Bundesanstalt für Arbeitsschutz
und Arbeitsmedizin
Federal Institute for Occupational
Safety and Health

SUBSTANCE EVALUATION CONCLUSION

as required by REACH Article 48

and

EVALUATION REPORT

for

Antimony trichloride
EC No 233-047-2
CAS No 10025-91-9

Evaluating Member State(s): Germany

Dated: December 2019

Template Version 2.1
March 2015

Evaluating Member State Competent Authority

BAuA
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Year of evaluation in CoRAP: 2018

Member State concluded the evaluation without any further need to ask more information from the registrants under Article 46(1) decision.
A compliance check has been initiated by ECHA in parallel to the substance evaluation to request missing standard information.

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

Antimony trichloride (ATC) was originally selected for substance evaluation in order to clarify the following concerns: suspected CMR (carcinogenicity and reproductive toxicity).

During the evaluation also additional concerns were identified: mutagenicity, repeated dose toxicity, endocrine disruptive activity (human health).

2. OVERVIEW OF OTHER PROCESSES / EU LEGISLATION

A compliance check has been initiated by ECHA in parallel to the substance evaluation to request missing standard information.

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	
Harmonised Classification and Labelling	
Identification as SVHC (authorisation)	
Restrictions	
Other EU-wide measures	
No need for regulatory follow-up action at EU level at this point	x

The evaluation of antimony trichloride (ATC) was conducted in parallel to evaluations for antimony metal (Sb metal, EC 231-146-5, CAS 7440-36-0), antimony trioxide (ATO, EC 215-175-0, CAS 1309-64-4), antimony sulphide (ATS, EC 215-713-4, CAS 1345-04-6) and 2,5,7,10,11,14-hexaoxa-1,6-distibabicyclo[4.4.4]tetradecane (ATEG, EC 249-820-2, CAS 29736-75-2). For the other four substances, draft decisions were prepared by the eMSCA according to Art. 46(1) and submitted to ECHA.

As of December 2019, the evaluation for these four cases is still ongoing. For all five Sb substances, a compliance check has been initiated in parallel by ECHA to assess whether standard information is missing.

4. FOLLOW-UP AT EU LEVEL

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

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)

Not applicable.

4.1.3. Restriction

Not applicable.

4.1.4. Other EU-wide regulatory risk management measures

Not applicable.

5. CURRENTLY NO FOLLOW-UP FORESEEN AT EU LEVEL

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

The concerns for ATC for repeated dose toxicity, carcinogenicity (section 7.9.7), mutagenicity (section 7.9.5), toxicity to reproduction (section 7.9.8), and endocrine disruption (human health) are predominantly based on the structural similarity to ATO and other antimony (Sb) compounds. However, due to lack of relevant studies on ATC and insufficient data to justify a read-across it is not possible to conclude on the hazard concerns. Endocrine activity was observed for ATC as well as for structurally similar Sb compounds. However, the data available are not sufficient to draw any final conclusion.

As there is no exposure of consumers indicated, occupational exposure of workers is regarded as very low and in light of the on-going dossier evaluation on this substance, the generation of new information by animal testing for ATC also under this process is considered not proportionate at this stage. Therefore, no further data are requested in the context of this substance evaluation and no further regulatory follow-up at EU level is currently (December 2019) proposed.

The need for further regulatory follow-up at EU level may be reassessed in case new information becomes available in the future, *e.g.* from the ongoing compliance check on this substance or in case new uses of the substance significantly change the potential for exposure.

5.2. Other actions

Based on the results from additional studies found in open literature during the evaluation, ATC fulfills the classification criteria for acute toxicity category 4, H302, and acute toxicity category 3, H311. The Registrant(s) are advised to update their registration dossiers accordingly.

6. TENTATIVE PLAN FOR FOLLOW-UP ACTIONS

Not applicable.

Part B. Substance evaluation

7. EVALUATION REPORT

7.1. Overview of the substance evaluation performed

ATC was originally selected for substance evaluation in order to clarify concerns about: suspected CMR properties (carcinogenicity and reproductive toxicity).

During the evaluation also additional concerns were identified: mutagenicity, repeated dose toxicity, endocrine disruptive activity (human health).

Table 2

EVALUATED ENDPOINTS	
Endpoint evaluated	**Outcome/conclusion**
Carcinogenicity	**No conclusion reached** There is concern that ATC may be carcinogenic, based on the structural similarity to ATO, which is currently classified as Carc. 2, H351. In a recent NTP study, ATO caused lung tumours in male and female mice and rats, adrenal medullary neoplasms in male and female rats, skin neoplasms in male mice and malignant lymphoma in female mice (NTP 2017). However, except for one old oral non-guideline study in guinea pigs, there are no RDT nor carcinogenicity studies with ATC and the available data are not sufficiently robust to conclude.
Mutagenicity	**No conclusion reached** ATC gave positive results in an *in vitro* micronucleus test (OECD 487) and caused DNA damage in several *in vitro* non-guideline studies. No valid *in vivo* genotoxicity studies are available for ATC. Thus, it is not possible to conclude on the endpoint.
Reproductive toxicity	**No conclusion reached** Several studies with different routes of exposure indicate reproductive (developmental) toxicity of Sb compounds including ATC. The substance potentially interferes with normal development of offspring in humans. However, the available data are not sufficiently robust to reach a conclusion.
Repeated dose toxicity	**No conclusion reached** There is concern that ATC may potentially cause target organ toxicity including haematotoxicity and cardiotoxicity after repeated oral or inhalation exposure based on an old oral non-guideline study with ATC in guinea pigs and from oral and inhalation studies with structurally related Sb compounds. While the available data are not sufficiently robust to conclude, they highlight

	substantial uncertainties regarding a DNEL derivation for ATC.
Acute toxicity	**No conclusion reached** Based on additional studies found in open literature during the evaluation it is concluded that ATC fulfills the classification criteria for acute toxicity category 4, H302, and acute toxicity category 3, H311. There are indications that ATC may also cause acute toxicity after inhalation, however the available data are not sufficiently robust to draw a conclusion.
Endocrine disruption – Human health	**No conclusion reached** There are indications for a potential interaction of Sb with the sex steroid as well as the thyroid hormone systems. However, no guideline studies investigating any endocrine parameters are available for ATC. Therefore, no conclusion can be drawn on the potential endocrine-disrupting effects of ATC.

No conclusion on hazard properties as listed above can be reached based on the available data. However, since no exposure of consumers could be identified, occupational exposure is regarded very low and in light of the on-going compliance check on ATC, the generation of new information by additional animal testing for ATC under this substance evaluation is currently considered not proportionate.

7.2. Procedure

Pursuant to Article 44(2) of the REACH Regulation, Antimony trichloride (ATC) was included on the Community rolling action plan (CoRAP) for evaluation in 2018. The substance evaluation commenced on 26 March 2018. ATC was evaluated as a member of a group consisting of antimony and four trivalent antimony compounds. The group members were Sb metal, ATO, ATS, ATC and ATEG.

The substance evaluation was conducted directly after the finalisation of the screening of eight Sb compounds in 2017 in the collaborative approach (COLLA) pilot project. The group of Sb compounds was proposed for the COLLA by the International Antimony Association (i2a), as there was already preparatory regulatory activity being carried out on some members of the substance group. The group of eight Sb compounds that were examined during COLLA was subdivided into a group containing Sb metal and four trivalent Sb compounds and a group containing three pentavalent Sb compounds which were not put forward for substance evaluation by the DE CA.

The outcome of the COLLA project was to follow a tiered approach for substance evaluation which will first include five substances, then the other three if necessary. Sb metal and two trivalent Sb compounds (ATO and ATS) were already included in the CoRAP for the evaluation in 2018 prior to the CoRAP update 2018-2020 and DE was chosen as the evaluating MS CA. Based on the COLLA project, two further trivalent Sb compounds (ATEG, ATC) were also suggested for the CoRAP for evaluation in 2018.

The initial concerns leading to regulatory scrutiny of the Sb compounds were carcinogenicity, as the structurally related ATO is classified as Carc. 2 – suspected human carcinogen, reported exposures lead to a high RCR, and reproductive toxicity, based on embryotoxic effects in a developmental toxicity study with the structurally related antimony metal. Consequently, ATC was included alongside other trivalent REACH-

registered Sb compounds and Sb metal for parallel evaluation to clarify the common concern.

The substance evaluation was conducted by assessing the registration dossiers[2], the CSRs and further scientific literature sources.

In June 2018, the eMSCA invited the registrant to clarify some questions and uncertainties in writing. The information provided by the registrant was assessed and taken into account while evaluating the substance. A meeting with the registrants also took place in June 2018.

Based on the available data, the evaluating MSCA concluded that there are remaining concerns for endocrine disruption, mutagenicity, carcinogenicity, toxicity to reproduction, and repeated dose toxicity. The available data are not sufficient to draw final conclusions on these hazard properties. However, since no exposure of consumers and very low exposure of workers has been identified based on the evaluation of the available information leading to a potential risk, no further data was requested in the context of this substance evaluation.

7.3. Identity of the substance

Table 3

SUBSTANCE IDENTITY of ANTIMONY TRICHLORIDE	
Public name:	Antimony trichloride
EC number:	233-047-2
CAS number:	10025-91-9
Index number in Annex VI of the CLP Regulation:	051-001-00-8
Molecular formula:	$SbCl_3$
Molecular weight range:	228.11 g mol^{-1}
Synonyms:	Trichlorostibine Antimony chloride Antimony(III) chloride

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

7.4. Physico-chemical properties

Table 4

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES of ANTIMONY Trichloride	
Property	**Value**
Physical state at 20°C and 101.3 kPa	Crystalline, white to yellow appearance, pungent odour
Melting point	72 – 78 °C (differential scanning calorimetry and capillary tube in a metal block according to EU A.1 and OECD Test Guideline 102)

[2] The latest dossier update considered for this conclusion document is from 24th May 2018

OVERVIEW OF PHYSICOCHEMICAL PROPERTIES of ANTIMONY Trichloride	
Property	**Value**
Boiling point	215 °C at 1013.25 hPa (differential scanning calorimetry according to EU A.2 and OECD Test Guideline 103)
Relative density	D^{23}_4 = 3.15 (air comparison pycnometer according to EU A.3 and OECD Test Guideline 109)
Vapour pressure	Handbook data: 1 mm Hg at 49.2 °C 10 mm Hg at 85.2 °C 40 mm Hg at 117.8 °C
Water solubility	Data waiver: According to Annex VII of the REACH Regulation, the water solubility is not required because the substance hydrolyses in water.
Partition coefficient n-octanol/water (Log Kow)	Data waiver: According to Annex VII of the REACH Regulation, the partition coefficient is not required because the substance is inorganic.
Flammability	-
Explosive properties	-
Oxidising properties	-
Granulometry	Particle size distribution determined by laser diffraction according to CIPAC MT 187 and ISO 13320-1: D10 = (440.3 ± 19.3) µm D50 = (897.2 ± 22.6) µm D90 = (1491.2 ± 35.9) µm Dustiness and MMAD determined using a Heubach dust meter according to DIN 55992-1:2006: 0.40 mg g^{-1} MMAD1 = (11.24 ± 4.01) µm (p1 = 43.2 %) MMAD2 = (11.51 ± 1.61) µm (p2 = 56.8 %)
Stability in organic solvents and identity of relevant degradation products	Data waiver: According to Annex IX of the REACH Regulation, the endpoint is not required because the substance is inorganic.

7.5. Manufacture and uses

7.5.1. Quantities

Table 5

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

Consumer

According to information from ECHA´s dissemination site, the brief profile of the substance and the CSR of the lead registrant no consumer-related uses nor article service life are known for ATC.

Table 6

USES	Use(s)
Uses as intermediate	Isolated intermediate
Formulation	-
Uses at industrial sites	Manufacture of ATO in the pigment industry
Uses by professional workers	-
Consumer Uses	Not identified
Article service life	

7.6. Classification and Labelling

7.6.1. Harmonised Classification (Annex VI of CLP)

Table 7

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 Code(s)	**Hazard statement code(s)**		
051-001-00-8		233-047-2	10025-91-9	Skin Corr. 1B; Aquatic Chronic 2	H314 H411	STOT SE 3; H335: C ≥ 5 %	

7.6.2. Self-classification

- In the registration(s)*:*

"Legal classification as laid out in regulation (EC) 1272/2008, Annex VI, Index No. 051-001-00-8. However, newly generated substance specific hazard data do not support the harmonised classification and labelling for this antimony compound as stated in Annex VI of regulation (EC) 1272/2008. Therefore, an alternative proposal for the classification and labelling of antimony trichloride (representative sample) is provided as well. ":

"conclusive but not sufficient for classification" for environmental hazards

- The following hazard classes are in addition notified among the aggregated self-classifications in the C&L Inventory*:*
One notification states Muta.2, H341, and Carc. 1B, H350, in addition to the harmonised hazard classes.

7.7. Environmental fate properties

The endpoint is not targeted and no further evaluation has been performed by the eMSCA.

7.8. Environmental hazard assessment

The endpoint is not targeted and no further evaluation has been performed by the eMSCA.

7.9. Human Health hazard assessment

7.9.1. General considerations: Structural alerts and read-across

ATC is a trivalent Sb compound (Sb(III)). For the endpoints repeated-dose toxicity, carcinogenicity, reproductive toxicity, and mutagenicity, a read-across approach has been applied by the registrants to fill information requirements in the registration dossier with ATO as source substance. Additionally, for reproductive toxicity a read-across has been applied with the following source substances: Sb metal (powder), meglumine antimoniate (EC 205-108-3, CAS 133-51-7) and sodium hexahydroxoantimonate (EC 251-735-0, CAS 33908-66-6)(i2a, 2018c). Some toxicokinetics information is provided for ATC, ATO, Sb metal, meglumine antimoniate, antimony potassium tartrate (EC 234-293-3, CAS 11071-15-1), [124]sodium antimonyl xylitol, and "field-measured Antimony".

The registration dossier did not contain a read-across justification for human health.[3] However, during the evaluation process the registrant(s) provided provisional read-across justifications for the endpoints "lung toxicity and carcinogenicity" (i2a, 2018b), reproductive toxicity (i2a, 2018c), and genotoxicity (i2a, 2018a). The registrants provided thereafter updated versions of the respective documents in a dossier update in June 2019 (i2a, 2019a; i2a, 2019b; i2a, 2019c). The proposed read-across justification is based on a category approach comprising i.a. the Sb compounds which have been subject to substance evaluation in 2018: Sb metal, ATO, ATS, ATC, and ATEG.

Structural similarity is claimed by the registrants on the basis of the common presence of Sb atoms in all substances. Regarding toxicity the hypothesis is based on the expectation that the substances would have a comparable release of "soluble metal (oxyan)ions" (metal being antimony [Sb]) and uptake by the body. The substances are further subcategorised according to the type of Sb ions that can be released, Sb(III) and Sb(V) forms, and by their solubility (i.a. water solubility and bio-accessibility as determined in *in vitro* bio-elution assays).

The eMSCA has analysed the available information. The hypothesis that trivalent Sb compounds share common toxicological properties raises concerns for ATC. However, the identity of the alleged "soluble metal (oxyan)ions" and the quantities of the uptake by the body are unknown. Therefore, there is currently insufficient supporting experimental evidence to verify this concern and support a qualitative and quantitative hazard and risk assessment.

7.9.2. Toxicokinetics

Djuric et al. (1962) studied the uptake and distribution of antimony-124 chloride ($Sb^{124}Cl_3$) after inhalation exposure in rats, rabbits, and dogs. The animals were sedated for the treatment (with pentobarbital, rats additionally with chloropromazine).

20 albino rats, female, (strain not specified) were exposed once by inhalation for a 30 minute period (nose-only) and sacrificed serially thereafter, four animals soon after removal, pairs of two on day 1, 2, 4, 8 and 15 days, one on day 22 and four on day 140. Whole body counting was performed daily on the two rats sacrificed on day 15 and on two rats sacrificed on day 140. Five animals were placed into metabolism cages for urine and faeces collection; two were sacrificed on day 8, one was sacrificed on day 22 and two were sacrificed on day 140. One rat was discarded from the experiment because of a handling error.

[3] The latest dossier update considered for this conclusion document is from 24th May 2018

In a 2nd experiment 20 rats were exposed in the same way and sacrificed in pairs daily for 10 days. Whole body counts were made on four rats, two of which were sacrificed on day 7 and two on day 9. Excreta were collected on two animals each over periods of 10 days. All animals were dissected for a complete tissue distribution.

Two rabbits and one dog were injected intratracheally to compare the Sb blood localization in these two species with the rat data. The rabbits were sacrificed on days 4 and 11, and the dog on day 8.

The highest percentage of radioactivity was found in the lungs. The rate of loss from the lung was very rapid at first and did not indicate a leveling off until about the 20th day, after which the rate of loss from the lung was a constant fraction of the body burden. ^{124}Sb was identified in the following organs: lungs, thyroid, adrenals, lymph nodes, trachea, heart, spleen, kidneys, muscle, liver, head, paws and tails, GI tract and contents, blood removed bone, and other.

Whole body counting showed a relatively long biological half-life in the body ($T_{1/2}$=~140 days after 20 days). A large fraction of the Sb determining the half-life resided in the circulating blood or highly vascularized tissue such as spleen and heart. The extremely high concentration in the red blood cells was very pronounced in the rat but not obvious in the rabbit and dog (Djuric et al., 1962). Although this study was done before the adoption of the particular guidelines and does not allow to derive dose levels as uptake and distribution are given as percentages of radioactivity it shows that ATC is absorbed via the lungs, distributed throughout the body, and that it has a long half-life in some organs.

In an oral study 18.5 Bq/feed were applied in diet to mice from day of vaginal plug until days 3, 5, and 7 of pregnancy. Thereafter, mice were sacrificed, tissues were removed and assayed for radioactivity. Intestinal absorption was 1.7% in non-pregnant and 15% in pregnant mice. Following organ distribution was found: 0.085% in lung, 0.14% in bone and 0.1-0.2% in ovaries and uterus; 0.1-0.4% in litter (Gerber et al., 1982).

After application of single doses of 800 µg $SbCl_3$/kg i.v., 200, 400 and 800 µg $SbCl_3$ i.p., to rats 45-55% of the radioactivity was excreted within four days (most on day 1) in urine and faeces (equal parts after i.v., 1:4 after i.p.) (Bailly et al., 1991).

Inaba et al. (1983) studied whole body retention and tissue distribution of ^{125}Sb as chloride form in rats after oral and i.v. application. After an initial fast excretion phase (in faeces after oral application, potentially indicating a low absorption, in urine after i.v.) the excretion rate of ^{125}Sb was extremely slow with a biological half-life of 125–200 days. In suckling rats, whole-body retentions of ^{125}Sb after oral dosing were much higher.

7.9.3. Acute toxicity and Corrosion/Irritation

Oral

No acute oral toxicity studies are provided in the registration dossier. According to information found in the open literature ATC has an oral LD_{50} of 50–400 mg/kg bw (Eastman Kodak Co, 1992) up to 675 (557.80-816.75) mg/kg bw in rats (Arzamastsev, 1964).

Inhalation

No acute inhalation toxicity studies could be located for ATC. Antimony pentachloride has an inhalation LC_{50} of 293 mg Sb/kg bw in rats and 252 mg Sb/kg bw in mice (exposure duration 2 hours) and is reported to cause damage to the liver, kidneys and the central nervous system in rats (Izmerov et al., 1982) - cited from (MAK, 2007).

For humans the minimal lethal concentration after 4-hour inhalation exposure to ATC was 131 mg/m^3 (Chemie, 1994; MAK, 2007). Taylor (1966) reported about a brief accidental

exposure of seven workers to fumes containing up to 146 mg ATC/m^3 air. There was no mortality in this incident but all exposed individuals had transient irritation of the upper respiratory tract, five of them also had delayed symptoms arising from the gastro-intestinal tract.

Dermal

The following study could be identified in the open literature. Death within one to two days was observed following dermal exposure to ATC in an old and poorly reported skin absorption and irritation study documented by Eastman Kodak (Eastman Kodak Co, 1992) who calculated an approximate LD_{50} of <0.1 mL/kg bw for guinea pigs (n=2) after application of undiluted deliquescent substance. According to MAK (2007) this corresponds to ~315 mg/kg bw (MAK, 2007).

Conclusion

ATC fulfils the criteria for classification as acute toxic Cat. 4, H302, and acute toxic Cat. 3, H311, according to CLP. The information from animal studies with antimony pentachloride and accidental exposure of humans as described above indicates that ATC may also be acute toxic after inhalation, however the available data are not robust enough to derive a classification.

Corrosion/irritation

ATC has a harmonized classification as skin corrosive 1B (due to release of hydrochloric acid when hydrolysed in contact with water) and STOT SE Cat.3 H335 'May cause respiratory irritation' (SCL C>5%).

7.9.4. Sensitisation

No studies are available which inform about potential sensitizing properties of ATC.

The endpoint was not in the scope of this substance evaluation.

7.9.5. Repeated dose toxicity

7.9.5.1. Non-human information

7.9.5.1.1. Repeated dose toxicity: oral

Repeated dose toxicity (oral)

There is no oral repeated dose toxicity study conducted with ATC included in the registration. One older, non-guideline study was identified in the open literature (Arzamastsev, 1964). Investigations in guinea pigs with application of about 0.0025, 0.025, 0.25 or 2.5 mg ATC per kg bw/d for 6 months in drinking water resulted in a NOAEL of 0.0025 mg/kg bw/d (Arzamastsev, 1964). A decrease of free SH-groups in serum was observed at 0.025 mg/kg bw/d and above. Changes in blood parameters (↓ haemoglobin, ↓erythrocytes, ↑ reticulocytes) and an increased stimulus threshold for action potential in the EEG were seen at doses of 0.25 mg/kg bw/d and above. At 2.5 mg/kg bw/d there were additional effects on serum proteins (↓ total serum protein, ↑ globulin fraction). Two month treatment with about 0, 12, 20 mg/kg bw/d resulted in reduced body weight gain, decreased haemoglobin and red blood cells, increased reticulocytes, increased globulin fraction of serum proteins, decreased free SH-groups in serum, decreased mitotic index in bone marrow (Arzamastsev, 1964).

Further studies are available with other Sb compounds. The studies by (Hext et al., 1999) and (Sunagawa, 1981) are also summarised on the ECHA dissemination site.

To assess the repeated dose toxicity of ATO, in a 90 day study (Hext et al. 1999) diets containing 0, 1000, 5000 and 20,000 ppm ATO were fed to groups of 12 Wistar rats (Alpk:APSD strain). The dose levels correspond to 84, 421 and 1686 mg/kg bw/d in males and 97, 494 and 1879 mg/kg bw/d in females. There was no substance-related effect on food intake, body weight gain or clinical signs of toxicity. A 10% increase in absolute and relative liver weight together with reductions in plasma alkaline phosphatase activity and increases in aspartate aminotransferase activity have been observed in high dose males and females. This is indicative for liver toxicity, however as there were no histological changes or other signs if intoxication the findings have been regarded as adaptive to treatment (EU, 2008). Increased incidences of pituitary cysts in both sexes at the high dose (4/12 males, 3/12 females compared to 1/12 male and female controls) are described as common spontaneous change in this strain of rats and as values were within the historical control range not regarded as treatment related. Three high dose males had slight (2/12) resp. moderate (1/12) plasma cell infiltration in the cervical lymph node. This change was not seen in controls or in females and regarded as incidental by the authors because of the sex specificity and its spontaneous occurrence in historical controls. Haematological findings (↑red cell count, ↓ in mean cell volume in males and females) were not statistically significant and/or too small to be regarded as relevant. The NOAEL derived from this study is 1686 mg/kg bw/d.

Indications for liver toxicity and adverse effects on red blood cell count were already observed at lower levels in another study (Sunagawa, 1981) in which diets with 0, 1% and 2% ATO were fed for 24 weeks to groups of 12-15 male Wistar rats (corresponding to about 500 and 1000 mg/kg bw/d). Serum biochemical parameters showed significantly increased glutamic-oxaloacetic transaminase (GOT) [= ASAT (aspartate aminotransferase)] values in both exposure groups. There was increasing tendency of GOT in the treated groups as compared to that of control group. The histopathological examinations of the livers showed slight disorder and cloudy swelling in hepatic cords in 3 out of 5 rats in the 1% treated group and 2 out of 5 rats in the 2% treated group.

The haematological examination showed a small but significant decrease of red blood cell count in the groups exposed to ATO (control = 9.6 ± 0.4 x 10*6/mm^3; 1.0% ATO = 7.5 ± 0.6 x 10*6/mm^3; 2.0% ATO = 8.0 ± 0.4 x 10*6/mm^3). However, all values seem to be within the normal range for rats (Harkness and Wagner, 1989). Laboratory specific historical control information is not reported.

Some older poorly described studies, obviously not following any guideline, describe reduced food intake and body weight gain at doses of about 1000 mg ATO/kg bw/d (Gross et al., 1955) and 1070 mg ATO /kg bw/d (Carnegie Mellon Institute of Industrial Research (Smyth and Thompson, 1945).

Higher oral toxicity is reported from other Sb compounds and from application to other species.

Poon et al. (1998) tested potassium antimony tartrate in concentrations of 0.5, 5, 50, and 500 ppm in drinking water applied to Sprague-Dawley rats (25/sex/dose in the control and high dose, 15/sex/dose in the intermediate dose groups) for 13 weeks. The doses roughly correspond to 0.06-42.17 mg/kg bw/d for males and 0.06-45.69 mg/kg bw/d for females. Potassium antimony tartrate in drinking water caused body weight reduction (at the highest dose), mild biochemical and hematological changes, and adaptive histological changes in the thyroid, liver, thymus, spleen, and pituitary gland. Histological changes in the thyroid (collapsed follicles) and liver (anisokaryosis) persisted in both sexes during the 4 week recovery period, after which new changes were detected in the thymus (mild reduction of cortical volume in both sexes and increased medullary volume in females) and spleen (sinus hyperplasia, congestion and hematopoesis, arteriolar cuff atrophy and reduced cell density in the periarteriolar lymphocyte sheaths in both sexes). The most sensitive target organ was the thyroid, although the relevance

of mild findings at 0.5 ppm for the setting of drinking water limit values was subject of a controversial debate (Lynch et al., 1999; Valli et al., 2000; WHO, 2003). Sb deposition in the thyroid has also been observed after exposure to ATC as described in section 7.9.2.

Conclusion

The available knowledge indicates that ATC may lead to toxicity after oral exposure. The abovementioned studies emphasise uncertainties to determine a point of departure for the DNEL derivation for ATC. The only available repeated dose toxicity study with ATC resulted in a NOAEL after exposure via drinking water of 0.0025 mg/kg bw/d (Arzamastsev, 1964), which is orders of magnitude lower than the NOAEL of ATO (1686 mg/kg bw/day (Hext et al., 1999)) but close to the LOAEL of 0.06 mg/kg bw/d derived with potassium antimony tartrate (Poon et al., 1998).

7.9.5.1.2. Repeated dose toxicity: inhalation

No repeated dose inhalation toxicity study is available for ATC. Several older long-term inhalation toxicity studies are available for ATO. They have been evaluated under the EU existing substances regulation (EU, 2008) and are described in detail in the risk assessment report. While many of these studies were considered inconclusive due to non-compliance with current test guidelines, lack of essential information regarding exposure conditions and statistical evaluation of the results, or both control and exposed animals showing signs of non-treatment related illness, the available studies still indicate that ATO is toxic to the respiratory tract (Groth et al., 1986; Newton et al., 1994; Unpublished experimental study 5, 2003; Watt, 1983). A NOAEC of 0.51 mg/m^3 is derived from the study by Newton et al. (1994) based on impaired lung clearance in rats at 4.50 mg/m^3 (EU, 2008). Effects at higher concentrations included chronic interstitial inflammation, granulomatous inflammation, and fibrosis.

More recently ATO underwent testing in the US National Toxicology Program. Male and female Wistar Han [Crl:WI (Han)] rats and B6C3F1/N mice were exposed to ATO (> 99.9% purity) by inhalation for 2 weeks or 2 years, resulting in a LOAEC of 3 mg/m^3 (NTP, 2017b).

In the 14 day rat study, groups of five male and five female core study rats were exposed by whole body inhalation to ATO aerosol at concentrations of 0, 3.75, 7.5, 15, 30, or 60 mg/m^3 for 6 hours plus T90 (12 minutes, theoretical value for the time to achieve 90% of the target concentration after the beginning of aerosol generation) per day, 5 days per week for 12 exposure days during a 16-day period. Additional groups of five female rats in the tissue burden study were exposed to the same concentrations for 16 days then held for 28 days without exposure. All rats survived up to the end of the study. The mean body weights of exposed groups of males and females were similar to those of the respective chamber control groups. Lung weights of 60 mg/m^3 males and 30 and 60 mg/m^3 females were significantly greater than those of the chamber controls. Incidences of chronic active inflammation in the lungs were significantly increased in 30 and 60 mg/m^3 males and females (NTP, 2017b).

In the 14 day mouse study, groups of five male and five female core study mice were exposed by whole body inhalation to ATO aerosol at concentrations of 0, 3.75, 7.5, 15, 30, or 60 mg/m^3 for 6 hours plus T90 (12 minutes) per day, 5 days per week for 13 exposure days during a 17-day period. Additional groups of five female mice in the tissue burden study were exposed to the same concentrations for 17 days then held for 28 days without exposure. All mice survived up to the end of the study. The mean body weights of exposed groups of males and females were similar to those of the respective chamber control groups. Lung weights were significantly increased in 60 mg/m^3 males and 15 mg/m^3 or greater females. In the larynx, there were significantly increased incidences of squamous metaplasia of the epiglottis in the 30 and 60 mg/m^3 males and females compared to those in the chamber control groups (NTP, 2017b).

In the 2 year study groups of 50 male and female rats and mice were exposed to aerosols containing 0, 3, 10, or 30 mg of ATO-particles per cubic meter of air for 6 hours per day, 5 days per week for 2 years. NTP summarises the outcome as follows:

"*In female rats exposed to antimony trioxide, increased incidences of lung neoplasms were observed, as compared to the control group. Higher incidences of lung tumors were also observed in exposed male rats compared to the control group. All exposed groups of male and female mice had markedly increased incidences of lung neoplasms compared to the respective control groups. There were increased incidences of a number of nonneoplastic lesions of the respiratory tract compared to the respective control groups in male and female rats and mice (e.g. inflammation, hyperplasia and fibrosis). There were also increases in nonneoplastic lesions in the nose of male and female rats and mice, in the larynx of female rats and male and female mice, and in the trachea in male mice. Foreign body, presumed to be antimony trioxide, was identified in the lung, nose, larynx, trachea, and bronchial and mediastinal lymph nodes of male and female rats and mice exposed to antimony trioxide.*

In male and female rats exposed to antimony trioxide, there were increased incidences of pheochromocytomas of the adrenal medulla and of adrenal medulla hyperplasia. In female mice, incidences of malignant lymphoma were increased in all exposed groups as compared to the control group. In male mice, incidences of fibrous histiocytoma and combined incidences of fibrous histiocytoma or fibrosarcoma were increased in males compared to controls.

There were increases in bone marrow hyperplasia in male and female rats and mice. Increased incidences of nonneoplastic lesions of the bronchial and mediastinal lymph nodes were observed in rats and mice (e.g. lymphoid hyperplasia). Lymphoid hyperplasia was also observed in the spleen of female mice, as was hematopoietic cell proliferation. Increases in cellular depletion of the thymus were observed in male and female mice.

In male and female rats, there were increased incidences of nonneoplastic lesions of the arteries, kidneys, and eyes. These included the combined incidences of arterial inflammation in the mediastinum, pancreas, mesentery, lung, and kidney in males and females, renal tubule hyaline droplet accumulation and nephropathy (females only), and acute inflammation of the eye and retinal atrophy (females only). In male and female mice, there were increased incidences of inflammation of the epicardium and forestomach (males only).

Conclusions

We conclude that exposure to antimony trioxide particles caused lung neoplasms in male and female rats and mice. A spectrum of other nonneoplastic lesions in the respiratory tract of male and female rats and mice was caused by antimony trioxide exposure. Adrenal medullary neoplasms in male and female rats, skin neoplasms in male mice, and malignant lymphoma in female mice were also attributed to antimony trioxide exposure. Nonneoplastic lesions of the bone marrow, adrenal medulla, arteries of multiple tissues (mediastinum, pancreas, mesentery, lung, and kidney), and the eyes of male and female rats; the thymus and heart of male and female mice; the forestomach of male mice; and the spleen of female mice were caused by antimony trioxide." (NTP, 2017b)

An overview on the incidence of the main non-neoplastic findings is presented in section 8, Annex 1.

Conclusion

The available knowledge leads to concerns that ATC may lead to toxicity after inhalation.

Structurally related trivalent Sb compounds, especially ATO, cause respiratory and systemic toxicity after repeated inhalation exposure.

According to the information provided on the ECHA dissemination site the particle size distribution and MMAD for the airborne fraction for ATC and ATO are in the same order of magnitude: ATO: MMAD 4.12±2.64 µm – 37.01±5.00 µm; ATC: MMAD 11.24±4.01 µm resp. 11.51±1.61 µm.

The same is true for the calculated fractional deposition in human respiratory tract (MPPD model, based on calculated MMAD): ATC: Head (ET): 76.6%, tracheobronchial (TB): 1.0%, pulmonary (PU): 1.9%; ATO: Head (ET): ~56-76%, tracheobronchial (TB): 0.39 - 2.44%, pulmonary (PU): 0.7-6.4%.

Systemic absorption of ATC after inhalation exposure is evident as described in section 7.9.2.

Thus it is likely that also ATC causes respiratory and systemic toxicity after inhalation. However the available evidence is not sufficient to support a read-across and does not allow a quantitative hazard and/or risk assessment and DNEL derivation.

7.9.5.1.3. Repeated dose toxicity: dermal

No relevant information available.

7.9.5.2. Human information

No human data are available for repeated dose toxicity of ATC. Several older reports describe effects on workers experiencing symptoms like rhinitis, perforation of the septa, pharyngitis, bronchitis, pneumonitis, pneumoconiosis, and symptoms of emphysema following inhalation exposure to ATO in ATS-ore mining and/or smelting plants (Cooper et al., 1968; Jones, 1994; Karajovic, 1957; Klucik et al., 1962; McCallum, 1963; McCallum, 1967; McCallum et al., 1970; Potkonjak and Pavlovich, 1983; Renes, 1953). Due to lack of detailed exposure data the studies cannot be used for quantitative risk assessment. They do however indicate that ATO, ATS, and possibly ATC have the potential to induce pulmonary inflammation, lung emphysema, and pneumoconiosis after repeated inhalation exposure.

7.9.5.3. Specific target organ toxicity: Cardiotoxicity

Cardiotoxicity is a well-known serious side effect from the medical use of tri- and pentavalent Sb compounds for the treatment of visceral leishmaniasis (Kala-azar) (Honey, 1960; O'Brien, 1959). With the regimen of 20 mg/kg per day sodium antimony gluconate for 28 days, cardiac toxicity has been reported in 8% to 17% of cases with 5% to 7% of them reporting fatal toxicity (Thakur and Narayan, 2004). The cardiovascular alterations induced by Sb compounds include ECG alterations such as ST segment inversion and QT interval prolongation, and consequently torsade de point arrhythmias and sudden cardiac arrest (Kuryshev et al., 2006; Maciel et al., 2010). *In vitro* investigations in HEK/hERG cells indicate that the underlying cellular mechanism may be an increase of cardiac calcium currents (Kuryshev et al., 2006).

Brieger et al. (1954) reported about Sb poisoning in a plant of the abrasives industry in which 8 of 125 workers died assumingly due to heart disease after 8 month to 2 year exposure to ATS (0.58 – 5.5 mg/m^3). Only two of these employees were known to suffer

from chronic heart disease. In the remaining workforce there was a high incidence of increased blood pressure and 37 out of 75 examined showed significant changes in the ECG, mostly of the T-waves. In addition, a large number of employees had gastrointestinal disturbances, in with ulcers diagnosed by X-ray in seven of 111, which was about four times higher than the incidence in other parts of the enterprise. No further deaths were reported after the use of ATS was discontinued.

The same authors further conducted some limited inhalation tests in rats, rabbits and dogs, which resulted in ECG changes (mainly effects on T-waves and unspecified indications of myocardial injury) as well as (histo)pathological findings (including heart dilatation, swelling of myocardial fibers and parenchymatous changes) after exposure to 3.07 resp. 5.6 mg/m^3 ATS for 6 weeks, 5d/wk, 7hr/d in male rats resp. rabbits thereby supporting the hypothesis that ATS may cause cardiotoxicity.

Nigra et al. (2016) conducted a systematic review of literature assessing the relationship between Sb (and some other metals) and cardiovascular diseases in adults but concluded that the current evidence is not sufficient to inform on the cardiovascular role of these metals because of the small number of studies.

There are several publications, based on the US National Health and Nutrition Examination Survey (NHANES) 1999-2010, reporting about associations between urinary Sb levels (source of exposure not specified) and increased prevalence of hypertension (Shiue, 2014), peripheral arterial disease (Navas-Acien et al., 2005) and cardiovascular disease (Agarwal et al., 2011). Guo et al. (2016) highlight that elevated urinary Sb levels are associated with increased likelihoods of heart disease and increased risk of heart disease mortality. However not all of the observations show a clear dose-response relationship.

Conclusion

In conclusion there is concern that trivalent Sb compounds including ATC may cause adverse cardiovascular effects. However based on the current evidence definite conclusions and precise risk estimates are not possible beyond medical applications.

7.9.6. Mutagenicity

The genotoxicity and mutagenicity of ATC as well as other trivalent Sb compounds has been assessed in various bacterial *in vitro* assays, mammalian cell *in vitro* assays, *in vivo* assays, and human exposure studies. Studies with other Sb compounds than ATC are considered in the substance evaluation in order to provide an overview of Sb induced genotoxic effects, also because registrants applied read-across for genotoxicity and other endpoints in the dossiers for ATO, Sb metal, ATEG, ATS, and ATC mostly with ATO and ATC as source substances but also with elemental Sb as well as pentavalent Sb compounds such as sodium hexahydroxo-antimonate and meglumin antimoniate. The term genotoxicity is used to cover also non-permanent DNA damages. Induction of oxidative stress is discussed in this section because oxidative damage is considered a major mutation inducing factor (Smith et al., 2016).

7.9.6.1. Genotoxicity *in vitro*, bacteria

Numerous studies are available, which tested ATC (Kanematsu et al., 1980; Kubo et al., 2002; Kuroda et al., 1991) and other Sb compounds (Arlauskas et al., 1985; Asakura et al., 2009; Elliott et al., 1998; Hartman et al., 1971; Zeiger et al., 1992) in the bacterial reverse mutation assay (Ames test), most of them according to or similar to OECD TG 471. The studies by Kuroda et al. (1991) and Kubo et al. (2002) are not guideline compliant because only tester strains TA98 and TA100 were used with and without metabolic activation. The study by Kanematsu et al. (1980), which is not included in the

dossier, is regarded as not reliable because the purity of test compound was not specified and no positive or negative controls were documented. ATC and other Sb compounds, except Sb metal (Asakura et al., 2009), were considered negative in the bacterial reverse mutation assay (Ames test, OECD TG 471), SOS umu test (ATC, (Yamamoto et al., 2002), not included in the dossier), and SOS chromotest (ATC, (Lantzsch and Gebel, 1997)). Consistent positive results were obtained with the rec assay, an indicator assay for genotoxic effects, for ATC, ATO, and other trivalent as well as pentavalent Sb compounds (Kanematsu et al., 1980; Kuroda et al., 1991; Nishioka, 1975). It is generally accepted that metals can produce false-negative results in bacterial genotoxicity assays, which suggests that genotoxicity assays with mammalian cells would be more appropriate (ECHA, 2017), in particular the XPRT test as discussed below (OECD TG 476). Despite a high prevalence of false-negative results with metals in bacterial assays, the rec assay delivered positive results indicating potential genotoxic effects of Sb compounds.

7.9.6.2. Genotoxicity and oxidative stress induction *in vitro*, mammalian cells, mammalian cells

Genotoxicity of ATC and other Sb compounds has been assessed in multiple mammalian cell *in vitro* studies by use of a variety of different cell lines. Two *in vitro* mammalian cell gene mutation studies with ATO (OECD TG 490, (Elliott et al., 1998)) and antimony thioantimonate (OECD TG 476, HPRT test, (Tu and Sivak, 1984), not included in the registration dossier) delivered negative results, confirming the negative Ames assay, which indicates that ATO does not cause gene mutations. However, metal ions can lead to large DNA deletions (ECHA, 2017a) and the HPRT test does not detect mutations resulting from large deletions (OECD, 2016a). Since the XPRT test (OECD TG 476) is supposed to detect also large DNA deletions, it might be more suitable as mammalian mutagenicity assay for the assessment of Sb compounds.

No OECD TG 473 study (*in vitro* mammalian chromosomal aberration test) is available for ATC. Chromosomal aberration assays according to or similar to OECD TG 473 were applied in four studies with different cell lines (Human leukocytes, Chinese hamster lung cells, Chinese hamster ovary cells) to assess the genotoxic potential of the Sb compounds ATO (Elliott et al., 1998), Sb metal (Asakura et al., 2009), antimony sodium tartrate (Paton and Allison, 1972), and the pentavalent antimony thioantimonate (Tu and Sivak, 1984). All four studies were positive and detected a dose-dependent increase of aberrant cells. The latter does not apply to the single dose study by Paton and Allison (1972). The lowest effective concentrations (significant increase of aberrant cells) ranged from 50 µg/mL for ATO and Sb metal to 60 µg/mL for antimony thioantimonate. The studies by Asakura et al. (2009), Paton and Allison (1972), and Tu and Sivak (1984) are not included in the dossier.

ATC (Gebel, 1998; Huang et al., 1998; Schaumlöffel and Gebel, 1998) and the pentavalent potassium antimonate (Migliore et al., 1999) have been tested positive in the micronucleus assay (similar to OECD TG 487) in four independent studies by use of various cell lines (Human bronchial epithelial cells (BES-6), Human fibroblasts (HF), Chinese hamster ovary cells, Human peripheral lymphocytes, and V79 Chinese hamster cells) with the lowest LOEC of 5 µM (Schaumlöffel and Gebel, 1998) and dose-dependent increases of micronucleus frequencies.

The sister chromatid exchange (SCE) assay, similar to OECD TG 479, shows positive effects in V79 Chinese hamster cells and human lymphocytes with a dose-dependent increase of SCEs for two trivalent Sb compounds, which have been assessed in the two studies, ATC and ATO (Gebel et al., 1997; Kuroda et al., 1991).

The comet assay was positive for ATC in two studies in V79 Chinese hamster cells (Gebel et al., 1998) and Human peripheral lymphocytes (Schaumlöffel and Gebel, 1998) with a LOEC from 0.23 to 11.4 µg/mL. The former study is not included in the dossier. Increase of γH2AX as marker for DNA double strand breaks was observed for ATC, confirming

results of the comet assay (Kopp et al., 2017). The latter study is not included in the registration dossier.

The impairment of DNA damage repair has been observed in three *in vitro* studies with ATC (Grosskopf et al., 2010; Koch et al., 2017; Takahashi et al., 2002) and one *in vitro* study with antimony potassium tartrate (Takahashi et al., 2002). Two of these studies (Grosskopf et al., 2010; Koch et al., 2017) demonstrated the impairment of proteins important for DNA damage repair. The study by Koch et al. (2017) is not included in the registration dossier.

The oxidative stress inducing potential of Sb compounds has been assessed *in vitro* in numerous studies for ATO (Jiang et al., 2016; Verdugo et al., 2017), Sb metal (Zhao et al., 2017), potassium antimony tartrate (Snawder et al., 1999; Tirmenstein et al., 1995; Tirmenstein et al., 1997; Wyllie and Fairlamb, 2006), sodium stibogluconate (Wyllie and Fairlamb, 2006), and potassium hexahydroxoantimonate (Verdugo et al., 2017). The *in vitro* studies with trivalent Sb compounds were positive, the ones with pentavalent Sb compounds negative. Inhibition of enzymes involved in GSH function, depletion of GSH, and disruption of mitochondrial membrane potential was reported. Also the formation of reactive oxygen species (ROS) was observed in several studies and could be a result of overstrained oxidative stress defence mechanisms (e.g., through glutathione depletion). None of these studies are included in the registration dossier.

In the ToxTracker assay (Hendriks et al., 2017), positive effects have been observed for oxidative stress induction and unfold protein response for ATC, ATO, Sb metal, ATS, and ATEG (Derr et al., 2017; Unpublished experimental study 3, 2017). All five compounds are negative in the DNA damage response and for activation of the p53-dependent cellular stress response. These results, including the reduced activity after metabolic activation and aforementioned studies showing induction of oxidative stress, emphasize the electrophilic character of the respective trivalent Sb compounds and hence the capacity to damage cellular structures.

7.9.6.3. Genotoxicity and oxidative stress induction *in vivo*

No reliable standard *in vivo* genotoxicity study is available for ATC. Genotoxicity of ATO and other Sb compounds has been assessed in various *in vivo* studies. As opposed to *in vitro* assays, *in vivo* tests on structural chromosomal aberrations (OECD TG 475) were negative in bone marrow in mice (Elliott et al., 1998) and rats (Kirkland et al., 2007). One positive study was regarded as not reliable (Gurnani et al., 1992a; Gurnani et al., 1992b; Gurnani et al., 1993) because the purity of test compound was not specified, no positive control was applied, and a very high mortality occurred after 20 days in the highest dose group. The latter is not plausible considering results of a 90-day oral repeated dose study (dietary exposure) where all rats survived the dosing period in good condition with a NOAEL of >1686 mg/kg bw/d (Hext et al., 1999). Another study, not included in the dossier, found positive effects after i.p. injection (single and repeated dose) of potassium antimony tartrate and Bilhardcid ($C_{12}H_{16}N_2O_{12}Sb_2$) in rats (El Nahas et al., 1982).

Tests with ATO on micronuclei formation were negative after oral application in mice (Elliott et al., 1998) and rats (Kirkland et al., 2007) in bone marrow. A 12 months inhalation study with ATO delivered negative results in peripheral erythrocytes in rats but positive effects in mice (NTP, 2017b). The increase in micronuclei was small but significant with a LOAEC of 30 mg/m³. The induction of micronuclei in erythrocytes after ATO inhalation requires systemic absorption of test compound. In the EU Risk Assessment report for ATO (EU, 2008), a systemic absorption of 6.82% after inhalation is proposed, which makes systemic effects conceivable. Four more studies, which are not included in the dossier, resulted in increased micronuclei formation in leukocytes of mice after intraperitoneal injection of the pentavalent meglumine antimoniate with a LOAEC of 212.5 mg/kg bw after single application and 20 mg/kg/d after daily application for 20 days (Cantanhede et al., 2015; de Jesus et al., 2018; Lima et al., 2010; Moreira et al.,

2017). Positive effects might be a result of Sb(III) residuals (Dzamitika et al., 2006; Kato et al., 2014) or Sb(V) metabolised to Sb(III) in the body (Friedrich et al., 2012).

The comet assay in lung cells was positive in a 12 months inhalation study with ATO in mice but negative in rats (NTP, 2017b). Despite this study being regarded as not reliable (because i. no positive control, ii. no historical negative/positive control data, iii. no cytotoxicity measurements), positive effects in lung cells after inhalation are plausible given the electrophilic character of Sb-compounds as discussed below. Consistent with results of micronucleus assays, intraperitoneal injection of meglumine antimoniate resulted in increased levels of DNA damage in leukocytes in the comet assay (Cantanhede et al., 2015; de Jesus et al., 2018; Lima et al., 2010; Moreira et al., 2017).

Conflicting results were also observed in studies assessing effects on the DNA repair system, which were positive for ATC in a study conducted by the Austrian Research Centre (EPA, 1988; Unpublished experimental study 1, 1988), which is not included in the registration dossier, and negative in Elliott et al. (1998) for ATO (unscheduled DNA synthesis (UDS) test with mammalian liver cells). The former is regarded as not reliable, mainly because no information on the systemic toxicity was reported, which is critical at doses from 500 – 1500 mg/kg given that an LD_{50} for mice of 50 – 400 mg ATC/kg has been reported before (MAK, 2007). Effects on the DNA repair system are plausible with regard to positive *in vitro* assays as discussed above.

Effects on oxidative stress were confirmed in several *in vivo* studies after i.p. or s.c. injection with ATC (Wang et al., 1998) and meglumine antimoniate (Bento et al., 2013; Cantanhede et al., 2015; de Jesus et al., 2018; Kato et al., 2014; Moreira et al., 2017). None of these studies are included in the dossier. In studies with meglumine antimoniate effects are most likely caused by Sb(III) residuals (Dzamitika et al., 2006; Kato et al., 2014).

7.9.6.4. Genotoxicity in humans

No human data for genotoxicty of ATC are available. Induction of chromosomal aberrations was tested negative in one study (not included in the dossier) with one patient in peripheral blood lymphocytes before and after treatment with meglumine antimoniate via intramuscular injection of 3 g/d over 15 days (Hantson et al., 1996). In the same study treatment with meglumine antimoniate increased frequency of binucleated cells 8-9-fold. This study is considered as not reliable because only one patient has been monitored who was in poor general condition, recovering from hemorrhagic shock and transient renal failure. Additionally, the patient had a relatively high frequency of chromosome type structural aberrations in three blood cultures before treatment, probably due to repeated diagnostic exposure to ionizing radiation. Cavallo et al. (2002) found no increase in micronuclei in peripheral lymphocytes from males occupationally exposed to ATO (n=23: 17 with high inhalation exposure (group A, mean exposure concentration: 0.12 µg/m³) and 6 with low exposure (group B, mean exposure concentration: 0.05 µg/m³)) compared to a control group (n=23, no exposure). Also the sister chromatid exchange assay was negative in both above-mentioned studies (Cavallo et al., 2002; Hantson et al., 1996).

One study delivered positive results in an enzyme (Fpg)-modified comet assay with peripheral lymphocytes after occupational inhalation exposure, pointing towards oxidative DNA damage (Cavallo et al., 2002). Co-exposure to other genotoxic chemicals cannot be excluded and therefore a causal relationship cannot be proven. Additionally, the exposure concentrations seem very low with 120 ng/m³ in the high exposure group, while ambient air concentrations are typically <20 ng/m³ but can exceed 1000 ng/m³ in the proximity of plants that convert Sb ores into metal or manufacture substances (ATSDR, 2017). Ambient air concentrations in the control group have not been monitored. Nevertheless, oxidative damages are plausible considering positive results in multiple *in vitro* and *in vivo* assays on genotoxicity and oxidative stress induction.

Another study (not included in the dossier) found a positive correlation between urinary Sb levels and DNA lesions (apurinic/apyrimidinic (AP) or abasic site) in ATO exposed workers (El Shanawany et al., 2017). In this study, the observed DNA lesions are not attributed to oxidative stress because DNA damage did not correlate with total oxidant capacity. AP sites are usually removed by base excision repair and hence impaired DNA repair could result in increased AP sites. Impaired base excision repair through Sb exposure has been observed before *in vitro* (Grosskopf et al., 2010). Again, a causal relationship cannot be established with certainty because co-exposure to other potentially genotoxic compounds cannot be excluded.

7.9.6.5. Discussion

The direct comparison of *in vitro* and *in vivo* results demonstrates that *in vitro*, ATC and other trivalent Sb-compounds (mainly ATO and antimony tartrate) are consistently tested positive with the rec assay, chromosomal aberrations assay, micronucleus assay, sister chromatid exchange assay, comet assay, assays to detect impairment of DNA repair mechanisms, and oxidative stress induction. *In vivo*, results of trivalent Sb compounds are much less consistent: negative for chromosomal aberrations and ambiguous or conflicting results for micronucleus formation, comet assay, and DNA repair. Pentavalent Sb compounds are mostly negative in *in vitro* assays (except in the rec assay, chromosomal aberration and micronucleus assay). For pentavalent Sb compounds only *in vivo* experiments with meglumin antimoniate injected intraperitoneally are available. Positive *in vivo* results with meglumin antimoniate are most likely caused by residual Sb(III).

In the ECHA Guidance on Information Requirements and Chemical Safety Assessment Chapter R.7a (ECHA, 2017) it is noted that highly electrophilic substances with positive results *in vitro* may react with proteins and water *in vivo* and hence be rendered inactive very quickly when distributed in the body and thus producing negative effects in most standard *in vivo* assays, in particular when systemic absorption is required to reach the target cells. However, such electrophilic compounds may be able to express their genotoxic potential at the initial site-of-contact with the body. Consequently, the use of test systems which detect effects in site-of-contact tissues might be necessary, e.g. comet assay with lung cells. A significant and dose-dependent decrease of glutathione levels (Snawder et al., 1999; Tirmenstein et al., 1995; Tirmenstein et al., 1997; Wyllie and Fairlamb, 2006), reactivity with proteins (Derr et al., 2017; Unpublished experimental study 3, 2017; Verdugo et al., 2017), significant reduction of protein thiols (Harvey, 1971; Tirmenstein et al., 1997), and induction of oxidative stress response (Derr et al., 2017; Unpublished experimental study 3, 2017) demonstrate the electrophilic properties of trivalent Sb compounds and the capacity to damage cellular structures. This could explain positive results in *in vitro* assays, predominantly negative results in *in vivo* assays which require systemic absorption, and positive results in the comet assay with lung cells after inhalation exposure in the NTP study (NTP, 2017b). Also the impairment of DNA repair processes might be a result of the electrophilic character of Sb(III).

Gene mutations (e.g., point or frame shift mutation), have not been observed in any of the provided studies except mild effects for Sb metal (Asakura et al., 2009). Chromosome mutations (structural chromosome changes) occurred consistently in several studies *in vitro* and with conflicting results *in vivo*. In light of the protein reactivity of ATO and other trivalent Sb compounds it seems plausible that trivalent Sb compounds exert genotoxic properties via non-DNA reactive mechanisms, such as inhibition of DNA synthesis, alterations in DNA repair, or overloading of anti-oxidants defence mechanisms (ECHA, 2017), all of which have been demonstrated *in vitro* and some of them *in vivo*. However, DNA reactive mechanisms could play a role in site-of-contact tissue and also systemic DNA reactive mechanisms cannot be excluded based on the available data.

7.9.6.6. Conclusion

Taking into account positive *in vitro* mutagenicity tests for ATC and other trivalent Sb compounds and the equivocal outcomes of *in vivo* genotoxicity assays as discussed above, a concern for potential genotoxic effects of ATC is evident. The available data are not sufficient to draw a final conclusion.

7.9.7. Carcinogenicity

7.9.7.1. Non-human information

7.9.7.1.1. Carcinogenicity: oral

No relevant information available.

7.9.7.1.2. Carcinogenicity: inhalation

No carcinogenicity studies with ATC are available. Until recently, three 12 months inhalation studies in rats were available for carcinogenicity assessment of ATO (Groth et al., 1986; Newton et al., 1994; Watt, 1983) and Sb ore (Groth et al., 1986). Two of these studies demonstrated increased rates of lung tumours in exposed animals (Groth et al., 1986; Watt, 1983). In one study, no benign or malignant tumours were observed (Newton et al., 1994). Some occupational inhalation exposure studies of workers from Sb or tin smelters observed elevated lung cancer risks while the causality of Sb exposure could not be conclusively established due to co-exposure to other carcinogenic compounds (Jones, 1994; Jones et al., 2007; Schnorr et al., 1995). Other occupational exposure studies did not find elevated lung cancer cases with inhalation exposure to ATO and/or ATS (McCallum, 1967; Potkonjak and Pavlovich, 1983). The available data at the time led to a harmonised classification as Carc 2 (H351) for ATO.

In a more recent 2-year whole body inhalation study, the US NTP found clear evidence of carcinogenic activity of ATO in B6C3F1/N mice and some evidence of carcinogenic activity of ATO in Wistar Han rats (NTP, 2017b).

In female mice, various neoplastic findings were observed with a LOAEC of 3 mg/kg bw/d: alveolar/bronchiolar adenoma (1/50, 10/50, 19/50, 8/50), alveolar/bronchiolar carcinoma (2/50, 14/50, 11/50, 11/50), alveolar/bronchiolar adenoma or carcinoma (3/50, 22/50, 27/50, 18/50), malignant lymphoma (7/50, 17/50, 20/50, 27/50), squamous cell carcinoma (skin) (0/50, 0/50, 0/50, 2/50). Also in male mice neoplastic findings were observed with a LOAEC of 3 mg/kg bw/d: alveolar/bronchiolar carcinoma (4/50, 18/50, 20/50, 27/50), fibrous histiocytoma (skin) (0/50, 1/50, 1/50, 4/50), fibrous histiocytoma or fibrosarcoma (skin) (0/50, 1/50, 3/50, 4/50).

In female rats, various neoplastic findings were observed: alveolar/bronchiolar adenoma (3/50, 4/50, 6/50, 8/50), alveolar/bronchiolar adenoma or carcinoma (3/50, 4/50, 8/50, 8/50), benign pheochromocytoma (adrenal medulla) (1/49, 0/50, 2/49, 7/50). Also in male rats neoplastic findings were observed: alveolar/bronchiolar adenoma (0/50, 2/50, 6/50, 5/50), cystic keratinizing epithelioma or squamous cell carcinoma (0/50, 0/50, 0/50, 3/50, equivocal finding), benign pheochromocytoma (adrenal medulla) (0/49, 2/49, 2/49, 6/50), benign or malignant pheochromocytoma (0/49, 2/49, 2/49, 7/50).

The results of the above summarised chronic inhalation toxicity studies with ATO and Sb ore raise concerns that ATC may lead to carcinogenicity after chronic inhalation exposure. Further, it is important to note that inhalation toxicity is not limited to effects on the lungs but includes upper respiratory tract symptoms as well as systemic effects after inhalation exposure. Systemic absorption of ATC after inhalation exposure is evident as described in section 7.9.2. Systemic genotoxic effects have been observed in a micronucleus assay in mice after inhalation exposure to ATO (section 7.9.6.3, (NTP,

2017b)). Systemic neoplastic effects after inhalation exposure to ATO have been observed in the 2-year NTP study (NTP, 2017b) in mice (malignant lymphoma) and rats (benign or malignant pheochromocytoma). Additionally, potential tumour promoting properties of antimony potassium tartrate have been found in a study by Zhang et al. (2018), which has not been observed in studies with other Sb compounds but the incidence of epithelial hyperplasia in the prostate of rats was increased in the 2-year inhalation study with ATO (NTP, 2017b).

7.9.7.1.3. Carcinogenicity: dermal

No relevant information available.

7.9.7.1.4. Carcinogenicity: other routes

No relevant information available.

7.9.7.2. Conclusion

There is concern for carcinogenicity of ATC, based on the structural similarity to ATO which is classified as Carc. Cat. 2 (H351). However, the available data are not sufficient to draw final conclusions about the qualitative and quantitative applicability of the above described findings for ATC.

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

7.9.8.1. Effects on fertility

There are no guideline studies available to specifically address effects of ATC on fertility and sexual function.

The available data from sub-chronic and chronic repeated dose-toxicity studies on ATO (oral route: (Hext et al., 1999; Sunagawa, 1981); inhalation route: (NTP, 2017b)), antimony potassium tartrate (James et al., 1966; NTP, 1992; Omura et al., 2002; Poon et al., 1998), and antimony dextran glycoside (Casals, 1972) do not indicate that Sb affects fertility. However, there are concerns from several other studies or human data that create a need for clarification on fertility effects. A non-guideline study with rats reported increased pre-implantation loss after inhalation exposure to ATO (Grin et al., 1987). Reduced incidence of pregnancies compared to controls has been observed in a rat inhalation study with Sb metal (Belyaeva, 1967). An occupational study with female workers of an Sb plant found increased incidences of disturbed menstrual cycles and increased incidences of spontaneous abortions and premature births (Belyaeva, 1967). However, no dedicated guideline studies specifically assessing fertility are available for any Sb compound. Mechanistic studies with potassium antimony tartrate and ATC indicate some endocrine activity of Sb compounds potentially affecting the reproductive system (Choe et al., 2003; Zhang et al., 2018) as described in section 7.10.2.

7.9.8.2. Developmental toxicity

7.9.8.2.1. Information from animal studies

Cumulative evidence from studies on several Sb compounds suggests some potential of Sb to interfere with normal development of offspring. However, no guideline-studies are available for ATC.

One inhalation prenatal developmental toxicity study in rat with ATO according to OECD TG 414 showed only local lung toxicity in dams but no developmental toxicity was observed (Unpublished experimental study 5, 2003). The preceding dose-range finder study (Unpublished experimental study 5, 2003) revealed no systemic maternal toxicity up to the highest dose tested. However, slightly reduced foetal body weights (8% lower; not significant), and a lower crown-rump distance (4% lower; significant) in the highest dose group (6.07 mg/m³) were observed. In contrast, a non-guideline inhalation study with ATO (rats, 0.027, 0.082, 0.27 mg/m³, 21 day whole body exposure around-the-clock) reported increased post implantation losses and gross macroscopic changes in the two highest exposure concentrations tested (increased bleeding in foetal brain membranes and liver; increased size of the kidney cavity and the cerebral ventricles) (Grin et al., 1987). However, this study has several shortcomings: i) it is not reported how the Sb oxide aerosol was generated, ii) no details on analytical method for verification of exposure levels, purity and particle size of the test compound, iii) few or no statistical calculations are available, iv) translation from Russian, v) unclear whether the studied substance is ATO or antimony pentoxide.

No definite conclusion on developmental toxicity can be drawn from these inhalation studies.

Non-guideline studies with ATC applied in the drinking water show decreased postnatal growth and alterations in vasomotor reactivity after gestational and lactational exposure (Angrisani et al., 1988; Marmo et al., 1987; Rossi et al., 1987). However, it is unclear whether these observations are developmental effects since no comparison was made to adult animals. Also the purity of tested substance is not known, and doses are estimated (Angrisani et al., 1988; Marmo et al., 1987; Rossi et al., 1987).

Oral prenatal developmental toxicity studies according to OECD TG 414 are available for the pentavalent substance sodium hexahydroxo-antimonate ($NaSb(OH)_6$) in rats (Unpublished experimental study 2, 2014) and for Sb metal in rabbits (Unpublished experimental study 4, 2017). In rats, $NaSb(OH)_6$ induced delayed ossifications in the absence of maternal toxicity (Unpublished experimental study 2, 2014). Exposure of rabbits to Sb metal resulted in developmental toxicity including decreased numbers of viable new-born (due to increased post-implantation losses and abortions), reduced foetal body weights and delayed ossifications (Unpublished experimental study 4, 2017). However, developmental toxicity was observed in the presence of maternal toxicity (reduced body weight gain and body weight, macroscopic changes in the liver and gastrointestinal tract, and mortality) (Unpublished experimental study 4, 2017). Maternal effects can impede the detection of reproductive hazards. The maternal toxicity in this study indicates that rabbits are very susceptible to adverse effects on the gastrointestinal tract. Therefore, an oral prenatal developmental toxicity study using rats is considered more appropriate to detect potential developmental effects of Sb substances.

Studies with i.p injected meglumine antimoniate reported decreased numbers of viable new-borns (due to increased post-implantation losses), lower birth weight, increased soft tissue and skeletal anomalies/variations in the absence of maternal toxicity (Coelho et al., 2014a; Miranda et al., 2006; Paumgartten and Chahoud, 2001). Furthermore, i.m. injection of sodium stibogluconate, meglumine antimoniate, as well as ATC during GD 6-15 resulted in increased resorption rates, decreased number of viable foetuses and decreased foetal weight (Alkhawajah et al., 1996). Teratological findings in this study comprised an increased frequency of palatal and ocular anomalies (undeveloped eyes), asymmetrical brain hemispheres, and rudimentary 14th ribs (Alkhawajah et al., 1996). However, this study is regarded as not reliable because i) there is no information on the degree of maternal toxicity and ii) no information about statistical analysis.

7.9.8.2.2. Information from human studies

In a prospective occupational cohort study with female workers from an Sb plant (161 women with high exposure, 157 women with lower exposure, 115 control women), increased incidences of late spontaneous abortions was observed (12.5% in the exposed

women vs 4.1% in the controls) as well as lower body weights of the children of exposed women after 3, 6, and 12 months (Belyaeva, 1967).

The analysis of trace elements (As, Cd, Co, Cr, Cu, Mn, Ni, Pb, Sb, Sr, Ti, Tl, V, Zn) in umbilical cord blood and the relation to the risk of adverse pregnancy outcomes has been studied by Zheng et al. (Zheng et al., 2014). Ti and Sb were found at higher levels with statistical significance in the cord blood samples of the adverse pregnancy group compared to the reference group.

In another study (Longerich et al., 1991), fourteen trace elements (Mg, Cu, Zn, Sr, Y, Mo, Cd, Sn, Sb, I, Ba, Ce, Pb, and U) were determined in drinking water of 28 women, who had given birth to an infant with a neural tube defect (NTD), along with 28 matched controls (C). For 13 of the 14 determined elements, the mean of the NTD group exceeded the mean of the C group. For most elements, there were more extremely high values in the NTD group than in the C group. For each individual element, the difference in the results of the 2 groups, while not significantly different at the 95% confidence level, suggest a relationship of trace elements in drinking water with NTD.

For all of these studies confounding factors are possible and a causal relationship between Sb exposure and adverse pregnancy outcome cannot be proven.

7.9.8.3. Conclusion

In conclusion, several studies with different routes of exposure demonstrate developmental effects of Sb compounds (Coelho et al., 2014a; Grin et al., 1987; Miranda et al., 2006; Paumgartten and Chahoud, 2001; Unpublished experimental study 4, 2017) including ATC (Alkhawajah et al., 1996; Angrisani et al., 1988; Marmo et al., 1987; Rossi et al., 1987). Thus, there is concern that ATC interferes with normal development of offspring in humans. Additionally, there is a concern for fertility effects. However, the available data are not sufficient to draw final conclusions.

7.9.9. Hazard assessment of physico-chemical properties

7.9.10. Selection of the critical DNEL(s)/DMEL(s) and/or qualitative/semi-quantitative descriptors for critical health effects

The available studies cannot provide reliable points of departure for DNEL derivation.

7.9.10.1. Workers

It can be taken from the ECHA dissemination site (consulted: 12/06/2019), that the inhalation DNEL of the Registrants for workers is based on read across to ATO. Currently it is not clear whether this should be considered reasonable. Based on the results of the ongoing dossier evaluations on ATC and other Sb compounds and the results of the ongoing substance evaluations on other Sb compounds an improved data base is expected to be available. Thus a discussion of DNELs is postponed and will be initiated later, if considered necessary.

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

Acute toxicity

Based on the available information, the registered substance can be regarded as acute toxic by the oral route with an LD_{50} of 50–400 mg/kg bw in rats and thus fulfils the criteria for classification as acute toxic Cat. 4, H 302, according to CLP.

The information from animal studies with antimony pentachloride and accidental exposure of humans, with a minimal lethal concentration of 131 mg/m^3 after 4-hour inhalation exposure to ATC (Chemie, 1994; MAK, 2007), indicates that ATC may also be acute toxic after inhalation, however the available data are not robust enough to derive a classification.

Corrosion/Irritation

ATC has a harmonized classification as skin corrosive 1B and STOT SE Cat.3 H335 'May cause respiratory irritation' (SCL C>5%), which is justified due to release of HCl when hydrolysed in contact with water.

Sensitisation

There is no information available to inform about potential skin sensitising properties of ATC and data on other Sb compounds do not give rise to such concerns.

Repeated dose toxicity

The eMSCA concludes that based on the available hazard information for ATC there is concern for repeated dose toxicity but the available data are insufficient to draw robust conclusions.

Mutagenicity

A concern for mutagenicity was identified from the available *in vitro* data where positive results were observed in bacterial and mammalian cell genotoxicity assays. The available data are insufficient to draw robust conclusions.

Carcinogenicity

The results of several chronic inhalation toxicity studies with ATO and Sb ore raise the concern that also ATC may lead to carcinogenicity after chronic inhalation exposure. However, insufficient information is available on the registered substance to draw robust conclusions about the potential carcinogenicity.

Toxicity to reproduction

The eMSCA concludes that based on the available hazard information for ATC and other Sb compounds there is concern for toxicity to reproduction but the available data are insufficient to draw robust conclusions.

Overall conclusion

As no exposure of consumers could be identified, occupational exposure was regarded as very low and in light of the on-going compliance check for ATC, the generation of new information by animal testing for ATC also under this process is considered not proportionate at this stage. Therefore, no further data were requested in the context of this substance evaluation.

7.10. Assessment of endocrine disrupting (ED) properties

7.10.1. Endocrine disruption – Environment

Not in the scope of this substance evaluation.

7.10.2. Endocrine disruption - Human health

Mechanistic studies with potassium antimony tartrate and ATC indicate some endocrine activity of Sb compounds potentially affecting the reproductive system (Choe et al., 2003; Zhang et al., 2018). Potassium antimony tartrate has been demonstrated to promote growth and invasion of the androgen-sensitive prostate cancer cell line LNCaP *in vitro* and *in vivo* after implantation into mice (Zhang et al., 2018). It is suggested by these authors that the promotion of tumour growth is mediated by Sb-induced phosphorylation of the androgen receptor. Furthermore, this study reports increased serum levels of Sb in prostate cancer patients and a correlation with poor therapy outcome (Zhang et al., 2018). It is important to note in this context that the incidence of epithelial hyperplasia in the prostate of rats was increased in a chronic inhalation study with ATO (NTP, 2017b). In addition, oestrogenic activity of ATC was demonstrated *in vitro* using an oestrogen receptor transactivation assay as well as an E-screen assay (Choe et al., 2003). Relative potency in the transactivation assay was 0.16% compared to 17β-estradiol and the relative proliferative effect in the E-screen was 0.43% compared to 17β-estradiol. However, since no guideline studies investigating ED-sensitive parameters are available for ATC, no conclusion can be drawn on potential estrogenic or androgenic ED effects of ATC *in vivo*.

Deposition of Sb in the thyroid gland after exposure to different Sb compounds including ATC has been documented in several studies (Coelho et al., 2014b; Djuric et al., 1962; Friedrich et al., 2012; Kramer, 1950) but studies on effects of Sb on the thyroid system are limited. Thyroid hypertrophy/hyperplasia was reported after dietary exposure to ATO in rats and this effect could be prevented by simultaneous application of thyroxine (T4) (Westrick, 1953). Furthermore, when co-applied, ATO augmented the stimulatory action of T4 on oxygen consumption. To the best of our knowledge, no other oral studies investigating thyroid parameters are available for ATO. On the other hand, several inhalative studies with ATO reported no effects on thyroid gland histology in rats (Groth et al., 1986; Newton et al., 1994; NTP, 2017a).

Histological findings in the thyroid of rats were reported for potassium antimony tartrate applied for 90-days via the drinking water (already at the lowest dose of 0.5 ppm) (Poon et al., 1998). These findings included reduced follicle size, collapsed follicles, increased epithelial height, and cytoplasmatic vacuolization and nuclear vesiculation in thyroid follicle cells of males and females. However, plasma total T4 was not significantly changed but a slight increase in plasma thyroid hormone-binding ratio was detected in the two highest doses in females. Histological changes in the pituitary were also observed (cytoplasmic vacuolization and inclusions). It remains unknown whether the pituitary findings are related to effects on thyroid-stimulating hormone (TSH) production or secretion since TSH plasma levels were not determined. It should be noted that in a 90-day study (NTP, 1992), i.p. injection of antimony potassium tartrate did not result in any histological effects in the thyroid or pituitary. The reasons for the discrepancies between the study by Poon et al. (Poon et al., 1998) and the NTP study (NTP, 1992) are not clear but are possibly related to the differences in the exposure regime (continuous exposure via the drinking water in (Poon et al., 1998) vs. i.p. injection 3 times per week in (NTP, 1992)). In rabbits, similarly no effects on thyroid histology and oxygen consumption or cholesterol levels (as read-out for changes in thyroid activity) where detected after 21-day exposure to antimony potassium tartrate (1 mg Sb/ bw/day) via i.v. injection (Kramer, 1950).

A human cross-sectional study found a negative correlation between Sb in blood (collected around 25 weeks gestation) and fT4 (n = 915 pregnant women, 11 metals analysed) (Guo et al., 2016). No causality can be derived from this study and no such correlation was found in Christensen (2013) (n = 1537 adults, Sb and other metals analysed in urine).

In summary, given the well documented deposition of Sb in the thyroid gland of different species combined with histological findings in the thyroid gland in some studies, there is a concern for a potential interaction of Sb with the thyroid system. However, no guideline studies investigating any thyroid parameters are available for ATC. Therefore, no conclusion can be drawn on the potential thyroid-disrupting effects of ATC.

7.10.3. Conclusion on endocrine disrupting properties (combined/separate)

The eMSCA concludes that based on the available hazard information for ATC there is concern for endocrine disruption (human health) but the available data are insufficient to draw robust conclusions.

As no exposure of consumers could be identified, occupational exposure was regarded as very low and in light of the on-going compliance check for ATC, the generation of new information by animal testing for ATC also under this process was considered not proportionate at this stage. Therefore, no further data were requested in the context of this substance evaluation.

7.11. PBT and VPVB assessment

Not assessed since the SEv was targeted to human health concerns.

7.12. Exposure assessment

7.12.1. Human health

7.12.1.1. Worker

Besides the manufacture of ATC, occupational exposure is limited to a single industrial use, the use of ATC for the manufacture of ATO in the pigment industry. The eMSCA concludes, that the potential for exposure is very low. This conclusion is supported by the low annual tonnage of 10 – 100 t.

7.12.1.2. Consumer

As there are no consumer uses known to the eMSCA, an exposure assessment is not applicable at this point.

7.12.2. Environment

Not in the scope of this substance evaluation.

7.13. Risk characterisation

7.13.1. Workers

The ongoing dossier evaluations on ATC and other Sb compounds and the ongoing substance evaluations on other Sb compounds are expected to generate further information on the hazardous properties of trivalent Sb and possible read across options. With respect to the evaluation of Sb as a constituent in ATC it is considered to be reasonable to await the results of these activities.

Since currently no DNELs can be derived for ATC (see 7.9.10), a provisional qualitative risk characterisation is performed according to the REACH guidance on information requirements and chemical safety assessment (Part E: Risk Characterisation, chapter E.3.4). Based on the harmonised classification (Skin Corr. Cat. 1B (H314), STOT SE Cat. 3 (H335)) and the additional classification derived in chapter 7.9.3 (Acute toxicity Cat. 3 (H311), acute toxicity Cat. 4 (H302)) ATC is assorted to the moderate hazard band of table E.3-1 of the guidance. As the occupational exposure of ATC is considered to be very low, the eMSCA considers that the corresponding risk management measures are acceptable. Only manufacture and uses at industrial sites (manufacture of ATO in the pigment industry) are mentioned on the ECHA dissemination site (consulted: 12/06/2019).

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7.15. Abbreviations

ASAT	aspartate aminotransferase
ATC	antimony trichloride (EC: 233-047-2)
ATEG	2,5,7,10,11,14-hexaoxa-1,6-distibabicyclo[4.4.4]tetradecane (EC: 249-820-2)
ATO	diantimony trioxide (EC: 215-175-0)
ATS	antimony trisulphide (EC: 215-713-4)
Bq	Becquerel
bw	body weight
CA	Competent Authority
CHO	Chinese hamster ovary
CLP	Classification, labelling and packaging (Regulation (EC) No 1272/2008)
CMR	Carcinogenic, Mutagenic, Reprotoxic
CoRAP	Community rolling action plan
CSR	Chemical Safety Report
d	day
DNEL	Derived no effect level
DEv	Dossier evaluation
ECG	electrocardiography
eMSCA	evaluating Member State Competent Authority
ET	endotracheal
fT4	free thyroxine
GOT	glutamic-oxaloacetic transaminase
i2a	International Antimony Association
i.m.	intramuscular
i.p.	intraperitoneal
i.v.	intravenous
LOAEC	lowest observed adverse effect concentration
LOAEL	lowest observed adverse effect level
MAK	Maximale Arbeitsplatz-Konzentration
MMAD	Mass Median Aerodynamic Diameter

MPPD	Multiple-Path Particle Dosimetry
MSCA	Member State Competent Authority
NOAEC	no observed adverse effect concentration
NOAEL	no observed adverse effect level
NTD	neural tube defects
NTP	National Toxicology Program
OECD	Organisation for Economic Cooperation and Development
OPCS	Office of Population, Censuses and Surveys
PU	pulmonary
RCR	Risk Characterization Ratio
ROS	reactive oxygen species
Sb	antimony
Sb metal	antimony metal (EC: 231-146-5)
s.c.	subcutaneous
SCE	sister chromatid exchange
SEv	Substance Evaluation
T3	triiodothyronine
T4	thyroxine
T90	theoretical value for the time to achieve 90% of the target concentration after the beginning of aerosol generation
TB	tracheobronchial
UDS	Unscheduled DNA synthesis

8. Annex 1: Incidence of selected non-neoplastic findings in the 2 year inhalation toxicity studies of ATO in rats and mice (NTP 2017)

Concentration in air 0, 3, 10 or 30 mg/m^3, 50 animals /sex/group

Target organ	**Male Wistar Han Rats**	**Female Wistar Han Rats**	**Male B6C3F1/N Mice**	**Female B6C3F1/N Mice**
Survival rates	30/50, 30/50, 28/50, 18/50	39/50, 38/50, 28/50, 20/50	38/50, 30/50, 27/50, 17/50	36/50, 31/50, 26/50, 15/50
Body weight	30 mg/m^3 group at least 10% less than the chamber control group after week 69 and decreased to 80% of that of the chamber controls by the end of the exposure.	3, 10, and 30 mg/m^3 groups at least 10% less than the chamber control group after weeks 99, 81, and 65, respectively; the 10 and 30 mg/m^3 groups were 20% and 28% less, respectively, than the chamber control group by the end of the exposure.	30 mg/m^3 group at least 10% less than the chamber control group after week 73 and 25% less than the chamber control group by the end of the exposure.	30 mg/m^3 group at least 10% less than the chamber control group after week 85 and 21% less than the chamber control group by the end of the exposure
Lung	foreign body (1/50, 50/50, 50/50, 50/50); inflammation, chronic active (18/50, 50/50, 50/50, 50/50); alveolus, inflammation, suppurative (0/50, 12/50, 24/50, 28/50); perivascular, infiltration cellular, lymphocyte (3/50, 25/50, 19/50, 9/50); proteinosis (0/50, 47/50, 50/50, 50/50); alveolar epithelium, hyperplasia (4/50, 50/50, 48/50, 49/50); bronchiole, epithelium, hyperplasia (3/50, 34/50, 36/50, 33/50); fibrosis (2/50, 50/50, 49/50, 49/50)	foreign body (0/50, 50/50, 50/50, 50/50); inflammation, chronic active (21/50, 50/50, 50/50, 50/50); alveolus, inflammation, suppurative (0/50, 5/50, 6/50, 5/50); perivascular, infiltration cellular, lymphocyte (0/50, 18/50, 11/50, 8/50); proteinosis (0/50, 50/50, 50/50, 50/50); alveolar epithelium, hyperplasia (5/50, 50/50, 49/50, 50/50); bronchiole, epithelium, hyperplasia (6/50, 26/50, 25/50, 27/50); alveolar epithelium, metaplasia, squamous (0/50, 5/50, 3/50, 1/50); fibrosis (1/50, 50/50, 50/50, 49/50)	infiltration cellular, lymphocyte (13/50, 47/50, 48/50, 45/50); foreign body (0/50, 50/50, 50/50, 50/50); inflammation, chronic active (0/50, 48/50, 50/50, 50/50); alveolus, fibrosis (0/50, 12/50, 30/50, 37/50); pluera, fibrosis (0/50, 36/50, 46/50, 50/50); pleura, inflammation (1/50, 40/50, 47/50, 48/50); alveolar epithelium, hyperplasia (6/50, 39/50, 45/50, 49/50); bronchiole, epithelium, hyperplasia (0/50, 32/50, 44/50, 44/50)	infiltration cellular, lymphocyte (7/50, 37/50, 37/50, 26/50); foreign body (0/50, 50/50, 50/50, 50/50); inflammation, chronic active (1/50, 50/50, 50/50, 50/50); alveolus, fibrosis (0/50, 13/50, 30/50, 38/50); pluera, fibrosis (1/50, 39/50, 50/50, 50/50); pleura, inflammation (4/50, 27/50, 42/50, 38/50); alveolar epithelium, hyperplasia (1/50, 36/50, 49/50, 48/50); bronchiole, epithelium, hyperplasia (1/50, 34/50, 48/50, 45/50)
Adrenal medulla	hyperplasia (1/49, 2/50, 4/49, 8/50)	hyperplasia (0/49, 0/49, 3/49, 5/50)		
Bone marrow	hyperplasia (0/50, 3/50, 4/50, 8/50)	hyperplasia (8/50, 5/50, 11/50, 20/50)	hyperplasia (10/49, 19/50, 27/48, 33/50)	hyperplasia (3/50, 5/50, 15/50, 28/50)

Target organ	Male Wistar Han Rats	Female Wistar Han Rats	Male B6C3F1/N Mice	Female B6C3F1/N Mice
Spleen				hematopoietic cell proliferation (17/50, 19/50, 20/50, 35/50)
Thymus			depletion cellular (15/41, 14/38, 32/43, 32/39)	depletion cellular (9/47, 18/49, 23/49, 29/49)
Nose	foreign body (0/50, 0/49, 17/50, 40/50); respiratory epithelium, hyperplasia	foreign body (0/50, 5/50, 26/50, 45/50); respiratory epithelium, hyperplasia (4/50, 6/50, 7/50, 16/50); respiratory epithelium, metaplasia, squamous (0/50, 2/50, 3/50, 5/50)	foreign body (0/50, 48/49, 48/49, 49/50); respiratory epithelium, inflammation, chronic active (3/50, 9/49, 9/49, 6/50)	foreign body (1/50, 44/49, 45/50, 48/50); respiratory epithelium, metaplasia, squamous (0/50, 3/49, 2/50, 4/50)
Larynx	foreign body (0/50, 50/50, 50/50, 50/50)	foreign body (0/50, 50/50, 50/50, 50/50); inflammation, chronic active (0/50, 8/50, 0/50, 3/50)	foreign body (0/50, 15/50, 29/50, 44/50); respiratory epithelium, hyperplasia (1/50, 3/50, 15/50, 30/50); respiratory epithelium, metaplasia, squamous (0/50, 0/50, 8/50, 18/50); squamous epithelium, hyperplasia (2/50, 0/50, 4/50, 13/50)	foreign body (0/50, 25/50, 39/50, 48/50); respiratory epithelium, hyperplasia (2/50, 0/50, 14/50, 18/50); respiratory epithelium, metaplasia, squamous (1/50, 0/50, 5/50, 24/50); squamous epithelium, hyperplasia (4/50, 1/50, 1/50, 12/50)
Trachea	foreign body (0/50, 28/50, 43/50, 48/50)	foreign body (0/50, 39/50, 47/50, 49/50)	foreign body (0/49, 3/50, 1/50, 20/50); epithelium, hyperplasia (0/49, 0/50, 2/50, 5/50)	foreign body (0/50, 7/50, 14/50, 20/50)
Lymph node bronchial	foreign body (0/41, 35/40, 45/48, 42/47); hyperplasia, lymphoid (0/41, 21/40, 29/48, 26/47); pigmentation (1/41, 4/40, 5/48, 10/47)	foreign body (0/35, 35/36, 23/28, 36/41); hyperplasia, lymphoid (0/35, 21/36, 9/28, 11/41)	hyperplasia, lymphoid (2/30, 21/43, 26/47, 13/41); foreign body (0/30, 34/43, 47/47, 38/41); infiltration cellular, histiocyte (0/30, 2/43, 4/47, 6/41)	hyperplasia, lymphoid (2/41, 15/47, 17/48, 11/49); foreign body (0/41, 34/47, 46/48, 43/49); infiltration cellular, histiocyte (0/41, 2/47, 7/48, 7/49)
Lymph node mediastinal	foreign body (0/42, 41/45, 41/49, 43/49); hyperplasia, lymphoid (1/42, 24/45, 30/49, 26/49)	foreign body (0/46, 27/46, 32/46, 33/46); hyperplasia, lymphoid (0/46, 14/46, 10/46, 15/46)	hyperplasia, lymphoid (2/37, 8/45, 17/48, 34/49); foreign body (0/37, 32/45, 42/48, 48/49); infiltration cellular, histiocyte	hyperplasia, lymphoid (0/46, 3/48, 16/49, 18/50); foreign body (0/46, 28/48, 45/49, 44/50); infiltration cellular, histiocyte (0/46, 6/48, 11/49, 16/50)
Mediastinum	artery, inflammation, chronic active (0/0, 1/1, 2/2, 10/10)	artery, inflammation, chronic active (0/0, 0/0, 2/2, 9/9)		
Heart			epicardium, inflammation, chronic active (0/50,	epicardium, inflammation, chronic active (0/50,

Target organ	**Male Wistar Han Rats**	**Female Wistar Han Rats**	**Male B6C3F1/N Mice**	**Female B6C3F1/N Mice**
			2/50, 7/50, 16/50)	2/50, 7/50, 7/50)
Stomach, forestomach			inflammation, chronic active (2/50, 4/50, 4/49, 7/50)	
Pancreas	artery, inflammation, chronic active (1/50, 0/50, 2/50, 8/50)	artery, inflammation, chronic active (0/50, 0/50, 3/50, 8/50); artery, necrosis (0/50, 0/50, 0/50, 4/50)		
Mesentery	artery, inflammation, chronic active (0/50, 0/50, 0/50, 6/50)	artery, inflammation, chronic active (0/50, 0/50, 0/50, 6/50)		
Lung (artery)	artery, inflammation, chronic active (0/50, 0/50, 1/50, 1/50)	artery, inflammation, chronic active (0/50, 0/50, 1/50, 2/50)		
Kidney	renal tubule, accumulation, hyaline droplet (0/50, 1/50, 3/50, 14/50); artery, inflammation, chronic active	renal tubule, accumulation, hyaline droplet (0/50, 0/50, 5/50, 11/50); nephropathy (16/50, 15/50, 20/50, 24/50); artery, inflammation, chronic active (0/50, 0/50, 0/50, 2/50)		
Artery (all tissues combines)	inflammation, chronic active (1/50, 1/50, 5/50, 16/50)	inflammation, chronic active (0/50, 0/50, 5/50, 15/50)		
Eye	ciliary body, inflammation, acute (0/49, 0/49, 1/50, 6/49)	retina, atrophy (6/49, 21/50, 18/49, 19/49); ciliary body, inflammation, acute (0/49, 0/50, 1/49, 6/49)		
Prostate gland	Epithelium, hyperplasia 9/50, 18/50, 21/50, 13/50	NA		NA