SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

ammonium perchlorate

EC No 232-235-1

CAS No 7790-98-9

Evaluating Member State(s): Germany

Dated: 10 August 2016

Evaluating Member State Competent Authority

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Year of evaluation in CoRAP: 2015

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.

Further information on registered substances here:

http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

DISCLAIMER

This document has been prepared by the evaluating Member State as a part of the substance evaluation process under the REACH Regulation (EC) No 1907/2006. The information and views set out in this document are those of the author and do not necessarily reflect the position or opinion of the European Chemicals Agency or other Member States. The Agency does not guarantee the accuracy of the information included in the document. Neither the Agency nor the evaluating Member State nor any person acting on either of their behalves may be held liable for the use which may be made of the information contained therein. Statements made or information contained in the document are without prejudice to any further regulatory work that the Agency or Member States may initiate at a later stage.

Foreword

Substance evaluation is an evaluation process under REACH Regulation (EC) No. 1907/2006. Under this process the Member States perform the evaluation and ECHA secretariat coordinates the work. The Community rolling action plan (CoRAP) of substances subject to evaluation, is updated and published annually on the ECHA web site[1].

Substance evaluation is a concern driven process, which aims to clarify whether a substance constitutes a risk to human health or the environment. Member States evaluate assigned substances in the CoRAP with the objective to clarify the potential concern and, if necessary, to request further information from the registrant(s) concerning the substance. If the evaluating Member State concludes that no further information needs to be requested, the substance evaluation is completed. If additional information is required, this is sought by the evaluating Member State. The evaluating Member State then draws conclusions on how to use the existing and obtained information for the safe use of the substance.

This Conclusion document, as required by Article 48 of the REACH Regulation, provides the final outcome of the Substance Evaluation carried out by the evaluating Member State. The document consists of two parts i.e. A) the conclusion and B) the evaluation report. In the conclusion part A, the evaluating Member State considers how the information on the substance can be used for the purposes of regulatory risk management such as identification of substances of very high concern (SVHC), restriction and/or classification and labelling. In the evaluation report part B the document provides explanation how the evaluating Member State assessed and drew the conclusions from the information available.

With this Conclusion document the substance evaluation process is finished and the Commission, the Registrant(s) of the substance and the Competent Authorities of the other Member States are informed of the considerations of the evaluating Member State. In case the evaluating Member State proposes further regulatory risk management measures, this document shall not be considered initiating those other measures or processes. Further analyses may need to be performed which may change the proposed regulatory measures in this document. Since this document only reflects the views of the evaluating Member State, it does not preclude other Member States or the European Commission from initiating regulatory risk management measures which they deem appropriate.

[1] http://echa.europa.eu/regulations/reach/evaluation/substance-evaluation/community-rolling-action-plan

Contents

Part A. Conclusion

1. CONCERN(S) SUBJECT TO EVALUATION

Ammonium perchlorate was originally selected for substance evaluation in order to clarify concerns about:

- Endocrine disruption in the environment
- Wide dispersive use
- Human health: Suspected CMR (carcinogenic) and thyroid toxicity
- Human health: potential endocrine disrupter
- Human health: high potential worker exposure

In parallel, the evaluating member state competent authority (eMSCA) evaluated sodium perchlorate, another perchlorate salt registered under REACH in a high tonnage band.

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

The substance is listed in Annex I of 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) and Annex I of 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).

3. CONCLUSION OF SUBSTANCE EVALUATION

The evaluation of the available information on the substance has led the evaluating Member State to the following conclusions, as summarised in the table below.

Table 1

CONCLUSION OF SUBSTANCE EVALUATION Conclusions	Tick box
Need for follow-up regulatory action at EU level	X
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	X
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level	

4. FOLLOW-UP AT EU LEVEL

4.1. Need for follow-up regulatory action at EU level

Environment

As a result of this substance evaluation, the endocrine mode of action of the perchlorate anion (i.e. inhibition of the thyroid sodium iodide symporter that transports iodide anion into the follicular cells and thereby downregulating the thyroid hormone production) and adverse endocrine effects evoked by this mode of action on organism-level (such as impaired metamorphosis and development, disturbed reproduction, hermaphroditism and skewed sex ratios, as well as reduced stress tolerance and impaired behaviour) could be demonstrated by the studies relevant for assessing effects in the environment evaluated in this report. This renders sodium perchlorate, other perchlorate salts and their precursor substances potential candidates for SVHC identification according to Art 57(f) of REACH regarding their environmental hazard aspects, which might be of equivalent concern like established for PBT-or vPvB-substances.

A SVHC identification and inclusion of perchlorate salts and precursors in Annex XIV would possibly affect the future production or import of perchlorates and their precursors. At least from the current registrations no significant releases are expected, thus the authorisation procedure would not be an effective risk reduction measure. Given the high background concentration of perchlorate (due to former releases or due to releases of perchlorate precursors), other EU-wide regulatory risk management measures might be appropriate to address the environmental concern. Thus, there is a need for a follow-up EU regulatory action, although the most effective legislative measures cannot yet be determined concluding on this substance evaluation. A possible SVHC identification of perchlorates and their precursors under Art. 57(f) could be an important first step to support EU-wide regulatory action also outside of the REACH framework. Accordingly, a subsequent RMOA prepared by the eMSCA should clarify the appropriate option(s) of risk management.

Worker

Ammonium perchlorate is manufactured and used as powders of low, medium or high dustiness, as a slurry (wet solid) or as an aqueous solution. For handling dusty materials, depending on the PROCs, exposure levels are often above the DNELs. For high dusty materials, the highest exposure levels are observed.

The combined RCRs for workers exceed in most exposure scenarios the value of 1 (maximum: 35) mainly caused by a high inhalation exposure. However, the risk characterization presented here is based on thyroidal iodine uptake inhibition which is a precursor effect for thyroid disorders. This precursor effect is not considered to be adverse by the eMSCA. Nevertheless, a dose-response relationship for adverse effects (e.g. changes in thyroid hormone levels) in humans is not available. Also there are no reliable human data on relationship between thyroidal iodine uptake inhibition and adverse effects on thyroid. Furthermore, a quantitative extrapolation from rodents to human is not possible due to substantial differences in thyroid hormone physiology. Based on the available human data RCRs above 1 were calculated by the eMSCA, but the eMSCA does not know to what degree these high RCRs really represent health risks to workers. However, it cannot be excluded by the eMSCA that a permanent inhibition of thyroidal iodine uptake by ammonium perchlorate leads to adverse effects on thyroid. For risk characterization it has further to be kept in mind that there are several parameters which could lead to a more critical situation for workers. Firstly, the dietary intake of iodine is a relevant factor. The inhibitory effects of perchlorate anion could have a greater impact on individuals with a low iodine dietary intake. EFSA stated that available data indicate that a substantial part of the EU population is subject to a mild to moderate iodine deficiency (EFSA, 2014). Furthermore, goitrogenous substances in foods, drinking water or cigarette smoke may inhibit the thyroidal iodine

uptake which will act on top of the inhibition by ammonium perchlorate exposure at workplace. Therefore, the eMSCA cannot exclude a health risk by ammonium perchlorate exposure for workers. Primarily, the eMSCA considers actions by the registrants as important risk management measures to ensure an adequate handling of ammonium perchlorate without a health risk (e.g. further risk management measures, occupational health checks). However, a future need for follow-up action cannot be excluded if new information on the dose-response relationship for adverse effects in humans becomes available.

4.1.1. Harmonised Classification and Labelling

Not applicable.

4.1.2. Identification as a substance of very high concern, SVHC (first step towards authorisation)

Based on the hazardous intrinsic properties of perchlorate, SVHC identification under Article 57 f of REACH seems to be well substantiated based on its endocrine disrupting effects in the environment which has been thoroughly evaluated in this report. Although an inclusion of perchlorates and precursor substances in the Annex XIV might not be an effective regulatory measure, to support follow-up EU regulatory actions outside of REACH, SVHC identification might be of high supportive relevance.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

See section 4.1.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

5.1. No need for regulatory follow-up at EU level

According to the available data for acute oral toxicity of ammonium perchlorate, the substance should be classified as Acute Tox 4. The eMSCA recommends that registrants reflect this classification in their self-classification.

5.2. Other actions

Not applicable.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS (IF NECESSARY)

Indication of a tentative plan is not a formal commitment by the evaluating Member State. A commitment to prepare a REACH Annex XV dossier (SVHC, restrictions) and/or CLP Annex VI dossier shall be made via the Registry of Intentions.

Table 2

FOLLOW-UP Follow-up action	Date for intention	Actor
Risk management option analysis	June 2016	Germany

The properties as an endocrine disruptor to the environment of the substance which necessitate the preparation of an RMOA analysis in the eyes of the eMSCA are related to the perchlorate anion which can be found in more substances apart from ammonium perchlorate which are registered under REACH and which can release perchlorate e.g. by dissociation. Therefore, an RMOA intention has been published by the eMSCA for "Perchloric acid and its salts" following the formal conclusion of the substance evaluation period. This RMOA is aimed to reflect the broader scope of the affected substances other than those which have undergone substance evaluation which may contribute to the burden of perchlorate measured in the environment.[2]

[2] ECHA PACT section on "Perchloric acid ant its salts": https://echa.europa.eu/addressing-chemicals-of-concern/substances-of-potential-concern/pact/-/substance-rev/13912/term?_viewsubstances_WAR_echarevsubstanceportlet_SEARCH_CRITERIA_EC_NUMBER=231-512

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

Ammonium perchlorate was originally selected for substance evaluation in order to clarify concerns about:

- Human health: Suspected CMR (carcinogenic) and thyroid toxicity,
- Human health: High potential for worker exposure due to high tonnage (> 1000t) and wide dispersive use
- Potential endocrine disruptor for the human health and the environment.

Table 3

EVALUATED ENDPOINTS **Endpoint evaluated**	**Outcome/conclusion**
Repeated dose toxicity	Repeated dose toxicity was evaluated due to a concern regarding specific target organs toxicity after repeated exposure (STOT-RE) with the thyroid as target organ. The eMSCA concludes that classification as STOT-RE Cat. 2 is appropriate. *Concern not substantiated. No further action.*
Mutagenicity	Mutagenicity was evaluated due to a concern regarding the potential of perchlorate to cause cancer in humans. The eMSCA concludes that non-classification for mutagenicity is appropriate. *No further action.*
Carcinogenicity	Carcinogenicity was evaluated due to a concern regarding the potential of perchlorate to cause cancer in humans. The eMSCA concludes that non-classification for carcinogenicity is appropriate. *Concern not substantiated. No further action.*
Endocrine disruption - Human health	Endocrine disrupting properties were evaluated due to a concern regarding the potential of perchlorate to act as an endocrine disruptor of thyroid hormone homeostasis in humans. *On the basis of the available human data the concern is not substantiated. No further action.*
Endocrine disruption - Environment	Endocrine disrupting properties were evaluated due to a concern regarding the potential of perchlorate to act as an endocrine disruptor of thyroid hormone homeostasis in wildlife animals. Endocrine disrupting properties of perchlorate were evaluated assessing endpoints of perchlorate interaction with the hypothalamus-pituitary- thyroid axis in fish, amphibians and mammals.

	Concern substantiated. RMOA and possible SVHC identification under Art. 57 f, as well as EU-wide regulatory measures are proposed.
Worker exposure	Actions by the registrants are considered as important risk management measures by the eMSCA to ensure an adequate handling of the substance without a health risk (e.g. further risk management measures, occupational health checks). On the basis of the currently available human data, no additional regulatory risk management measures regarding occupational risks are currently in order. A re-evaluation may be required in case new information becomes available regarding the dose-response relationship for adverse effects in humans. *No further action.*

Considerations on read-across by the eMSCA applied during the evaluation

The eMSCA considers read-across between the two registered substances ammonium perchlorate and sodium perchlorate which were evaluated in 2015 in parallel as possible for the endpoint of concern, i.e. toxicity to the thyroid (including carcinogenicity) after repeated exposure.

According to the registration dossiers both substances are mono-constituents without impurities preventing the proposed read-across approach. Both substances share the perchlorate anion and are readily soluble in water. In aqueous solutions they are expected to dissociate into the according cation and the perchlorate anion, resulting in a lower pH for an ammonium perchlorate solution. In general, perchlorates are readily absorbed and become systemically available in experimental animals and humans. The proposed mode-of-action model, suggests inhibition of the thyroidal iodide uptake as initial step of thyroid effects (NRC, 2005). This could be demonstrated with sodium, ammonium and also potassium perchlorate determining thyroidal radioactive iodine uptake (Eskin et al. 1975, Greer et al. 2002, Lawrence et al. 2000, and Lawrence et al. 2001). Further outcomes such as decreases in thyroid hormones, increases in thyroid stimulating hormone, adaptive thyroid hypertrophy and thyroid hyperplasia could be established in experimental animals with ammonium and potassium perchlorate, pointing to the relevance of the perchlorate anion as toxic moiety (Siglin et al., 2000, York et al. 2001a, b, Gauß, 1972, EFSA 2015). Therefore the eMSCA considers the read across approach to be justified and included relevant data on potassium perchlorate for purpose of this substance evaluation. These further steps are as well proposed for humans, but have not been demonstrated so far (NRC 2005).

Although the endpoints of acute toxicity were not included in the substance evaluation they have been consulted in order to gain further insight into the appropriateness of the read across approach. Except for acute oral toxicity, information is only available with sodium perchlorate. The information was used for read-across to ammonium perchlorate and ammonium perchlorate was accordingly self-classified as eye-irritating cat. 2. For acute oral toxicity data on sodium, ammonium and potassium perchlorate are available, pointing to a difference in the acute oral toxicity of ammonium perchlorate. In view of the eMSCA there is a reliable source indicating an LD50 below 2000 mg/kg bw in mice based on a range finding study for a micronucleus test (Sharma, 1998). This is supported by a study with incomplete reporting (Shigan, 1963), where LD50 of 1900 mg/kg for mice and rabbits (and >2000 for rats and Guinea pigs) were determined. The read across for acute oral toxicity is not acceptable and ammonium perchlorate should be classified as acutely toxic Cat. 4 by the oral exposure route.

7.2. Procedure

The two perchlorate salts ammonium perchlorate and sodium perchlorate were included in the Community Rolling Action Plan for substance evaluation 2015-2017 which was published on 17 March 2015, their evaluation scheduled for immediate evaluation in 2015. The member state competent authority of Germany was appointed to carry out the evaluation.

7.2.1.1. Environment

Regarding the environmental effects of the perchlorate anion, the eMSCA focused on the endocrine disrupting effects in this substance evaluation. The evaluation was based on the registration dossiers and peer-reviewed publications from the scientific literature on perchlorate interaction with the hypothalamus-pituitary-thyroid axis assessing aquatic organisms as they are the most vulnerable taking into account potential environmental exposure routes.

7.2.1.2. Human Health

The evaluation of the toxicity of perchlorate has been based on the registration dossiers as well as on reviews by a variety of international bodies/regulatory programs and original publications. Data available up to November 2015 for all endpoints have been assessed. The potential of perchlorate to act as an endocrine disruptor, the classification for thyroid toxicity and the non-classification of perchlorate for carcinogenicity provided by the lead registrant were reviewed.

7.2.1.3. Worker exposure

The exposure assessment is based on the data provided in the registration. The German CA considers the following aspects of particular importance for exposure scenarios for worker:
- Sufficient description of operational conditions and risk management measures including personal protective equipment.
- The order of priority for protective and prevention measures shall comply with the order as laid down in Directive 98/24/EG Art.6(2) (EC, 2014a).
Information provided by the Registrants after a meeting during the evaluation period was received and taken into account.

7.3. Identity of the substance

Table 4

SUBSTANCE IDENTITY	
Public name:	Ammonium perchlorate
EC number:	232-235-1
CAS number:	7790-98-9
Index number in Annex VI of the CLP Regulation:	017-009-00-0
Molecular formula:	NH_4ClO_4
Molecular weight range:	117.49 g/mol
Synonyms:	Perchloric acid, ammonium salt

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

Structural formula:

NH_4^+ ClO_4^-

Table 5

READ ACROSS SUBSTANCE IDENTITY	
Public name:	Sodium perchlorate
EC number:	231-511-9
CAS number:	7601-89-0
Index number in Annex VI of the CLP Regulation:	017-010-00-6
Molecular formula:	$NaClO_4$
Molecular weight range:	122,44 g/mol
Synonyms:	Perchloric acid, sodium salt

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

Structural formula:

Na^+ ClO_4^-

7.4. Physico-chemical properties

Table 6

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES OF AMMONIUM PERCHLORATE	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Solid white powder, odourless
Vapour pressure	calculated: 8.3E-12 Pa at 25°C
Water solubility	205.9 g/L at 20°C
Partition coefficient n-octanol/water (Log Kow)	calculated: Log K_{OW} -5.84 at 25°C
Flammability	idem
Explosive properties	idem
Oxidising properties	idem
Granulometry	Different sizes in µm range are manufactured
Stability in organic solvents and identity of relevant degradation products	Substance is inorganic. No test required.
Dissociation constant	Substance is an inorganic salt, which dissociate in water
Density	1.95 g/mL at 20°C
Melting point	≥150°C under decomposition

7.5. Manufacture and uses

Ammonium perchlorate is produced by reaction between ammonia and perchloric acid, or by reaction of ammonium salts with sodium perchlorate.

Ammonium perchlorate is mainly used for the production of solid fuel propellants. These composite propellants are composed of fuel and oxidizer mixed with a rubbery binder, all combined into a homogeneous mixture. The perchlorate serves as the oxidizer, while the binder and e.g. aluminium serve as the fuel.

7.5.1. Quantities

Table 7

AGGREGATED TONNAGE (PER YEAR)				
☐ 1 – 10 t	☐ 10 – 100 t	☐ 100 – 1000 t	☒ 1000- 10,000 t	☐ 10,000-50,000 t
☐ 50,000 – 100,000 t	☐ 100,000 – 500,000 t	☐ 500,000 – 1000,000 t	☐ > 1000,000 t	☐ Confidential

7.5.2. Overview of uses

Table 8

USES	Use(s)
Uses as intermediate	See formulation
Formulation	Handling of dry ammonium perchlorate (manufacture or formulation), PROC 3, 4, 5, 8b, 9, 14, 21 Handling of ammonium perchlorate in laboratory, PROC 15
Uses at industrial sites	Manufacture of propellant blocks (grains) or composite explosives or other energetic components containing Ammonium perchlorate PROC 3, 14 ,21 Handling and transforming reticulated propellant blocks (grains) containing Ammonium Perchlorate, Proc 21, 24
Uses by professional workers	Service life of pyrotechnic articles containing ammonium perchlorate (including burning) – downstream use by worker and consumer PROC 0 (other)
Consumer Uses	-
Article service life	-

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 9

HARMONISED CLASSIFICATION ACCORDING TO ANNEX VI OF CLP REGULATION (REGULATION (EC) 1272/2008)							
Index No	**International Chemical Identification**	**EC No**	**CAS No**	**Classification**		**Spec. Conc. Limits, M-factors**	**Notes**
				Hazard Class and Category Codes	**Hazard statement codes**		
017-009-00-0	ammonium perchlorate [containing ≥ 80 % of 0-30 µm particles]	232-235-1	7790-98-9	Expl. 1.1 Ox. Sol. 1	H201 H271		Note T

7.6.2. Self-classification

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

  Eye Irrit. 2, H319
  STOT RE 2, H373 (thyroid)
  EUH044

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

  none

7.7. Environmental fate properties

Not in the scope of this evaluation.

7.8. Environmental hazard assessment

Not in the scope of this evaluation.

7.9. Human Health hazard assessment

7.9.1. Toxicokinetics

7.9.1.1. Absorption

Oral:
Perchlorate is readily and extensively absorbed from the gastro-intestinal tract in humans and rats. (ATSDR 2008, JECFA 2011): rapid in rat: peak blood concentrations by 3 h,

human: perchlorate in urine from 10 minutes after ingestion) and nearly complete (human 95 %, rat 99.5 %)

Dermal:
Expected to be low based on physico-chemical data and as electrolytes applied from aqueous solutions do not readily penetrate the skin (Scheuplein and Bronaugh 1983). From the skin irritation data and the acute dermal toxicity data there are no contrary indications. Supporting evidence was provided on read-across substance sodium chlorate. The registrants concluded dermal absorption of the substance is 1.85 %, and based on the available information the eMSCA can support this conclusion.

Inhalation:
No studies were found regarding quantitative absorption of perchlorate after inhalation exposure. Pulmonary absorption may occur (Lamm et al. 1999), if perchlorate particles were suspended in air, depending on the particle size, small particles reaching the alveoli would dissolve and readily enter the systemic circulation due to the aqueous solubility of perchlorate salts.

7.9.1.2. Distribution

Following absorption, perchlorate is widely distributed in the body (human serum, plasma, urine, saliva and breast milk) with the highest concentrations occurring in the thyroid. (EFSA 2015)

7.9.1.3. Metabolism

Evidence indicates that perchlorate undergoes very little, if any metabolism (Wolff, 1998; Fisher et al., 2000; ASTDR, 2008).

7.9.1.4. Excretion

Perchlorate is rapidly excreted mainly in the urine as unchanged parent compound (EFSA 2015); main pathway of elimination is via urine: half-live rat: 8-20 h, humans: 8-12 h (ATSDR 2008). Almost all radiolabelled perchlorate (99.5 %) was recovered from urine within 48 hours following intravenous administration in rats. (EFSA 2015)

7.9.2. Acute toxicity and Corrosion/Irritation

Not relevant for clarification of the concern.

7.9.3. Sensitisation

Not relevant for clarification of the concern.

7.9.4. Repeated dose toxicity

7.9.4.1. Animal data on repeated dose toxicity after oral exposure

Table 10

OVERVIEW OF EXPERIMENTAL STUDIES ON REPEATED DOSE TOXICITY, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
OECD TG 408 (deviations regarding the housing temperature. No histological examination of Peyer's patches.)	LOAEL: 10 mg AP/kg bw per d	LOAEL/NOAEL based on thyroid hyperplasia	Siglin et al., 2000

Ammonium Perchlorate (purity 99.8 %) Oral route 90 d (terminal and 30d recovery groups) 14 d (satellite groups) **rat** (Sprague-Dawley) Main: 10m + 10f per group Satellite/recovery Nominal in diet 0, 0.01, 0.05, 0.2, 1, 10 mg AP/kg per d "Highest dose chosen with the aim to induce antithyroid effects, but not based on dose-limiting toxicity."	NOAEL: 1 mg AP/kg bw per d LOEL: 0.01 mg AP/kg bw per d (thyroid hormone levels) <u>10 mg AP/kg bw per d:</u> thyroid: hypertrophy and hyperplasia in F and M, reversible, thyroid weights ↑ <u>≥0.2 mg AP/kg bw per d:</u> TSH ↑ (M, 90d sacrifice) <u>≥0.05 mg AP/kg bw per d:</u> TSH ↑ (F, recovery group) <u>≥0.01 mg AP/kg bw per d:</u> T3↓ T4↓ statistically significant	T3 (F), T4 (M) and TSH (F) not fully reversible No treatment related effects on haematology, clinical chemistry, ophthalmology, sperm parameters and oestrous cyclicity no effects on investigated tissues and organs (including mammary gland)	
OECD TG 416 (one litter per generation) **Ammonium perchlorate** (purity 99.8%) oral: drinking water P1: 113 to 137 days F1 adults: 125 to 142 days **Rat** (Sprague-Dawley) 30 M / 30 F per dose and group 0, 0.3, 3, 30 mg AP/kg bw per day	NOAEL (Reproductive toxicity): ≥ 30 mg AP/kg bw per d LOAEL P1/F1 (Antithyroid effects): 3 mg AP/kg bw per d ≥ <u>3 mg AP/kg bw per d:</u> follicular hyperplasia/hypertrophy (number of small follicles↑ /enlarged follicular epithelium) ≥ <u>30 mg AP/kg bw per d:</u> thyroid follicle hypertrophy and hyperplasia, ↑ TSH F1: thyroid follicular-cell adenomas (2/30)	no effects on reproductive function, fertility and pup growth no effects on investigated tissues and organs (including mammary gland) no general parental toxicity	York et al. 2001a
OECD TG 414/ EPA OPPTS 870.3700 **Ammonium perchlorate** (purity 99.8%) oral: drinking water 23 days: GD 6 – 28 **Rabbit** (New Zealand White) 25 F 0, 0.1, 1, 10, 30 and 100 AP mg/kg bw per day	NOAEL (Maternal toxicity): 1 mg AP/kg bw per d LOAEL (Antithyroid effects): 10 mg AP/kg bw per d ≥ <u>10 mg AP/kg bw per d:</u> thyroid follicle hypertrophy and hyperplasia (↑ incidence) ≥ <u>30 mg AP/kg bw per d:</u> T4↓, ↓ abs. + rel. thyroid weight	Maternal MTD is above 100 mg/kg per d. No other effect than antithyroid effects at any dose, in does. no developmental effects	York et al. 2001b
No GL followed **Ammonium perchlorate** (purity not given) Oral: drinking water 14 d **rat** (Sprague-Dawley)	NOAEL: Females: 0.12 mg/kg bw per day Males: 0.44 mg/kg bw per day LOAEL: Females: 0.47 mg/kg bw per day	No info on GLP; data scattered in a total of 4 sources without a comprehensive report	Caldwell et al. 1995

F + M 6/group Females: 0, 0.12, 0.47, 1.2, 3.1, 4.9, 11 and 25 mg/kg bw per day Males: 0, 0.11, 0.44, 1.1, 2.3, 4.3, 11 and 22 mg/kg per day basis for dose levels unclear (ammonium perchlorate or perchlorate ion)	Males: 1.1 mg/kg bw per day ≥4.7 mg/kg bw per day: T3↓, T4↓, thyroglobulin↑, TSH↑, rT3↑, thyroid follicle hypertrophy ↑ (incidence and severity) 1.1/3.1 mg/kg bw per d (M/F): see above, but unaffected thyroid weight 0.11/0.12 mg/kg bw per d: T3↓, T4↓, thyroglobulin↑ (F+M) and follicular hypertrophy↑ (M only).		
No GL followed **Sodium perchlorate** (purity not given) Oral: drinking water 8 weeks **rat** (Sprague-Dawley) 6 F/group 0 and 4 g/L (corresponding to ≈340-500 mg/kg bw per d based on reported bw and default drinking water consumption according to CLP Guidance) basis for dose levels unclear (SP or perchlorate) i.p. injections of ^{125}I, investigation of RAIU in thyroid, mammary gland	Radioactive iodine uptake ↓ in thyroid (by 95%) and mammary gland (by 52%) leading to mild atrophy, atypia of the lobular epithelium and scattered foci of marked hyperplasic activity of the mammary gland LOAEL equals the administered dose of ≈340-500 mg/kg bw per d	Only one dose tested, no investigation of thyroid hormones or TSH	Eskin et al. 1975
No GL followed **Potassium perchlorate** (purity given as "p. a.") Oral in feed and drinking water for up to 160 d (43 Females) 35 d of treatment and 31 recovery (17 Females) 64 d of treatment for bw (21 Females) **mouse** (NMRI) 1% in feed plus drinking water as saturated perchlorate solution (1.675 g PP/100 ml H_2O)	LOAEL equals the administered dose of ≈ 5000 mg PP/kg bw (based on reported mean bw and feed consumption and default water consumption according to CLP GD) thyroid volumes↑ follicular proliferation↑ body weight loss, exophthalmos, goitre, reduced reactivity (described as apathy), ragged fur, hair loss, hunched postures, and paralysis of the hind limbs >110 d of treatment leads to pituitary compensated hyperplasia and to benign cystadenoma	Actual dose somewhat uncertain due to missing data on water consumption authors conclude that perchlorate causes iodide deficiency goitre after prolonged exposure	Gauß, 1972

7.9.4.2. Human Data from short-term and chronic studies

Table 11

OVERVIEW OF CRITICAL STUDIES ON REPEATED DOSE TOXICITY IN HUMANS			
Method	**Results**	**Remarks**	**Source**
cross sectional study in occupational population **Ammonium perchlorate** (AP, purity not given) inhalation 35 M / 2 F (in AP production), (mean age 30 y.) 19 M / 2 F (in azide production, 'control'), (mean age 35 y.) Division into 'control'/low/mid/high dose group based on presumptive exposure by visible dust generated depending on types of activities, verified by air sampling and perchlorate determination in serum and urine. exposure duration: 12h/shift (**42 h within 6 d**) 40% of AP and 50% of azide worker employed for > 5y, no further information on total exposure duration/worker complete blood count and T3, T4, free T4 index (FTI), thyroid hormone binding ratio, TSH, and thyroid peroxidase antibodies in post-shift samples urinary perchlorate, iodine, creatinine in pre- and post-shift samples	mean T3, T4, FTI, thyroid hormone binding ratio, TSH, Anti-TPO red and white blood cell and platelet counts within normal ranges. No stat. sign. differences between exposure groups TSH elevated (above reference range) in azide-exposed and high perchlorate-exposed group (4th quartile, each), but not in low and mid exposure No differences in urine iodine between pre- and post-exposure or compared to azide-exposed. No clinical evidence of thyroid abnormalities or evidence of haematotoxicity in any perchlorate-exposure group. exposures to airborne perchlorate ranged from 0.004 to 167 mg/day Mean absorbed perchlorate: 1, 4, 11, and 34 mg/shift for the azide-exposed and low, medium, and high perchlorate-exposed groups, respectively.	'control' group invalid, as exposed to perchlorate as well The sample sizes in each group were small, so it was difficult to detect meaningful differences between exposure groups. Exposure groups do not unequivocally reflect differences in exposure levels as actual ranges of perchlorate exposure (absorbed doses) are overlapping within the groups	Lamm et al., 1999
cross sectional study in occupational population **Ammonium perchlorate** (AP, purity not given) inhalation 29 volunteers (in AP production), (mean age 33.6 y) 12 'community controls': non randomly selected community volunteers who were not working in the plant (mean age 39.5 y) dose estimation based on serum perchlorate concentrations exposure duration: 3x 12h/shift (**42 h within 6 d**)	T3, T4, FTI, Tg, and TSH in workers during exposure and pre-exposure and in controls within normal ranges. T4↑, FTI↑, and TT3↑ during exposure compared to pre-exposure and controls; urine iodine excretion↑ compared to pre-exposure Thyroid radioactive iodine uptake ↓ (38%) in workers during perchlorate exposure compared to pre-exposure. Thyroid volumes unaffected and patterns were not significantly different between workers and volunteers.	Detected changes in T4, FTI and TT3 are in opposite direction to an antithyroid effect of perchlorate Authors conclude that 'thyroid may be concentrating less of the dietary iodine during perchlorate exposure'	Braverman et al., 2005

minimum duration of employment of AP volunteers: 1.7 y, median 5.9 y 14-h RAIU, T3, T4, FTI, TSH, thyroglobulin, urinary perchlorate pre- and during exposure, urinary iodine excretion; thyroid volume (ultrasound)	No apparent long-term effects on thyroid size or function. **NOAEL** corresponds to the median absorbed doses of **0.167 mg perchlorate/kg bw per d**		
study in healthy adult volunteers **Potassium perchlorate** ('pharmaceutical grade') oral (in lemon juice and drinking water) 16 M / 21 F (mean age 38 y, range 18 -57 y) 0.007, 0.02, 0.1, and 0.5 mg perchlorate/kg per day daily for **14 d** (8-10 subjects per group) TSH, FT4, TT4, TT3 pre-, during and post-exposure (10 x), urinary perchlorate pre-, during and post-exposure, Anti-Tg, Anti-TPO 8- and 24-h RAIU: pre-exposure, exposure day 2 and 14, and post-exposure 15 d	0.5 mg perchlorate/kg bw per d: TSH ↓ compared to pre-exposure baseline, recovery after 15 d post exposure; baseline TSH was stat. sign. higher than in mid exposure group (0.1 mg/kg bw per d) ≥0.02 mg perchlorate /kg bw per d: 24-h thyroid radioactive iodine uptake ↓ (by 16.4, 44.7 and 67.1 %) FT4, TT4, TT3 levels within the normal range in all dose groups (except one subject with high TSH in the 0.007 mg/kg bw per d group) 2 subjects with elevated anti-TPO (clinically euthyroid) **NOEL**: **0,007 mg perchlorate/kg bw per d** based on radioactive iodine uptake	Dose response relationship for perchlorate induced decrease in thyroid RAIU with a known exposure The lowest dose was included subsequently when the originally intended lowest dose of 0.02 mg/kg proved to inhibit the thyroid radioactive iodine uptake	Greer et al., 2002
study in healthy volunteers **Potassium perchlorate** (purity 'reagent grade') oral in capsules 13 subjects placebo, 0.5 and 3.0 mg perchlorate/ d (estimated as 0.007 and 0.04 mg/kg bw per d based on 70 kg 'default bw' by ATSDR, 2008) (4-5 subjects per group) daily for **6 month** 24-h thyroid RAIU and serum Tg and Tg antibodies at baseline, 3 and 6 months. Monthly: serum thyroid function tests, perchlorate; urine iodine, perchlorate, and creatinine	all thyroid parameters within reference range; no significant changes in serum total T3, FTI, TSH, or Tg concentrations, thyroid radioactive iodine uptake up to the highest tested dose of 0.04 mg perchlorate/d (NOEL)	Small number of subjects per dose group. Equivocal reporting regarding participants and dose levels in methods and results.	Braverman et al. (2006)
study in healthy volunteers **Potassium perchlorate** (purity not given) oral in drinking water 9 M	No adverse effects of perchlorate on hepatic, renal, or hematologic parameters Thyroid radioactive iodine uptake ↓ stat. sign. after 14 d of exposure (mean decrease of 38%)	Only one dose tested	Lawrence et al. 2000

10 mg perchlorate/d (corresponding to 0.14 mg/kg per d: source Braverman et al. 2005) daily for **14 days** 4-, 8-, and 24-hour thyroid RAIU at baseline, 14 d of exposure and 14 d post-exposure serum T3, T4, FTI, thyroid hormone binding ratio, TSH, urine and serum perchlorate pre-exposure (baseline), after 7 and 14 d of exposure and 14 d post-exposure	and increased 2 weeks post exposure compared to baseline no effect on circulating thyroid hormone or TSH concentrations		
study in healthy volunteers **Potassium perchlorate** (purity not given) oral in drinking water 8 M 3 mg perchlorate/d (corresponding to 0.04 mg/kg bw per d: source Braverman et al. 2005) daily for **14 days** 8- and 24-hour thyroid RAIU, serum T3, T4, FTI, thyroid hormone binding ratio, TSH, urine and serum perchlorate at baseline, 14 d of exposure and 14 d post-exposure	Thyroid radioactive iodine uptake ↓ Mean 24-hr thyroid RAIU was 16.1% at baseline and 14.5% during perchlorate ingestion, and the mean 8-hr uptake values were 13.8% and 11.8%, respectively, not stat. significant No significant changes in thyroid function tests or in urinary iodine or creatinine excretion	Only one dose tested	Lawrence et al. 2001
study in healthy volunteers **Perchlorate** (identified as Irenat, no information on actual compound, purity not given) oral 5 M (age 25-28 y) 900 mg perchlorate/d (estimated as ≈ 13 mg/kg bw per d based on a default bw of 70 kg for male humans) daily for **4 weeks** thyroidal iodide, T3, FT3, T4, FT4, reverse T3, thyroxine-binding globulin (TBG), TSH, iodine trapping, TOP, and Tg gene expression, thyroid volume (ultrasound) pre- and posttreatment perchlorate administration preceded by 4 weeks of iodine supplementation (200 µg/d)	T3, T4, FT3, FT4, rT3, Tg and TBG within normal range and no differences between pre- and post-exposure post-exposure FT4↓, Tg↑, TSH↓, but within normal range Thyroidal iodide↓ (25 %)	Only one relatively high dose tested in a very small number of subjects	Brabant et al. 1992

7.9.4.3. Conclusion on repeated dose toxicity

For the assessment of effects of concern, information was obtained from repeated dose toxicity studies with perchlorates performed in rats, mice and rabbits with repeated oral administration for various exposure durations. A guideline-compliant subchronic (90 d) toxicity study in rats, a guideline-compliant 2-generation reproductive toxicity study in rats and a prenatal developmental toxicity study in rabbits are considered most relevant for the assessment of repeated dose toxicity of perchlorates (Siglin et al., 2000 and York et al., 2001a, b). In these studies the tested doses were chosen based on effects in the primary target organ, the thyroid. In all three studies several doses were tested orally and a clear dose response for antithyroid effects of perchlorate was observed. Effects on the determined hormones of the hypothalamic–pituitary–thyroid axis occurred at lower doses than morphological changes. Treatment with ammonium perchlorate resulted in statistically significantly decreased T3 and T4 levels at doses of ≥ 0.01 mg AP/kg bw per d and decreased T4 at doses of ≥ 0.3 mg AP/kg bw per d (F1 adults) or at the highest tested dose of 30 mg AP/kg bw per d (P1) rats as well as decreased T4 levels ≥ 30 mg AP/kg bw per d in rabbits (dams) (Siglin et al., 2000; York et al., 2001a; York et al., 2001b). TSH was significantly increased in rats at doses of ≥ 0.05 mg AP/kg bw per day (recovery group), ≥ 0.2 mg AP/kg bw (90-d sacrifice), or at 30 mg AP/kg bw per d (Siglin et al., 2000; York et al., 2001a). Histological findings such as hypertrophy and hyperplasia of the thyroid were observed in rats at ≥ 3 mg AP/kg bw per day (York et al. 2001a), and in rabbits at 10 mg AP/kg bw per day (Siglin et al., 2000; York et al. 2001b). In rabbits, absolute and relative thyroid weights were decreased in dams in a dose related manner (not stat. sign.) (York et al., 2001b).

Very high perchlorate doses resulted in an almost completely inhibited thyroidal iodide uptake as well as effects on the mammary gland in female rats (reduced iodide uptake, mild atrophy, atypia of the lobular epithelium, scattered foci of marked hyperplasic activity) (Eskin et al., 1975). The latter were not seen in other studies in rats with longer exposure (Siglin et al., 2000; York et al., 2001a). Further effects of prolonged administration of a high perchlorate dose in mice were described as increased thyroid volumes and follicular proliferation, goitre, exophthalmos, body weight loss, reduced reactivity (described as apathy), ragged fur, hair loss, hunched postures, and paralysis of the hind limbs (Gauß, 1972).

Overall, the animal studies consistently show antithyroid effects due to repeated perchlorate exposure leading to changes in levels of thyroid hormones and thyroid-stimulating hormone (TSH), thyroid weight increases, and histological findings in the thyroid (colloid depletion, follicular cell hypertrophy and hyperplasia) and goitre (EFSA 2015). Perchlorate has an antithyroid effect on rats at high doses. There are no data to suggest that perchlorate has effects that are not mediated through inhibition of iodide transport into the thyroid gland (NRC 2005).

Effects of repeated exposure to perchlorates were investigated in studies with healthy volunteers, and in occupational studies with exposure to perchlorates in the workplace. As evidenced from these studies exposure to perchlorates decreases the thyroidal iodide uptake after oral administration or exposure by inhalation (Brabant et al. 1992, Lawrence et al. 2000, Lawrence et al. 2001, Greer et al., 2002, Braverman et al., 2005; Braverman et al., 2006). In the majority of studies this did not result in changes in thyroid hormone levels (Lawrence et al. 2000, Lawrence et al. 2001, Greer et al., 2002, Braverman et al., 2006). In two studies with oral exposure although in the normal range, slight decreases in TSH levels were observed when compared to pre-exposure levels (Brabant et al. 1992, Greer et al., 2002). Braverman et al. (2005) observed increases in thyroxine, total triiodothyronine and the free T4 index when compared to controls and pre-exposure which is a deviation in the opposite direction of an antithyroid effect as observed in experimental animals. Despite changes in serum hormone levels they prevailingly remained within the reference ranges. No adverse effects such as thyroid hyperplasia, e. g. indicated by increased thyroid volumes, were reported in any of the studies. However, the referred studies included only small numbers of subjects and those with well controlled exposure were of short durations.

It is not possible to extrapolate data quantitatively from rodents to humans for purposes of human health risk assessment. Most experimental studies in animals designed to characterize the effects of perchlorate exposure have been done in rats, but the biochemical and physiologic differences between rats and humans related to the thyroid affect their responses to goitrogens, such as perchlorate. For example serum T3 concentrations were significantly decreased in male rats at 14 days from 0.009 mg perchlorate/kg per day (Siglin et al., 2000) whereas administration of 0.1 mg perchlorate/kg per day to healthy men for 14 days resulted in no changes in serum thyroid hormone or TSH concentrations during the exposure period (Lawrence et al. 2000). Serum TSH concentrations were significantly increased from 0.16 mg perchlorate/kg per day in male rats and from 0.04 mg perchlorate/kg per day in female rats at 14 days (Siglin et al., 2000). Studies in adult humans found no decreases in serum thyroid hormones or increases in serum TSH in healthy men and women given perchlorate at up to 0.5 mg/kg per day for 14 days (Greer et al., 2002). This shows that based on the available data at comparable doses rats are much more sensitive to disturbance of thyroid homeostasis by perchlorates than are humans, so the relevance of rat studies - in quantitative terms - to humans is limited. Therefore the human data provide the most reliable point of departure for the risk assessment than the animal data (NRC 2005).

Overall, the evidence from chronic, occupational-exposure studies and ecologic investigations in adults is not consistent with a causal association between perchlorate exposure at the doses investigated and hypothyroidism or other thyroid disorders in adults. While high doses of perchlorate can decrease thyroid hormone production in laboratory animals by inhibiting the uptake of iodide by the thyroid, in euthyroid humans perchlorate exposure does not reduce iodide uptake to an extent that would cause adverse health effects, such as hypothyroidism. It cannot be excluded that rather high doses of perchlorate can produce hypothyroidism as only data up to 13 mg/kg bw per d are available. As there was no adverse effect in humans indicating an hypothyroidic response, the clinical studies of iodide uptake in humans were taken forward for determining a reference dose from **NOEL** of **7 µg perchlorate/kg bw per day** based on the non-adverse thyroid iodide uptake inhibition by perchlorate from 0.02 mg perchlorate/kg bw per day (Greer et al. 2002).

7.9.5. Mutagenicity

7.9.5.1. In vitro data

Table 12

OVERVIEW OF EXPERIMENTAL IN VITRO GENOTOXICITY STUDIES						
Method **Guideline**	**Test system** **(Organism, strain)**	**Concentrations tested (give range)**	**Results** **+ S9**	**– S9**	**Remarks (give information on cytotoxicity and other)**	**Reference**
OECD TG 471 (GMbact)	**Sodium Perchlorate** (purity 98.21%) S. typhimurium TA 1535, TA 1537, TA 98, TA 100, TA 102	312.5-5000 µg/plate with and w/o metabolic activation: S9 vehicle: water	neg	neg	doses producing toxicity: none no information on the kind of S9 mix given, no detailed information on test results	TL 2008a
EPA OTS 798.5265 (GMbact)	**Ammonium perchlorate** (purity 99.8%)	312.5-5000 µg/plate with and w/o metabolic activation:	neg	neg	doses producing toxicity: none	Sharma, 1998

	S. typhimurium TA 1535, TA 1537, TA 98 and TA 100	S9 from Aroclor-induced rat liver vehicle: sterile distilled saline			deviations: 2nd experiment carried out by direct incorporation in-std. of preincubation; invalid solvent control (not the right solvent), no detailed information on test results	
OECD TG 476 (GMvitro)	**Sodium perchlorate** (purity 98.21%) Mouse lymphoma L5178Y cells exposure period: 3 and 24 h w/o S9; 3h w S9	preliminary test: 10-5000 µg/mL; main test: 156.3-5000 µg/mL with and w/o metabolic activation: S9 from Aroclor 1254 induced rat liver vehicle: water	neg	neg	doses producing toxicity: 5000 µg/mL in the second experiment shown by a a 39% decrease in adjusted relative total growth	TL 2009
OECD TG 473 (Cytvitro)	**Anhydrous sodium perchlorate** (purity 98.21%) Cultured Human Lymphocytes exposure period: 3, 20 and 44 h w/o S9; 3h w S9	1st test: 39.06-5000 µg/mL 2nd test: 156.3-5000 µg/mL w and w/o S9 from Aroclor 1254 induced rat liver vehicle: water	neg	neg	concentration producing toxicity: ≥ 1250 µg/ml (44h), ≥ 2500 (20h) decrease in mitotic index. no detailed information on results of the single tests	TL 2008b

7.9.5.2. In vivo data

Table 13

OVERVIEW OF EXPERIMENTAL IN VIVO GENOTOXICITY STUDIES						
Method Guideline	**Test substance Route of exposure Duration**	**Species, Strain, Sex, No/group**	**Dose levels**	**Result Target organs**	**Remarks (give information on cytotoxicity and other)**	**Reference**
EPA OTS 798.5395 (Cytvivo, MNT)	**Ammonium Perchlorate** (purity 99.8%) oral: gavage 3x at 24h-intervalls	Mouse (CD-1) F + M 5/group	0, 62.5, 125, 250, 500 and 1000 mg/kg per d vehicle: water	neg no induction of micronulei in femoral bone marrow	lethal at 2000 and 4000 mg/kg (4/6 and 5/6, resp.) in a range finding study (sex not known)	Sharma, 1998
Combined in vivo Micronucleus study with OECD TG	**Ammonium Perchlorate** (purity 99.8 %) Oral: drinking water	Rat (Sprague-Dawley) 10m + 10f per group	Nominal in diet 0 and 10 mg/kg per d	neg no induction of micronuclei in bone marrow	sampling upon sacrifice 10 mg/kg bw per d was top dose of the 90-d study (but not MTD)	Siglin et al., 1998

408 (Cytvivo)	90 d, continuous treatment 90 d, continuous treatment + 30 d recovery		vehicle: water			

7.9.5.3. Conclusion on genotoxicity

The registrants concluded that the substance is not genotoxic, and based on the available information, the eMSCA can support this conclusion. This is in line with evaluations of other risk assessment bodies such as EFSA (2015), and ATSDR (2008).

7.9.6. Carcinogenicity

7.9.6.1. Animal Carcinogenicity Data

Table 14

OVERVIEW OF EXPERIMENTAL STUDIES ON CARCINOGENICITY, NON-HUMAN DATA			
Method	**Results**	**Remarks**	**Source**
No GL followed **Potassium perchlorate** (purity not given) oral: drinking water 2 years (interim sacrifices at 40, 120, 220 days) **Rat** (Wistar) 20 M control, 11 M treated 0 or 1 % $KClO_4$ in water	LOAEC: (carcinogenicity): 1 % $KClO_4$ in drinking water (male) LOAEL (carcinogenicity): 1139 mg/kg bw per d (male) estimated by EPA 2002 Thyroid nonneoplastic lesions: increased absolute and relative weights at all sacrifice time points, diffuse goitre evolving into fibrosis Thyroid neoplastic lesions: adenomas in 4/11 rats at 2 years sacrifice no tumours were observed in the 20 control rats	Only one dose; only one sex; only one organ investigated for lesions incl. tumours; only 11 rats treated for 2 years limited details on the study with unclear pathological diagnoses (NRC 2005)	Kessler FJ, Krüskemper HL (1966)
No GL followed **Sodium perchlorate** (purity not given) oral: drinking water 46 weeks **Mouse** (BALB/c) 72 (12/group) 0 or 1.2 % $NaClO_4$ in water	LOAEL ≈ 2 147 mg $NaClO_4$/kg bw per day (EPA 2002a) Hypertrophy and hyperplasia of thyroid follicular and pituitary thyrotropic cells, thyroid follicular cell carcinomas were noted in five out of six treated mice No thyroid follicular-cell carcinomas were observed in the control animals.	42 animals were sacrificed, while 30 animals died during the experimental period; details about the cause of death were not provided.	Pajer and Kalisnik (1991)

Increased thyroid tumour incidence was observed in rats and mice following chronic exposure to perchlorate. Rats are sensitive to the development of thyroid tumours because their thyroid function is disrupted by RAIU caused by perchlorate exposure (Table 10) and tumours are thought to occur from the constant stimulation by TSH (due to reduced iodine levels) of the thyroid gland to synthesise and secrete T3 and T4 (EFSA 2015). On the other

hand, perchlorate is non-mutagenic under standard tests (Table 12 and Table 13). Therefore thyroid-pituitary disruption is considered to be the sole mode of action for the observed thyroid tumours caused by perchlorate in rodents. (EPA 2005)

7.9.6.2. Human Carcinogenicity Data

Epidemiological evidence is considered insufficient to determine whether or not there is an association between perchlorate exposure and thyroid cancer. (EPA 2005) Three measures have been used to assess whether there is an increased risk of thyroid cancer in areas with perchlorate-containing water (perchlorate ions in the range of 5 to 24 ppb) in comparison to non-perchlorate areas: thyroid cancer prevalence, mortality, and incidence. None of the three thyroid cancer measures showed an association with perchlorate exposure (Soldin 2001).

Potassium perchlorate was introduced in human pharmacology in the 1950s for the treatment of thyrotoxicosis (EFSA 2015). Under appropriate clinical circumstances doses as high as approximately 10 mg perchlorate/kg bw per day are used to bring thyroid hormone levels under control. The duration of perchlorate exposure in these patients ranged from a single dose to several weeks of treatment. One case study reported treating a single patient with perchlorate for 22 years (Soldin 2001). There are no reports of the appearance of a new thyroid disorder, thyroid nodules, or thyroid carcinoma in any patient treated with potassium perchlorate for hyperthyroidism (NRC 2005).

7.9.6.3. Conclusion on Carcinogenicity

Based on the non-genotoxic mode of action of perchlorate and the available human data from long term clinical use and epidemiological studies thyroid tumours found in rats and mice following chronic exposure to perchlorate the eMSCA concluded there is no indication for carcinogenic concern to humans. This is in line with evaluations of other risk assessment bodies such as EFSA (2015).

7.9.7. Toxicity to reproduction (effects on fertility and developmental toxicity)

The registrants concluded the substance is not toxic to reproduction, and based on the available information, the eMSCA can support this conclusion.

7.9.8. Hazard assessment of physico-chemical properties

Because of the classification as strong oxidizer a risk assessment of the likelihood and the severity of an event occurring due to physicochemical properties is needed.

Depending of the critical particle size under which ammonium perchlorate is explosive the risk of detonation will increase. Upon the critical particle size only the hazard as a strong oxidizer have to be considered in the risk assessment. The eMSCA recommends that the Registrant(s) determine the critical particle size and report it both in the registration and along their supply chain.

7.9.9. Selection of the critical DNEL and/or qualitative/semi-quantitative descriptors for critical health effects

A review of available dose descriptors per endpoint indicates that the major concern associated with sub-acute to chronic exposures to perchlorate is toxicity to the thyroid. Changes in thyroidal hormones in experimental animals, thyroid hypertrophy and follicular hyperplasia (not observed in humans) and inhibition of iodide uptake in epidemiological studies are the most prominent effects observed from the lowest exposure levels.

The available animal studies are not considered suitable for quantitative assessment of human health risk for perchlorate, due to differences in the dynamics of the pituitary-thyroid system between the species, and thus they cannot provide a reliable starting point for the quantitative risk assessment

Several human studies investigate the relationship between occupational exposures as well as short-term (0.5 to 6 months) administration of perchlorate and inhibition of iodide uptake by the thyroid in exposed workers and healthy subjects, respectively (reviewed in Table 11). Most of them are not considered as a reliable basis for risk quantification. Major deficiencies are the uncertainties associated with exposure assessment in occupational studies, the handling of confounding factors such as iodide and health status, and the absence of clear data on the thyroid iodide uptake inhibition levels that could be associated to the development of goitre or multinodular toxic goitre.

In agreement with the assessment of EFSA (2015) the critical toxicity endpoint for perchlorate in human studies is the dose-dependent increase of iodide uptake inhibition. Taking into account the information published in reviews of international bodies and regulatory programs (EFSA 2015, ATSDR 2008, JECFA 2011, NRC 2005) suitable human studies and typical dose descriptors identified for risk characterisation and derivation of long-term systemic DNEL values is selected (Table 15).

Table 15

DOSE DESCRIPTORS PER ENDPOINT				
Endpoint of concern	**Type of effect**	**Critical studies**	**Corrected dose descriptors (e.g. NOAEL, NOAEC)**	**Justification/ Remarks**
Repeated dose toxicity: sub-acute	thyroid iodide uptake inhibition by perchlorate	human clinical 14-day study in healthy adult volunteers by **Greer et al. (2002)**	No observed-effect level (**NOEL**) of **7 µg perchlorate/kg bw per day** as the point of departure provides a reasonable and transparent approach to the perchlorate risk assessment. (NRC, 2005)	non-adverse effect selected as the point of departure was considered a conservative, health-protective approach (NRC, 2005)

Inhibition of iodide uptake by the thyroid through the NIS clearly is not an adverse effect; if the key effect iodide deficiency does not occur (independent of its cause), there is no progression to adverse health effects. Transient and mild changes in serum thyroid hormone and TSH concentrations are also not considered as adverse health effects, but they represent biochemical changes that could precede long term adverse effects (goitre). The first expected adverse health effect that could result from perchlorate exposure would be hypothyroidism. Inhibition of iodide uptake by the thyroid is the key biochemical event as it is the obligatory initial step of possible effects of perchlorate exposure, and thyroid uptake of iodide (as radio iodide) can be measured easily and reliably. Therefore to use inhibition of iodide uptake by the thyroid as the basis of the perchlorate risk assessment is the most health-protective and scientifically valid approach (NRC 2005).

7.9.9.1 Workers

Relevant scenarios for worker exposure are long-term inhalation exposure and long term dermal exposure. Rat and human dose-response data are available for evaluation.

The most sensitive target is the thyroid. Perchlorate competitively inhibits uptake of iodine in the thyroid. The perchlorate anion interacts with the sodium-iodide symporter protein (NIS). As consequence a sustained inhibition of iodine uptake could cause depletion of thyroid stores of hormones T_3 and T_4 and lower thyroid hormone serum levels. Decrease in circulating levels of thyroid hormones, will trigger the hypothalamic-pituitary-thyroid

(HPT) feedback pathway, resulting in an increase in secretion of TSH (thyroid stimulating hormone). Persistent stimulation of the thyroid gland by elevated levels of TSH results in increases in thyroid size and weight (goitre) (ATSDR, 2008a). In addition during prolonged inhibition of NIS, adequate thyroid hormone and TSH production are not the most sensitive indicators of a biological effect in human. The thyroid glands adapts in several ways to low thyroid iodine content whereby the thyroid hormone production can be kept adequate. This is independent whether the low thyroid iodine content is caused by low dietary iodine intake or intake of compounds that inhibit iodine transport or utilization by the thyroid gland. The adaptive process, if longstanding, may lead to goitre and the generation of thyroid nodules with autonomously functioning hormone synthesis and secretion (toxic multinodular goitre, TMNG) (EFSA, 2014).

The HPT feedback pathway is qualitatively similar in rats and humans. However, the dynamics of the system in both species differ substantially. Rats have a shorter half-life for T_4 (12-24 h) than humans (5-9 days) because the rat binding proteins for thyroid hormones have a lower binding affinity than the binding protein TBG (thyroxine-binding globulin) in humans. The follicles in the rat contain much less colloid than primate follicles which serves as a reserve pool of thyroid hormone precursor. So, rat thyroid gland appears more sensitive to perchlorate exposure than human (Fisher et al., 2012; Lewandowski et al., 2004). But no data is available for scaling from rodents to humans related to aspects of the HPT axis. Due to the limitations in quantitative extrapolation rat data are of limited use and human data were considered for evaluation.

Greer et al. studied the effect of perchlorate on thyroid uptake of radiolabelled iodine (RAIU) in human volunteers after oral administration of potassium perchlorate in drinking water for 14 days and determined a dose response relationship. The radioiodine uptake was measured on exposure day 2 and exposure day 14 at either 8 or 24 hr after radioiodine administration. There was no statistically significant difference between the suppression of radioiodine uptake indicating the achievement of quasi-steady-state inhibition by exposure day 2 and the absence of a cumulative effect. The authors identified a NOEL of 0.007 mg/kg bw per d (7 µg/kg bw per d) for inhibition of thyroidal RAIU with no statistically significance. The suppression of radioiodine uptake was linearly related to the logarithm of perchlorate dose. Table 16 illustrates the dose response relationship which is based on the regression analysis of the 8 hr relative radioiodine uptake (RU_8) for 14 day exposure (E14) against the logarithm of the perchlorate dose (D) in mg/kg bw per d by Greer et al. which yielded equation 1 (Greer et al., 2002).

$(RU_8)_{E14} = -0.337 \times \log_{10} D + 0{,}229$ [equation 1]

Table 16

DOSE RESPONSE RELATIONSHIP FOR PERCHLORATE INHIBITION OF THYROIDAL IODINE UPTAKE BASED ON GREER ET AL. (2002).

Thyroidal iodine uptake inhibition [%][a]	Perchlorate dose [mg/kg bw per d]
0	0.005[b]
10	0.010
20	0.020
30	0.040
40	0.079
50	0.157
60	0.311
70	0.616
80	1.219
90	2.414

a: calculation 100% - ((RU_8)E_{14} x 100%); b: NEL (no effect level)

Braverman et al. also observed in worker exposed to perchlorate a reduced thyroid iodine uptake during the work shift (Braverman et al., 2005). This data is appropriate to establish a dose response relationship between perchlorate dose and inhibition of thyroidal iodine uptake which is comparable to the results of the experimental study by Greer et al.. However, the experimental study by Greer et al. is considered more reliable by eMSCA to establish a dose response relationship than the occupational exposure study by Braverman et al..

The eMSCA calculated a DNEL for iodine uptake inhibition in human (Table 17 and Table 18). The oral NOEL of 0.007 mg/kg bw per d was obtained from Greer et al. and set as point of departure. The DNEL for iodine uptake inhibition of 10 µg perchlorate/m^3 after inhalation can be calculated by multiplying the NOEL by 70 kg (the standardized average worker's body weight) and divided by 10 m^3 (the volume of air breathed in a 8-hours working day); equal rate of oral absorption and absorption via inhalation route is assumed. The default factor of 5 was applied to adjust for intraspecies differences as outlined in Chapter R8 of the REACH Guidance (ECHA, 2012).
The dermal DNEL for iodine uptake inhibition of 70 µg perchlorate/kg bw per d can be calculated using the oral NOEL as starting point and considering the lower dermal absorption rate compared to oral absorption. Oral absorption of perchlorate occurs nearly complete in humans (ATSDR, 2008a). The absorption rate for human via dermal route is not known for perchlorate. Therefore, absorption by dermal route was set as 2 % based on justified read across from sodium chlorate (Kane, 2007) as discussed in section 7.9.1. The default factor of 5 for intraspecies differences was also applied.

Table 17

DETAILED OVERVIEW OF THE DNEL DERIVATION FOR INHALATION ROUTE ($DNEL_{WORKER, INHALATION, LONG-TERMN, SYSTEMIC}$) FOR IODINE UPTAKE INHIBITION BY PERCHLORATE CONDUCTED BY THE EVALUATING MSCA.		
Descriptor	**Value**	**Remarks**
Relevant dose descriptor	NOEL: 0.007 mg perchlorate/kg bw per d	The NOEL results from a volunteer study where potassium perchlorate was given in drinking water for 14 days (Greer et al., 2002). The relevant effect is inhibition of thyroidal iodine uptake.
Modification of the relevant dose descriptor	70 kg bw 10 m^3/d respiratory volume	Route-to-route extrapolation is needed from the oral to the inhalation route. For this purpose a default body weight of 70 kg and a respiratory volume of 10 m^3 per person and day are applied for workers according to the REACH guidance R.8. Oral absorption occur nearly complete in humans and animals (ATSDR, 2008a). The absorption rate for human via inhalation route is not known for perchlorate. It is assumed that absorption rate via inhalation route is similar to absorption rate via oral route.
Corrected dose descriptor	0.007 mg perchlorate/kg bw per d x 70 kg bw / 10 m^3/d = 0.049 mg perchlorate/m^3	
Assessment factor (AF)	**AF Value**	**Remarks**
Interspecies (allometric scaling)	-	Not applicable.
Interspecies (remaining differences)	-	Not applicable.

Intraspecies	5	The default factor for workers is applied according to the REACH guidance R.8.
Exposure duration	-	Not applicable.
Dose-response	-	Not applicable.
Quality of database	-	Not applicable.
DNEL$_{worker}$, inhalation, long-term, systemic (iodine uptake inhibition)	0.049 mg perchlorate/m^3 / 5 = 0.0098 mg perchlorate/m^3 ≈ **10 µg perchlorate/m^3**	

Table 18

DETAILED OVERVIEW OF THE DNEL DERIVATION FOR DERMAL ROUTE (DNELW$_{ORKER,}$ DERMAL, LONG-TERM, SYSTEMIC) FOR IODINE UPTAKE INHIBITION BY PERCHLORATE CONDUCTED BY THE EVALUATING MSCA.		
Descriptor	**Value**	**Remarks**
Relevant dose descriptor	NOEL: 0.007 mg perchlorate/kg bw per d	The NOEL results from a volunteer study where potassium perchlorate was given in drinking water for 14 days (Greer et al., 2002). The relevant effect is inhibition of thyroidal iodine uptake.
Modification of the relevant dose descriptor	2 % dermal absorption	Route-to-route extrapolation is needed from the oral to the dermal route. Oral absorption occur nearly complete in humans and animals (ATSDR, 2008a). The absorption rate for human via dermal route is not known for perchlorate. Experimental data on dermal absorption rates is available for sodium chlorate (Kane, 2007). Based on a justified read-across from sodium chlorate the dermal absorption for perchlorate was set at 2 %.
Corrected dose descriptor	0.007 mg perchlorate/kg bw per d x 100 % / 2 % = 0.35 mg perchlorate/kg bw per d	
Assessment factor (AF)	**AF Value**	**Remarks**
Interspecies (allometric scaling)	-	Not applicable.
Interspecies (remaining differences)	-	Not applicable.
Intraspecies	5	The default factor for workers is applied according to the REACH guidance R.8.
Exposure duration	-	Not applicable.
Dose-response	-	Not applicable.
Quality of database	-	Not applicable.
DNEL$_{worker}$, dermal, long-term, systemic (iodine uptake inhibition)	0.35 mg perchlorate/kg bw per d / 5 = 0.07 mg perchlorate/kg bw per d ≈ **70 µg perchlorate/kg bw per d**	

DNEL derivation by eMSCA is based on the thyroid iodine uptake inhibition data from Greer et al.. Thyroid iodine uptake inhibition is the earliest systemic effect. It should be considered that the inhibition of iodine uptake in the thyroid is not per se an adverse effect and can be compensated by HPT feedback control. However as described above a sustained inhibition of iodine uptake could cause depletion of thyroid stores of hormones and further result in goitre. But no clear data is available to eMSCA to conclude at what level of thyroidal iodine uptake inhibition the compensation cannot longer be maintained.

No statistically significant changes were observed in the monitored thyroid hormones during the study period in any treatment group in the human volunteer study (Greer et al., 2002) which is understandable due to the short exposure period of 14 days. The human thyroid gland contains a huge store of hormone and it will take several weeks of perchlorate exposure to detect a decrease in blood levels of thyroid hormones.
Furthermore occupational exposure studies are available. Lamm et al. (1999) and Braverman et al. (2005) studied occupational exposure in a perchlorate production plant and no adverse effects on thyroid function and size were observed in these cross-sectional studies (Braverman et al., 2005; Lamm et al., 1999). Details in study design and results are described in section 7.9.4. However, both studies are not suitable to exclude adverse effects on thyroid after long-term exposure to perchlorate since they do not sufficiently quantify the previous exposure (Lamm et al., 1999) or they do not adequately take the previous exposure into account in their analysis (Braverman et al., 2005), respectively. These occupational exposure studies were used by the registrant for DNEL derivation which is not supported by eMSCA.

EFSA gives a summary of previous risk assessments in its scientific opinion on the risks to public health related to the presence of perchlorate in food where it is stated that JECFA (Joint FAO/WHO Committee on Food Additives) concluded that the inhibition of thyroid iodine uptake of 50 % is not associated with any changes in TSH or thyroid hormone levels and NRC (National Research Council) suggested that an inhibition of at least 75 % for several month or longer seems to be necessary in order to cause a decrease in thyroid hormone production that would have adverse effects in healthy adults (EFSA, 2014). The eMSCA cannot understand on which database these conclusions are based. In addition a long-lasting adaptive process to compensate lower thyroid iodine uptake to keep the thyroid hormone production adequate may result in goitre or TMNG. EFSA concluded that a prolonged inhibition of 50 % by exposure to NIS inhibitors such as perchlorate may lead to such effect (EFSA, 2014). The database for this conclusion was not reviewed by eMSCA. However, no clear data is available on the effects of a prolonged thyroidal iodine uptake inhibition lower than 50 %.

In summary no relationship for thyroidal iodine uptake inhibition and adverse effects on thyroid in human could be established for DNEL derivation. Therefore thyroidal iodine uptake inhibition as non-adverse precursor effect for adverse effects on thyroid was selected as the point of departure for DNEL derivation. This choice is considered a conservative, health-protective approach.

An overview of hazard conclusion by the eMSCA can be found in Table 19. A long-term systemic DNEL of 10 µg perchlorate/m^3 for inhalation route as well as a long-term systemic DNEL of 70 µg perchlorate/kg bw per d for dermal route was calculated for the precursor effect of thyroidal iodine uptake inhibition. The equivalent DNELs for ammonium perchlorate were calculated by multiplying by factor 1.18 (molecular weight of ammonium perchlorate divided by molecular weight of perchlorate).

Table 19

HAZARD CONCLUSIONS FOR WORKERS MADE BY THE EVALUATING MSCA FOR PERCHLORATE AND AMMONIUM PERCHLORATE.				
Route	**Type of effect**	**Hazard conclusion for perchlorate**	**Hazard conclusion for ammonium perchlorate**	**Endpoint**
Inhalation	Systemic effects – long-term	DNEL = 10 µg/m^3	DNEL = 12 µg/m^3	Inhibition of thyroidal iodine uptake (precursor effect).
Dermal	Systemic effects – long-term	DNEL = 70 µg/kg bw per d	DNEL = 83 µg/kg bw per d	Inhibition of thyroidal iodine uptake (precursor effect).

As supporting information for risk assessment the eMSCA also derived reference values for 50 % thyroidal iodine uptake inhibition by perchlorate. The calculation was performed on the same method as described above. A reference concentration of 220 µg/m^3 for inhalation route and a reference dose of 1570 µg/kg bw per d for dermal route were derived which are equivalent to 260 µg/m^3 ammonium perchlorate and 1854 µg/kg bw per d ammonium perchlorate, respectively. Assuming the data presented in the EFSA report are valid it could be concluded that a ammonium perchlorate exposure exceeding 260 µg/m^3 for inhalation route and 1854 µg/kg bw per d for dermal route lead to changes in TSH or thyroid hormone levels and further result in goitre.
However, adaptive processes possibly resulting in TMNG would also occur at an ammonium perchlorate exposure lower than 260 µg/m^3 for inhalation route and 1854 µg/kg bw per d for dermal route, respectively.

7.9.10. Conclusions of the human health hazard assessment and related classification and labelling

7.9.10.1. Specific target organ toxicity – repeated exposure

Upon assessment of the existing information on the thyroid toxicity of perchlorate in humans and experimental animals the eMSCA considers the proposed self-classification of perchlorate as STOT RE 2 with the thyroid as target organ appropriate. The existing information on perchlorate is sufficient to conclude that perchlorate produces disturbances in the hypothalamus-pituitary-thyroid axis and thyroid hormone homeostasis in experimental animals following repeated oral exposure leading to clear morphological changes in the thyroid (Chapter 7.9.4.1). Antithyroid effects on rats like thyroid weight increases, and histological findings in the thyroid (colloid depletion, follicular cell hypertrophy and hyperplasia) at and above the guidance value of 10 mg NH4Cl/kg bw per d in a 90-day study and an NOAEL value below the guidance value might result in category 1 classification after interpolation (CLP Guidance 2015).

Whereas thyroid function and regulation are qualitatively similar in rats and humans (Bianco et al. 2002), important differences in serum thyroid hormone binding and clearance rates lead to important quantitative differences between the two species (NRC 2005): rats have more than 100 times lower serum thyroid hormone binding affinity contributing to higher thyroid hormone clearance rates and the need for a higher rate of thyroid hormone production per unit of body weight (Dohler et al. 1979). Therefore the potency of perchlorate is lower in humans than in animals, because of the substantial differences in the dynamics of the two systems (NRC 2005).

According to the Guidance on the Application of the CLP Criteria, chapter 3.9.2.3.2 "Any information pertaining to the relevance of findings in animals to humans must be taken into account and may be used to modify the classification from how it would be if based on the available animal data (CLP Guidance 2015). The availability of sufficient human data on thyroid toxicity of perchlorate (Chapter 7.9.4.2) demonstrated that humans are much less susceptible to disruption of thyroid function and antithyroid effects, leading to a decrease in the classification assigned, if taken into account. Weight of evidence of all data merits classification as STOT RE 2; H373 (affected organ: thyroid).

7.9.10.2. Carcinogenicity

Upon assessment of the existing information on the carcinogenicity of perchlorate in humans and experimental animals the eMSCA considers the non-classification of perchlorate appropriate. Perchlorates have induced benign tumours in experimental animals but there is strong evidence that the hormonally mediated mode of action of tumour formation is not relevant for humans (Chapter 7.9.6 and 7.9.10.1).

In case the available information on carcinogenicity is from animal studies the relevance of the findings in animals to humans must be considered (CLP Guidance 2015). Thyroid follicular-cell tumours in rats are not an unexpected finding at doses that are goitrogenic

by stimulating the thyroid tissue by TSH (NRC 2005), whereas iodide deficiency in the thyroid gland of humans, as possible consequence of perchlorate administration or exposure, is not associated with an increase in thyroid cancer (Schlumberger 1998). In humans the thyroid appears to be less sensitive to increased TSH caused by iodine deficiency (Fisher et al., 2012). Studies in humans have shown no increase in serum TSH levels or decreases in T3 and T4 levels following exposure to perchlorate for 14 days (Table 11) compared with the same duration of exposure in rats (NRC, 2005).

Substances are classified according to their potential to cause cancer in humans (CLP Guidance 2015). In the absence of genotoxicity and on the basis of the species differences in the physiology of thyroid hormones, it can be concluded that the neoplastic changes observed in rodents are not relevant for humans and therefore that perchlorate is not of carcinogenic concern to humans (EFSA 2015). Therefore perchlorate classification according to Annex I of the CLP Regulation is not warranted.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Perchlorate inhibits the NIS (sodium iodide symporter) mediated iodide uptake in rodents, rabbits and humans (see Section 7.9 and 7.10.2). However, this molecular mode of action has not been explicitly confirmed for fish and amphibians but indirect *in vitro* effects (e.g. inhibition of T4 release from amphibian follicular cells after perchlorate incubation) provide strong evidence that the mode of action is comparable to those in rodents and humans. Additionally, given the evolutionary conserved hypothalamus-pituitary-thyroid axis in vertebrate species (Zoeller et al., 2007) studies discussed in this section postulate this mode of action also for fish, amphibians and birds. In vertebrates, the transport of iodide into the follicular cells of the thyroid gland is a key step of thyroid hormone synthesis (Blanton and Specker, 2007; Fort et al., 2007; Zoeller et al., 2007). By inhibiting the iodine uptake to the thyroid follicles, the production of thyroid hormones is downregulated affecting the thyroid hormonal homeostasis of the body, as shown for fish, amphibian, lamprey and bird species by studies discussed in this section. This might result in adverse effects listed for different biological organisation level in Table 20. For several amphibian and teleost species it has been shown that the reduced serum thyroid hormone level triggers a negative feedback response via the hypothalamus-pituitary-thyroid axis to produce more thyroid hormones to compensate for the reduced hormone levels (Blanton and Specker, 2007; Denver, 2013).

Table 20

ADVERSE EFFECTS* OF THE ALTERED THYROID HORMONE SIGNALING CAUSED BY PERCHLORATE EXPOSURE IN FISH, LAMPREY AMPHIBIAN AND BIRD SPECIES		SPECIES	REFERENCE
Molecular interaction	• Competitive inhibition of the Na-I symporter	• Not reported for fish, lamprey, amphibian or bird species.	• -
Cellular responses	• Reduced thyroid hormone production due to the lack of intrafollicular iodine • Upregulation of genes/enzymes playing a role in the synthesis of thyroid hormones due to the negative feedback autoregulatory loop	• *Danio rerio/ Xenopus laevis/ Colinus virginianus* • *Gobiocypris rarus*	• Thienpont et al. (2011)/ Hu et al. (2006)/ McNabb et al. (2004a) • Li et al. (2011)

Extracellular responses	• Altered serum thyroid hormone concentration • Negative feedback response to the hypothalamus/pituitary to trigger the secretion of thyroid hormones	• *Danio rerio/ Lampetra appendix / Xenopus laevis/ Colinus virginianus* • *Gobiocypris rarus*	• Mukhi and Patino (2007) / Holmes et al. (1999) / Goleman et al. (2002a)/ McNabb et al. (2004a) • Li et al. (2011)
Organ responses	• Follicular hyperthrophy, hyperplasia • Angiogenesis • Thyroid colloid depletion • Altered organ weights and somatic indices	• *Danio rerio/ Xenopus laevis/ Colinus virginianus* • *Danio rerio* • *Danio rerio*	• Mukhi et al. (2005)/ OECD, 2007/ Gentles et al. (2005) • Mukhi et al. (2005) • Mukhi et al. (2005)
Organism responses	• Impaired metamorphosis • Impaired embryonal/larval development (reduced length/wet weight, craniofacial malformations, uninflated swim bladder) • Retarded pigmentation • Crosstalk with other endocrine axes	• *Xenopus laevis* • *Danio rerio* • *Pimephales promelas* • *Gasterosteus aculeatus*	• Goleman et al. (2002a) • Mukhi and Patino (2007) • Crane et al. (2005) • Petersen et al. (2015)
Higher tier organism responses	• Impaired reproduction (lower fertilisation rate, poor spawning performance, poor hatching rate) • Impaired (reproductive/swimming) behaviour • Altered sex ratios • Hermaphroditism • Reduced stress tolerance	• *Danio rerio* • *Gasterosteus aculeatus* • *Gasterosteus aculeatus* • *Gasterosteus aculeatus*	• Patino et al. (2003) • Bernhardt and von Hippel (2008) • Furin et al. (2015) • Bernhardt et al. (2006)

*This Table provides only examples for adverse effects found by studies discussed in this section. An exhaustive list of observed endpoints can be found in the Annex 1.

The endocrine disrupting potential of perchlorate was evaluated by the registrants by using mostly non-standard tests on aquatic organisms taking into account additional scientific publications aiming at the assessment of thyroid disruption potencies of perchlorate. For supporting evidences of thyroid disruption provoked by perchlorates, the scientific literature regarding endpoints listed above was also reviewed.

For the environmental hazard assessment of endocrine effects, studies testing different salts of perchlorate ($NaClO_4$, NH_4ClO_4, $KClO_4$, $Mg(ClO_4)_2$) were taken into account. Once dissolved, the salts of perchlorate completely dissociate into the perchlorate anion and a cation (Na^+, NH_4^+, K^+, Mg^{2+}). Thus, in order to evaluate the read-across between the different perchlorate salts, it has to be investigated whether the cation influences the endocrine effect of perchlorate. None of the cations mentioned has endocrine or endocrine modulating effects or show other systemic toxic effects in the concentration range tested. However, in aqueous solution the ammonium cation exists in a temperature and pH dependent balance with the toxic ammonia. Differences in toxicity to amphibians have been shown by Goleman und Carr (2006) at very high test concentrations (>100 mg/L) of perchlorate salts indicating five times higher LC_{50} values for $NaClO_4$ than for NH_4ClO_4.(2780 vs. 510 mg/L). Regarding endocrine disruption related endpoints (thyroid histopathology and gonadal differentiation), there are just subtle differences to be observed. Given that the majority of investigated endocrine related endpoints were analyzed in non-toxic concentration ranges, a read-across between the different perchlorate salts in the course of environmental hazard assessment of endocrine effects is appropriate. For the comparability, effect

concentrations listed in the annex 1 are normalized to the concentration of the perchlorate anion while the text refers to the concentrations tested of the different salts used by the studies.

7.10.1.1. *In vitro test systems*

The potential *in vitro* thyroid disruption potencies of perchlorate were not covered by the registration dossiers. In the scientific literature Hornung et al. (2010) reports on inhibitory effects of sodium perchlorate on the T_4 (thyroxine) release measured in thyroid gland cultures from prometamorphic Xenopus tadpoles with an IC_{50} of 1.2 µM (=147 µg/L). Thyroidal activity of potassium perchlorate was assessed in larval lamprey endostyle (which gives rise to follicular thyroid tissue during metamorphosis *in vitro*) by Manzon und Youson (2002) investigating the iodide uptake. According to the findings of the study, the uptake of iodide was significantly reduced after the treatment with 0.72 mM (=99.8 mg/L) or 3.6 mM (=498.8 mg/L) potassium perchlorate.

7.10.1.2. *In vivo* test systems using fish

Endocrine effects of perchlorate in fish were assessed in the registration dossier based on the studies of Mukhi et al. (2005). In this paper a non-standard test with 12 week exposure and 12 week of recovery was conducted using adult zebrafish (*Danio rerio*) for the investigation of time-course and concentration-dependent effects of sodium perchlorate on thyroid follicle hypertrophy, colloid depletion, and angiogenesis as well as alterations in whole-body thyroxine (T_4) levels. At 12 weeks of exposure, LOECs for colloid depletion, hypertrophy, angiogenesis, and colloidal T_4 ring intensity were 11.48 mg/L, 1.131 mg/L, 90 µg/L, and 11 µg/L sodium perchlorate, respectively. However, whole-body T_4 concentration and body growth (length and weight) were not affected by perchlorate. The former might have been balanced out by the body with the help of the autoregulatory feedback mechanism. After the recovery period, all changes were reversible, although effects on angiogenesis and colloidal T_4 ring intensity could still be observed (with higher LOECs). The registrants claim that these LOECs cannot be considered given that these endpoints on angiogenesis and colloidal T_4 ring intensity are not established. However, all endpoints gave an indication to perchlorate's mode of action on disruption of thyroid hormone signalling.

Furthermore, a doctoral thesis of Mukhi (2006) -with two additional studies on perchlorate- was cited by the registrants, although none of them was discussed in the registration dossier. In the first study (also published as Mukhi und Patino (2007), reproductive performance and effect on the thyroid system were evaluated using adult zebrafish (*Danio rerio*) and the offsprings thereof treating them with sodium perchlorate over 10-16 weeks. Thyroid histology, thyroid hormone level, reproductive and developmental parameters (spawning performance, fertilisation rate, fertilized egg diameter, hatching rate, standard length, and craniofacial development) were assessed. T_4 but not the T_3 (triiodothyronine hormone) concentrations were changed both in adults and in the offspring for both studied sodium perchlorate concentrations (10 and 100 mg/L). Female body weight, spawning performance (given as cumulative packed egg volume) and egg diameter were affected in both concentrations, while fertilization and hatching rates were unaffected. Offsprings of adults exposed to 100 mg/L sodium perchlorate showed craniofacial malformation and also reduced length. This study gives an indication that altered thyroid hormone signalling might be related to higher apical effects such as growth, reproductive success and embryonal/larval development. The second study (also published as Mukhi et al. (2007) investigates the effect of larval-juvenile exposure to perchlorate on sex ratios using zebrafish (*Danio rerio*) using concentrations of ammonium perchlorate of 100 and 250 mg/L. Thyroid histology but not fish mortality was affected. Co-treatment with exogenous T_4 worsened the effects both on mortality and fork length. Perchlorate skewed the sex ratios to female and this effect could be rescued using exogenous T_4 that shifted the sex ratios to male causing also earlier onset of spermatogenesis. This experiment gives indication that thyroid hormone plays a role in the establishment of gonadal sex phenotype. However, effects on length and mortality could not be clearly associated with altered thyroid hormone signalling.

The registrants provided furthermore a study on $PNEC_{freshwater}$ derivation reviewing the literature on aquatic toxicity of perchlorate. Thyroid functions were studied by Bradford et al. (2005) in eastern mosquitofish (*Gambusia holbrooki*) exposed over 30 days to 0.1-1000 mg/L sodium perchlorate. Histopatological endpoints showed a concentration-dependent severity starting from the lowest concentration, where also significant whole-body T_4 changes could be observed, although not in a dose-dependent manner. Further study on thyroid functions was performed by Crane et al. (2005) investigating developing fathead minnows (*Pimephales promelas*) exposed to ammonium perchlorate (1-100 mg/L). Histopathological alterations could be observed in all tested concentrations. T_4 was significantly elevated in the highest test concentration, while T_3 levels did not show alterations. In concentrations of 10 and 100 mg/L ammonium perchlorate, retarded growth (both length and wet weight) and pigmentation could be observed. Liu et al. (2006) showed also histopathological alterations following to 10-90 day of exposure to 10-100 mg/L sodium perchlorate in zebrafish (*Danio rerio*). Patino et al. (2003) reported histopathological alterations of the thyroid follicles in concentrations of 18 and 677 mg/L perchlorate. In addition, reproductive performance was also investigated: 677 mg/L perchlorate affected the reproduction, which might not be related to altered thyroid hormone signalling given that no alterations in thyroid hormone levels could be observed.

Higher tier apical effects on reproduction were investigated by Bernhardt und von Hippel (2008) and Bernhardt et al. (2006) in three-spined stickleback (*Gasterosteus aculeatus*) using sodium perchlorate showing impaired reproductive behaviour in the second generation of exposed fish (with LOEC of 32 mg/L perchlorate) or hermaphroditism (histologically proven for 102.92 mg/L perchlorate) and dose-dependent reduced survivorship in case of stress, respectively. In addition to histopathological effects, Park et al. (2006) reports on affected reproduction, growth and survival in exposed mosquitofish (*Gambusia holbrooki*). However, no dose-dependent changes of reproduction and growth could be observed, thus these apical effects cannot be linked to the thyroid (or other endocrine) disruption potency of perchlorate. Toxic effect of perchlorate on exposed fries could be observed at high concentrations (LC_{50}=404.4 mg/L perchlorate) indicating presumably the narcotic effect of perchlorate and not a specific mode of action.

From the scientific literature, numerous studies give indications on the thyroid disruption potency of perchlorate. Schmidt et al. (2012) found histopathological changes starting from 250 µg/L potassium perchlorate in a modified early-life stage test with zebrafish (*Danio rerio*). 180 µM (25 mg/L) potassium perchlorate completely abolishes the T_4 production in zebrafish embryos identified by an immunofluorescence assay (Raldua und Babin, 2009). Using the same assay, Thienpont et al. (2011) derived an EC_{50} value of 2.5 µM (346.1 µg/L) for potassium perchlorate. Li et al. (2011) found altered gene expression of the sodium-iodide symporter and two deiodinases in Chinese rare minnow (*Gobiocypris rarus*) in concentrations of 5 and 50 µg/L perchlorate. Moreover, in both concentrations larvae showed impaired development of swim-bladder. Thyroid functions and reproductive fitness were investigated at different temperatures using medakas (*Oryzias latipes*) by Lee et al. (2014) finding that exposure to sodium perchlorate (100 mg/L) could influence both endpoints, and these effects could be aggravated under high water temperatures. Furin et al. (2015) showed that an early onset of perchlorate exposure (30 and 100 mg/L sodium perchlorate) has profound effects on reproductive and thyroid tissues of three-spined stickleback (*Gasterosteus aculeatus*). Petersen et al. (2015) hypothesised that developmental and reproductive effects on three-spined stickleback might not be fully related to altered thyroid hormone signalling. According to that study, although perchlorate (10-100 mg/L) modified the thyroid histology, levels of thyroid hormones were balanced presumably because the increased number of thyroid follicles compensated for the disruptive effects. However, gonadal development showed dose-dependent alterations with early stage ovarian follicles in females and of advanced spermatogenic stages in males. Moreover, androgen hormone levels were also altered.

The only field study on perchlorate contaminated area was conducted by Theodorakis et al. (2006) investigating thyroid histopathology of central stonerollers (*Campostoma anomalum*). Water concentrations of perchlorate ranged from 10.78-70.23 µg/L, while internal

concentrations measured in the fish and in periphyton (serving as food for the fish) were one order of magnitude higher. Thyroidal histological indicators were correlated to levels of perchlorate in the fish, water, and periphyton and they were also season dependent.

7.10.1.3. *In vivo* test systems using lampreys

Effects on metamorphosis of perchlorate were widely investigated on lampreys. Potassium perchlorate was found to induce the metamorphosis of American brook lamprey (*Lampetra appendix*) (Holmes et al., 1999) and of see lampreys (*Petromyzon marinus*) (Kao et al., 1999). Same findings were made for sea lampreys exposed to potassium and ammonium perchlorate (Manzon et al., 2001). According to these studies, the reason for the induced metamorphosis is the decreased thyroid hormone concentration (which is caused by perchlorate) that is naturally required for the onset of metamorphosis.

7.10.1.4. *In vivo* test systems using amphibians

The registrants refer to an OECD validation report of the amphibian metamorphosis assay (AMA) involving five laboratories (OECD, 2007). In this study several thyroid related endpoints of perchlorate were measured. However, the registrants refer only to the developmental effects (measured as hind limb length and developmental stage) in the registration. The participating five laboratories measured the following NOECs: 485, 474, 87, 238, and 524 µg/L, respectively. However, two laboratories did not provide or measured very low iodine concentration for the exposure medium, thus proper interpretation and interlaboratory comparison of their results is not possible. The registrants calculated the geometric mean of those values where iodine concentration was also measured giving the 216 µg/L NOEC value. Histopathological changes were detected already at the lowest perchlorate concentration tested (61-87 µg/L perchlorate). Growth related effects were measured only by certain laboratories, from perchlorate concentration of 117 µg/L. The registrants claim that effect concentrations for thyroid histopathology might not be indicative for higher tier apical endpoints given the negative autoregulatory mechanism of the hypothalamus-pituitary-thyroid axis. This is supported by other studies (Petersen et al., 2015) discussed above showing normal thyroid hormone concentrations despite histopathological alterations. However, long-term effects and species differences of such alterations are not yet explored.

Furthermore, the registrants discussed three scientific papers on thyroid disrupting effects of perchlorate on Xenopus. The study of Goleman et al. (2002a) aimed at determining the concentration-dependent effects of ammonium perchlorate on Xenopus lethality, developmental abnormalities and metamorphosis during the 70 days of exposure giving LOECs of 18 µg/L (tail resorption/hindlimb length) and 5 µg/L (forelimb emergence) ammonium perchlorate. The second study of Goleman et al. (2002b) applied similar exposure conditions with a 28 day recovery phase. Besides endpoints on lethality, development, metamorphosis and thyroid histopathology effects on gonadal differentiation were assessed. While no effects on mortality and hatching success were observed, alterations in gonadal differentiation, metamorphosis and thyroid histopathology were evident in both concentrations (59 µg/L and 14.14 mg/L perchlorate). The latter two effects could be reversed during the recovery period. Both studies of Goleman et al. have been disregarded by the registrants as they were conducted in iodine free medium which leads to lower effect concentration of perchlorate, thus overestimated thyroid toxicity. However, sufficient iodine might have been available to the test organisms via the food. The effects described by the study clearly support the thyroid mode of action of perchlorate and deliver evidence that long-term thyroid disruption might cause also adverse effect on other endocrine axes. The third study cited by the registrants was conducted by Olmstead et al. (2009) describing histopathological effects on the thyroid and impairment of reproduction and metamorphosis. The study concludes that histopatological alterations are compensatory mechanism of the nature and not indicative for higher tier apical effects (which could not be find by the study up to the highest sodium perchlorate concentration of 1.5 mg/L). This statement is in accordance with the previous findings. However, data are still lacking on perchlorate concentrations causing only histopathological effects on the thyroid but no higher tier effects.

The registrants provided furthermore a study on $PNEC_{freshwater}$ derivation reviewing the literature on aquatic toxicity of perchlorate. Several studies were conducted to assess perchlorate effects on the metamorphosis. Tietge et al. (2005) showed a LOEC of 250 µg/L and 16 µg/L perchlorate for impaired metamorphosis or thyroid histology in a short term exposure to sodium perchlorate, respectively, while exposure throughout the metamorphosis gave LOEC values of 125 and 63 µg/L perchlorate, respectively. Hu et al. (2006) exposed Xenopus for 38 or 69 days with sodium perchlorate finding a LOEC for metamorphosis and for classical histological endpoints (38 day exposure) of 93 µg/L perchlorate. An additional biomarker on histology, the colloidal T_4 ring intensity analysed immunohistochemically gave a LOEC of 8 µg/L perchlorate for both exposure window tested. However, no histopathological changes could be seen after 96 day of exposure. Brausch et al. (2010) investigated the effect of surface water or artificial exposure media on the outcome of the exposure experiments. Indeed, no effects on metamorphosis of New Mexico spadefoot toad (*Spea multiplicata*) or on Xenopus was found up to 1 mg/L or 80 µg/L of measured perchlorate concentration, respectively, when exposed in surface water. The reason might rely on the physicochemical properties of the surface water (e.g. the presence of iodide). In the study of Semlitsch und Gibbons (1988) also higher tier effects indirectly related to thyroid disruption are discussed, such as higher predation hazard given the smaller size of the organism. However, no experiments on perchlorate have been conducted for studying this indirect effect.

The field study mentioned above conducted by Theodorakis et al. (2006) assessed also cricket frogs (*Acris crepitans*) in perchlorate contaminated and reference sites finding follicle cell hyperthrophy and affected follicle cell height but no evidence for colloid depletion or hyperplasia in frogs.

7.10.1.5. *In vivo* test systems using birds

There are few scientific studies of perchlorate effects on birds. However, the registrants did not discuss any of them. The chronic exposure of Japanese quail (*Coturnix coturnix japonica*) chicks to 2000 mg/L ammonium perchlorate via drinking water caused hypothyroidism (lower thyroid hormone level, thyroid gland hypertrophy) (Chen et al., 2009). Chronic exposures to ammonium perchlorate via drinking water with northern bobwhite quails (*Colinus virginianus*) indicated alterations of thyroid gland morphology at the highest tested concentrations (1 mM=117.5 mg/Lammonium perchlorate) but no effects on egg production, or body/organ weights (Gentles et al., 2005). Early life stages of bobwhite quails were exposed up to 500 mg/L ammonium perchlorate to study of the negative feedback autoregulatory loop over 8 weeks using thyroid hormone concentrations and histopathological endpoints (McNabb et al., 2004a). The compensatory mechanism of the chicks showed a dose-dependent manner, whereby at the highest concentration no compensation of perchlorate effects could be seen. The compensatory mechanism were also shown by McNabb et al. (2004b) using the similar test conditions pointing out the complexity of this mechanism depending on the exposure length. Growth and behavioural investigations on zebra finch (*Taeniopygia guttata*) were studied by Rainwater et al. (2008) showing a dose-dependent alteration of multiple growth and behavioral endpoints in zebra finches exposed to environmentally relevant concentrations of sodium perchlorate.

7.10.2. Endocrine disruption - Human health

The studies in experimental animals listed in Table 10 contain sufficient endpoints relevant for the assessment of endocrine activity. The effects of perchlorate result from its ability to competitively inhibit iodide uptake via the sodium-iodide symporter protein (NIS). Inhibition of the iodide uptake by the thyroid gland leads to a reduction in the synthesis of thyroid hormones (T3 and T4) in rodents and rabbits. As a result increased TSH and thyroid hyperplasia are observed leading to the induction of thyroid tumours in rats (OECD 2012). On the other hand, studies on healthy adult volunteers as well as information from occupational studies, showed no correlation between the exposure to perchlorate and any adverse effects or changes in the thyroid hormone levels, even at exposure levels associated

with a substantial inhibition of thyroid iodide uptake (Table 11). No direct correlation between the diverse animal studies to human endocrine systems is provided therefore these animal studies are not indicative or representative of humans (NAS 2005, ATSDR 2008).

7.10.3. Conclusion on endocrine disrupting properties

7.10.3.1. Environment

The WHO/IPCs definition was used to assess whether or not the perchlorate anion can be considered to be an endocrine disruptor in the environment. This concluding section summarizes data, which provide evidence that the perchlorate anion acts via an endocrine mode of action and – as a consequence of this mode of action – leads to adverse effects in organisms in wildlife species.

"An endocrine disrupter is an exogenous substance or mixture that alters function(s) of the endocrine system and consequently causes adverse health effects in an intact organism, or its progeny, or (sub)populations" (WHO/ILO/UNEP, 2002).

In this context, the information provided by the registrants and freely available literature was assessed based on the following questions:

• Does the perchlorate anion interact with the endocrine system of wildlife animals?

• Are the adverse effects observed likely to be a consequence of this interaction?

Perchlorate is known from mammalian studies (Section 7.9 and 7.10.2) to be a potent inhibitor of the thyroid sodium iodide symporter that transports iodide anions into the follicular cells, which is a key step of thyroid hormone synthesis. This mode of action has also been postulated for fish, lamprey, amphibian and bird species given the evolutionary conserved HPT axis in vertebrates and the reduced follicle/plasma thyroid hormone levels reported in case of perchlorate exposure. In case of a reduced thyroid hormone production due to the inhibitory action of perchlorate, several adverse effects on organ and organism level were reported, such as various histopathological alterations of the thyroid, impaired metamorphosis and development. Furthermore, a crosstalk with other endocrine axes was observed, resulting in a disturbed reproduction, hermaphroditism and skewed sex ratios, as well as reduced stress tolerance and impaired behaviour in different species. Hence, the available lower-tier *in vivo* data consistently point to an endocrine mode of action mediated via the thyroid pathway, while higher-tier *in vivo* data demonstrate adverse effects provoked by this mode of action.

Regarding the studied fish species the lowest observed effect concentrations (~1-100 mg/L) are three orders of magnitude higher than those for amphibians (~4-400 µg/L) when considering higher apical effects such as effects on growth, reproduction or metamorphosis. While biomarkers of lower relevance - such as gene expression alterations - show effects of perchlorate on the HPT axis already in the µg/L concentration range in fish. This might rely on differences in fish and amphibians regarding iodide accumulation, transport and metabolism or the autoregulatory feedback mechanism of the HPT axis (Blanton and Specker, 2007; Fort et al., 2007). Due to the negative autoregulatory feedback mechanism, transient effects might be balanced out by the body and thus preventing irreversible effects. This might be the same for endpoints of medium relevance, such as histopathological alterations, where after elongated exposure the thyroid concentrations in the blood are re-established indicating that the altered structure of the thyroid follicles represents a regulatory response to perchlorate exposure. However, long-term and population relevant impacts of such an alterations have not been investigated. Furthermore, perchlorate, although in higher concentrations, interfered with other endocrine axis exhibiting such as effects on the HPG axis. More studies reported on population relevant effects like skewed sex ratios or impaired behavioral effect and stress survival. Some of them could have been rescued applying exogenous thyroid hormones, indicating the specificity of this endpoint for thyroid hormone signaling.

In conclusion, the available data from different fish species support the proposed thyroidal mode of action of the perchlorate anion. Furthermore, the studies show some evidence for possible adverse effects mediated by this mode of endocrine action, however the observed effect concentrations here are relatively high, which can be explained by differences in iodide accumulation, transport and metabolism or autoregulatory feedback loop in fish.

Amphibians are known to be particularly sensitive to thyroid disruption given that thyroid hormones orchestrate several molecular, biochemical and morphological changes during metamorphosis (Denver, 2013). The data evaluated in this report confirm this trend as effect concentrations observed for the tested amphibian species are orders of magnitudes lower than in the fish assays. Also in amphibians, the assessed biomarkers clearly point to an endocrine mode of action mediated via the thyroid axis. Several studies investigating the early life stage of tadpoles (starting from NF 9-10) show effects on metamorphosis, like delayed hind limb growth or tail resorption after incubation with perchlorate in the µM range. Furthermore, one study exposing NF 9-10 tadpoles to perchlorate could show a significant influence on the male/female ratio in the µM (59 µM) range after 70 days of exposure. Summing up the amphibian data, a clear endocrine mode of action of the perchlorate anion can be demonstrated. Exposing especially sensitive life stages to micromolar, i.e. environmentally relevant, perchlorate concentrations can lead to adverse effects like delayed metamorphosis or even sex ratio disturbances on the organism level.

Regarding effect concentrations it should be noted that iodine concentration in the exposure media plays a pivotal role in the effect propagation of perchlorate as iodine might mitigate perchlorate effects. The importance of the iodine concentration in the exposure media has been verified by studies with amphibians, where for example effects in surface water (where iodine was present) were lower. However, the iodine concentration of the exposure media was not reported for the majority of the evaluated studies, thus more research is needed to explore environmental relevance of perchlorate, especially in case of high iodine background concentrations. Although it has to be noted that iodine concentration in surface waters is very variable: 0.6-212 µg/L with a median value of 10 µg/L regarding 39 European and North-American rivers according to Moran et al. (2002). Thus, environmental hazard posed by perchlorates might not be mitigated in aquatic environments with low iodine background concentration.

In summary, both the endocrine mode of action and adverse endocrine effects of perchlorate could be demonstrated by the studies evaluated in this substance evaluation report. Hence, there is scientific evidence of probable serious effects to the environment, which might give rise to an equivalent level of concern based on perchlorate endocrine disrupting effects in the environment. This has to be, however, investigated in an upcoming SVHC identification process. The evaluated studies in this report present an adequate basis for the identification of perchlorate salts and precursors under Art. 57 f. The persistency and high mobility of the perchlorate in aqueous media strengthen this concern, since transient exposure scenarios - allowing for recovery and autoregulation - are assumed to be unrealistic.

7.10.3.2. Human Health

Perchlorates are endocrine active substances in rodents and rabbits, with respect to disruption of thyroid hormones (OECD 2012). In comparison with rodents, healthy adult humans have lower thyroid hormone turnover rates and larger reserves of iodinated thyroglobulin, allowing them to compensate for reduced hormone synthesis in the thyroid (see also chapter 7.9.10.1). Due to these differences in thyroid hormone physiology, the data from toxicological studies in rats are of limited use for extrapolating to humans (EFSA 2015). Based on the currently available human data, the human health endocrine disruptor concern is not substantiated.

7.11. PBT and VPVB assessment

Not relevant for clarification of the concerns, therefore PBT/vPvB assessment was not part of this substance evaluation.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

Ammonium perchlorate is handled either as powders of different grain sizes leading to low, medium or high dustiness or it is handled as a wet solid, a concentrated aqueous solution or as a slurry. The latter three options are mostly applied in the production and further processing as an intermediate e.g. crystallisation.

In order to identify possible risks the CSRs were checked whether the exposure scenarios for workers are complete, plausible and well documented regarding relevant uses and exposure routes. The efficiency of the proposed risk management measures was evaluated in order to clarify whether further risk management options are needed.

7.12.1.2. Overview of uses and exposure scenarios

7.12.1.3. Ammonium perchlorate is used in a variety of industrial and professional settings.

According to the registrants the use of ammonium perchlorate can lead to long-term inhalation and dermal exposure of workers. In the CSRs the registrants provided worker assessments based on modelled data.

Monitoring data

The registrants did not provide any monitoring data for the substance in the CSR.

Modelled data

The registrants have estimated the workplace exposure to ammoium perchlorate using the tier 1 model MEASE. MEASE (Metal-EASE-Model) has been developed based on already existing models (EASE, ECETOC TRA) for special situations in the metals industry and is a 1st tier screening tool for the estimation of occupational inhalation and dermal exposure to metals and inorganic substances.

For inhalation exposure, the tool follows a PROC-specific approach and selects initial exposure estimates from three so-called "fugacity classes". The initial exposure estimates in MEASE are based on measured data from the metals industry which have been validated in EU Risk assessment procedures under the Existing Substances Regulation. For powders, the fugacity classes depend on the potential of staying airborne. As a result, MEASE gives the user the possibility to choose between several RMMs instead of only LEV as an implemented RMM.

The assessment of dermal exposure is based on the classification system applied in the EASE model. However, the assessments have been compared with measurement data, which were collated and plotted against the EASE exposure classes and the EASE exposure bands have been replaced. The reduction of dermal exposure by use of protective gloves can be considered.

7.12.1.4. Consumer

Not relevant for clarification of concern and no consumer uses.

7.12.1.5. Risks from physical-chemical properties

The handling and processing of ammonium perchlorate as an explosive constitutes a high risk. Each ES with a particle size distribution under the intrinsic critical one has a very high risk if the decomposition temperature is reached.

7.12.2. Environment

The initial concern for performing a substance evaluation of ammonium perchlorate was the endocrine disrupting potential of the perchlorate anion in the environment. Thus, all available exposure information has been evaluated to clarify the environmental relevance of ammonium perchlorate with respect to the hazard concern mentioned above. Taking into account all available data, including data from various literature studies, it is concluded that the perchlorate anion can enter environmental compartments via different applications and pathways, including precursor substances like chlorate and hypochlorite and natural sources of perchlorate like fertilizers or evaporite deposits. Only the registered uses were evaluated in depth.

Hence, the data analysed with respect to exposure issues during the substance evaluation of ammonium perchlorate support our conclusion that the perchlorate anion is an environmentally relevant contaminant in aqueous media.

The detailed non confidential aspects of our exposure assessment regarding ammonium perchlorate are discussed in the following paragraphs.

The total amount of registered ammonium perchlorate is in the tonnage band of 1.000 – 10.000 tonnes per annum.

Due to this indicated high tonnage (> 1000 t) in the registration wide dispersive use of ammonium perchlorate with a high potential of environmental exposure can be assumed.

However, in addition to production and formulation exclusively industrial uses have been registered. The uses as propellant blocks (grains) or composite explosives or other energetic components containing ammonium perchlorate are registered and covered with exposure scenarios in the CSR. Effluent data from production sites demonstrate a constant release of perchlorate from production and formulation. This finding is supported by further literature data e.g. presented in an Article of Technology & Regulatory Council Washington D.C. (ITRC, 2005), which reported findings of perchlorates to sites of production and use.

The use of ammonium perchlorate as explosive has to be considered separately. Ammonium perchlorate has the technical function of an oxidizing agent – so it will be mostly consumed during combustion. Hence, from this application only minor releases of the perchlorate anion to environmental media are expected. This assumption is supported by literature data (Oxley et al., 2009), which report the efficiency of perchlorate consumption.

Overall, an environmental release of perchlorate emanating from the production and use of ammonium perchlorate cannot be excluded. The initial assumption of an environmentally open wide dispersive use is confirmed by the data analysed during this substance evaluation.

7.13. Risk characterisation

7.13.1. Worker exposure

For quantitative risk characterization of ammonium perchlorate, exposure data from inhalation and dermal exposure were compared with the derived long-term systemic dermal and inhalation DNELs, respectively. The exposure assessment was made based on the estimations given in the CSRs. Furthermore, for several exposure scenarios (ES), additional risk management measures (RMM) were taken into considerations based on analogous ES described for sodium perchlorate presented as footnotes in the confidential annex to this report.

The risk characterization ratios (RCR) per each route of exposure are based on the DNELs calculated for thyroidal iodine uptake inhibition as the earliest systemic effect (see section 7.9.9 for details). For ammonium perchlorate, a long-term systemic DNEL for inhalation route of 12 µg/m^3 and a long-term systemic DNEL for dermal route of 83 µg/kg bw/d were calculated. Both DNELs are based on data derived from a volunteer study where the read across substance potassium perchlorate was given via drinking water (Greer et al., 2002). The read across is justified by the fact that the inhibition of thyroid iodine uptake is caused by the perchlorate anion. The RCR were then added to calculate the combined RCR for each exposure scenario.

The relation of exposure and the corresponding DNELs results in combined RCRs which exceed in most exposure scenarios the value of 1 up to a maximum of about a factor of 35 per process category mainly caused by a high inhalation exposure. There are only a small number of exposure scenarios where the dermal exposure is relevant. The manufacture of ammonium perchlorate is the most critical exposure scenario. Furthermore for risk characterization the dustiness is relevant. Low dustiness does not result in RCR above 1. However the risk by medium or high dustiness persists despite applying further RMM like integrated LEV. Based on the existing data the eMSCA cannot assess the need to combine RCRs for different process category. However, a combination of PROCs of exposure scenario 2 results in a markedly higher RCR than 35. An overview of some calculated RCRs per exposure route and the corresponding combined RCRs per process category is provided in the confidential annex to this report. Exemplary the highest exposure value per exposure scenario is presented as well as some exposure data to illustrate the impact of different dustiness.

For risk evaluation it has to be considered that the recalculated RCRs by eMSCA are based on the non-adverse precursor effect thyroidal iodine uptake inhibition which is not per se an adverse effect. Taking into account a reference value of 260 µg/m^3 for inhalation route and 1850 µg/kg bw/d for dermal route, respectively only the RCR for high dust exposure scenarios considering further RMM would be slightly above 1. As explained in section 7.9.9.1 these reference values could be possibly associated with changes in TSH or thyroid hormone levels resulting in goitre based on data of secondary literature. However, no clear data are available to confirm this assumption. For scenarios with an exposure of ammonium perchlorate between 12 µg/m^3 and 260 µg/m^3 for inhalation pathway and 83 µg/kg bw/d and 1854 µg/kg bw/d there seems to be a risk for worker to develop toxic multinodular goitre in consequence of adaptive processes, which however cannot be quantified. This applies to most exposure scenarios.

In conclusion, the eMSCA is not able to provide a reliable risk characterization. However, based on the available data it cannot be excluded by the eMSCA that a permanent inhibition of thyroidal iodine uptake leads to adverse effects on thyroid.

7.13.2 Risk of physico-chemical properties

The risk characterisation of physicochemical properties by a description of the risk factors, adequate RMM and an estimation of the severity and a conclusion was made in some registration dossiers. Nevertheless, in some registrations the assessment of explosive properties was not assessed. The eMSCA could not evaluate if other critical particle sizes of the remaining registrants will be communicated down the supply chain. To secure a high quality of the safety data sheets the eMSCA recommends an update of the dossiers of registrants with other critical particle sizes for explosive for the physicochemical risk assessment and characterization on which to base the recommendation for risk management measures to be communicated down the supply chain.

7.14. References

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7.15. Abbreviations

abs.	absolute
AP	Ammonium Perchlorate
ATSDR	Agency for Toxic Substances and Disease Registry
bw	body weight
C&L	Classification and Labelling
CMR	Carcinogenic, Mutagenic, Toxic for reproduction
conc.	concentration
d	day(s)
DNEL	Derived No Effect Level
EC_{50}	Half maximal effect concentration
ES	Exposure Scenario
IC_{50}	Half maximal inhibitory concentration
EFSA	European Food Safety Authority
EPA	Environmental Protection Agency
F	Female
GD	Gestational Days
GL	Guideline
GLP	Good laboratory praxis
h	hour(s)

HPT	Hypothalamus-Pituitary-Thyroid
HPG	Hypothalamus-Pituitary-Gonad
LO(A)EL	lowest-observed (adverse) effect level
M	Male
NO(A)EL	no-observed (adverse) effect level
NRC	National Research Council
OECD	Organisation for Economic Co-operation and Development
PNEC	Predicted no effect concentration
PROC	Process Category
RCR	Risk characterization ratio
rel.	relative
SVHC	Substances of very high concern
TG	Test Guideline
TL	Test Laboratory
TMNG	toxic multinodular goitre
TSH	thyroid-stimulating hormone
T4	thyroxin
TT4	total T4
T3	triiodothyronine
TT3	total T3
w	week
WHO	World Health Organization

ANNEX 1: Effect concentrations to endpoints on environmental endocrine disruption

Table A1:

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN FISH AND LAMPREYS									
Reference	**Provided by the registrants?**	**Guideline/Method**	**Reliability of the study**	**Substance**	**Endpoint**	**Relevance**	**Effect concentration type**	**Effect concentration ($\mu g/L$ ClO_4^-)**	**Remark**
Bernhardt and von Hippel (2008)	in PNEC study	two generation test with three-spined stickleback (*Gasterosteus aculeatus*)	2	$NaClO_4$	Reproductive effects (generation 0)	high	LOEC	>18600	Very objective endpoints, hard to recognise a real dose-dependent relationship for all endpoints measured only two concentrations tested
					Behavioural effects (generation 0)	high	LOEC	>18600	
					Behavioural effects (swimming performance, generation 1)	high	LOEC	32000	
					Behavioural effects (courtship, generation 1)	high	LOEC	32000	
Bernhardt et al. (2006)	in PNEC study	two generation test with three-spined stickleback (*Gasterosteus aculeatus*)	2	$NaClO_4$	Reproductive effect (interference with nuptial colouration)	medium	LOEC	32000	only three concentrations tested
					Reproductive effect (hermaphroditism)	high	LOEC	102920	
					Survival in case of stress	high	LOEC	32000	
Bradford et al. (2005)	in PNEC study	eastern mosquitofish (*Gambusia holbrooki*) exposed over 30 days	2	$NaClO_4$	Whole-body T_4 level	low	LOEC	81	non concentration-dependent only nominal concentrations given
					Histopathology of the thyroid follicles (multiple endpoints)	medium	LOEC	81	

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN FISH AND LAMPREYS									
Reference	**Provided by the registrants?**	**Guideline/Method**	**Reliability of the study**	**Substance**	**Endpoint**	**Relevance**	**Effect concentration type**	**Effect concentration (µg/L ClO_4^-)**	**Remark**
Crane et al. (2005)	in PNEC study	exposure of developing fathead minnow (*Pimephales promelas*) over 28 days (similar to FELST)	2	NH_4ClO_4	Whole-body T_4 level (adult)	low	LOEC	8500	only three concentrations tested, only nominal concentrations given
					Whole-body T_3 level (adult)	low	LOEC	>85000	
					Histopathology of the thyroid follicles	medium	LOEC	850	
					Growth (lenght)	high	LOEC	8500	
					Wet weight	high	LOEC	8500	
					Developmental effects (retarded pigmentation, absence of scales)	high	LOEC	8500	
Furin et al. (2015)	no	Exposure of three-spined stickleback (*Gasterosteus aculeatus*) starting at 0, 3, 7, 14, 21, 42, 154 and 305 days post fertilization until approximately one year old age	2	$NaClO_4$	Histopathology of the thyroid follicles	medium	LOEC	24300	only two concentrations tested, only nominal concentrations given
					Reproductive effects (skewed sex ratios to males)	high	LOEC	81000	
					Reproductive effects (delayed gonadal maturity)	high	LOEC	24300	
Holmes et al. (1999)	no	American brook lamprey (*Lampetra appendix*) larvaes were	2	$KClO_4$	Whole-body T_4/T_3 level	low	LOEC	72000	only two concentrations tested, only

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN FISH AND LAMPREYS									
Reference	**Provided by the registrants?**	**Guideline/Method**	**Reliability of the study**	**Substance**	**Endpoint**	**Relevance**	**Effect concentration type**	**Effect concentration (µg/L ClO_4^-)**	**Remark**
		exposed until metamorphosis			Effect on metamorphosis (earlier onset)	high	LOEC	72000	nominal concentrations given
Hornung et al. (2010)	no	*In vitro* assessment of T4 inhibition using thyroid gland cultures from prometamorphic Xenopus tadpoles	2	$NaClO_4$	Inhibition of T_4 production	low	IC_{50}	119	only nominal concentrations given
Kao et al. (1999)	no	Landlocked lamprey (*Petromyzon marinus*) larvae were exposed over 16 weeks	2	$KClO_4$	Altered organ weights and somatic indices (kidney, liver)	medium	LOEC	36000	only one concentration tested, only nominal concentration given
					Effect on metamorphosis (earlier onset)	high	LOEC	36000	
Lee et al. (2014)	no	Temperature and perchlorate interactions were studied using medakas (*Oryzias latipes*)	2	$NaClO_4$	Gene expression changes	low	LOEC	81000	only one concentration tested, only nominal concentration given
					Whole-body T_4 level (adult)	low	LOEC	81000	
					Whole-body T_3 level (adult)	low	LOEC	>81000	
					Reproductive parameters (total number of eggs)	high	LOEC	81000	

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN FISH AND LAMPREYS

Reference	Provided by the registrants?	Guideline/Method	Reliability of the study	Substance	Endpoint	Relevance	Effect concentration type	Effect concentration (µg/L ClO_4^-)	Remark
Li et al. (2011)	no	Chinese rare minnow (*Gobiocypris rarus*) larvaes and adults were exposed over 21 days	2	$Mg(ClO_4)_2$	Gene expression alteration (larvae, deiodinase 2 gene)	low	LOEC	5	only nominal concentrations given [1]concentration-dependent responses after 7 and 14 days but not after 21 days [2]concentration-dependent responses after 7 and 21 days but not after 14 days [3]concentration-dependent effects were seen only for d3 in females [4]concentration-dependent effects were seen only in females after 21 days [5]just in males [6]just in females
					Gene expression alteration (larvae, nis gene)	low	LOEC	50 [1]	
					Gene expression alteration (adult liver, deiodinase 1,2,3 gene)	low	LOEC	>50	
					Gene expression alteration (adult liver, nis gene)	low	LOEC	5 [2]	
					Gene expression alteration (adult brain, deiodinase 2,3 gene)	low	LOEC	5 [3]	
					Gene expression alteration (adult brain, nis gene)	low	LOEC	5 [4]	
					Developmental effects (impaired swimbladder)	medium	LOEC	50	
					Whole-body T_4 level (adult)	low	LOEC	>50	
					Whole-body T_3 level (adult)	low	LOEC	50 [5]	
					Gonadosomatic index	medium	LOEC	>50	
					Hepatosomatic index	medium	LOEC	50 [6]	

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN FISH AND LAMPREYS									
Reference	**Provided by the registrants?**	**Guideline/Method**	**Reliability of the study**	**Substance**	**Endpoint**	**Relevance**	**Effect concentration type**	**Effect concentration (µg/L ClO_4^-)**	**Remark**
					Body length	high	LOEC	>50	
Liu et al. (2006)	in PNEC study	Zebrafish (*Danio rerio*) were exposed over 10-90 days	2	$NaClO_4$	Histopathology of the thyroid follicles (multiple endpoints)	medium	LOEC	8100	only nominal concentrations given, only two concentrations tested
					Growth (wet weight)	high	LOEC	>81000	
Manzon and Youson (2002)	no	*In vitro* assessment of iodide uptake by larval lamprey endostyle	2	$KClO_4$	Inhibition of iodide uptake	low	LOEC	71856	only two concentrations tested, only nominal concentrations given
Manzon et al. (2001)	no	Landlocked lamprey (*Petromyzon marinus*) larvae were exposed until metamorphosis	2	$KClO_4$	Whole-body T_4/T_3 level	low	LOEC	7200	only two concentrations tested, only nominal concentrations given
					Effect on metamorphosis (earlier onset)	high	LOEC	72000	

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN FISH AND LAMPREYS									
Reference	**Provided by the registrants?**	**Guideline/Method**	**Reliability of the study**	**Substance**	**Endpoint**	**Relevance**	**Effect concentration type**	**Effect concentration (µg/L ClO_4^-)**	**Remark**
Mukhi and Patino (2007)	yes	10-16 week of exposure using adult zebrafish (*Danio rerio*) and the offsprings thereof (effects measured weekly, LOECs given for week 16)	2	$NaClO_4$	Whole-body T_4 level (embryonic)	low	LOEC	8100 [1]	only two concentrations tested, only nominal concentrations given after maternal exposure
					Whole-body T_3 level (embryonic)	low	LOEC	>81000 [1]	
					Histopathology of the thyroid follicles	medium	LOEC	8100	
					Whole-body T_4 level (adult)	low	LOEC	8100	
					Whole-body T_3 level (adult)	low	LOEC	>81000	
					Reproductive effects (cummulative packed egg volume)	medium	LOEC	8100	
					Developmental effects (hatching rate)	medium	LOEC	>81000 [1]	
					Developmental effects (egg diameter)	medium	LOEC	8100 [1]	
					Developmental effects (craniofacial marformation)	medium	LOEC	81000 [1]	
					Reproductive effects (fertilisation rate)	high	LOEC	>81000	
					Growth (female body weight)	high	LOEC	8100	

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN FISH AND LAMPREYS									
Reference	**Provided by the registrants?**	**Guideline/Method**	**Reliability of the study**	**Substance**	**Endpoint**	**Relevance**	**Effect concentration type**	**Effect concentration (µg/L ClO_4^-)**	**Remark**
Mukhi et al. (2005)	yes	12 weeks of exposure and 12 weeks of recorvery using adult zebrafish (*Danio rerio*) (effects measured at weeks 2, 4, 8, 12; LOECs given for week 12)	2	$NaClO_4$	Immunohistochemistry on follicular T_4 (colloidal ring intensity)	low	LOEC	11 [1,3]	[1] not established endpoint [2] possible effect of the autoregulatory feedback mechanism [3] after 12 weeks of recovery the effect could have been mitigated
					Histopathology of the thyroid follicles (colloid depletion)	medium	LOEC	11480	
					Histopathology of the thyroid follicles (hyperthrophy)	medium	LOEC	1131 [3]	
					Histopathology of the thyroid follicles (angiogenesis)	medium	LOEC	90 [1, 3]	
					Whole-body T_4 level	low	LOEC	>11480 [2]	
					Growth (length/weight)	high	LOEC	>11480	
					Mortality	high	LOEC	>11480	

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN FISH AND LAMPREYS

Reference	Provided by the registrants?	Guideline/Method	Reliability of the study	Substance	Endpoint	Relevance	Effect concentration type	Effect concentration (µg/L ClO_4^-)	Remark
Mukhi et al. (2007)	yes	larval/juvenile exposure of zebrafish (*Danio rerio*) over 30 day	2	NH_4ClO_4	Fish mortality	high	LOEC	212500 [1]	only two concentrations tested, only nominal concentrations given [1] more serious effect when co-treated with T_4 [2] could be rescued using exogenous T_4
					Growth (lenght)	high	LOEC	85000 [1]	
					Histopathology of the thyroid follicles	medium	LOEC	85000 [2]	
					Reproductive effects (skewed sex ratios)	high	LOEC	85000 [2]	
Park et al. (2006)	in PNEC study	Adult and fry mosquitofish (*Gambusia holbrooki*) were exposed over 8 week (adults) or 5 days (fries), resp.	2	$NaClO_4$	Histopathology (adult)	medium	LOEC	1150	[1] non-clear dose-response [2] estimated LC_{50}=404400
					Survival (adult)	high	LOEC	>99250	
					Growth (adult)	high	LOEC	>99250	
					Reproductive effects (GSI)	medium	LOEC	1150 [1]	
					Reproductive effects (embryo mass)	medium	LOEC	99250 [1]	
					Reproductive effects (fecundity)	high	LOEC	1150 [1]	
					Survival (fries)	high	LOEC	427000 [2]	
					Growth (fries)	high	LOEC	800 [1]	

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN FISH AND LAMPREYS									
Reference	**Provided by the registrants?**	**Guideline/Method**	**Reliability of the study**	**Substance**	**Endpoint**	**Relevance**	**Effect concentration type**	**Effect concentration (µg/L ClO_4^-)**	**Remark**
Patino et al. (2003)	in PNEC study	8 weeks of exposure of zebrafish (*Danio rerio*)	2	NH_4ClO_4	Histopathology of the thyroid follicles (multiple endpoints)	medium	LOEC	18000	only two concentrations tested
					Reproductive effects (packed egg volume)	medium	LOEC	667000	
Petersen et al. (2015)	no	exposure of three-spined stickleback (*Gasterosteus aculeatus*) starting at various developmental stage after fertilization until reproduction	2	$NaClO_4$	Whole-body T_4 level (adult)	low	LOEC	>100000	[1] only the lowest dose affected showing a non-monotonic concentration-response curve. During development, no significat alterations [2] early stage ovarian follicles, earlyier onset of spermatogenesis
					Whole-body T_3 level (adult)	low	LOEC	10000 [1]	
					Survival, morphology, growth	high	LOEC	>100000	
					Crosstalk with other endocrine pathway (elevated androgen hormone levels)	medium	LOEC	10000	
					Reproductive effects (gonadal development)	high	LOEC	10000 [2]	
Raldua and Babin (2009)	no	exposure of zebrafish embryos (*Danio rerio*) from 2-5 day post fertilisation	2	$KClO_4$	Follicular T_4 changes measured with immunohistochemistry	low	LOEC	17901	only nominal concentrations given
Schmidt et al. (2012)	no	modified FELST with zebrafish (*Danio rerio*)	2	$KClO_4$	Growth (condition factor)	high	LOEC	90 [1]	only nominal concentrations given

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN FISH AND LAMPREYS									
Reference	**Provided by the registrants?**	**Guideline/Method**	**Reliability of the study**	**Substance**	**Endpoint**	**Relevance**	**Effect concentration type**	**Effect concentration (µg/L ClO_4^-)**	**Remark**
					Whole-body T_4 level	low	LOEC	3600	[1] calculated as a function of lenght and weight. No dose dependency for length and weight alone
					Histopathology of the thyroid follicles (multiple endpoints)	medium	LOEC	180	
Theodorakis et al. (2006)	no	Field study on central stonerollers (*Campostoma anomalum*)	2	ClO_4^-	Histopathology of the thyroid follicles	medium	-	no different dilutions of surface water were tested.	Effects were seen as low as 23.61 µg/L perchlorate in surface water
Thienpont et al. (2011)	no	exposure of zebrafish embryos (*Danio rerio*) from 2-5 day post fertilisation	2	$KClO_4$	Follicular T_4 changes measured with immunohistochemistry	low	EC_{50}	249	only nominal concentrations given

Table A2:

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN AMPHIBIANS									
Reference	**Provided by the registrants?**	**Guideline/Method**	**Reliability of the study**	**Substance**	**Endpoint**	**Relevance**	**Effect concentration type**	**Effect concentration (µg/L ClO_4^-)**	**Remark**
Brausch et al. (2010)	in PNEC study	The effect of surface water or artificial exposure media on the outcome of the experiments was tested on Xenopus and New Mexico spadefoot toad (*Spea multiplicata*)	2	$NaClO_4$	Interference with metamorphosis (Xenopus in FETAX)	high	LOEC	80	only two concentrations tested
					Interference with metamorphosis (Xenopus in stream)	high	LOEC	>80	
					Interference with metamorphosis (Spadefoot in stream)	high	LOEC	> 1038	only three concentrations tested
Goleman et al. (2002a)	yes	Xenopus embryos were exposed over 70 days followed by a recovery period of 28 days. LOECs are given for day 70	2	NH_4ClO_4	Mortality of adults (70d)	high	LOEC	>14140	FETAX medium was used (no iodide added), just two concentrations tested
					Development	high	LOEC	>14140	
					Histopathology of the thyroid follicles (multiple endpoits-70d)	medium	LOEC	59	
					Interference with metamorphosis (hindlimb lenght)	high	LOEC	59	
					Interference with metamorphosis (forelimb emergence)	high	LOEC	14140	
					Interference with metamorphosis (completing tail resorption)	high	LOEC	14140	
					Interference with metamorphosis (snout-vent lenght)	high	LOEC	>14140	

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN AMPHIBIANS

Reference	Provided by the registrants?	Guideline/Method	Reliability of the study	Substance	Endpoint	Relevance	Effect concentration type	Effect concentration (µg/L ClO_4^-)	Remark
					Whole-body T_4 level (adult)	low	LOEC	14140	
					Reproductive effects (male/female ratio)	high	LOEC	59	
Goleman et al. (2002b)	yes	Xenopus embryos were exposed over 70 days	1	NH_4ClO_4	Mortality of embryos (5d)	high	LC_{50}	433500	FETAX medium was used (no iodide added)
					Mortality of adults (70d)	high	LC_{50}	189550	
					Interference with metamorphosis (snout-vent lenght)	high	LOEC	361250	
					Interference with metamorphosis (forelimb emergence)	high	LOEC	4,25	
					Interference with metamorphosis (hindlimb lenght)	high	LOEC	15,3	
					Interference with metamorphosis (completing tail resorption)	high	LOEC	15,3	
Hu et al. (2006)	in PNEC study	Xenopus tadpoles were exposed for 38 and 69 days	1	$NaClO_4$	Interference with metamorphosis (multiple endpoints)	high	LOEC	93	FETAX medium was used (no iodide added) no tadpoles completed metamorphosis in concentration 1131 µg/L
					Histopathology of the thyroid follicles (exposure 38 d)	low	LOEC	93	

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN AMPHIBIANS									
Reference	**Provided by the registrants?**	**Guideline/Method**	**Reliability of the study**	**Substance**	**Endpoint**	**Relevance**	**Effect concentration type**	**Effect concentration ($\mu g/L$ ClO_4^-)**	**Remark**
					Histopathology of the thyroid follicles (exposure 96 d)	medium	LOEC	>93	colloidal T_4 ring intensity was responsive for both exposure period tested
					Immunohistochemistry on follicular T_4	low	LOEC	8	
OECD, 2007	yes	OECD 231 - AMA prevalidation study by five laboratories; measurments of lab 2 and 5 are excluded due to the lack of iodide measurement effect concentrations are given for day 21	1	$NaClO_4$	whole body lenght	high	LOEC	117	laboratory 1
							LOEC	284	laboratory 3
							LOEC	>446	laboratory 4
					Interference with metamorphosis (snout-vent lenght)	high	LOEC	117	laboratory 1
							LOEC	284	laboratory 3
							LOEC	>446	laboratory 4
					wet weight	high	LOEC	117	laboratory 1
							LOEC	149	laboratory 3
							LOEC	>446	laboratory 4
					Interference with metamorphosis (hindlimb lenght)	high	LOEC	>485	laboratory 1
							LOEC	284	laboratory 3
							LOEC	238	laboratory 4
					Histopathology of the thyroid follicles (multiple endpoits)	medium	LOEC	61	laboratory 1
							LOEC	87	laboratory 3
							LOEC	65	laboratory 4
	yes		4	$NaClO_4$	Histopathology of the thyroid follicles	medium	LOEC	500	

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN AMPHIBIANS

Reference	Provided by the registrants?	Guideline/Method	Reliability of the study	Substance	Endpoint	Relevance	Effect concentration type	Effect concentration (µg/L ClO_4^-)	Remark
Olmstead et al. (2009)		40 weeks of exposure of Xenopus embryos			Interference with metamorphosis	high	LOEC	>1500	just a presentation (only abstract available)
					Reproductive effects (male/female ratio)	high	LOEC	>1500	
Semlitsch and Gibbons (1988)	in PNEC study	Indirect effect of perchlorate exposure was tested on predation: smaller animals are more susceptible to predators	2	-	Susceptibility to predators	high	-	-	-
Theodorakis et al. (2006)	no	Field study on cricket frogs (*Acris crepitans*)	2	ClO_4^-	Histopathology of the thyroid follicles (follicle cell hyperthrophy)	medium	LOEC	10	no evidence of colloid depletion or follicle hyperplasia
Tietge et al. (2005)	in PNEC study	Two experiments performed using lake water: study 1_short-term exposure of stage 51-54 tadpoles and study 2_exposure of stage 54 Xenopus tadpoles throughout the metamorphosis	2	$NaClO_4$	Interference with metamorphosis	high	LOEC	250	in study 1
					Histopathology of the thyroid follicles	medium	LOEC	16	in study 1
					Interference with metamorphosis	high	LOEC	125	in study 2
					Histopathology of the thyroid follicles	medium	LOEC	63	in study 2

Table A3:

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN BIRDS

Reference	Provided by the registrants?	Guideline/Method	Reliability of the study	Substance	Endpoint	Relevance	Effect concentration type	Effect concentration (µg/L ClO_4^-)	Remark
Chen et al. (2009)	no	Chronic exposure (7.5 weeks) of Japanese quail (*Coturnix coturnix japonica*) chicks via drinking water	2	NH_4ClO_4	Histopathology of the thyroid follicles (hyperthrophy)	medium	LOEC	1700000	only one concentration tested, only nominal concentration given
					Whole-body T_4 level	low	LOEC	1700000	
Gentles et al. (2005)	no	Chronic exposure (30 days) of northern bobwhite quails (*Colinus virginianus*) via drinking water	2	NH_4ClO_4	Histopathology of the thyroid follicles (hyperthrophy)	medium	LOEC	99450	deionized tapwater used; only one concentration tested, only nominal concentration given significant accumulation was seen in eggs
					Toxicological endpoints (body/organ weights, reproduction)	high	LOEC	>99450	
McNabb et al. (2004a)	no	Chronic exposure (2,4 and 8 weeks) of northern bobwhite quails (*Colinus virginianus*) via drinking water	2	NH_4ClO_4	Whole-body T_4 level	low	LOEC	21250	distillated water used, only nominal concentrations given after 2 weeks-no clear dose response
					Follicular T_4 changes	low	LOEC	425	after 2 weeks- clear dose response
					Whole-body T_4 level	low	LOEC	25,5	after 4 weeks-no clear dose response
					Follicular T_4 changes	low	LOEC	42500	after 4 weeks- clear dose response
					Whole-body T_4 level	low	LOEC	8,5	after 8 weeks-no clear dose response

LIST OF EVALUATED STUDIES ON ENDOCRINE DISRUPTING EFFECTS OF PERCHLORATE IN BIRDS

Reference	Provided by the registrants?	Guideline/Method	Reliability of the study	Substance	Endpoint	Relevance	Effect concentration type	Effect concentration (µg/L ClO_4^-)	Remark
					Follicular T_4 changes	low	LOEC	212500	after 8 weeks-no clear dose response
McNabb et al. (2004b)	no	Chronic exposure (1, 2 and 8 weeks) of northern bobwhite quails (*Colinus virginianus*) via drinking water	2	NH_4ClO_4	Whole-body T_4 level	low	LOEC	212500	distillated water used, only nominal concentrations given LOECs given for 8 weeks of exposure
					Follicular T_4 changes	low	LOEC	212500	
					Thyroidal weight	medium	LOEC	850000	
Rainwater et al. (2008)	no	Oral exposure of zebra finch (*Taeniopygia guttata*) from 3-14 days post hatch to day 72 post hatch	2	$NaClO_4$	Growth (weight/lenght)	high	LOEC	100 µg/g	only three concentrations tested, only nominal concentrations given
					Mean liver mass	medium	LOEC	100 µg/g	
					Mean brain mass	medium	LOEC	>1000 µg/g	
					Behavioural effects	high	LOEC	1000 µg/g	