# Justification for the selection of a substance for CoRAP inclusion

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|---|---|
| **Substance Name (Public Name):** | Ammonium perchlorate |
| **Chemical Group:** | |
| **EC Number:** | 232-235-1 |
| **CAS Number:** | 7790-98-9 |
| **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**

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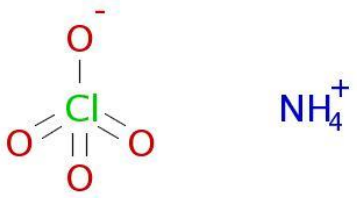
|---|---|
| **EC name:** | Ammonium perchlorate |
| **IUPAC name:** | Ammonium perchlorate |
| **Index number in Annex VI of the CLP Regulation** | 017-009-00-0 |
| **Molecular formula:** | $ClHO_4.H3N$ |
| **Molecular weight or molecular weight range:** | 117.49 $g \cdot mol^{-1}$ |
| **Synonyms/Trade names:** | Perchloric acid, ammonium salt |

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

**Structural formula:**



# 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) | | |
| 017-009-00-0 | | 232-235-1 | 7790-98-9 | Expl. 1.1<br>Ox. Sol. 1 | H201<br>H271 | | * |

* This substance may be marketed in a form which does not have the physical hazards as indicated by the classification in the entry in Part 3. If the results of the relevant method or methods in accordance with Part 2 of Annex I of this Regulation show that the specific form of substance marketed does not exhibit this physical property or these physical hazards, the substance shall be classified in accordance with the result or results of this test or these tests. Relevant information, including reference to the relevant test method(s) shall be included in the safety data sheet.

## 2.2 Self classification

- In the registration (*deviations from Annex VI)*

  STOT RE 2 H373
  (May cause damage to organs through prolonged or repeated exposure. Affected organs: thyroid)

  Eye Irrit. 2H319: Causes serious eye irritation.

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

## 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 |

| ☒ Industrial use | ☒ Professional use | ☒ Consumer use | ☒ Closed System |
|---|---|---|---|

Ammonium perchlorate is registered for uses as an intermediate in synthesis, in additive formulations for plastic processing and as comburant for explosives (e. g. pyrotechnic articles).

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

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|---|---|
| ☐ 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 an 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

# 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<br>☐C ☐M ☐R | Suspected CMR[1]<br>☒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) |

[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

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 of the ecotoxicological key studies (long term toxicity to fish according to OECD Guideline 215) in the registration dossier[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 ammonium perchlorate is an environmentally relevant endocrine disrupting chemical. Additionally, the reproduction toxicity study performed with rats cited in the registration dossier shows a clear antithyroidal effect (on the biomarker level) of ammonium perchlorate 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 at high dosages by competitive inhibition of the sodium iodide symporter (NIS) 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 with potassium perchlorate. Similar to 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 for changes in TSH or thyroid hormones not before 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. Therefore, certain conditions during pregnancy, such as maternal hypothyroxinanemia and/or maternal iodine deficiency may be at an increased risk for adverse effects from perchlorate exposure because of the possible impact on thyroid hormone homeostasis. Although in epidemiological studies [5, 6, 7] perchlorate exposures have 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[8] by inducing or aggravating underlying thyroid dysfunctions during pregnancy and accordingly affect growth and neurological and cognitive development of human offspring.

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

Results from a two-generation reproduction toxicity study (OECD 416) indicate a possible carcinogenic potential of ammonium perchlorate since thyroid follicle adenomas were observed in two male rats. Data from a carcinogenicity study are provided from a study conducted with the analogous substance potassium perchlorate (CAS 7778-74-7). However, only a reliability grade of Klimisch 4 is assigned to this study. When evaluating the carcinogenic potential of ammonium perchlorate, the registrants state that a causal relationship between perchlorates and malignant thyroid tumours "is not established and seems unlikely". In order to clarify whether carcinogenic properties can be ruled out or not and whether exposure to the substance poses risks to workers a substance evaluation is proposed for ammonium perchlorate.

Sodium perchlorate has a harmonised classification for Acute Tox. 4*, H302. If read across to ammonium perchlorate is justified, a classification on the hazard class may also be relevant for ammonium perchlorate.

There are significant differences in self classifications between notifiers with regard to the hazard classes 'eye irritation' and 'STOT RE'. Considering read-across to sodium perchlorate and inconsistencies in the self-classification on eye irritation it is necessary to check whether harmonized classification should be proposed.

Sufficient information from animal tests (90-d drinking water repeat dose toxicity study, two-generation reproduction toxicity study) and from human data (e.g. human volunteer study Greer et al., 2002, Draft EFSA Opinion) is available. Some notifiers classified the substance as STOT RE 2, H373 (Thyroid) while others did not. The self-classification of the registrants 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 marketed tonnage (> 1000 t/a) and identified uses in industrial and professional (handling of pyrotechnic articles) settings a wide dispersive use situation and a large collective of exposed worker 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) |

Ammonium perchlorate is suspected of possessing potential endocrine disrupting properties in the environment and for humans. The ecotoxicological data provided in the registration dossier is insufficient 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 ammonium perchlorate needs to be classified as a 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.