International Antimony Association

Scientific opinion, weight of evidence and read-across assessment, and further research opportunities
-
Human Health: Lung toxicity and carcinogenicity

Version 2

18 June 2019

Version management

Version	Date	Main change	Sections affected
1	31 July 2018	/	/
2	18 June 2019	Electrophilicity considered, ECHA's stepwise weight of evidence template followed, research strategy adjusted in consideration of REACH Evaluations Draft Decisions dated 18 April 2019	All

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1. Introduction

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Lung toxicity/carcinogenicity studies have been performed for only a few of the 10 mono-constituent antimony (Sb) substances that are registered under REACH. Overall, around 15 studies have assessed the lung effects since the 1980's. Most of the information is available on a few trivalent Sb substances, and recent animal data is only available for Sb trioxide. This dataset is used as the starting point to perform the ***weight of evidence-based lung toxicity assessment*** of Sb substances.

Annex XI of the REACH Regulation also opens the possibility of predicting properties of substances for which no data is available, on the basis of data available on other related substances, by applying read-across (so-called 'read-across approach') between one or more source and target substances. The ***read-across assessment*** is built upon the physico-chemical similarities and differences that can be observed among the Sb substances, and which are of relevance to the toxicological property to be assessed.

Along these two related assessments, a number of information gaps are identified and are the targets of a phased research program being conducted over the next several years, identified as further research options.

This "scientific opinion, weight of evidence and read-across assessment, and further research options" document therefore outlines the approach followed to assess and predict the lung toxicity properties of Sb substances under REACH. It implements the recommendations and principles laid down in relevant ECHA documents[1], in order to facilitate the examination of the read-across and weight of evidence justification by REACH authorities.

This document refers to evidence which is available in the REACH Registration dossier of the Sb substances and therefore avoids repetition of detailed description of evidence which is available in the dossier and/or the Chemical Safety Reports (CSRs). Reading it in conjunction with the REACH dossiers and/or Chemical Safety Reports (CSRs) will bring a more complete picture to the reader.

i2a, on behalf of the registrants of its ten (10) Sb substances in scope, requests that the opinions and conclusions presented in this document, including the further research options that are outlined, are taken into account when preparing REACH Evaluation decisions. Future data generation may alter this scientific opinion and the REACH dossiers and CSRs. Accordingly, this document (and any updates of it) will be attached to the next REACH Dossier updates.

About i2a

The mission of the International Antimony Association is to inspire product stewardship along the antimony value chain. This mission is accomplished by generating and sharing information concerning the environmental and health safety and societal benefits of antimony and antimony compounds. Through a common evidence base, i2a promotes a harmonized risk management and continued safe use of antimony and antimony substances across the value chain and geographical borders.

For further information: www.antimony.com.

[1] ECHA Guidance on grouping of substances (2017), ECHA's Read-Across Assessment Framework (RAAF) (2017), and ECHA's Weight of evidence/uncertainty in hazard assessment background document and template (no date specified). Where necessary, the concepts and terms used in ECHA Documents are adapted to have greater compatibility with the unique properties of metals and metalloid substances.

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2. Assessment of lung toxicity applying a weight of evidence approach

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ECHA's recommendation for documenting a weight of evidence approach includes the following steps:

1) Problem formulation (cf. subsection 2.1 below)
2) Collection and documentation of all information (cf. subsection 2.2 below)
3) Assessment of quality of individual evidence (cf. subsection 2.2 below)
4) Integration and weighing of evidence (weight of evidence analysis), including the application of levels of confidence (cf. subsection 2.3 below)
5) Uncertainty analysis (cf. subsection 2.3 below)
6) Conclusion (cf. subsection 2.3 below)

2.1 Problem formulation

Establishing the carcinogenic potential of Sb and its compounds is central to a determination of the cancer risk that may be associated with the production, use, or disposal of Sb compounds.

The weight of evidence assessment therefore aims to respond to the following questions:

- Is the available evidence sufficient to assess the lung toxicity and carcinogenicity potential of Sb substances?
- What indication does the available evidence provide as to the potential lung toxicity and carcinogenicity potential of Sb substances?
- What research would increase the confidence/reduce the uncertainty of the lung toxicity and carcinogenicity assessment of Sb substances?

2.2 Lung toxicity and carcinogenicity information on Sb substances

This section covers steps 2) collection and documentation of all information, and 3) assessment of quality of individual evidence (reliability, relevance, adequacy) of ECHA's weight of evidence approach.

Literature addressing these issues was located by searching bibliographic data bases (ToxLine, PubMed). Initial literature searches focused on the period 1990 to May 2017. Supplemental searching to identify more recent publications were conducted in May of 2019, and focused upon May 2017 to May 2019. The capture of literature was broadened by reliance upon the primary search terms "antimon* followed by manual inspection of papers identified for relevance to Sb lung toxicity, carcinogenicity, and other key toxicological properties. Approximately 200 papers concerned the use of antimonial compounds in the treatment of parasitic diseases. This clinical literature was included in the analysis since it potentially helped define toxic or toxicokinetic properties of antimonial compounds. Table 1 summarizes this literature search strategy.

Table 1: Toxicology literature search criteria for Sb substances.

Search dates covered	Number of papers identified	Search criteria	Substances included
1990 – May, 2017	~2500	"antimon*"	Antimony metal, Diantimony trioxide, Antimony sulfide, Antimony trichloride, Antimony tris (ethylene glycolate), Sodium hexahydroxoantimonate, Potassium hexahydroxoantimonate, Sodium antimonate, Antimony pentachloride, Diantimony pentoxide
May 2017 – May 2019	612	"antimon"	

Approximately 2500 publications were identified from 1990 to May 2017. Supplemental searching of more recent literature identified approximately 600 additional papers published from May 2017 to May 2019. Papers

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were sorted by date, the Sb substance evaluated, and characterization of the toxicological endpoints evaluated. Of the total 3100 candidate papers for evaluation, approximately one half merited more in-depth evaluation (although not all were used in CSR preparation).

Tables 2, 3 and 4 below provide an overview of the Klimisch score 1 or 2 lung toxicity and carcinogenicity data that is available for the ten Sb substances registered under REACH. Typical effects reported are pneumoconiosis or stibiosis (synonyms[2]) without significant progressive pathological changes (e.g. fibrosis) in humans; and inflammation, fibrosis and cancer in rodents.

Table 2: Overview of Sb-related observations on lung toxicity in humans.

Cohort Studied	Results	Remarks	Reference
51 males (aged of 31 – 54) employed in a smelter and exposed to dust containing predominantly Sb trioxide with small amounts (2.1 – 7.8%) of Sb pentoxide. As co-exposure documented. Duration of employment was from 9-31 years. All workers exhibited symptoms of pneumoconiosis.	X-rays confirmation small, dense, roundish or polygonal opacities typical of pneumoconiosis in the majority of workers but little evidence for fibrosis. Clinical respiratory symptoms observed included permanent or periodic breathlessness in effort, coughing and wheezing Pulmonary function tests showed obstructive changes that were mild in most cases.	2 (reliable with restrictions)	Potkonjak V., Pavlovich M. (1983b) **KEY STUDY**
274 men at an Sb processing plant with exposure to Sb trisulfide, Sb trioxide, process slags	X-ray examination revealed simple pneumoconiosis in 97 workers. No clinically significant changes in lung function tests.	2 (reliable with restrictions)	McCallum RI (1967) **KEY STUDY**

Several long-term historical occupational inhalation exposures to Sb compounds have been associated with impairments of lung function resulting from chronic inflammation and fibrosis. Two studies of relatively good quality (Table 2), and other studies of lower quality (summarized in the CSRs) document such effects in Sb-exposed workers. In general, however, the pneumoconiosis observed in workers tends to be benign with only little evidence of pathological changes (e.g. fibrosis) that would indicate progressive reactivity of the Sb burden in the lungs of workers.

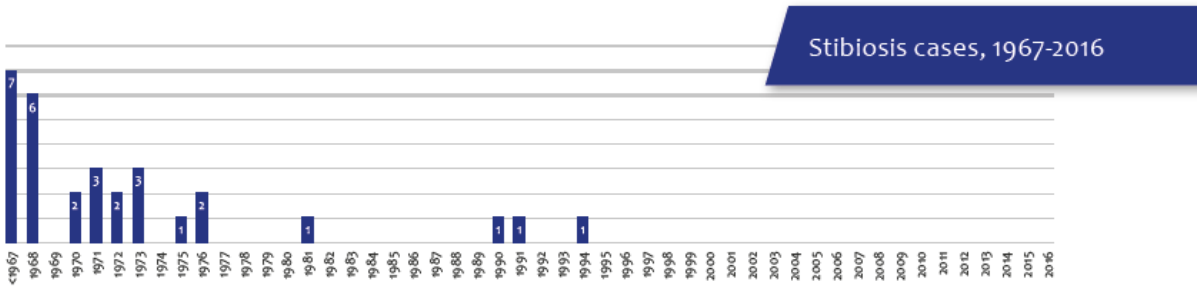

Figure 1. Decrease in pneumoconiosis/stibiosis cases at an Sb trioxide production facility following the implementation of the OEL

[2] Pneumoconiosis is the term for lung diseases caused by inhalation of mineral or inorganic dust. When it is associated with inhalation of Sb dusts, it is called stibiosis.

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Studies confirm the historical incidence of pneumoconiosis in workers employed at Sb processing facilities, with an exposure exceeding the current Occupational Exposure Limit of 0.5 mg/m^3 by a factor of 10 or more. This is consistent with medical surveillance data reported to the International Antimony Association by its membership and with the decrease of the incidence of pneumoconiosis at an Sb trioxide production facility after the implementation of OELs (Figure 1).

Table 3: Summary of epidemiology studies workers of occupationally exposed to Sb trioxide.

Cohort	Results	Remarks	Reference
Prospective cancer mortality study of 1420 men employed at an Sb smelter which converted to Sb trioxide production in 1973. Selection criteria entailed 3 months of employment between 1961 and 1992	Elevated lung cancer risk (37 observed vs. 23.9 expected). Lung cancer excess (32 cases) confined to workers with employment history prior to 1961. Significant exposures to arsenic and lead were present until the early 1970s, precluding assumptions of causality between Sb exposure and lung cancer. No data on cigarette smoking rates	2 (reliable with restrictions)	Jones, R.D. (1994) **KEY STUDY**
Mortality study of 1014 men employed at an Sb smelter between 1937 and 1971. Worker population was largely Hispanic and an appropriate referent group was difficult to assemble. Occupational exposures included Sb ores, metal and Sb trioxide.	Elevated incidence of lung cancer (SMR 1.39) when it was assumed that Hispanics have a lower incidence of smoking. Pneumoconiosis also elevated (SMR 1.22) but ethnic specific rates were not available for comparison. Significant co-exposure to known lung carcinogens such as arsenic precludes attribution of health risk to Sb. No data available on cigarette smoking rates.	2 (reliable with restrictions)	Schnorr et al., 1995
Mortality study of 1,462 male workers employed at a tin smelter over an employment period of 1937 - 2001	Elevated risk of lung cancer in the overall smelter population. However, co-exposures to lead, arsenic and cadmium were documented in air sampling conducted from 1972 – 1991. Personal exposure measurements for exposure to Sb trioxide not available for lung cancer cases– air samples from different process areas indicated relatively low Sb (presumable Sb trioxide) levels in occupational aerosols ranging from 0.01 to 0.11 mg/m^3. Median exposure prior to 1972 estimated at 0.63 mg/m^3. No control for smoking or other lifestyle confounders. Attribution of lung cancer to Sb exposure not possible.	2 (reliable with restrictions)	Jones et al., 2007 **KEY STUDY**
Cohort mortality study of 5498 men (employed 1950 – 1982) of whom 887 were identified as glassblowers with potential exposure to Sb trioxide as well as metals such as arsenic, cadmium, chromium and lead.	Employment as a glassblower was associated with moderate increases in total cancer, stomach cancer (OR=2.6), colon cancer (OR=3.1), lung cancer (OR=2.3) and cardiovascular disease (OR=1.3). Metal exposures were estimated from job titles – no measured values of exposure were available. Sb exposure was said to be associated with a modest increase in stomach and colon cancer but no data were presented to confirm this or to ascertain the impacts of co-exposures to known human carcinogens.	3 (not reliable)	Wingren and Axelson, 1987
Health study of 360 male coke oven workers exposed to polycyclic aromatic hydrocarbons and multiple different metals,	360 male coke oven workers (238 controls and 122 exposed) aged 20 – 60 years) at a steel foundry. 23 urinary metals were monitored and compared to urinary metabolites of carcinogenic and noncarcinogenic polycyclic aromatic hydrocarbons, DNA strand breaks (Comet assay on lymphocytes), oxidative stress (urinary 8-hydroxydeoxyguanosine excretion, heart rate variability, microRNA expression and micronucleus induction. Urinary Sb was higher in controls then in exposed subjects and was not associated with any health endpoints assessed except for enhanced expression of microRNAs associated with the metabolism of	2 (reliable with restrictions)	Deng et al., 2019

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Cohort	Results	Remarks	Reference
	carcinogenic PAHs. This could indicate Sb enhances PAH metabolism although effects of co-exposures cannot be precluded.		
A prospective study of the "Sister Cohort", 50,884 cancer-free woman (aged 35 – 74) studied 2003 – 2009 who had a sister with breast cancer.	Essentially an ecological epidemiology study, breast cancer incidence was related to a census tract level data base of air pollution established by the United States Environmental Protection Agency (National Air Toxics Assessment data base containing estimates of air exposure for Sb, As, Cd, Cr, Co, Pb, Mn, Hg, Ni and Se. Exposure quintiles were established for each metal and compared to 2,587 breast cancer cases diagnosed during the study period. No consistent or significant association with Sb was observed.	2 (reliable with restrictions)	White et al, 2019

Although epidemiology studies in smelter environments (Jones et al., 1994; Schnorr et al., 1995 and Jones et al., 2007) have reported small increases in lung cancer in workers occupationally exposed to Sb trioxide (Table 3), attribution to Sb compounds has not been possible due to significant levels of co-exposure to known lung carcinogens such as arsenic and cadmium. An older study of glassblowers suggested an association with colon and stomach cancer (Wingren and Axelson, 1987) but measurements of Sb exposure were not available and the association with the cancer data not presented. An ecological study of breast cancer incidence in the United States (White et al., 2019) failed to find an association with airborne Sb levels (although exposure levels were low). Finally, Deng et al (2019) observed no impacts upon early biomarkers of potential health effects (e.g. the Comet Assay) except for altered expression of microRNAs associated with the metabolism of polycyclic aromatic hydrocarbons. Urinary Sb levels served as the index of exposure and, curiously enough, was higher in the non-exposed controls. No consistent association between cancer incidence and Sb exposure is evident in these studies.

Table 4: Overview of inhalation exposure impacts upon experimental animals.

Method	Results	Remarks	Reference
Rat (Fischer 344) male and female exposed (65/sex/group) 6 h per day, days per week for 52 weeks to 0.0, 0.055, 0.511 or 4.50 mg/m^3 Sb trioxide followed by 12 months of observation. MMAD of particles was 3.76 microns.	Interstitial inflammation, fibrosis and granulomas in treated animals and controls. No induced benign or malignant tumors observed. Evidence of particle overload being attained at highest dose tested. LOAEC of 4.5 mg/m^3 based upon 80% inhibition of particle clearance. NOAEC of 0.51 mg/m^3 based upon diminished clearance impacts.	2 (reliable with restrictions)	Newton et al., (1994) **KEY STUDY**
Rat (Wistar) male and female exposed in groups of 90 /sex/substance to 45.0 mg/m^3 Sb2O3 (MMAD 2.8 microns) or 36.0 mg/m^3 Sb ore (MMAD 4.78 microns) for up to 52 weeks. (7 h/d and 5 d/wk) and then held for observation. Purity of Sb203 only 80% with significant lead and arsenic contamination.	Lung tumors in 25% of female rats exposed to Sb2O3 and 27% of female rats exposed to ore. No lung tumors in exposed males or controls. Lung pathology showed interstitial fibrosis hyperplasia and metaplasia in response to treatment	2 (reliable with restrictions)	Groth et al., (1986)
Groups of 20 female CDF rats exposed to 0, 1.9 and 5.0 mg/m^3 Sb2O3 6 h/day, 5 days /week for one year followed by one year of observation. MMAD of 5.06 microns	Focal fibrosis at 3 months in high dose group that increased with exposure duration. Evident in the low dose group at 12 months. No malignant lung tumors in controls or low dose group but scirrhous carcinoma of the lung found in 9 out of 18 high dose rats and squamous cell carcinomas in 2 out of 18 animals.	2 (reliable with restriction	Watt (1983)
Rats (Wistar Han) male and female exposed in groups of 60 per sex per treatment concentration to Sb trioxide	Reduced body weight gain and survival at all treatment levels indicating MTD approached or exceeded. Dose dependent increase in benign and	1 (reliable without restriction)	NTP (2017) **KEY STUDY**

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Method	Results	Remarks	Reference
(MMAD 0.9 – 1.5 microns) at concentrations of 0, 3, 10 and 30 mg/m^3 6 h per day, 5 days per week for up to two years.	malignant lung tumors and adrenal pheochromocytomas in both sexes. Significant lung inflammation and fibrosis accompanied by abnormal breathing and cyanosis indicative of hypoxia		
Mice (B6C3F1) male and female exposed in groups of 60 per sex per treatment concentration to Sb trioxide (MMAD 0.9 – 1.5 microns) at concentrations of 0, 3, 10 and 30 mg/m^3 6 h per day, 5 days per week for up to two years.	Reduced body weight gain and survival at all treatment levels indicating MTD approached or exceeded. Dose dependent increase in benign and malignant lung tumors in both sexes. Dose dependent lymphoma increase (predominately B cell) especially in female mice. Benign and malignant skin neoplasms also observed. Significant lung inflammation, fibrosis and abnormal breathing.	1 (reliable without restriction)	NTP (2017) **KEY STUDY**

Animal studies (Table 4) using exposures of sufficient duration and respirable particle aerosols with a small size facilitating penetration to the deep lung (< 4 µm) confirmed that Sb trioxide can have toxic impacts upon the lung. This affirmation needs to be placed within the appropriate context regarding workers exposed in industrial facilities since the occupational aerosols possess a larger particle size distribution (Hughson, 2005) with larger particles (the inhalable fraction) that preferentially deposit in the nose, throat and upper airways. The total mass of the respirable fraction is, on average, only about one third the mass of inhalable fraction.

Animal inhalation studies are thus designed to maximize the likelihood of damage to tissues of the deep lung. Although three initial experimental inhalation studies deviate from standard protocols (one year of exposure opposed to the two years specified by most cancer bioassay guidelines), it has been demonstrated that Sb trioxide could impair particle lung clearance. More recently, a two-year cancer bioassay (NTP, 2017) reported evidence of a relationship between exposure to respirable Sb trioxide and lung tumors in the mouse and, to a lesser extent, the rat.

Table 5: Overview of lung toxicity and carcinogenicity data available for Sb substances considered for grouping and read-across for lung toxicity and carcinogenicity endpoints (only Klimisch 1 or 2 studies).

Name	CAS #	Human		Rodent	
		Workplace observations	Epidemiology studies	Rat	Mice
Sb metal					
Sb –powder	7440-36-0		x		
Sb – massive	7440-36-0				
Trivalent Sb compounds					
Diantimony trioxide	1309-64-4	x, x	x, x, x	x, x, x, x	x
Antimony sulfide	1345-04-6	x	x		
Antimony tris(ethylene glycolate)	29736-75-2				
Antimony trichloride	10025-91-9				
Pentavalent Sb compounds					
Sodium hexahydroxoantimonate	33908-66-6				
Sodium antimonate	15432-85-6				
Antimony pentachloride	7647-18-9				
Antimony pentoxide	1314-60-9				
Potassium hexahydroxoantimonate	12208-13-8				

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Table 5 above presents an overview of the available lung and carcinogenicity toxicity studies per Sb substance. The table shows that evidence is only available for Sb metal, Sb trioxide, and Sb trisulfide. There is no information on the potential to cause lung toxicity or cancer for any other Sb substance. While all studies have reported some degree of lung toxicity, only one reports clear evidence of cancer (in mice). Evidence in rats is either less clear or may be attributable to a pulmonary overload response.

2.3 Weight of evidence analysis of the lung toxicity and carcinogenicity potential of Sb substances

This section covers step 3) integration and weighing of evidence (weight of evidence analysis of the weight of evidence approach.

In order to assess the potential lung toxicity and carcinogenicity of Sb substances, it is important to carefully define the nature of the effects which have been reported and try to understand the mechanism(s) by which Sb compounds may damage the lung, and the chemical species involved in the induction of such a response.

Lung toxicity

The historical medical surveillance literature, documenting the impacts of inhalation exposure to Sb trioxide in occupational setting, is concordant with the animal studies in that impairments of pulmonary function (e.g. spirometry deficits and radiographic indications of mild pulmonary damage) were associated with occupational exposures experienced prior to the adoption of modern OELs (McCallum, 1967; Potkonjak and Pavlovich, 1983). Although the pulmonary changes associated with occupational exposures were much less severe than those evident in rats and mice, they confirm that the human lung can be adversely impacted by inhalation exposure to Sb trioxide and ore materials containing Sb trisulfide (stibnite). **The combined animal and human exposure data support a STOT RE classification for impacts upon the lung after repeated inhalation exposure to Sb trioxide and Sb trisulfide.**

STOT RE classifications are further assigned either category 1 or category 2 (ECHA, 2017). Category 1 classifications are indicative of high potency for the product of significant to severe health effects whereas a category 2 classification indicates moderate potency to induce significant health effects. Although the ECHA Classification and Labelling guidance indicates that Category 1 designations are often indicated when there is "good quality evidence from human case or epidemiology studies", it is further noted that "*In exceptional cases human evidence can also be used to place a substance in Category 2*" (ECHA, 2017). Category assignment of a STOT RE substance thus entails a weight of evidence analysis that results in a classification which accurately conveys both the potency of the substance and the severity of the health effects observed.

STOT RE Category 1 designations are triggered by the observation of significant or severe impacts in rats at aerosol concentrations less than 0.02 mg/liter/6h/day (20 mg/m^3) in a 90-day exposure study, whereas category 2 is indicated for effects induced between 0.02 and 0.2 mg/liter/6r/day (20 – 200 mg/m^3). These values are not intended as strict demarcation points but as general guidance to be used in conjunction with expert judgement. Adjustment of these values in accordance with Haber's rule is also suggested – thus the demarcation value of 20 mg/m^3 would be reduced by a factor of at least 4 (to < 5 mg/m^3) in comparing results of a 90-day study and to those from a 1 – 2-year inhalation study.

The comprehensive two-year inhalation studies of NTP (2017) observed a LOAEL for pulmonary impacts of 3 mg/m^3, just below the Haber's law adjusted Category 1 demarcation value. However, the NTP (2017) studies

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utilized experimentally generated respirable Sb trioxide aerosols capable of deep lung penetration and deposition. Studies of real-world occupational aerosols indicate that their particle size distribution has a relatively low content of respirable particles. On average, for exposed humans, inhalable aerosols capable of yielding pulmonary deposition fractions comparable to those produced by experimentally generated Sb trioxide aerosols used in rodent inhalation studies would require a 5-fold higher concentration of Sb trioxide in air (Hughson, 2005; Vetter, 2018).

Using the Multiple-Path Particle Dosimetry Model (v. 3.01) described by Ashgarian and Price (2009), one can further compare the pulmonary deposition of the experimental aerosols used by NTP (2017), with those of the real-world occupational Sb trioxide aerosols measured by Hughson (2005). Whereas the NTP aerosols (MMAD 1.2 µm +/- 1.9 GSD) would yield a pulmonary deposition rate in rats of 7.6%, the average particle size distribution of the aerosols sampled by Hughson (2005), as calculated by Vetter (2018) had an MMAD of 17.2 µm with a GSD of 2.7. This would yield a pulmonary deposition rate in the rat of 0.3%. In terms of potency for the rat, a real-world Sb trioxide occupational aerosol of 75 mg/m^3 would be required to produce the pulmonary impacts observed by NTP (2017) at their airborne LOAEL of 3 mg/m^3. This total aerosol Sb trioxide concentration is significantly above the 5 mg/m^3 demarcation point for chronic exposure potency in establishing category 1 vs. category 2 in STOT RE inhalation classifications.

Granulometry studies are described in the CSRs for Sb metal powder and Sb trisulfide, and predict the characteristics of the aerosols each would produce. Sb metal powder would be expected to generate an occupational aerosol with an MMAD of 19.05 µm +/- 2.75 GSD. A bimodal distribution is predicted for Sb trisulfide aerosols with 11% of the particle mass having an MMAD of 2.69 µm +/- 2.38 GSD, and 88.7% of the aerosol mass with a MMAD of 28.48 µm +/- 1.56 GSD). MPPD modelling predicts that pulmonary deposition rates of 0.05% and 0.22% would result from aerosols of Sb metal powder and Sb trisulfide, respectively. Pulmonary deposition rates equivalent to those for rats exposed to 3 mg/m^3 of Sb trioxide in the NTP studies would thus require Sb metal powder aerosols of approximately 100 mg/m^3 and Sb trisulfide aerosols of 450 mg/m^3. Real-world aerosols of Sb trioxide, Sb trisulfide and Sb metal powder would be judged to have a moderate to low potency as pulmonary toxicants when viewed from the perspective of deposition rates in the lung regions that are the targets for pulmonary toxicity.

Historical exposures capable of producing human pulmonary impacts after years of chronic exposure, although not precisely defined, were most likely in significant excess of 10 mg/m^3 (ECHA, 2008). The historical exposure levels associated with changes to lung pathology and function confirm that Sb trioxide has only moderate potency for inducing pulmonary impacts in humans. The nature of the pulmonary alterations associated with exposure of humans to Sb trioxide provides further indications that Sb trioxide has only moderate potency as a pulmonary toxicant.

Inhalation of Sb trioxide by rats and mice produced severe impairment of both pulmonary structure and function (NTP, 2017). The severity of the impacts in rodents, contrasts with the observed impacts in humans. Although impacts upon human lung function are judged as clinically significant, the pulmonary function impacts observed are generally mild. The underlying alterations to human lung tissue that mediate these modest functional changes are in turn associated with comparatively modest inflammatory responses and rather benign and generally non-progressive fibrotic changes.

The concentrations of Sb trioxide associated with pulmonary toxicity in both humans and rodents indicate moderate potency that is consistent with a STOT RE category 2 classification. The relatively benign and non-progressive nature of the structural alterations documented in workers with high-level historical occupational exposures similarly indicates relatively mild potency consistent with STOT RE category 2 classification for lung toxicity from inhalation exposure. **Modelling of the alveolar deposition fractions predicted for rats exposed to aerosols of Sb metal powder and Sb trisulfide further indicates that the**

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potency of these substances could be lower than Sb trioxide and thus also consistent with a category 2 STOT RE classification.

(Lung) carcinogenicity

As just noted, chronic inhalation of Sb trioxide by rats and mice can produce damage to the lungs characterized by the progressive development of pulmonary inflammation, tissue damage and fibrotic changes. These dose-dependent changes, at sufficiently high exposures, can produce significant impairment of pulmonary function and severe systemic hypoxia that induces adaptive physiological changes (e.g. erythroid hyperplasia).

Activation and alteration of oncogenes

NTPs (2017) analysis of mouse and rat lung tumors extended to an evaluation of oncogene alterations associated with tumor formation. The presence of activated oncogenes in tumors is informative but can be the result of a myriad of direct and indirect processes. Focusing on the mouse lung tumors, which were observed with far higher frequency, permits more robust analysis of the "molecular pathology" responsible for activated oncogenes in spontaneous and induced neoplasms. Spontaneous lung tumors were found to contain altered Kras genes with the activating mutations generally mapping to established "hot spots" (i.e. G to A transitions in codon 12). Altered Kras oncogenes were detected in 43% of the tumors observed in Sb trioxide treated animals. NTP notes that tumors in Sb trioxide treated animals possessed base sequence changes in hot spots similar to those observed in spontaneous tumors, and suggests that the Kras altered genes observed in the tumors of Sb trioxide treated animals were the result of spontaneous lesions, permitted to undergo clonal expansion by the pulmonary toxicity of Sb trioxide. This suggestion is consistent with the observation that spontaneous activated oncogenes are now known to be present in the normal tissues of animals used in cancer bioassays (Parsons *et al.*, 2009), exhibiting both tissue and animal strain specificity with respect to the prevalence of different activated oncogenes.

In addition to Kras alterations, 46% of lung tumors in Sb trioxide treated mice were observed to contain altered Egfr oncogenes. The high prevalence of tumors with Egfr alterations in exposed animals could be interpreted as evidence of mutagenic oncogene alterations induced by Sb trioxide. However, the origin of Egfr alterations is potentially more complex than is described. In humans, lung cancer tumors are increased in subjects with disease syndromes (e.g. chronic obstructive pulmonary disease) that impair lung function and lead to hypoxic conditions. Signaling pathways involving EGFR appear to play a role in the growth of such tumors under hypoxic condition (Karoor *et al.*, 2012). Egfr alterations are further linked to the ability of cancer cells to survive in hypoxic microenvironments (Murakami et al., 2014). The prevalence of Egfr alterations in Sb trioxide treated animals may thus be a result of selection for tumors capable of undergoing rapid clonal expansion, under the hypoxic conditions associated with the pulmonary toxicity produced by Sb trioxide. The activated Egfr oncogenes may thus be spontaneous in origin or produced by a variety of indirect processes during tumor progression (e.g. ROS generation, error prone DNA repair) with an increased prevalence in tumors that is more indicative of the conditions that permitted clonal expansion of neoplastic lesions. The mere observation of an activated oncogene in a tumor, in and of itself, confers little information that permits determination of the mechanism(s) that may have produced it.

These oncogene structural alterations do not represent the only potential means by which Sb trioxide might influence the expression of oncogenes or other cellular constituents. The electrophilic nature of Sb is such that binding to a variety of cellular macromolecules occurs (Verdugo et al., 2017) and could facilitate neoplastic development. For example, although Sb has not been linked to prostate cancer, Sb 3+ ions will activate signaling pathways that stabilizes the c-myc oncogene that stimulates cell proliferation (Zhang et al., 2018).

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Whereas NTP suggests that many of the lung tumors in mice originate from cells with spontaneous Kras oncogene activation that are permitted to undergo clonal expansion in response to the pulmonary toxicity induced by Sb trioxide, mouse lung tumors with Egfr lesions may similarly reflect selection for, and clonal expansion of, cells with enhanced proliferative capacity under hypoxic conditions. It is not possible to ascertain whether Egfr alterations are spontaneous or induced. The etiology of Kras and Egfr oncogene alterations observed in lung tumors merits investigation to determine if they are pre-existing spontaneous lesions, lesions induced by Sb via indirect mechanisms of genotoxicity and/or lesions selected for clonal expansion as a consequence of pulmonary toxicity and hypoxia.

Body weight suppression

The impacts of Sb trioxide exposure upon the overall health status of rats and mice should not be neglected, and may explain other adverse effects observed in the NTP studies. Exposure of rats to 3, 10 or 30 mg/m³ Sb trioxide was associated with end of study body weight suppression of 7, 8 and 20% in male rats; and 10, 20 and 28% in female rats, respectively. Corresponding body weight suppression in male mice was 8, 11 and 25%; and 3, 8 and 21% in female mice. Much of the data generated by the NTP bioassays reflects effects near, or in excess of, the maximum tolerated dose for Sb trioxide. This conclusion is bolstered by the observations of labored breathing, hypoxia and premature mortality due to pulmonary inflammation in exposed animals. These observations do not negate the induction of pulmonary lesions, but indicate that care must be exercised in the interpretation of systemic effects that might be associated with inhalation exposure to Sb trioxide.

Pheochromocytomas

Adrenal gland neoplasms (pheochromocytomas) lesions are expected to develop under conditions of pulmonary inflammation and hypoxia. As reviewed by Greim *et al.* (2009), the association of this adrenal lesion with pulmonary impairment is sufficiently robust that, within the context of the EU REACH process, pheochromocytomas secondary to pulmonary impairment are not considered as relevant for cancer classification or risk assessment. The adrenal lesions are a response to pulmonary damage induced by Sb trioxide and not a direct substance-specific effect of Sb trioxide. Indeed, they can be interpreted as confirmation that maximum tolerated doses have been exceeded in the rat.

Lymphomas

Sb trioxide exposures in mice were also associated with an increase in lymphomas. Interpretation of increased lymphoma incidence in female mice poses diagnostic challenges that were not addressed by NTP's histopathological analysis. Whereas lymphomas induced by chemicals are usually T cell in origin (Ward, 2005), those associated with Sb trioxide exposure were predominantly B-cell or mixed B- and T-cell in origin, and many appeared to be reactive lesions responding to Sb trioxide lung toxicity. Mouse B-cell lymphomas are further difficult to interpret due to their high spontaneous incidence and complex etiology that likely includes endogenous retrovirus activity. In NTP inhalation studies, the average historical control incidence of lymphomas in B6C3F1 female mice is 25.2% (range 14 – 36%). Thus, lymphoma incidence at 10 and 30 mg/m³ Sb trioxide, but not 3 mg/m³, was significantly elevated over historical controls. The complex and diverse mechanisms for B-cell lymphoma induction have prompted the development of histopathological diagnosis and classification strategies to distinguish between spontaneous and induced lesions (Ward, 2005). Unfortunately, none of these diagnostic criteria were applied in the NTP study. Based upon the limited data provided, the excess lymphomas associated with Sb trioxide exposure appear to be similar to the naturally occurring spontaneous lesions in the B6C3F1 mouse; it can be plausibly postulated that the chronic inflammation and hypoxic conditions in the Sb trioxide exposed lung produced adaptive responses in the lung and spleen that promoted the development of what is already a high incidence spontaneous neoplasm in the

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female mouse. As such, the increased incidence of lymphomas would not provide clear evidence of carcinogenicity.

Skin lesions

Neoplastic skin lesions were also observed in mice exposed to Sb trioxide and different types of skin lesions were pooled to yield statistical significance. Given the high-level whole-body inhalation exposures employed by NTP, the appearance of histiocytomas (a benign skin lesion) is mostly likely an immunological response, as opposed to neoplastic response, and not a precursor lesion to fibrosarcoma (malignant tumors of fibrous tissues). Histiocytomas are not generally known to be precursor lesions to fibrosarcoma and there appears to be no legitimate scientific rationale to support data pooling. The observation of two squamous cell carcinomas in Sb trioxide treated female mice is unusual but is similarly difficult to interpret in the absence of preneoplastic precursor lesions. Moreover, no other study has suggested skin as a target organ for Sb trioxide carcinogenesis. There is no legitimate scientific rationale to support that skin tumors are induced by Sb trioxide.

Lung cancer

According to the experimental studies, Sb compounds might pose a carcinogenic risk to the lungs of rats through particle overload (Newton et al., 1994; Schroeder, 2003). Rat's lungs do not have the capacity to remove excessive quantity of respirable particle and this triggers a cascade of inflammatory responses leading to a tumor formation, resulting from the accumulation of inert particles. This response to inflammation from particle overload is not observed in mice or humans. There is no statistically significant increase in rat lung tumors at Sb trioxide concentrations (3 mg/m3) that do not produce pulmonary overload. Rat lung tumor incidence at higher exposure levels is low, lacking in dose-response and most likely the result of pulmonary overload. As such, the rat pulmonary lesions are not reflective of human risk. Therefore, rat lung tumors, if induced by particle overload, would be of questionable significance for hazard classification or risk assessment.

NTP (2017) concluded that overload did not occur in rats at an Sb trioxide exposure of 3 mg/m³ and therefore that pulmonary overload is not required for the induction of lung neoplasms in the rat lung. The rationale for this conclusion is tenuous in that 3 mg/m³ is indeed associated with impaired clearance in the rat in the NTP studies – the departure from modeled clearance rates is just not sufficient to attain the lung burden levels that meet an arbitrary criterion for overload. Moreover, significant impairment of clearance has been reported at levels much lower than those used in the NTP studies (e.g. Newton *et al.*, 1994). Finally, the incidence of lung neoplasms in both male and female rats is not statistically elevated over that in controls at 3 mg/m³ Sb trioxide exposures. The lack of both overload and a carcinogenic response in the rat at 3 mg/m³ Sb trioxide cannot be taken as an indication that tumors produced in the rat lung at higher levels of exposure were not the result of the pulmonary overload. Particle overload and the subsequent cascade of inflammatory responses leading to a tumor formation can be retained as a possible mode of action for lung cancer in rats, but would be of questionable relevance for hazard classification or risk assessment.

As discussed in the scientific opinion on genotoxicity, any Sb genotoxicity that might facilitate neoplastic development is likely mediated by indirect mechanisms, such as induction of oxidative stress or interference with DNA repair processes. The available data do not permit discrimination between alternative mechanisms, nor do the mechanisms need to be mutually exclusive, but there is relatively high confidence that the lung carcinogenicity is not a result of direct genotoxicity of Sb. Excess tumors observed may reflect the clonal expansion of pre-existing preneoplastic cells with activated oncogenes in the absence of genotoxicity (direct or indirect). If lesions are induced, it is most likely via a local indirect genotoxic mode of action. The most probable indirect modes of action (e.g. overload in the rat, inflammation and ROS generation in the mouse)

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would be expected to exhibit effect thresholds that produce neoplastic response only above a given level of inhalation exposure.

Sb trioxide appears to induce cancer at tissue sites (adrenal, lymphoma and skin) that are likely side-effects of pulmonary toxicity or the irritant properties of Sb trioxide. These lesions are not relevant to an evaluation of the carcinogenic properties of Sb trioxide. **The primary target organ of inhaled Sb substances appears to be the lung, and mode of action considerations should look at local effects in the lung rather than systemic effects. The inhalation exposure route is the only route of exposure relevant for the assessment of carcinogenicity properties.** Exposure route specificity (the lung by inhalation exposure) is further evidenced by lack of pulmonary changes after sub-chronic oral exposures to high doses of Sb trioxide (Hext et al., 1999) and high sub-chronic i.p. dosing with the Sb (III) potassium tartrate (Dieter, 1992).

Data from experimental animal studies do not yield compelling evidence of cancer risk at exposure levels, or via mechanisms, that are likely to be relevant to present occupational or consumer exposure scenarios. Epidemiological studies have failed to demonstrate elevated cancer risk that can be attributed to Sb trioxide exposure. **According to the ECHA Guidance on the Application of CLP criteria, the present evidence satisfies, and likely exceeds, that required for a Category 2 cancer via inhalation classification.** Indeed, according to the ECHA Guidance on the Application of the CLP Criteria (July 2017), suspected human carcinogens are those for which the evidence obtained from human and/or animal studies is not sufficiently convincing to place the substance in Category 1A or 1B, in particular, when e.g. the data suggest a carcinogenic effect but are limited for making a definitive evaluation because there are unresolved questions regarding the adequacy of the interpretation of the results of the studies. In light of the discussion presented above, there are clear interpretation issues which do not permit to conclude on a category 1 carcinogenicity, and rather suggest maintaining the current Category 2 cancer classification:

- Tumour background incidence - comparison of the tumour incidence with historical control tumour data. This can be particularly relevant for animal strains which have a propensity to develop a particular type of tumour spontaneously with variable and potentially high incidence. In such a case, the tumour incidence may not be providing reliable evidence of treatment related carcinogenicity;
- Routes of exposure - the classification shall take into consideration whether or not the substance is absorbed by a given route(s); or whether there are only local tumours at the site of administration for the tested route(s), and adequate testing by other major route(s) show lack of carcinogenicity. The hazard statement allows for identifying the route of exposure '*if it is conclusively proven that no other routes of exposure cause the hazard*' (CLP Annex I, Table 3.6.3). In this case the hazard statement may be modified accordingly;
- The possibility of a confounding effect of excessive toxicity at test doses. In lifetime bioassays, compounds are routinely tested using at least three dose levels, of which the highest dose needs to induce minimal toxicity, such as characterized by an approximately 10% reduction in body weight gain (maximal tolerated dose, MTD dose). The MTD is the highest dose of the test agent during the bioassay that can be predicted not to alter the animal's normal longevity from effects other than carcinogenicity. If a test compound is only found to be carcinogenic at the highest dose(s) used in a lifetime bioassay, and the characteristics associated with doses exceeding the MTD are present, this could be an indication of a confounding effect of excessive toxicity/excessive loading. This may support a classification of the test compound in Category 2 or no classification;
- Mode of action and its relevance for humans, such as cytotoxicity with growth stimulation, mitogenesis, immunosuppression, mutagenicity. The various international documents on carcinogen assessment all note that mode of action in and of itself, or consideration of comparative metabolism, should be evaluated on a case-by-case basis and are part of an analytic evaluative approach. One must look closely at any mode of action in animal experiments taking into consideration comparative toxicokinetics/toxicodynamics between the animal test species and humans to determine the

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relevance of the results to humans. The criteria for a Carcinogenicity Category 1B classification are not met due to the uncertain relevance of both rat and mouse lung tumors for humans.

2.4 Conclusion of the weight of evidence assessment of the lung toxicity and carcinogenicity potential of Sb substances

This section covers steps 4) application of levels of confidence, 5) uncertainty analysis, and 6) conclusion of the weight of evidence approach.

Based on the available evidence and the assessment of it made above, questions formulated in section 2.1 above can be answered as follows:

- **Is the available evidence sufficient to assess the lung toxicity and carcinogenicity potential of Sb substances?**
  Yes, although with a relatively medium level of confidence, due to the general lack of lung toxicity or carcinogenicity evidence on most Sb substances except Sb trioxide.

- **What indication does the available evidence provide as to the potential lung toxicity and carcinogenicity potential of Sb substances?**
  - The combined animal and human exposure data support a STOT RE 2 classification for impacts upon the lung after repeated inhalation exposure to Sb trioxide and Sb trisulfide.
  - The combined animal and human exposure data support a Carcinogenicity category 2 via inhalation classification for Sb trioxide.
  - The main uncertainty underpinning the above pertains to the mode of action related to the carcinogenicity, but the conclusion can be established (based on human exposure evidence), with a relatively high level of confidence.

- **What research would increase the confidence/reduce the uncertainty of the lung toxicity and carcinogenicity assessment of Sb substances?**
  - Determine whether the Kras and Egfr oncogene alterations observed in lung tumors are pre-existing spontaneous lesions, lesions induced by Sb via indirect mechanisms of genotoxicity, and/or lesions selected for clonal expansion as a consequence of pulmonary toxicity and hypoxia;
  - Clarify the (local) genotoxicity of Sb substances (cf. scientific opinion on genotoxicity);
  - Run one or more in vivo inhalation study to confirm the observations gathered so far.

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3. Assessment of lung toxicity and carcinogenicity applying a grouping/read-across approach

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ECHA's recommendation for documenting a read-across approach includes the following steps:

1) Properly identify and characterize the source and target substance(s)
2) Select of the most appropriate scenario to be used for the read-across assessment
3) Address each common assessment element (AE) of the selected scenario
4) Establish the read-across assessment based on the conclusions derived for all of the AEs

3.1 Identification and characterization of the source and target substance(s)

Metal and metalloid compounds are typically defined on the basis of the valence or oxidation state of the ion contained in the substance. In Table 6, the Sb substances and their corresponding CAS number are listed in order of valence state, namely 0, 3+ and 5+. The oxidation state (IUPAC Definition: the charge of the atom after ionic approximation of its heteronuclear bonds) will dictate the affinity and potential for interaction and chemical bonding of a given metal/metalloid substance with biological systems. As explained by Hashimoto et al. (2003), Zheng, Zhi and Chen (2006), and ATSDR (2017), Sb 3+ or 5+ will exhibit strong electrophilic characteristics, and be taken up as the (oxyan)ion after release from the parent compound due to hydrolysis of ionic bonds. ***Considering the specificity of interactions between a chemical and a cell, the differences in valence/ionic species may need to be considered for the purpose of read-across for lung toxicity and carcinogenicity evidence.***

Table 6 also provides information on the moiety (functional group) of each Sb substance that will normally influence the physico-chemical properties, and the bio-availability of the substance. The functional groups will dictate the ease with which Sb oxyanions are released from a substance and their residence time in the lung.

Given the essential or metabolite nature of the moieties, the anticipated local lung toxicity impact of these moieties, compared to the possible local lung impact of Sb, is expected to be negligible. The chemical nature of the ligand moiety may exert its own toxicity in rare cases, but this is the exception and not the rule, and particularly not for the moieties reported in Table 6. The notable exception to this generalization will be moieties (e.g. chlorides) which, when administered in pure or concentrated doses, will have corrosive or irritant properties that will disrupt essential functions such as food ingestion or breathing.

Except for Sb trichloride and Sb pentachloride, which are classified as STOT SE 3 due to the corrosive nature of their chloride moiety, ***the difference in moieties can be omitted for the purpose of read-across for lung toxicity and carcinogenicity evidence***. Sb chlorides likely merit separate consideration in read across. The trivalent form is supplied in the form of crystals, and the pentavalent form is supplied as a liquid. Although these are not respirable 'particles', their corrosive nature may cause respiratory irritation, which is why these chlorides already carry a harmonized STOT SE3 classification. This corrosive property differs from the lung toxicity carcinogenic effects and mode of action described for other Sb compounds in this document. The chlorides, or any other Sb compound with a moiety expressing such a distinct adverse in the lung, should hence be considered as a separate subgroup for the purpose of read-across.

As regards the molecular weight and structure of each substance, the information in Table 6 shows that there are no specific trends or patterns among the molecular weight or structure that can inform the read-across approach. ***Considering the specificity of interactions between a chemical and a cell however, the difference in molecular weight may need to be considered for the purpose of estimating dosimetry in read-across comparisons of lung toxicity evidence.***

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Impurities in Sb substances are commonly arsenic and lead (in the relevant speciation)[3], but typically in concentration levels below 0,1% or their respective Specific Concentration Limits (SCL)[4]. This means that the assessment and read-across of the toxicity hazard and effect of the Sb substance will be driven by the Sb, and **not** by the impurities in the substances; and that the various *pure* Sb substances do not need to be distinguished on the basis of their impurities for the purpose of read-across. Table 6 confirms that ***the impurity profile is relatively comparable across the various Sb substances, and that there is no reason to discriminate between these on the basis of (im)purity for purposes of read-across for lung toxicity and carcinogenicity evidence.***

Finally, the table provides information on the physical form (powder, particle size) of each Sb substance. The physical form, and particle size, is relevant to the consideration of the exposure routes through which the various Sb substances may enter the body under realistic use conditions. Lung toxicity and carcinogenicity would require the inhalation of a relatively large amount of a given substance, able to yield deep lung deposition where inflammatory responses will typically take place. In this context, the inhalation route offers the main physiological entry point for Sb substances into the respiratory system; physical forms (and sizes) that can be inhaled are those of relevance to lung toxicity and carcinogenicity.

The lung toxicity and carcinogenicity evidence further show that toxicity is triggered in the deep lung, only accessible to *respirable* particles at or below 4µm. However, because the actual cascade of events leading to the lung toxicity remains to be clarified, it is recommended to consider *inhalable* particles, rather than retain respirable ones only. ***Only the Sb substances with particle sizes of 100 µm or below can be inhaled; thus only Sb metal powder, Sb trioxide, Sb trisulphide, Sb pentoxide and Sodium hexahydroxoantimonate merit attention for the purpose of lung toxicity and carcinogenicity assessment***. This will be further informed by the planned genotoxicity research (cf. scientific opinion on genotoxicity).

As a general principle, the fact that a substance is inhalable or respirable however, does not imply it can then accumulate in and damage the lung. It would need to be insoluble too. Even if the substance is able to reach the alveoli of the deep lung, it may express no (cyto)toxic or carcinogenic effects if the rate of dissolution and bioavailability preclude its accumulation in the deep lung. Assessment of each Sb compound for its ability to yield deposition and persistence in the deep lung is key to the hypothesized mode of action for both toxicity and carcinogenicity.

The content of Table 6 shows that physical form, possibly followed by valency and molecular weight, are the main parameters to be considered for the purpose of reading across lung toxicity and carcinogenicity evidence across Sb substances.

[3] Because of the geological affinity there is between the Sb, As and Pb in the predominant natural source of Sb (stibnite), As and Pb will typically be present as impurities in any Sb substance. Indeed, even following the transformation of stibnite into Sb "metal", and then into subsequent Sb compounds, these impurities will remain, albeit in controlled quantities. In Sb metal, the impurities will be present in metallic form whereas in e.g. Sb oxides or sulfides, they will be present in oxidic or sulfidic form, respectively.

[4] For carcinogens category 1A such as As oxides or acid the cut-off level is 0.1 %. For reprotoxicants category 1A such as Pb oxides the cut-off is 2.5 %, for Pb metal massive the SCL is 0.3 %, and for Pb metal powder the SCL is 0.03%.

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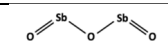
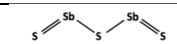
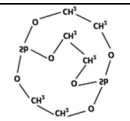
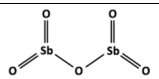
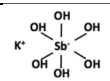
Table 6: Identity, characterization and structural (dis)similarity of Sb substances considered for grouping and read-across.

Name	CAS #	Form and typical particle size	Molecular weight (g/mol)	Chemical formula	Structure	Moiety	Purity (% w/w)	Impurities
"Metallic" Sb								
Sb – powder	7440-36-0	Powder (< 1 mm)	121.76	Sb	Sb	--	>89.45 - <100	As: <2.5 Pb: <9
Sb – massive	7440-36-0	Massive (> 1 mm)[3]	121.76	Sb	Sb	--		
Trivalent Sb substances								
Diantimony trioxide	1309-64-4	Powder 0.2-0.44 µm	291.5	Sb_2O_3		--	>97 - <100	As_2O_3: <0.1 PbO: <2.5
Antimony sulfide	1345-04-6	Powder D_{50}: 32.7 µm	339.7	Sb_2S_3		SO_4^{2-}		
Antimony tris(ethylene glycolate)	29736-75-2	Crystal D_{50}: 1600 µm	495.7	$Sb_2(C_2H_4O_2)_3$		$(C_2H_4O_2)^{2-}$	>99	n.s. [2]
Antimony trichloride	10025-91-9	Crystal D_{50}: 897 µm	190.7	$SbCl_3$		Cl^-	>99	n.s. [2]
Pentavalent Sb substances								
Sodium hexahydroxoantimonate	33908-66-6	Powder MMAD: 26.2 µm[1]	246.8	$Na(Sb)(OH)_6$		Na^+	>94.8 – <99.75	PbO: <2.5
Sodium antimonate	15432-85-6	Powder/Crystals: 1-180 µm	192.7	$NaSbO_3$		Na^+	>95 – <99.9	n.s. [2]
Antimony pentachloride	7647-18-9	Liquid	299,02	$SbCl_5$		Cl^-	>98	$SbCl_3$: <1 As: <0.1 Pb: <0.1
Antimony pentoxide	1314-60-9	Powder/colloidal suspension D_{50}: 24.4 µm	323.5	Sb_2O_5		--	>87 - <99.9	As_2O_3: <0.1 PbO: <0.25
Potassium hexahydroxoantimonate	12208-13-8	Crystal	262.9	$K(Sb)(OH)_6$		K^+	> 94 - < 97	n.s. [2]

[1] Mass Median Aerodynamic Diameter; [2] Non-specified impurities for which the individual composition does not exceed 0.1% and/or which are not classified; [3] Cf. Guidance on the Application of the CLP Criteria Version 5.0 – July 2017, page 600, Section IV.5.5 Particle size and surface area.

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3.2 Selection of the most appropriate scenario to be used for the read-across assessment

As lung toxicity and carcinogenicity information is available from more than one source substance, and used for more than one target substance, the read-across approach applied to fill in lung toxicity and carcinogenicity data gaps for Sb 3+ and 5+ substances is a ***category*** (as opposed to analogue) or group one.

The read-across hypothesis is that different Sb 3+ or 5+ substances, respectively, will ***give rise to/release (the same) common compound*** to which an organism will be exposed. On this basis the substances can actually be grouped into two subgroups which are each releasing a valence-specific (3+ or 5+) metal (oxyan)ion. The release of the specific Sb ion can be considered a common transformation product within each subgroup (no matter how the transformation occurs).

As concluded in section 2.4 above, the lung toxicity and carcinogenicity data available on the Sb substances reveal a general trend of mild lung toxicity in humans and animals, and low potency carcinogenicity in animals. Mechanistic information indicates that lung toxicity requires high amounts of a given species of Sb to deposit in the deep lung, and carcinogenicity would result from a number of possible indirect mechanisms, which may differ between Sb 3+ and Sb 5+ substances. As discussed in the scientific opinion on genotoxicity, whereas Sb 3+ substances appear to induce oxidative stress or interfere with DNA repair processes, Sb 5+ substances are of lower potency and refractile to binding to DNA. It is too early to demonstrate a (dis)similarity of effects between the five Sb substances which have the relevant physical form to penetrate the respiratory system.

As a result, the read-across approach applied to the lung toxicity and carcinogenicity assessment of Sb substances potentially corresponds to Scenario 5:
"*This scenario covers the category approach for which the read-across hypothesis is based on (bio)transformation to common compound(s). For the REACH information requirement under consideration, the property investigated in studies conducted with different source substances is used to predict the property that would be observed in a study with the target substance if it were to be conducted. Similar properties are observed for the different source substances; this may include absence of effects for every member of the category. No relevant differences in predicted properties are observed for several source substances.*"

3.3 Common assessment elements for the selected scenario

This section will cover the following assessment elements of scenario 5: 1) Formation of common (identical) compound(s); 2) Biological target(s) for the common compound(s); 3) Exposure of the biological target(s) to the common compound(s); and 4) Impact of parent compounds.

Assessment element 5) Formation and impact of non-common compounds was addressed in section 3.1, in the discussion about the moieties and functional groups of the Sb substances in scope.

The local toxicity of most metal(loid)s and their compounds occurs upon: i) the release of soluble metal ions; and ii) their interaction at their target organ sites. In addition to the speciation (valency), it is the bioavailability of the released metal at the site of action (for local effects) or uptake (for systemic effects) in the organism that can be the most important determining factor modulating the toxicity. This information is important as the hypothesized mode of action behind lung toxicity and carcinogenicity involves 1) inhalation and deposition of a given small sized Sb substance, and 2) prolonged residence time of in the deep lung, i.e. the substance is poorly soluble or insoluble in lung fluids or within cells present in the deep lung. Comparable Sb substances in terms of potential lung toxicity would thus be expected to release a common species/valency of Sb ion, with a comparably (low) solubility or systemic uptake potential or bio-availability.

Various sources of solubility data (water solubility, bio-accessibility in artificial alveolar fluid, in vitro lung cell/tissue testing conditions, in vivo tests, etc.) need to be taken into account to assess the potential for deep lung persistence.

Information on bioavailability can be predicted using in vitro models, such as bioelution, that simulate processes governing dissolution rates in vivo. Bio-elution measures the bio-accessibility of a substance in simulated biological fluids. A bio-elution test will therefore measure the amount of released metal "available for absorption" under relevant physiological conditions. There are artificial fluids for every relevant route of exposure to be assessed. Unfortunately, the bio-elution assays for the inhalation route have not yet been validated (the bio-elution assay for the oral route is undergoing validation first). In the absence of lung bio-elution data, Table 7 provides information on the release and behavior of Sb species in water and cell culture medium.

Figure 1 indicates where, on the basis of water solubility only (second table), and the definition of approximate solubilities described by the US Pharmacopeia and National Formulary[5] (first table), the cut-off or subgroup delimitation between the Sb substances with inhalation potential could be positioned. The substances which decompose in water have not been included in this provisional subgrouping. Sb trisulfide, Sb metal powder[6], and Sb trioxide can be considered to be insoluble, whereas Sb pentoxide and Sodium hexahydroxoantimonate are either only very slightly soluble or sparingly soluble. The latter two Sb substances would be expected to solubilize in the lung and be removed, while Sb metal powder, Sb trioxide and Sb trisulphide which are insoluble, are more likely to reside longer in the lung and reach both the necessary concentrations and deep lung tissues to cause the lung toxicity and carcinogenicity.

Three subgroups can be identified based on physical form and water solubility:

1. **Inhalable and insoluble Sb substances: Sb substances supplied in physical forms at or below 100 µm and considered slightly or sparingly soluble (water solubility between 0.1 and 33 mg/ml);**
2. **Inhalable and soluble Sb substances: Sb substances supplied in physical forms at or below 100 µm and considered to be water soluble (water solubility > 33 mg/ml);**
3. **Other Sb substances: Sb substances having moieties with a lung toxicity potential worse than that of the Sb ion (e.g. chlorides).**

Table 7: Solubility data of Sb substances considered for grouping and read-across.

Name	CAS #	Solubility in water(1)	Extraction in culture medium(2)
Sb – metal powder	7440-36-0	18.2 µg/ml	60 µg Sb/ml
Sb – massive metal	7440-36-0		
Diantimony trioxide	1309-64-4	0.370 µg/ml	0,8 µg Sb/ml
Antimony sulfide	1345-04-6	43.5 µg/ml	5.6 µg Sb/ml
Antimony tris(ethylene glycolate)	29736-75-2	0.4 µg/ml	32 µg Sb/ml
Antimony trichloride	10025-91-9	Technically not feasible	30 µg Sb/ml*
Sodium hexahydroxoantimonate	33908-66-6	594 µg/ml	30 µg Sb/ml
Sodium antimonate	15432-85-6	247 µg/ml	2.5 µg Sb/ml
Antimony pentachloride	7647-18-9	Decomposes in water	29 µg Sb/ml
Antimony pentoxide	1314-60-9	453 µg/ml	4.7 µg Sb/ml
Potassium hexahydroxoantimonate	12208-13-8	17,100 µg/ml	42 µg Sb/ml

(1) Extracted from the Chemical Safety Reports (2019)
(2) ToxTracker test reports on Sb substances – Hendriks (2017 and 2018)
* Comparison between water solubility and extraction results under examination

[5] Available from: https://www.uspnf.com/sites/default/files/usp_pdf/EN/USPNF/usp-nf-notices/usp38_nf33_gn.pdf and repository.uobabylon.edu.iq/2010_2011/4_10975_328.doc. ECHA does not provide any quantitative reference to water solubility thresholds. The only Q&A addressing water solubility ('What are the criteria for deciding if a substance is highly insoluble in water or poorly water soluble?', ID: 0836, dated November 2016) relates to determining aquatic toxicity testing requirements.

[6] This further suggests that the reported effects of Sb metal powder, which was administered orally to rabbits, is most probably associated to maternal toxicity, and not to a systemic uptake and direct developmental toxicity.

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Table I. Description and Relative Solubility of US Pharmacopeia and National Formulary Articles

Description form (Solubility definition)	*Parts of solvent required for one part of solute*	*Solubility range (mg/mL)*	*Solubility assigned (mg/mL)*
Very soluble (VS)	< 1	> 1000	1000
Freely soluble (FS)	from 1 to 10	100 – 1000	100
Soluble	from 10 to 30	33 – 100	33
Sparingly soluble (SPS)	from 30 to 100	10 – 33	10
Slightly soluble (SS)	from 100 to 1000	1 – 10	1
Very slightly soluble (VSS)	from 1000 to 10000	0.1 – 1	0.1
Practically insoluble (PI)	> 10000	< 0.1	0.01

Table II. Solubility of Sb substances according to US Pharmacopeia and National Formulary Articles' definition

Sb Substance	Water solubility from Table 3 (µg/ml)	Recalculated water solubility (mg/ml)	Solubility definition according to US Pharmacopeia
Sb glycolate	0.0004-0.0012	0.0000004-0.0000012	Practically insoluble
Sb trisulfide	0.944	0.000944	Practically insoluble
Sb metal powder	18.2	0.0182	Practically insoluble
Sb trioxide	19.7-28.7	0.0197-0.0287	Practically insoluble
Sb triacetate	'Moderately soluble'	Not applicable	Very slightly soluble?
Sodium antimonate	247	0.247	Very slightly soluble
Sb pentoxide	453	0.453	Very slightly soluble
Sodium hexahydroxoantimonate	594	0.594	Very slightly soluble
Potassium hexahydroxoantimonate	20,000	20	Sparingly soluble
Sb potassium tartrate	83,000	83	Soluble
Sb pentavalent drugs	'Very soluble'	Not applicable	Freely soluble?

Figure 1: Provisional subgrouping of Sb substances based on water solubility, for the purpose of lung toxicity and carcinogenicity read-across assessment.

3.4 Consistency of the lung toxicity and carcinogenicity information for Sb substances

The assessment of the lung toxicity and carcinogenicity dataset on Sb substances is made in Section 2.3 above and concludes the following:

- The combined animal and human exposure data support a STOT RE 2 classification for impacts upon the lung after repeated inhalation exposure to Sb trioxide and Sb trisulfide.
- The combined animal and human exposure data support a Carcinogenicity category 2 via inhalation classification for Sb trioxide.

There is some indication of consistency that fine and insoluble Sb compounds have lung toxicity and carcinogenicity effects. The consistency will be confirmed upon assessment and consideration of the evidence which will be completed with the research options described in Section 2.3.

3.5 Read-across analysis of the lung toxicity and carcinogenicity of Sb substances

Table 8 below summarizes the evidence available for each one of the common and specific assessment elements to be considered to justify the read-across approach applied to predict the lung toxicity and carcinogenicity potential of each subgroup of Sb substances.

Table 8: Assessment elements and read-across justification evidence.

Assessment Element/Details	Supporting evidence
Characterization of source and target substances	
Identity and characterization of all substances in category	**Subgroup inhalable, insoluble Sb substances:** Source substances: Any Sb substance supplied in physical forms at or below 100 µm and having moieties or impurities which do not have a more severe lung toxicity profile than the Sb ion. Target substances: Any substance supplied in physical form at or below 100 µm and having moieties or impurities which do not have a more severe lung toxicity profile than the Sb ion. **Subgroup inhalable, soluble Sb substances:** Source substances: Any Sb substance supplied in physical forms above 100 µm and having moieties or impurities which do not have a more severe lung toxicity profile than the Sb ion. Target substances: Any substance supplied in physical form above 100 µm and having moieties or impurities which do not have a more severe lung toxicity profile than the Sb ion. **Subgroup other Sb substances:** Sb substance having moieties or impurities which have more severe lung toxicity profile than the Sb ion (e.g. chlorides) Cf. Table 6 for more detailed identification and characterization information.
Structural similarity and dissimilarity within the category (category description)	
The structural similarities and differences identified for all category members	**Subgroup inhalable, insoluble Sb substances:** All substances in the category have in common that they have one or more Sb atoms bond through ionic or covalent bonding with moieties, many of which are essential nutrients or Essential Trace Elements (ETEs), with none or negligible lung toxicity potential, or normal metabolites (NM), which are expected to be rapidly metabolized. **Subgroup inhalable, soluble Sb substances:** All substances in the category have in common that they have one or more Sb atoms bond through ionic or covalent bonding with moieties, many of which are essential nutrients or Essential Trace Elements (ETEs), with none or negligible lung toxicity potential, or normal metabolites (NM), which are expected to be rapidly metabolized. **Subgroup other Sb substances:** All substances in the category have in common that they have one or more Sb atoms bond through ionic or covalent bonding with moieties with a more severe lung toxicity profile than the Sb ion (e.g. chlorides). Cf. Table 6 for more detailed identification and characterization information.
Structural differences that are allowed within the category are specified	**Subgroup inhalable, insoluble Sb substances:** Differences in molecular weight, moieties and release rates are allowed as long as there is evidence that the final speciation of the released (oxyan)ions, remains comparable. **Subgroup inhalable, soluble Sb substances:** Differences in molecular weight, moieties and release rates are allowed as long as there is evidence that the final speciation of the released (oxyan)ions, remains comparable. **Subgroup other Sb substances:** Differences in molecular weight, and release rates are allowed as long as the moiety has a more severe lung toxicity profile than the Sb ion.

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Assessment Element/Details	Supporting evidence
	Cf. Table 6 for more detailed identification and characterization information.
Link of structural similarities and structural differences with the proposed regular patterns (presence of hypothesis) - It is explained why and how the category members should behave in a predictable manner	
Formation of common (identical) and non-common compounds	**Subgroup inhalable, insoluble Sb substances:** All substances in the category have in common that they release a common Sb (oxyan)ion form that will be insoluble and reside long in the lung. This Sb form can be considered as a common transformation product. Lung exposure will be to this common transformation product, no matter the original form of the substance originally present and/or administered. **Subgroup inhalable, soluble Sb substances:** All substances in the category have in common that they release a common Sb (oxyan)ion form that will be soluble and not reside long in the lung. This Sb form can be considered as a common transformation product. **Subgroup other Sb substances:** All substances in the category have in common that they have a moiety that has a lung toxicity profile that is more severe than that of Sb. Cf. Section 3.3 for more information on transformation products.
Degradation, bioaccumulation and impact of non-common compounds	**Subgroup inhalable, insoluble and soluble Sb substances:** All substances in the category have in common that they have a moiety that has a lung toxicity profile that is less severe than that of Sb. **Other substances:** All substances in the category have in common that they have a moiety that has a lung toxicity profile that is more severe than that of Sb. Cf. Section 3.2 for more information.
Impact of impurities on the prediction	
The identified impurities have an impact on the prediction	**All:** All Sb substances will typically have some levels of As and/or Pb as impurities, because of the geological affinity/common primary origin of these three elements in nature. These impurities are not expected to have an impact on the (predicted) effect as long as they are present in concentrations below the classification threshold. Cf. Table 7 for more detailed information on impurities.
Consistency of properties in the data matrix	
A data matrix with experimental data for source and target substances is needed to support the read-across	**Subgroup inhalable, insoluble and soluble Sb substances:** The lung toxicity and carcinogenicity dataset available for Sb metal, Sb trioxide and Sb trisulphide is not really comparable in terms of endpoints covered, but overall indicates that these Sb substances cause lung toxicity following significant exposures to inhalable fractions. **Subgroup inhalable, soluble Sb substances:** There is no lung toxicity and carcinogenicity evidence for Sb pentoxide and Sodium hexahydroxoantimonate. Genotoxicity evidence (cf. scientific opinion on genotoxicity) however indicates that these have a low direct carcinogenicity potential. **Subgroup other Sb substances:** There is no lung toxicity and carcinogenicity evidence for the other Sb substances More information in Sections 2.2 and 2.3 of this document.
Reliability and adequacy of the source data	
The source study(ies) needs to be reliable and adequate as requested for any other key study	Only adequate and reliable data has been used to support the read-across justification. More information in Section 2.2 of this document.

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3.6 Conclusion of the read-across assessment of the lung toxicity and carcinogenicity of Sb substances

Table 9 provides, for each Sb substance, the result of the hazard assessment and classification constructed on the basis of the read-across approach

Table 9: Classification resulting from provisional read-across approach for Sb substances.

Name	CAS #	Lung toxicity / Carcinogenicity classification	Further testing needs
Subgroup inhalable, insoluble Sb substances:			• Determine whether the Kras and Egfr oncogene alterations observed in lung tumors are pre-existing spontaneous lesions, lesions induced by Sb via indirect mechanisms of genotoxicity, and/or lesions selected for clonal expansion as a consequence of pulmonary toxicity and hypoxia; • Clarify the (local) genotoxicity of Sb substances (cf. scientific opinion on genotoxicity); • Run one or more in vivo inhalation study to confirm the observations gathered so far.
Sb –powder	7440-36-0	STOT RE 2 Carcinogenicity 2	
Diantimony trioxide	1309-64-4	STOT RE 2 Carcinogenicity 2	
Antimony trisulfide	1345-04-6	STOT RE 2 Carcinogenicity 2	
Subgroup inhalable, soluble Sb substances:			
Sodium hexahydroxoantimonate	33908-66-6	Not classified	
Antimony pentoxide	1314-60-9	Not classified	
Subgroup other Substances:			
Sb – massive	7440-36-0	Not classified	
Antimony tris (ethylene glycolate)	29736-75-2	Not classified	
Antimony trichloride	10025-91-9	STOT SE 3[7]	
Sodium antimonate	15432-85-6	Not classified	
Antimony pentachloride	7647-18-9	STOT SE 3[6]	
Potassium hexahydroxoantimonate	12208-13-8	Not classified	

[7] Due to its low pH and high corrosivity.

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4. References

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