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Helsinki, 12 March 2020

Registered substance subject to this decision, hereafter 'the Substance': Antimony metal (Sb metal)
EC number: 231-146-5
CAS number: 7440-36-0
Date of latest submission(s) considered[1]: 20 June 2019
Decision/annotation number: Please refer to the REACH-IT message which delivered this communication (in format SEV-D-XXXXXXXXXX-XX-XX/F)
Addressee(s): Registrant(s)[2] of Antimony metal (Sb metal)

DECISION ON SUBSTANCE EVALUATION

In accordance with Article 46(1) of the REACH Regulation (Regulation (EC) No 1907/2006), you must submit the following information on the Substance:

Human Health

1. 90-day (subchronic) inhalation toxicity study in rats (test method: OECD TG 413) with the Substance, including

i) BAL and measurements of lung burden[3], which inform on pulmonary deposition and retention of particles in the lung,

ii) cardiovascular effect evaluations, including electrocardiogram, cardiac biomarkers (myoglobin, cardiac troponins, creatine-kinase isoenzyme MB (CK-MB), brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-ProBNP)) and histopathology comprising standard HE and histomorphological and quantitative investigations for fibrosis (e.g. Sirius Red/Fast Green Staining) at representative localisations (further specifications see Appendix 1) and

iii) toxicokinetic assessment covering the test parameters according to test method OECD TG 417 using a satellite group at the high exposure level (as specified in Appendix 1). The toxicokinetic studies shall include quantification of the parent compound and – by means of metal speciation – trivalent (Sb(III)), pentavalent (Sb(V)), and alkylated (e.g. methylated) Sb species, which might be formed from the parent compound.

[1] This decision is based on the registration dossier(s) on the day until which the evaluating MSCA granted an extension for submitting dossier updates which it would take into consideration.

[2] The terms registrant(s), dossier(s) or registration(s) are used throughout the decision, irrespective of the number of registrants addressed by the decision.

[3] As described in the latest update of OECD 413 of 25 June 2018

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You must provide an update of the registration dossier(s) containing the requested information, including robust study summaries and, where relevant, an update of the chemical safety report by **20 December 2021**.

In addition to the robust study summaries, you must submit the full study report by the same deadline, by attaching it to the relevant endpoint study record in IUCLID.

The deadline for provision of the requested data takes into account the time that you may need to agree on which of the registrant(s) will perform the required tests (3 months is allocated for this) and include the time required for developing an analytical method, conduct of the study, preparation of the study report and reporting in IUCLID.

The reasons of this decision and any further test specifications of the requirements are set out in Appendix 1. The procedural history is described in Appendix 2. Further information, observations and technical guidance as appropriate are provided in Appendix 3. Appendix 4 contains a list of registration numbers for the addressees of this decision. This appendix is confidential and not included in the public version of this decision.

Based on Article 53 of the REACH Regulation, you are requested to inform ECHA who will carry out the study on behalf of all registrant(s) within 90 days. Instructions on how to do this are provided in Appendix 3.

Appeal

This decision can be appealed to the Board of Appeal of ECHA within three months of its notification. An appeal, together with the grounds thereof, has to be submitted to ECHA in writing. An appeal has a suspensive effect and is subject to a fee. Further details are described under: http://echa.europa.eu/regulations/appeals

For your information

Overall, there is evidence that after exposure to antimony containing substances an unidentified antimony species (e.g. Sb3+, Sb5+, or methylated Sb (Me-Sb) becomes systemically available and causes effects independently of the route of exposure. Therefore, this substance evaluation is conducted in parallel to evaluations for diantimony trioxide (ATO,EC 215-175-0, CAS 1309-64-4), antimony sulphide (ATS, EC 215-713-4, CAS 1345-04-6), antimony trichloride (ATC, EC 233-047-2, CAS 10025-91-9) 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 which similar initial concerns need to be clarified. For all cases, including yours, a compliance check has been initiated in parallel to assess whether standard information is missing.

Authorised[4] by Christel Schilliger-Musset, Director of Hazard Assessment

[4] As this is an electronic document, it is not physically signed. This communication has been approved according to ECHA's internal decision-approval process.

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Appendix 1: Reasons

Based on the evaluation of all relevant information submitted on antimony metal (Sb metal)[5] and other relevant available information, ECHA concludes that further information is required to enable the evaluating Member State competent authority (MSCA) to complete the evaluation of whether the Substance constitutes a risk to human health.

The evaluating MSCA will subsequently review the information submitted by you and evaluate if further information should be requested to clarify any remaining concerns in the follow up process.

The identification of a potential risk is based on a combination of exposure and hazard information.

According to information in the registration dossier the Substance is used in electrical and carbon products, the seal and pump industry, as an impregnating agent for porous carbon and graphite ceramics, in recordable media (see below) and for further processing to diantimony trioxide (ATO) and antimony sulphide (ATS).

Therefore, significant exposure of workers and consumers cannot be excluded.

In the comments you provided, you indicate that you "disagree with this assumption/claim". You further elaborate that this was not justified, as in the CSRs "low/controlled exposures have been demonstrated for all these substances" and "that the exposure of workers to antimony metal is well controlled below the DNEL and can therefore not be claimed to be significant".

ECHA notes that there is evidence of exposure of humans, as mentioned above, to a substance that is suspected to cause repeated dose toxicity and carcinogenicity via inhalation exposure and your risk assessment does not account for that. ECHA emphasises that there is exposure and expects that the information requested by this decision will make possible the assessment of the significance of it.

Overall description of the concern

Based on the structural similarity between Sb metal and ATO and other trivalent Sb compounds, there is a concern that Sb metal may cause respiratory tract and systemic toxicity and potentially cancer after prolonged inhalation exposure.

However, the available data are not sufficient to draw a robust conclusion.

Consumer exposure via the oral, dermal, and inhalation route is evident based on the use of Sb metal in metal articles, such as [redacted], in addition to the use in ammunition and solder.

Workers are exposed at a variety of industrial and professional settings: the production and use of the Substance itself and its further processing to e.g. ATO and ATS and to different alloys. Sb metal is used in electrical and carbon products, the seal and pump industry, as an impregnating agent for porous carbon and graphite ceramics, and in recordable media. Tasks leading to potential high exposures are low energy manipulation of pure Sb or Sb bound in materials or articles, potentially closed industrial processing

[5] The registered substance antimony metal will be named Sb metal in the following text

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with minerals/metals at elevated temperature (e.g. smelters, furnaces, refineries, coke ovens), handling and high energy work-up of alloys and ores, mixing and blending of powders (e.g. hot rolling/forming, grinding, mechanical cutting, drilling or sanding) and production of mixtures or articles by tabletting, compression, extrusion or palletisation. Exposure is observed for several involved PROCs e.g. PROC 5, 14, 26, 28.

Explanation of the testing strategy

In your comments on the draft decision, you request awaiting the outcome of ECHA's compliance check and the assessment of the information submitted subsequently before further information is requested from you under substance evaluation.

ECHA considers that there is no need to postpone substance evaluation as the concerns that lead to further information requests in this decision are already established. Specifically for this case, substance evaluation aims at addressing the concerns for repeated dose toxicity and carcinogenicity after inhalation exposure. The tests requested under compliance check do not resolve this concern.

From effects seen after exposure to antimony containing substances such as Sb metal, ATO, ATS, and ATC, it is suspected that a common soluble and systemically available antimony species is causing these effects. Information on the identity and availability of this soluble species, *i.e.* the toxophore, will help to understand the underlying molecular mechanisms of the identified concerns.

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1. 90-day (subchronic) inhalation toxicity study in rats (test method: OECD TG 413)

The concern(s) identified

There is a concern that Sb metal causes toxicity after repeated inhalation exposure in occupational settings. Observations from occupational exposure during mining and smelting of ATS ore (Jones, 1994; Karajovic, 1957; McCallum, 1963; McCallum, 1967; McCallum et al., 1970; Potkonjak and Pavlovich, 1983; Renes, 1953) indicate that Sb (different forms) causes toxic effects after inhalation. For some of these case studies it is likely that workers were also exposed to Sb metal (Jones, 1994; McCallum, 1963). There is evidence from several studies that repeated inhalation exposure with the structurally related ATO causes toxicity in the respiratory tract (EU, 2008; NTP, 2017) and systemic effects (NTP, 2017). The concern is thus partly based on evidence that the toxicity observed after various routes of administration of structurally similar Sb compounds such as ATO, ATS, and others may be due to common antimony species causing these effects.

Occupational exposure:

Workers are exposed at a variety of industrial and professional settings: the production and use of the Substance itself and its further processing to e.g. ATO and ATS and to different alloys and other products. Tasks leading to potential high exposures are low energy manipulation of pure Sb or Sb bound in materials or articles, potentially closed industrial processing with minerals/metals at elevated temperature (e.g. smelters, furnaces, refineries, coke ovens), handling and high energy work-up of alloys and ores, mixing and blending of powders (e.g. hot rolling/forming, grinding, mechanical cutting, drilling or sanding), production of mixtures or articles by tableting, compression, extrusion or palletization.

Several involved PROCS as reported in the CSR are indicative for exposure. Such are, e.g. 8a, 23-26 and 28.

Consequently, there is a concern that Sb metal cause toxicity via inhalation exposure.

Why new information is needed

The registration dossier contains the following results of studies conducted with Sb metal:

Toxicokinetics

No information on standard toxicokinetic studies performed with Sb metal was provided in the registration dossier or could be located from other sources.

The registration dossier does however contain a study assessing solubility of Sb metal in different body fluids (Hedberg et al., 2010). The study is summarised as follows: *"Antimony metal (Sb) was exposed to five different synthetic body fluids for two different time periods, 2 and 24 hours. In parallel to the generation of bioaccessibility data, particle and surface characterisations were conducted.*

- The Sb sample revealed a large number of smaller sized particles (about 1µm) and a large size distribution (up to > 100µm).

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- A solution composition dependence were observed for the dissolution.

- Particles of Sb dissolved at least in parts in all test media after 24 h of exposure in the following order: ALF (82%) > ASW (61%) > GMB (57%) > PBS (42%) > GST (14%).

- Release rates of antimony (independent of the calculation method) decreased with time in all media at least by a factor of 2 as follows (release rates in mg /cm2/h corrected for measured surface area after 2 and 24 h): ALF (0.064 to 0.026) > ASW (0.04 to 0.012) > GMB (0.024 to 0.011) > PBS (0.03 to 0.007) > GST (0.024 to 0.002)."

The information provides indications that a soluble antimony species might be systemically available after exposure to antimony metal.

Repeated dose toxicity: Sb metal

The registration dossier does not contain any repeated dose toxicity studies conducted with Sb metal and none could be found from other sources.

In the registration dossier read-across has been applied to predict a toxicological property of Sb metal using data generated with ATO.

While the read-across cannot be used without further supporting information to predict the properties of Sb metal for a conclusive risk assessment and classification, these data on ATO strengthen the concern for toxicity of Sb metal after inhalation. This concern is further supported by occupational case studies where it is likely that effects seen in workers were caused by exposure to Sb metal (Jones, 1994; McCallum, 1963).

Repeated dose toxicity (inhalation): ATO

ATO is classified under CLP Regulation 1272/2008 as Carc. 2 H351.

Several older long-term inhalation toxicity studies for ATO have previously been evaluated under the EU existing substances regulation (for detail see risk assessment report (EU, 2008)). 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 indicated that ATO is toxic to the respiratory tract (Groth et al., 1986; Newton et al., 1994; [redacted], 2003; [redacted], 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.

The risk assessment report (EU, 2008) also describes case reports on workers experiencing symptoms like rhinitis, perforation of the septa, pharyngitis, bronchitis, pneumonitis, pneumoconiosis and symptoms of emphysema following 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 these studies cannot be used for quantitative risk assessment. They do however indicate that ATO has the potential to induce pulmonary inflammation, lung emphysema, and pneumoconiosis after repeated inhalation exposure (EU, 2008).

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 (greater than 99.9% pure) by inhalation for 2 weeks or 2 years, resulting in a LOAEC of 3 mg/m^3.

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 were exposed in a tissue burden study to the same concentrations for 16 days then held for 28 days without exposure. All rats survived until 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, 2017).

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 were exposed in a tissue burden study to the same concentrations for 17 days then held for 28 days without exposure. All mice survived until 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, 2017).

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. There were clear signs of systemic toxicity in addition to local effects on the respiratory tract. NTP summarises the outcome as follows:

"*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, 2017).

Cardiotoxicity

Cardiotoxicity is a well-known serious side effect from the medical use of tri- and pentavalent Sb compounds for the parenteral 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 and ulcers were diagnosed by X-ray in seven of 111, which was about four times higher than in other parts of the enterprise. No further deaths were reported after the use of ATS was discontinued.

The same authors conducted further, limited inhalation tests in rats, rabbits and dogs. The study 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 disease 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 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) highlighted 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.

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

The available knowledge leads to the concerns that Sb metal may be systemically available and toxic after inhalation.

Consequently, a sub-chronic study (90-day), inhalation route (test method OECD TG 413) in rats, with investigation of BAL and measurements of lung burden, which inform on pulmonary deposition and retention of particles in the lung, cardiovascular effects evaluations and toxicokinetic assessment to determine the systemic absorption and distribution of the test substance is needed to address the concern.

What is the possible regulatory outcome?

Information from a repeated dose inhalation toxicity study can be used for deciding on classification for STOT RE 1 or 2 and is needed for risk assessment of Sb metal. It may lead to the derivation of an occupational exposure limit (OEL) for Sb metal in air. The toxicokinetic information may inform about identity and systemic availability of soluble

antimony species. Comparison of the toxicological and toxicokinetic information gained from this study will further allow assessing potential read-across from the carcinogenicity studies with ATO, which is classified as Carc Cat 2 H351.

Considerations on the test method and testing strategy

The sub-chronic study (90-day), inhalation route (test method OECD TG 413) in rats, must include the determination of BAL/lung burden, cardiovascular assessment and toxicokinetic investigations.

These investigations are necessary for the following reasons:

- BAL/lung burden

Knowledge about particle distribution and retention is essential to assess the mode of action of lung toxicity, where lung burden and potential overload are important parameters to determine the toxicological significance of adverse findings.

- Cardiovascular investigations

There are indications from animal studies and human observations as described above that exposure to Sb compounds may cause cardiac and/or vascular toxicity. The current evidence however is not conclusive. The cardiovascular alterations need to be quantitatively described for managing the risks resulting from the uses of the Substance.

Therefore, cardiovascular investigations must be included in the OECD TG 413 as also indicated in the test guideline.

Therefore, at all exposure levels:

These investigations must include an electrocardiogram, because ST segment inversion and QT interval prolongation and consequently torsade de point arrhythmias and sudden cardiac arrest belong to the cardiovascular alterations induced by Sb compounds as described above.

Furthermore, as a minimum, the following cardiac toxicity biomarkers must be determined in serum samples: myoglobin, cardiac troponins, creatine-kinase isoenzyme MB (CK-MB), brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-ProBNP). Serum biomarkers provide an additional non-invasive measure for diagnosing cardiac injury. Their use has been increasingly standardised and validated in the recent years (Clements et al., 2010; Kim et al., 2016; O'Brien, 2008; Walker, 2006). Histopathology shall comprise standard HE and histomorphological and quantitative investigations for fibrosis (e.g. Sirius Red/Fast Green Staining) at representative localisations. Best practice guidance on organ sampling and trimming and interpretation of findings shall be followed (Berridge et al., 2016; Morawietz et al., 2004).

- Toxicokinetic investigations

There are no reliable toxicokinetic studies available to assess uptake, speciation, distribution, metabolism and excretion of Sb metal after inhalation or any other exposure route. The requested toxicokinetic data will enable to quantitatively assess the uptake, distribution, metabolism and excretion of the parent substance Sb metal and its potential

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metabolites. The design also enables to conclude on the antimony-species involved (e.g. Sb(III), Sb(V), Me-Sb) which are possibly responsible for the observed toxicity. Furthermore, toxicokinetics may also serve for route-to-route extrapolations.

Thus, toxicokinetic information is necessary as an indispensable prerequisite for data interpretation, *e.g.* with regard to systemic effects as observed after inhalation exposure to ATO (NTP, 2017), for quantitative risk assessment and DNEL derivation as well as to gain an understanding of the toxicological mode(s) of action.

Information on availability in tissues is of relevance for the interpretation of in vivo mutagenicity tests. Furthermore, insight can be gained whether the parent compound and / or metabolites should be considered as the toxic agent. The requested study will allow a comparison between the different trivalent Sb compounds under substance evaluation and enable the eMSCA to decide whether read-across can be applied for the assessment of the carcinogenic potential or when requesting further higher tier studies.

The study by de Bie and Salmon-te Rietstap (2005) demonstrates an increasing systemic concentration of Sb after oral ATO exposure over time. Thus it is necessary to investigate substance concentrations at several time points in order to assess the bioaccumulation potential. Two recent studies identified methylated Sb species in vivo pointing to alkylation as an important metabolic pathway in rats, by use of three different Sb compounds (ATO, antimony potassium tartrate, potassium pyroantimonate) (Wu et al., 2018) as well as in humans, where alkylated species were detected in urine and saliva (Ye et al., 2018). Both studies contradict the previous assumption that Sb is not methylated in the organism (EU, 2008). Biotransformation to common compound(s) seems plausible based on these two studies, which have not been cited in the registration dossier (Wu et al., 2018; Ye et al., 2018). Nonetheless, these studies demonstrate that metabolism of Sb compounds is not fully understood and further data are critical to increase the understanding of Sb toxicokinetics and mechanism of action.

In order to obtain the toxicokinetic information considered relevant based on the above arguments, for animal welfare reasons that information is requested by assessing toxicokinetic parameters within the requested OECD TG 413 study. Uptake, bioavailability, distribution, metabolism and excretion of the parent compound and metabolites shall be determined on the basis of OECD TG 417 using a satellite group at the high exposure level of the OECD TG 413 study. A minimum of four animals of one sex should be used for each time point of analysis. Reasonable efforts should be made to identify all metabolites present at 5 % or greater of the administered dose and to provide a metabolic scheme for the Substance (OECD TG 417).

The parent compound, Sb(III) and Sb(V) species as well as alkylated (e.g. methylated) Sb species shall be quantified after one day, one week, six weeks and at the end of the exposure period of the OECD TG 413 study in plasma and blood cells as well as in urine and faeces.

In line with OECD TG 417, section 38, tissue distribution shall be determined at the time of peak blood concentration and at the end of the exposure period. The parent compound, Sb(III) and Sb(V) species as well as alkylated (e.g. methylated) Sb species shall be quantified in whole blood, erythrocytes, heart, lung, thyroid, thymus, spleen, liver, kidney, bone marrow, skin, fat, GI tract, gonad tissue and residual carcass. This information is needed for the interpretation of target organ toxicity and in order to interpret data from other toxicological studies.

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Methods to detect Sb(III) and Sb(V) as well as alkylated Sb species are described in several publications and the most suitable method shall be selected by you, e.g., (Friedrich et al., 2012; He et al., 2019; Viñas et al., 2006; Wang et al., 2018; Wu et al., 2018; Ye et al., 2018).

You must submit the full study report for the information requirement by dossier update. Considering the complexity of the case as described above, the submission of the full study report (implemented method, raw data collected, interpretations and calculations, consideration of uncertainties, argumentation, etc.) is required. This will be instrumental in clarifying the concern for toxicity after repeated inhalation exposure.

Consideration of alternative approaches

The request for an OECD TG 413 study is suitable and necessary to obtain information that will allow clarifying whether there is a potential risk for toxicity after repeated exposure by inhalation. More explicitly, there is no equally suitable alternative way available in order to obtain this information. Inclusion of investigations of lung burden measurement, cardiotoxicity and toxicokinetics are required for the reasons detailed above. ECHA notes that there is currently no validated method available that could generate the necessary information without the use of vertebrate animals.

Consideration of your comments on the draft decision

ECHA notes that you are not in principle questioning the concern for systemic toxicity.

Testing strategy

In your comments on the draft decision, you question the need of the 90-day (sub-chronic) inhalation toxicity study in rats (OECD TG 413) with Sb metal and generally the need for studies to assess the systemic toxicity of Sb substances "*before having clarified a number of inhalation and oral toxicity related questions*." More specifically, you demand "*that the request for inhalation sub-chronic studies be suspended until the mode of action for genotoxicity has been clarified.*" You indicate further, how you intend to proceed in your provisional testing strategy.

You suggest to perform *in vitro* research comparing and ranking all Sb substances in terms of bioelution (gastric and lung cells), cytotoxicity and viability impacts, intracellular reactive oxygen species (ROS) generation, ROS-induced damage, pro-inflammatory responses, Sb particle surface reactivity, oxidative potential, oxidative stress (intracellular glutathione and gene expression of HO-1), and genotoxicity in lung cells. Then you intend to refine the hypothesis for the genotoxicity mechanism(s) of action (direct or indirect) presumed to be involved in lung carcinogenicity, identify the ideal test items for further inhalation testing and finally run the most optimal (combined) *in vivo* inhalation genotoxicity study(ies). Only thereafter you plan, according to the visual overview of your testing strategy, to conduct OECD 413 90 day inhalation repeated dose study(ies?) (test material not specified).

ECHA notes your efforts to assess a wider category of Sb compounds but observes the following deficiencies of your strategy that do not address the concern for this substance and which overall usefulness is unclear and the outcome uncertain:

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- The refinement of the hypothesis for the genotoxicity mechanism of actions does not inform the design of the OECD 413 nor does it clarify the concern for inhalation toxicity after prolonged exposure.

- the bio-elution assays for the inhalation route have not yet been validated and thus the usefulness of this information is unpredictable. The *in vitro* bio-accessibility data do not provide information on *in vivo* systemic absorption and bioavailability. Bio-accessibility results cannot provide on their own the basis for predicting *in vivo* toxicity.

- You have not yet determined the test materials to be used in the future testing program.

ECHA notes that your testing strategy does not address the concern of systemic toxicity upon inhalation immediately. Instead, it delays further the generation of necessary information required to clarify the concern. As the concerns are already manifested for this Substance, ECHA needs to clarify them as soon as possible. The testing strategy is thus not a suitable alternative to the information requested.

Route of exposure for systemic toxicity testing

You express the view that systemic toxicity should be investigated in oral studies. You suggest further a set of oral *in vivo* studies before you "*decide on the need and design of an oral 90-day sub-chronic repeated dose oral study with the most suitable substance*".

ECHA notes that the study according to OECD TG 413 detects both, local toxicity at the point of entry (respiratory system) as well as systemic toxicity. It is designed to provide robust data for quantitative inhalation risk assessments. Evidence from epidemiological observations and limited experimental studies with Sb metal as well as the alerts from the structurally related ATO raise the concern that Sb metal may cause adverse local and systemic effects, including cardiotoxicity, following repeated inhalation exposure. ECHA maintains therefore the request for this study via the inhalation route.

Cardiotoxicity

You requested to remove the specific investigations for cardiotoxicity "*unless and until the organ weight and histopathology in the OECD 422 study indicates adverse effects following relevant (oral route of administration"*.

ECHA notes that there is no need for additional animal studies to decide on the need of investigating cardiotoxicity. The available information related to different routes of exposure is sufficient to raise the concern.

Dossier update

In the updated dossier you included_a revised version of the "Scientific opinion, weight of evidence and read-across assessment, and further research opportunities – Human Health" for the endpoint "Lung toxicity and carcinogenicity" (i2a, 2019). In this document you have provisionally grouped ATO and Sb metal together and suggest a classification as STOT RE2 and Carc. 2. The document does not address systemic toxicity resp. target organ toxicity to other organs than the lung.

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ECHA notes that the STOT self-classification applied to Sb metal in the registration dossier is limited to lungs (STOT RE 2, H373, lungs). Further, there is no information to support a quantitative inhalation hazard and risk assessment for Sb metal, which is needed for the derivation of a DNEL and in order to decide about the appropriate classification (i.e. STOT RE 1 or 2). Thus, the self-classification does not eliminate the need to conduct further testing to clarify the concern.

The new information in your dossier from ToxTracker and the bioelution tests do not allow for conclusions on properties such as toxicity, uptake, distribution, excretion or metabolism. In addition, there are some inconsistencies between the information provided in IUCLID compared to data in the above mentioned scientific opinion (i2a, 2019). In conclusion, the additional data provided in the dossier update do not replace the animal studies requested in this decision.

Conclusion

Therefore, in accordance with Article 46(1) of the REACH Regulation, you must carry out the following study using the Substance subject to this decision:

90-day (subchronic) inhalation toxicity study in rats (test method: OECD TG 413) as specified above, including

i) BAL and measurements of lung burden[3], which inform on pulmonary deposition and retention of particles in the lung,

ii) cardiovascular effect evaluations including electrocardiogram, cardiac biomarkers (myoglobin, cardiac troponins, creatine-kinase isoenzyme MB (CK-MB), brain natriuretic peptide (BNP) and N-terminal pro-brain natriuretic peptide (NT-ProBNP)) and histopathology comprising standard HE, histomorphological and quantitative investigations for fibrosis (e.g. Sirius Red/Fast Green Staining) at representative localisations (further specifications as described above) and

iii) toxicokinetic assessment covering the test parameters according to test method OECD TG 417 as specified above. The toxicokinetic studies shall include quantification of the parent compound and – by means of metal speciation – trivalent (Sb(III)), pentavalent (Sb(V)), and alkylated (e.g. methylated) Sb species, which might be formed from the parent compound.

A satellite group to the high dose group must be used for the toxicokinetic investigations that should include all relevant parameters from OECD TG 417.

Based on the results of the range-finding study the study director shall decide on the need for additional post-exposure intervals for determining pulmonary retention as described in OECD TG 413 (see especially sections 1, 14, 22-28 and the Annex).

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Appendix 2: Procedural history

On the basis of an opinion of the ECHA Member State Committee and due to initial grounds for concern relating to suspected carcinogenicity, wide dispersive use, high RCR, exposure of workers and high aggregated tonnage, Sb metal CAS No 7440-36-0 (EC No 231-146-5) was included in the Community rolling action plan (CoRAP) for substance evaluation to be evaluated in 2018. The updated CoRAP was published on the ECHA website on 20 March 2018. The competent authority of Germany (hereafter called the evaluating MSCA) was appointed to carry out the evaluation.

In accordance with Article 45(4) of the REACH Regulation, the evaluating MSCA carried out the evaluation of the above substance based on the information in your registration(s) and other relevant and available information.

In the course of the evaluation, the evaluating MSCA identified additional concerns regarding repeated dose toxicity, mutagenicity and reproductive toxicity.

The evaluating MSCA considered that further information was required to clarify the abovementioned concerns. Therefore, it prepared a draft decision under Article 46(1) of the REACH Regulation to request further information. It subsequently submitted the draft decision to ECHA on 20 March 2019.

ECHA notified you of the draft decision and invited you to provide comments.

Registrant(s)' commenting phase

ECHA received comments from you and forwarded them to the evaluating MSCA without delay.

The evaluating MSCA took the comments from you which were sent within the commenting period as well as a dossier update received on 20 June 2019 into account. They are reflected in the reasons (Appendix 1). The requests were not amended.

Proposals for amendment by other MSCAs and ECHA and referral to the Member State Committee

The evaluating MSCA notified the draft decision to the competent authorities of the other Member States and ECHA for proposal(s) for amendment.

As no proposals for amendment were received, ECHA took the decision accordingly.

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Appendix 3: Further information, observations and technical guidance

1. This decision does not imply that the information provided by you in the registration(s) is in compliance with the REACH requirements. The decision neither prevents ECHA from initiating compliance checks on your dossier(s) at a later stage, nor does it prevent a subsequent decision under the current substance evaluation or a new substance evaluation process once the present substance evaluation has been completed.

2. Failure to comply with the request(s) in this decision, or to otherwise fulfil the information requirement(s) with a valid and documented adaptation, will result in a notification to the enforcement authorities of your Member State.

3. In relation to the required experimental study/ies, the sample of the substance to be used ('test material') has to have a composition that is within the specifications of the substance composition that are given by all registrant(s). It is the responsibility of all the registrant(s) to agree on the tested material to be subjected to the test(s) subject to this decision and to document the necessary information on the composition of the test material. The substance identity information of the registered substance and of the sample tested must enable the evaluating MSCA and ECHA to confirm the relevance of the testing for the substance subject to substance evaluation.

4. In relation to the experimental stud(y/ies) the legal text foresees the sharing of information and costs between registrant(s) (Article 53 of the REACH Regulation). You are therefore required to make every effort to reach an agreement regarding each experimental study for every endpoint as to who will carry out the study on behalf of the other registrant(s) and to inform ECHA accordingly within 90 days from the date of this decision under Article 53(1) of the REACH Regulation. This information should be submitted to ECHA using the following form stating the decision number above at: https://comments.echa.europa.eu/comments_cms/SEDraftDecisionComments.aspx?CaseNumber=SEV-231-146-5-1

   Further advice can be found at http://echa.europa.eu/regulations/reach/registration/data-sharing. If ECHA is not informed of such agreement within 90 days, it will designate one of the registrants to perform the stud(y/ies) on behalf of all of them.