidal uptake of iodide by competitive inhibition at the sodium iodide symporter (NIS) at high dosages, thus potentially contributing to disturbances in the HPT axis and thyroid hormone homeostasis. This property had been used in the past pharmacologically for the treatment of hyperthyroidism. In the same way as common alimentary iodine deficiency also the inhibition of iodide uptake into thyrocytes - e.g. following exposure to perchlorate - can potentially limit the availability of iodide required for the production of the thyroid hormones T3 and T4. This shortage in available iodide may cause depletion of thyroidal/extrathyroidal stores of these hormones and lower the hormone serum levels. Clinical data from healthy adults following both short-term and chronic exposure to perchlorate have shown that the inhibition of iodide uptake in humans is dose-dependent and that inhibition of iodide uptake may be operant to changes in TSH or thyroid hormone levels not before

[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

an NIS inhibition level of 50% is attained[4]. While these data are derived from healthy euthyroid adults, there are nevertheless populations and life stages which are considered more sensitive to iodine deficiencies, such as pregnant women and their fetuses, because of an increased demand for iodide during gestation to support growth and neurodevelopment. Appropriate levels of thyroid hormones during pregnancy are essential for normal fetal growth and for differentiation of many organs. In particular, neurological and cognitive development is dependent on adequate supply of thyroid hormones from fetal life until at least 2 years after birth. Fetal supply of thyroid hormones is completely dependent on the maternal thyroid hormones transferred via the placenta during early and mid-gestation gestation. Therefore, certain conditions during pregnancy, such as maternal hypothyroxinaemia and/or maternal iodine deficiency may be at an increased risk for adverse outcomes from perchlorate exposure because of the possible impact on thyroid hormone homeostasis. Although in epidemiological studies [5, 6, 7] perchlorate exposure has not yet been associated with substantial changes in maternal thyroid function in pregnant women, there is increasing concern that low level environmental perchlorate exposure might pose a health hazard by inducing or aggravating underlying thyroid dysfunction during pregnancy and accordingly affect growth and neurological and cognitive development of human offspring[8].

The data provided in the dossier regarding the persistency and mobility of sodium perchlorate in aqueous and terrestrial environments indicate that this substance must be considered as persistent and highly mobile in the environment.

The registration dossier includes a waiver for carcinogenicity testing even though thyroid follicle adenomas were observed in two male rats when tested with the analogous substance ammonium perchlorate (CAS 7790-98-9) in a two-generation reproduction toxicity study. In his justification for a waiver the registrant does acknowledge that perchlorates are substances which are known to stimulate thyroid tissues and which may induce benign tumours under specific circumstances but he also considers a "causal relationship with malignant thyroid tumours not established and unlikely". Within the framework of a substance evaluation it shall be clarified whether the registrants' conclusion regarding sodium perchlorate's carcinogenic potential can be supported or not. The proposed self-classification for STOT RE 2 with the thyroid as target organ might need to be changed to STOT RE 1 based on evidence in humans.

Due to the high tonnage (> 1000 t) wide dispersive use with high potential of exposure is anticipated.

[1] Brucker-Davis F. Effects of environmental synthetic chemicals on thyroid function. *Thyroid* 1998, 8, 827-856.
[2] UNEP Report: Endocrine disrupting chemicals – 2012. Chapter 2.5 Endocrine disruptors and thyroid-related disorders and diseases. 2012, 91-108.

[3] Mukhi S, Carr JA, Anderson TA, Patino R. Novel biomarkers of perchlorate exposure in zebrafish. 2005, 24(5), 1107-1115.

[4] JECFA 2011: Safety evaluation of certain contaminants in food, prepared by the Seventy-second meeting of the Joint FAO/WHO Expert Committee on Food Additives (JECFA), WHO food additives series: 63; FAO JECFA monographs, 8; FAO & WHO, 685-762, 2011 ; WHO technical report series 959: 64-73, 2011

[5] Pearce EN, Lazarus JH, Smyth PP, He X, Dall'amico D, Parkes AB, Burns R, Smith DF, Maina A, Bestwick JP, Jooman M, Leung AM, Braverman LE. Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women. J Clin Endocrinol Metab. 2010 Jul;95(7):3207-15. doi: 10.1210/jc.2010-0014

[6] Pearce EN, Alexiou M, Koukkou E, Braverman LE, He X, Ilias I, Alevizaki M, Markou KB. Perchlorate and thiocyanate exposure and thyroid function in first-trimester pregnant women from Greece. Clin Endocrinol (Oxf). 2012 Sep;77(3):471-4. doi: 10.1111/j.1365-2265.2012.04407.x..

[7] Pearce EN, Spencer CA, Mestman JH, Lee RH, Bergoglio LM, Mereshian P, He X, Leung AM, Braverman LE. Effect of environmental perchlorate and thyroid function in pregnant women from Cordoba, Argentina, and Los Angeles, California. Endocr Pract. 2011 May-Jun;17(3):412-7. doi: 10.4158/EP10293.OR.

[8] Leung AM, Pearce EN, Braverman LE Perchlorate, iodine and the thyroid. Best Pract Res Clin Endocrinol Metab. 2010 Feb;24(1):133-41. doi: 10.1016/j.beem.2009.08.009

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)

Sodium perchlorate is suspected of possessing potential endocrine disrupting properties in the environment and for humans. The ecotoxicological data provided in the registration dossier is not sufficient to come to a final conclusion on this concern since in the cited long term fish study only some hints on the biomarker level are presented and especially vulnerable life stages (e.g. fish embryo) are not covered. Additionally, there are literature data (e.g. AMA) available addressing thyroid specific endpoints but without allowing for a conclusion on apical endpoints.

Thus, additional information from non-standard tests may be necessary to clarify the concern. This information could be provided by e.g. a FFLC study addressing thyroid specific endpoints to link the effects observable at the biomarker level with adverse effects on the organism and population level.

It is unclear whether sodium perchlorate needs to be classified as carcinogen and whether further toxicological information is needed to clarify this endpoint. If the substance evaluation indicates that risks for workers arise, further information on exposure might be necessary.

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 substance evaluation and further studies a harmonized classification for carcinogenicity and STOT RE might be necessary or the identification as an environmental endocrine disruptor. An analysis of risk management options will be carried out, taking into account information on use and exposure. Potential options are the inclusion in the Candidate List with or without Authorisation, but also Restriction.