International Antimony Association

Scientific opinion, weight of evidence and read-across assessment, and further research options

Human Health: Reproductive Toxicity

Version 2

17 June 2019

Version management

Version	Date	Main change	Sections affected
1	31 July 2018	/	/
2	17 June 2019	New bio-elution data included, 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

International Antimony Association

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1. Introduction

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Reproductive toxicity studies have been performed for only a few of the 10 mono-constituent antimony (Sb) substances that are registered under REACH. Some toxicity data is also available on more 'exotic' forms of Sb, which are not subject to REACH. Overall, around 15 studies have assessed the reproductive toxicity of Sb substances since 1967. However, this comprises an incomplete dataset both in terms of quality of data, and of coverage of endpoints and Sb substances. This dataset is used as the starting point to perform the ***weight of evidence-based reproductive 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 reproductive 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 reproductive 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 reproductive toxicity potential of Sb and its compounds is central to determinations of whether Sb substances are capable of inducing adverse effects on the reproductive potential or function, or on the embryofetal development.

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

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

2.2 Reproductive toxicity evidence 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, Toxnet DART, and 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*; Sb; toxic; fertil; reproduct; fetus; fetal; foetal; foetus; pregnan; baby; chid; infant; development; sex; sperm; semen; seminol; ovarian; ovary; rat; mouse; mice; dog; primate; monkey and combinations thereof. Papers were selected and manually inspected on the basis of relevant animal or data for relevance to Sb relating to reproductive function and foetal development. Table 1 summarizes the 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

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 were sorted by date, the Sb substance evaluated, and characterization of the toxicological endpoints

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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 and 3 below provide an overview of the reproductive toxicity data that is available for the Sb substances considered for grouping and read-across, and the assessment performed by i2a as to the specific and general deficiencies and conclusions which can be reached in each case.

Available reproductive toxicity data shows that the assessment of the reproductive toxicity of Sb substances commenced in 1967, with most recent, GLP and guideline compliant studies dating from 1999 onwards. A mix of Sb substances have been tested, most often in rats. Data available include inhalation, oral administration and injection studies of Sb compounds, including one oral administration study of Sb metal powder. Data are available for the 0, +3 and +5 valence states, but some data are for exposure routes which are not relevant for chemical safety assessment. There are mainly oral studies for Sb 3+ substances, and parenteral studies for Sb 5+ ones.

Approximately 200 papers concerned the use of Sb compounds in the treatment of parasitic diseases. Studies have been conducted to evaluate pentavalent Sb drugs applied parenterally in the treatment of parasitic diseases, including leishmaniasis. These Sb drugs are not within the remit of REACH, but the data may elucidate the mode of action of Sb substances, since the therapeutic action of the drugs requires the release of Sb ions and the parenteral administration route is necessary to achieve highest bioavailability (e.g. WHO recommended dose regimen for Glucantime ® of 20 mg/kg/day by the intramuscular route up to a maximum of 850 mg for 8 weeks).

Indeed, disease treatment requires systemic Sb concentrations that cannot be achieved via oral routes of administration due to: i) the very limited rate of uptake of Sb compounds from the gastrointestinal tract (ATSDR, 2017), and ii) the emetic effects that would be associated with oral administration of Sb substances. Injection studies administering for example 100 mg/kg bw/day of an Sb compound would require oral administration of at least 10,000 mg/kg bw/day. Such high levels of oral administration would not be technically feasible.
Therefore, data on Sb drugs administered via injection represent scenarios of maximum systemic presence/uptake, and highest ion release and bioavailability of Sb in animals and would not be relevant for the purpose of REACH hazard assessment or classification, but only possibly to understand and define toxic or toxicokinetic properties of Sb compounds and mode of action aspects. Despite decades of use in clinical treatments however, there is not yet any detailed mode of action explaining any of the effects of these antimonial drugs. In light of this, these data are used to inform further research options.

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Table 2: Overview of relevant reproductive toxicity studies available for Sb substances and i2a assessment of reliability and remaining knowledge gaps

Reference	Sb chemical form	Animal	Exposure route	Doses Vehicle	OECD Guideline	GLP	Reliability [Klimisch score]	Summary	Conclusions	Knowledge Gaps	Recommendation
Hansen, B. (2014)	SHHA	Rats	Oral, gavage	Daily, Day 6 to 19 of gestation, 100, 300, 1000 mg/kg bw/d, in aqueous hydroxypropyl methyl cellulose 0.8%	414	Yes	1	Maternal NOAEL 1000 mg/kg bw/d Fetal NOAEL 100 mg/kg bw/d	No adverse litter/fetal effects except skeletal ossification delays at 300 and 1000 mg/kg bw/d	Is skeletal retardation an effect caused by Sb? Is the retardation reversible, in that normal ossification takes place by weaning?	Check influence of Sb on Ca metabolism, and investigate reversibility of delay in 421/422 study
Hansen, B. (2017)	Sb	Rabbits	Oral, gavage	Daily, Day 6 to 28 of gestation, 30, 100 and 230/300 mg/kg bw/d	414	Yes	1	Maternal and Fetal NOAELs not reported	Excessive maternal toxicity at highest dose, based on deaths, abortions and periods or zero/negligible food intake. Evidence of delayed ossification in fetuses	Do ECHA agree that excessive toxicity the high dose precludes evaluation of this dose level? Are the reduced foetal weight and retarded ossification in the intermediate dose group secondary to maternal toxicity? Is there evidence that the retardation reversible?	Calculate maternal toxicity based on weight gain adjusted for gravid uterus weight and examine frequency of periods of zero/low food intake., Add maternal and fetal NOAELs. Explore influence of Sb on Ca metabolism, and reversibility of delay by double staining (i.e. cartilage as well as bone) in future studies. Explore reversibility in rat 421/422 study
Schroeder et al. (2003)	ATO	Rats	Inhalation	6h Daily, Days 0-19 of gestation - 0, 2.6, 4.4 and 6.3 mg/m^3	414	Yes	1	Maternal NOAEL 2.6 mg/M3, Fetal NOAEL 6.3 mg/M3	Effects on dam lung weight/ =pathology, but no developmental toxicity	Can this study be used as read-across for other Sb substances by the oral route?	

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Hext, Pinot and Rimmel (1999)	ATO	Rats	Oral, diet	0, 1000, 5000 and 20000 ppm in the diet, equivalent to 84, 421 and 1686 mg/kg bw in males or 97, 494 or 1879 mg/kg bw in females daily for 90 days	408	Yes	1	NOAEL high dose in both sexes	NOAEL for reproductive organs exceeds the limit dose		Include organ weights and detailed histopathology of the reproductive organs and thyroid.

Table 3: Overview of other reproductive toxicity studies available for Sb substances and i2a assessment of relevance, reliability and remaining knowledge gaps

Reference	Sb chemical form	Animal	Exposure route	Doses Vehicle	OECD Guideline	GLP	Reliability [Klimisch score]	Summary	Conclusions	Relevance	Inadequacies/data gaps
Miranda et al. (2006)	Meglumine antimonate		Subcutaneous injection	0, 75, 150, 300 mg/kg bw/d by variable dose volume from Day 1 to 20 of gestation	None	No	3		Reported as embryotoxic at ≥75 mg/kg bw/d and no maternal toxicity at highest dosage	Non-standard methodology, Interpretation limited, some conclusions questionable. High dose dams showed 19% reduction in weight gain when adjusted for gravid uterus. Fetal effects cannot be demonstrated as secondary to maternal effects as no individual data.	Test should include minimum of 20 pregnant females as per OECD 414 guideline. Visceral abnormalities and skeletal abnormalities should be examined in 50:50 of fetuses, not 33:67. Ensure that females used are not siblings or mated with siblings and use well-characterized strain from commercial supplier Record individual data, not only means or medians. Compare results with historical

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											control data, not only concurrent control group. Assess local irritancy and non-standard vehicle
Rossi et al. (1987)	ATC	Rats	Oral, drinking water	Dams 0.1 or 1 mg/dL water from Day 1 of gestation to Day 21 post-partum: Pups Day 22 to 60 post-partum. Dose cannot be determined in absence of water intake data	None	No	3	Maternal toxicity characterized by dose-related reduction in maternal body weight at Day 20 of gestation, 10% at high dose	Reduced pup weight at birth and day 60 post-partum, no effect on litter size. No 'teratogenic' effect reported but changes in vasomotor reactivity	Interpretation limited, actual dosage, pups randomized between dams in group, unclear experimental design	
Grin et al. (1987)	ATO	Rats	Inhalation, whole body	0, 0.027, 0.082, 0.27 mg/M3 continuously from Day 0 to 20 of gestation	~414	No	3		Various maternal and fetal effects, possibly stress-related owing to continuous exposure	Group size of 6 or 7 inadequate. Potential Ingestion from exposed diet/water. Unsuitable for evaluation	Ensure purity and particle size are properly reported. Clearly report animal strains and exposure levels.
Paumgarten et al. (2001)	Meglumine antimonate	Rats	Subcutaneous injection	0 or 300 mg/kg bw/d daily from Day 6 to 15 of gestation, or 900 mg/kg bw on Day 11 only	~414 pre 2001	No	3		No maternal toxicity at either dosage. Fetal effects limited to increased incidence of resorptions at 300 mg/kg bw/d and misshapen atlas bone	Various deficiencies, cannot be fully analyzed without individual data	Test should include minimum of 20 pregnant females as per OECD 414 guideline. Dosing period not as current guidance. Use double staining to differentiate bone and cartilage, and retarded ossification from permanent structural alterations. Report individual data for retardation of ossification, to determine if

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											associated with low weight and any individual maternal toxicity
Alkhawajah et al. (1996)	SSG + Meglumine antimonate + SbCl3	Rats	Intramuscular injection	0, 30, 100, 300, 900 mg/kg bw/d intramuscular Days 6-15 of gestation	~414 pre 2001	No	3		Increased resorption reported, in absence of assessment of maternal effects, other than all died at 900 mg/kg bw	In-house rat, strain not identified, no mention of avoidance of siblings in pairings or group allocations. Group size and dosing period not to current guidance. No assessment of maternal effects, no historical control data. Limited reporting of anomalies suggests inexperienced examiners.	Ensure commercial rat strain with adequate historical control data selected. Use current guidance for dosing period and group size. Report maternal effects on individual basis, referring to gestation day. Examination by registered fetal pathologists
Alkhawajah et al. (1996)	ATC	Rats	Intramuscular injection	100 mg/kg bw/d	~414 pre-2001		3		Increased incidence of resorptions and low fetal weight. Relationship to maternal toxicity unknown as no report of maternal parameters. Higher incidence of hematoma reported likely associated with handling/low fetal weight	Inadequate group size and dosing period not as current guidance. No assessment of maternal effect.	As above

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Belyaeva, AP. (1967)	Sb, ATO, APS	Women	Inhalation of workplace dust		None	No	3		Low birth weight, increased incidence of premature birth and spontaneous abortions	Case reports. Controls not defined. No control of confounding factors, exposure to other chemicals possible	
Belyaeva, AP. (1967)	ATO	Rats	Inhalation	209 mg Sb/M3 prior to mating and throughout gestation	None	No	3			Original paper cannot be found, citations only.	
Coelho et al. (2014)	Meglumine antimonate	Rats	Subcutaneous injection	0, 75, 150, 300 mg/kg bw/d, parental females only from Day 0 of gestation to Day 31 post-partum	None	No	3	Maternal NOAEL 300 mg/kg/day; Fetal NOAEL 150 mg/kg bw/d owing to reduced litter size and pup weight at birth	No effect on fertility of offspring	Group size only 14/16. Dosage determined by volume. Untreated males, premating dosing in parental females therefore no assessment of fertility in parental generation. Offspring reproductive capacity assessed by age at puberty and mating at sexual maturity. Sperm assessment in Male pups at 100-110 days old.	Guideline studies required to cover inadequate assessment of male fertility, pre-mating dosing in females, reproductive organs and thyroid hormones and pathology for adults and pups, in an appropriate Sb compound. Preliminary dose-range finding/screening study required in preparation for definitive study.
Omura et al. (2002)	ATO	Rats and mice	Oral, water	0, 12 and 1200 mg/kg bw/d suspended in distilled water Rat 3 d/wk for 4 wks, mouse 5d/wk for 4 wks	None	No	3	NOAEL 1200 mg/kg bw/d	No adverse effects on bw or male reproductive organ weights, histopathology, sperm count, motility or morphology	Intermittent dose regimen. Group size 8 (rat) or 10 (Mouse). Actual dosage not determined, no water intake data	No detailed histopathology of male reproductive organs and seminology.

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Omura et al. (2002)	APT	Rats and mice	Oral, water	27.4 mg/kg bw/d suspended or dissolved in distilled water	None	No	3	NOAEL 27.4 mg/kg bw/d	as above	Non-standard dose regimen. Group size 8 (rat) or 10 (Mouse)	As above
Dieter 1992	APT	Rats & Mice	intraperitoneal injection	Rat 0, 1.5, 3, 6, 12 or 24 mg/kg bw/d 3d/wk for 13 wks Mouse 0, 6, 12 or 24 mg/kg bw/d	~ 408	Yes	1	NOAEL 24 mg/kg bw/d for both species	No effect on oestrous cycles or sperm count, motility or morphology or reproductive organ pathology	Non-standard dose regimen. Group size 10 for oestrous cycle/sperm evaluations, 20 for pathology	

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Effects on fertility

For fertility, there are three non-standard studies in animals, one on female rats (Belyaeva, 1967) and one on male rats and mice (Omura et al., 2002); and one human occupational report study (Belyaeva, 1967). At a first glance, the inhalation study in female rats by Belyaeva (1967) appears to suggest that Sb trioxide might have an adverse effect on fertility after repeated exposure to 250 mg/ m^3. However, the results must be regarded as inconclusive and cannot be used for risk assessment, since the study report does not provide a valid description of the overall experimental conditions and the purity of the test substance. Furthermore, since it is well-established that rats are particularly sensitive to inert particle overload (in contrast to humans) which occurs in sub-chronic studies at levels approximately 50-fold below the level in Belyaeva (1967), it can reasonably be assumed that the rats in this study suffered from a massive, non-substance-specific impairment of their respiratory system by overload of lung macrophages and breakdown of their lung clearance, so that any adverse effects can easily be explained as of secondary nature. Significant pulmonary damage, impaired pulmonary function (hypoxia) and secondary changes related to hypoxia (e.g. renal lesions, erythroid hyperplasia) have subsequently been noted in recent chronic inhalation studies with rats and mice at exposure levels ranging from 3 to 30 mg/m^3 (NTP, 2017).

The gavage study on male rats and mice (Omura, 2002) showed no testicular toxicity after 4 weeks repeated exposure up to 1200 mg/ kg bw. The human case report study on women occupationally exposed to Sb trioxide indicates that Sb trioxide might affect the fertility of female workers. However, this study is inconclusive due to the lack of information on the control group, the exposure situation and the overall workplace environment. Based on these fertility studies in animals and humans, no conclusion on female fertility can be derived.

However, a 90-day oral feeding study in male and female rats with Sb trioxide reported no effects on reproductive organs up to a dose of 1686 mg/kg in males and 1879 mg/kg in females. The effects of Sb trioxide, Sb potassium tartrate and sodium hexahydroxoantimonate upon the fertility of rats and/or mice have been evaluated after oral exposure (Hext, et. al., 1999; Omura et al. 2002; Hansen, 2014a), and i.p. injection (Dieter, 1992). No significant adverse functional or structural impacts upon the reproductive systems of male or female animals have been observed. The NOAEL for effects upon fertility via oral exposure (adjusted for the Sb content of compounds evaluated) is in excess of 1000 mg/kg bw/day.

Data evaluating fertility impacts after inhalation exposure are lacking, but the overall profile of Sb compounds indicates low potential for reproductive toxicity. Fertility effects via inhalation exposure would not be expected given the high oral NOAEL for fertility impacts, coupled with the lack of developmental impacts from high (6.3 mg/m^3) inhalation exposure to Sb trioxide (Schroeder, 2003).

In summary, focusing on the very few GLP-compliant, guideline (Klimisch score 1) studies that should be used as the basis for effects assessment and classification, there are no definitive guideline studies which assess **reproductive function**, and data are limited to evaluations performed on chronic toxicity studies. Such studies are available on two Sb 3+ compounds: Sb trioxide and Sb potassium tartrate, and one Sb 5+ compound: sodium hexahydroxoantimonate:

- In 90-day studies with intraperitoneal injection of Sb potassium tartrate up to 24 mg/kg bw/d for 3 days/week in rats and mice, there were no adverse effects on estrous cycles or sperm count, morphology or motility and no adverse effect on histopathology of the reproductive organs.
- In a 90-day dietary study in the rat with Sb trioxide, no adverse histopathology was reported for reproductive organs at dosages which exceed the limit dose (1686 mg/kg bw/d in males and 1879 mg/kg bw/d in females).
- A further published 4-week intermittent dosing study with Sb trioxide and Sb potassium tartrate in rats and mice reported no effect on reproductive organ weight, histopathology, sperm count, motility and

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morphology at target dosages of 12 or 1200 mg/kg bw/d Sb trioxide and 27.4 mg/kg bw/d Sb potassium tartrate.

Developmental toxicity effects

The developmental toxicity of oral exposure of rabbits to Sb metal powder (Hansen, 2017) and inhalation exposure of rats and mice to Sb trioxide (Schroeder, 2003) has been studied with little evidence of significant developmental deficits. Oral exposure studies of rabbits to Sb metal powder were complicated by maternal toxicity at the higher levels of Sb exposure. These exposures were associated with lethality, gastric irritation and reductions in maternal food intake and maternal body weight gain. Reductions in fetal weights, increased post-implantation losses and delayed vertebral ossification were observed in parallel to this maternal toxicity and have been documented to result from reduced maternal food intake and growth in the rabbit (Cappon et al., 2005). No impacts of Sb, independent of maternal toxicity, were observed.

Hansen (2014) evaluated the effects of oral gavage with 100, 300 and 1000 mg/kg bw/d sodium hexahydroantimonate upon developmental toxicity in Sprague Dawley rats. No evidence of maternal toxicity was evident up to 1000 mg/kg bw/d of sodium hexahydroantimonate (Sb 5+) although slight retardation of fetal skeletal ossification was observed at 300 and 1000 mg/kg bw/d. The significance of this mild effect is difficult to assess, particularly when contrasted with the observations from injection studies with other Sb 5+ compounds projected to yield systemic Sb 5+ concentrations approximately 10 - 100-fold higher than those achieved via oral gavage. This observed delayed ossification can provisionally be dismissed as not relevant as per Carney and Kimmel (2007).

A separate but growing body of literature has focused upon the therapeutic intravenous administration of Sb 5+ compounds such as meglumine antimoniate for the treatment of leishmaniasis - a parasitic disease state endemic in tropical countries that in and of itself poses health risk to pregnant women and their fetuses. After more than 5 decades of therapeutic use of pentavalent antimonials, a small number of anecdotal case studies have suggested embryotoxicity during treatment for leishmaniasis. Rodent studies have thus evaluated the developmental toxicity of meglumine antimoniate administered to the rat by injection (Miranda et al., 2006; Coelho et al, 2014):

Miranda et al. (2006) evaluated the developmental toxicity of daily subcutaneous injections of 75 – 300 mg Sb(V) /kg bw/day throughout gestation. Reductions in fetal weight and some skeletal and soft tissue abnormalities were evident at 300 mg/kg bw/day and attenuated at 150 mg/kg bw/day, yielding a NOAEL of 75 mg/kg bw/day. The authors suggest that maternal toxicity was not evident in the study but reductions in maternal weight gain during gestation were evident at the highest dose tested, and do indicate the presence of maternal toxicity.

Coelho et al. (2014) expanded upon the work of Miranda et al (2006), essentially conducting an extended one-generation reproductive test study (EOGRTS). Subcutaneous injection of 75 – 300 mg Sb(V)/kg bw/day to pregnant rats was conducted from day 0 to 20 of gestation and through parturition and lactation to post-natal day 21. Embryotoxicity, manifesting as decreases in pup weight and reductions in litter size, were noted to have occurred in the absence of maternal toxicity. However, suppression of maternal weight gain (minus the weight of the uterus) was observed and indicates the subtle onset of maternal toxicity at 300 mg/kg bw/day. Impacts upon pregnancy outcome had an apparent NOAEL of 150 mg Sb 5+/kg bw/d. Post-natal developmental impacts were present but minor. Other than modest decrements in female pup weight gain and exploratory behavior in female pups, no detrimental impacts of treatment were observed on neurobehavioural development, sexual maturation, male fertility or female reproductive performance. The authors concluded that meglumine antimoniate was a weak developmental toxicant and further postulated that

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the minor effects seen in offspring were potentially the result of decrements in maternal weight gain during gestation that had subsequent negative impacts upon lactation and pup nutrition.

The subcutaneous injection studies with meglumine antimoniate are relevant to pharmacological applications in the treatment of leishmaniasis. Coelho et al. (2014) further note that the injection doses used in the rat reproduction studies are much higher than those employed therapeutically in the treatment of leishmaniasis in humans– typically on the order of 20 mg Sb (V)/kg bw/d – and yield rat blood antimony levels approximately 100-fold higher than therapeutic human blood antimony levels. The systemic Sb levels achieved via s.c. injection are also strikingly higher than systemic levels that will result from physiological routes of exposure. For example, blood Sb levels of 160 µg/g result one hour after s.c. injection of 300 mg/kg bw meglumine antimoniate in the rat (Miranda et al., 2006). In contrast, oral administration of rodents at similar dosing rates is indicated to yield no detectable increases in Sb levels in blood (Coelho et al., 2014). Rodent blood Sb levels after injection are also approximately 10,000-fold higher than the blood Sb levels of humans occupationally exposed to Sb compounds (Wu and Chen, 2017). The mild developmental impacts observed after administration of antimony compounds by injection are thus elicited by systemic antimony levels many-fold higher than can conceivably be produced via physiological routes of exposure due to a combination of extremely limited uptake and/or irritating and emetic effects of highly soluble compounds (Dieter et al., 1991).

Sb compounds administered via physiological exposure routes do not produce developmental toxicity independent of maternal toxicity. The NOEC for effects from inhalation exposure is in excess of 6.3 mg/m^3 for Sb trioxide.

In summary, as regards **developmental toxicity**, no adverse effects on embryofetal development were observed in a rat inhalation study with Sb trioxide, despite the expected adverse lung pathology in dams. Studies in rats and rabbits using oral administration, effects reported include **maternal toxicity**, especially in groups exposed to high/excessive quantities of Sb, demonstrated by mortalities, abortions, reduced weight gain and periods of negligible food intake in the dams, with reduced food intake in some individual animals at the intermediate dose level, and **retardation of fetal ossification**. In rats treated with sodium hexahydroxoantimonate, fetal effects were limited to ossification delays (which are generally accepted as reversible).

The overview of reproductive toxicity data available is also presented in another format in Table 4 below. This table also shows the main gaps to be addressed, or where the assessment requires further investigation or justification.

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Table 4: Overview of toxicity data available for Sb substances considered for grouping and read-across for reproductive toxicity endpoints (x = Klimisch score 1 or 2 OECD guideline/GLP compliant, x = Klimisch score 3 or 4 studies of non-standard design/limited data, and ~x = not strictly OECD guideline compliant but similar). NOTE: Clinical studies with parenteral administration of Sb have not been included in this overview.

Name	CAS #	Acute Toxicity	Repeated dose toxicity		Reproductive toxicity			
		(OECD 403)	28-day (OECD 407)	90-day[a] (OECD 408)	Fertility / Developmental (OECD 421)	Pre-natal developmental[b] (OECD 414)	Combined Toxicity with Reproduction / Developmental Toxicity Screening (OECD 422)	Extended One Generation (OECD 423)
Metallic Sb								
Sb –powder	7440-36-0					X		
Sb – massive	7440-36-0							
Trivalent Sb substances								
Diantimony trioxide	1309-64-4	~x, ~x, ~x, ~x, ~x, x, ~x, x, ~x		x, ~x, ~x, ~x, ~x, ~x, ~x, ~x, ~x,		x, ~x		
Antimony sulfide	1345-04-6							
Antimony tris(ethylene glycolate)	29736-75-2							
Antimony trichloride	10025-91-9					~x, ~x		
Antimony triacetate	6923-52-0							
Pentavalent Sb substances								
Sodium hexahydroxoantimonate	33908-66-6	x		x, x		X		
Sodium antimonate	15432-85-6							
Antimony pentachloride	7647-18-9							
Antimony pentoxide	1314-60-9	x						
Potassium hexahydroxoantimonate	12208-13-8							
Trivalent Sb drug								
Antimony potassium tartrate	28300-74-5			~x				
Pentavalent Sb drugs								
Glucantime (meglumine antimonite)	133-51-7					~x, ~x		x
Pentostam (sodium stibogluconate)	16037-91-5					~x		

[a] Includes assessment of reproductive organ histopathology; [b] Includes "screening" studies of small group size

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2.3 Weight of evidence analysis of the reproductive toxicity of Sb substances

This section covers step 3) integration and weighing of evidence (weight of evidence analysis), 4) application of levels of confidence, and 5) uncertainty analysis of the weight of evidence approach.

In order to assess the potential reproductive toxicity of Sb substances, it is important to understand the mechanism(s) by which Sb compounds seem to cause some level of adverse effects in a number of studies, and the chemical species involved in such a response. The following hypothesis have been put forward based on the available reproductive toxicity information:

Maternal toxicity has been demonstrated by excessive exposure to Sb substances. As indicated previously, extensive rapid dissolution of Sb substances can produce a disruption of gastrointestinal tract function. It is necessary therefore to distinguish between: i) the adverse effects of disruption of normal food intake, including secondary effects on reproductive outcome, and ii) direct reproductive toxicity.

Published studies investigating fetal effects in an array of Sb substances and routes have limitations (not least the excessive exposure profile achieved by parenteral administration of Sb in the investigation of Sb 5+ compounds designed for medicinal use and not relevant for non-therapeutic human exposures). These available data are also not fully GLP or OECD guideline compliant, and even for the most recent studies, do not provide sufficient detail on maternal adverse effects, and there are no individual data records to assess how such effects may influence embryofetal development.

It is not clear how exposure to Sb influences **fetus ossification** nor whether the delay is reversible, in that normal ossification takes place by weaning. Unless studies include a dedicated assessment of the Ca metabolism of animals exposed to Sb substances, the actual role of Sb and the resulting developmental toxicity assessment cannot be confirmed.

The limited Klimisch score 1 relevant, reliable studies together with the less reliable ones, leave a number of questions unaddressed. There is little indication of effects on reproduction or fertility, but this statement has a relatively low confidence level, and is shadowed by at least two uncertainties: maternal toxicity vs direct developmental toxicity, and the influence of Sb exposure on the fetus' Ca metabolism and its skeletal ossification.

The overall confidence/uncertainty of the weight of evidence assessment would be increased/decreased upon verification of i) the maternal toxicity of Sb substances; ii) the influence of Sb in the Ca metabolism and ossification delays, and the reversibility of this effect; and iii) the developmental effects of Sb observed independent of any sign of maternal toxicity.

To address these knowledge gaps, the following research options appear relevant:

1) **Array of 2-week dose-range finding/tolerance[2] studies** in rats in a comparative analysis that permits selection of the most representative test item/source substances for further oral testing (based on the general reaction of the test animals to the treatments/substances, their specific gastric tolerance/irritation[3], and the systemic uptake/exposure levels obtained). This will involve selection of the most appropriate (non-standard?) vehicles, demonstrated to cause no local irritancy either;
2) **OECD 422 in vivo Combined Repeat Dose Screening Reproductive studies** on one or two Sb substances to screen for toxicokinetics and relevant systemic and reproductive toxicity parameters,

[2] In light of Sb's reported emetic properties, this step is important before any *in vivo* oral study is considered.

[3] Sb have known emetic properties, but rats cannot vomit, so the assessment has to be done on the basis of their general reaction and specific gastric tolerance/irritation observations.

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including maternal effects of Sb exposures, and Ca metabolism to investigate the cause of the ossification delays and their (ir)reversibility.
Maternal toxicity should be determined on the basis of weight gain adjusted for gravid uterus weight and examination of the frequency of periods of zero/low food intake. The study should include weighing and detailed histopathology of the reproductive organs and the thyroid.
The effects on the fetus ossification should be assessed by using double staining (i.e. cartilage and bone tissues). Visceral and skeletal abnormalities should be examined in 50:50 of fetuses (not the standard 33:67). The (ir)reversibility of the eventual delayed ossification should be explored by examining some post-delivery pups.
In any case, the study should be designed to explore possible endocrine disrupting effects too, and enable derivation of both maternal and fetal NOAEL. For this, individual data should be recorded, not only means or medians, and results should be compared with historical control data, not only data from the concurrent control group.

3) **OECD 414 in vivo Prenatal Developmental Toxicity studies** on one or more Sb substances (including the most representative test item/source substance) if necessary. Study design will have to maximize the information that can be collected from the observations, along the lines of specifications provided for the OECD 422 studies above;
4) **Additional higher tier oral study** to clarify any pending reproductive toxicity properties, if necessary.

2.4 Conclusion on the weight of evidence assessment of the reproductive toxicity of Sb substances

This section covers steps 4) application of levels of confidence, 5) uncertainty analysis (again), 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 reproductive toxicity of Sb substances?**
  Not fully, especially as the existing evidence is not guideline compliant and leaves a number of interpretation questions open.

- **What indication does the available evidence provide as to the potential reproductive toxicity of Sb substances?**
  - The available data (none of which is an OECD 421 study) support the conclusion that **Sb substances are not considered to impact fertility**.
  - The available developmental evidence allows to provisionally conclude that the effects observed do not to constitute severe and irreversible reproductive toxicity, and that **Sb substances do not have a direct adverse effect on the development of the conceptus**.
  - In light of this, no reproductive toxicity classification is warranted.

- **What research would increase the confidence/reduce the uncertainty of the reproductive toxicity assessment of Sb substances?**
  - Array of 2-week dose-range finding/tolerance studies;
  - OECD 422 in vivo Combined Repeat Dose Screening Reproductive studies;
  - OECD 414 in vivo Prenatal Developmental Toxicity studies, if necessary;
  - Additional higher tier oral study, if necessary.

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3. Assessment of reproductive toxicity 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 5, the Sb substances and their corresponding CAS number are listed in order of valence state, namely 0, 3+ and 5+. This table contains both Sb substances having REACH Registration obligations, and Sb substances which are not in scope of REACH but which may provide information relevant to the read-across justifications for reproductive effects.

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 reproductive toxicity evidence.***

Table 5 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 made available for systemic uptake. The primary impact of the moiety will be in determining the dissolution rate of compounds in the gastrointestinal tract (US EPA, 2007). The actual uptake of Sb ions/oxyanions from the gastrointestinal tract appears to be mediated by saturable carrier protein transport systems and will occur with low (<1 %) efficiency (ATSDR, 2017)[4].

The released moieties, many of which are essential nutrients or Essential Trace Elements (ETEs), may also be subject to independent gastrointestinal uptake (in many instances regulated by homeostatic control mechanisms). Given their essential nature, the anticipated reproductive toxicity impact of these moieties, compared to the possible reproductive toxicity impact of Sb, is expected to be negligible. Other moieties are normal metabolites (NM), often of carbohydrate metabolism, and are expected to be rapidly metabolized.

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 5. 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 serve to limit substance administration due to local effects that disrupt essential functions such as food ingestion or breathing. But again, this is not a reasonable and foreseeable situation under REACH. ***The difference in moieties can be omitted for the purpose of read-across for reproductive toxicity evidence.***

As regards the molecular weight and structure of each substance, the information in Table 5 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***

[4] This low uptake rate combines with the emetic properties of Sb compounds (ATSDR, 2017) to limit the systemic levels of Sb that can be achieved via oral exposure.

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difference in molecular weight may need to be considered for the purpose of estimating dosimetry in read-across comparisons of reproductive toxicity evidence.

Impurities in Sb substances are commonly arsenic and lead (in the relevant speciation)[5], but typically in concentration levels below 0,1% or their respective Specific Concentration Limits (SCL)[6]. 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 5 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 reproductive toxicity 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. Reproductive toxicity would require the systemic uptake of a relatively large amount of a given substance, able to reach and/or interact with endogenous molecules in cells or tissues of the reproductive organs or those involved in the development of the conceptus. In this context, the oral exposure route offers the main physiological entry point for Sb substances into the human body; physical forms (and sizes) that can be ingested are those of relevance to reproductive toxicity (in theory, any of the Sb substances in Table 5). The ingestion route is also the route through which consumers will be more likely to be exposed to Sb substances. ***The differences in physical form and particle sizes can be omitted for the purpose of read-across of reproductive toxicity evidence.***

The content of Table 5 shows that on the basis of identity or characterization, beyond valency and molecular weight, there are no major differences between the Sb substances subject to REACH that would challenge a grouping or read-across approach. In short, any Sb substance which does not contain a moiety with a more severe systemic toxicity than that of the moieties in Table 7, could in principle be part of the Sb substances read-across group for reproductive toxicity.

[5] 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.

[6] 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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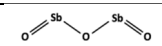
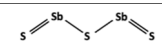
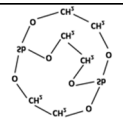
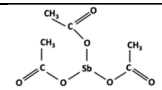
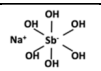
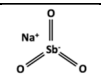
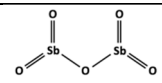
Table 5: Identity and characterization of Sb substances considered for grouping and read-across, or as sources of read-across relevant information.

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)[4]	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]
Antimony triacetate[3]	6923-52-0	>100 µm	298.9	$Sb(CH_3COO)_3$		CH_3COO^-	n.a.[3]	n.a. [3]
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]

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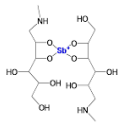
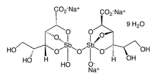
Name	CAS #	Form and typical particle size	Molecular weight (g/mol)	Chemical formula	Structure	Moiety	Purity (% w/w)	Impurities
Trivalent Sb drugs								
Antimony potassium tartrate	28300-74-5	MMAD: 30 µm	667.87	$K_2Sb_2(C_4H_2O_6)_2$				
Pentavalent Sb drugs								
Glucantime (meglumine antimonite)	133-51-7	Liquid	366	$C_7H_{18}NO_8Sb$		N-methyl-D-glucamine		
Pentostam (sodium stibogluconate)	16037-91-5	Liquid	910.9	$C_{12}H_{37}Na_3O_{26}Sb_2$				

(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) Not available, ATA has not been REACH registered so far; (4) 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 reproductive toxicity 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 reproductive toxicity 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+) soluble 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 reproductive toxicity data available on the Sb substances reveal a general trend of no adverse effects on fertility and relatively mild impacts on the ossification of the fetus. This seems to be the result of maternal toxicity, possible influence on the Ca metabolism, and should constitute a reversible effect. The information available does not enable to confidently judge on the actual (dis)similarity of effects inside each subgroup, but the effects do appear to the relatively similar across all Sb substances studied.

As a result, the read-across approach applied to the reproductive toxicity assessment of Sb substances 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 systemic toxicity of most metal(loid)s and their compounds occurs upon: i) the release of soluble metal ions; and ii) their uptake by the body and/or interaction at their target organ sites. 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.

Information on bioavailability can be predicted using in vitro models, such as bioelution, that simulate processes governing uptake 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 physiological conditions.

There are artificial fluids for every relevant route of exposure to be assessed. For the oral exposure route, which is relevant for the systemic uptake of Sb substances, fluids exist which simulate the stomach and the intestinal conditions. A key difference between these two fluids is the pH they mimic: pH of 1.5 for gastric, and

pH of 7.4 for intestinal. Although the uptake of metals is known to occur in the intestine, at neutral pH, the highest release of metal can be expected to take place in the stomach, at acidic pH. Because of this, the gastric fluid is often selected for bio-accessibility testing, as it represents 'worst-case conditions' for release following ingestion.

A relationship can be assumed between in vitro bio-accessibility in an artificial biological fluid, and relative in vivo bioavailability. Bio-accessibility methods are generally considered to overestimate absolute bioavailability and toxicity of inorganic compounds since bio-elution tests do not assess absorption after release. Based on this overestimation, it can be safely assumed that a (worst-case) relationship can be defined between in vitro bio-accessibility in the artificial fluid and relative in vivo bioavailability of the ions that may additionally be absorbed systemically following release.

Table 6: Solubility and bio-accessibility data of Sb substances considered for grouping and read-across.

Name	CAS #	Solubility in water	Bio-accessibility in artificial gastric fluid [2]
Sb – metal powder	7440-36-0	18.2 µg/ml	29.6 µg Sb/ml
Sb – massive metal	7440-36-0		
Diantimony trioxide	1309-64-4	0.370 µg/ml	8.15 µg Sb/ml
Antimony sulfide	1345-04-6	43.5 µg/ml	14.6 µg Sb/ml
Antimony tris(ethylene glycolate)	29736-75-2	0.4 µg/ml	15.3 µg Sb/ml
Antimony trichloride	10025-91-9	Technically not feasible	15.9 µg Sb/ml
Sodium hexahydroxoantimonate	33908-66-6	594 µg/ml	260 µg Sb/ml
Sodium antimonate	15432-85-6	247 µg/ml	325 µg Sb/ml
Antimony pentachloride	7647-18-9	Decomposes in water	580 µg Sb/ml
Antimony pentoxide	1314-60-9	453 µg/ml	1.16 µg Sb/ml
Potassium hexahydroxoantimonate	12208-13-8	17,100 µg/ml	184 µg Sb/ml

[1] Extracted from the Chemical Safety Reports (2019)
[2] 2 hours Bio-elution Study on 10 Sb substances at a 0.2 and 2 g/L loading in a simulated gastric fluid (Brouwers, 2019)

Table 6 provides information on the release and behavior of Sb species in a number of physiologically relevant media.

Bio-elution assays in artificial gastric fluid (0.07 N HCl) have been (repeated or) launched on all ten (10) Sb substances in scope in 2018, with results reported in 2019. The assays were conducted according to the Standard Operating Procedure for Bio-elution Testing of Metals, Inorganic Metal Compounds (Eurometaux, October 31, 2018) currently in the process for validation by ECVAM; as well as in artificial gastric fluid supplemented with physiological constituents, naturally present in the human gastric juice, such as: urea, glucuronic acid, glucose, glucosamine, mucin, bovine serum albumin and pepsin.

The results of these assays provide various observations:

- All substances release a minimum amount of Sb ions (Sb3+ for the trivalent substances and Sb5+ for the pentavalent substances), except Sb pentoxide which releases at levels near the limits of analytical detection in such conditions.
- The trivalent substances seem to be less bio-accessible than the pentavalent substances, and could be foreseen as a sub-group for further systemic toxicity assessment.
- The pentavalent substances, excluding Sb pentoxide, present a significantly higher bio-accessibility, and could constitute a second sub-group in terms of read-across for systemic toxicity endpoints.
- The presence of physiological gastric proteins did not cause any significant difference in the dissolution of the Sb compounds except for the Sb tris(ethylene glycolate) and Sb trichloride, for which the capacity to release Sb3+ ions was three times higher than in a medium without proteins. This last observation could be explained by the fact that the molecular structure and moieties of these two Sb substances could increase their chemical affinity for proteins, resulting in a further redox reaction, resulting in a higher release of Sb ions.

There is little data detailing speciation or changes in valency following uptake of Sb into mammalian systems (ATSDR, 2017). The information in Table 7 below may however provide an indication of general trends.

Table 7: Summary of available ADME information on Sb substances.

Absorption	Distribution	Metabolization	Excretion
The valence state of Sb compounds has been suggested to impact uptake from the gastrointestinal tract but differences reported are generally small (ATSDR, 2017). As a generalization, uptake efficiency is very low (less than 1%) and likely nonlinear, with saturation of uptake processes as administered doses increase.	Valency (and changes in valency) of systemic Sb in mammalian systems, has not been well characterized but appears to influence Sb distribution within the body and subsequent excretion. Systemic Sb 5+, after ingestion or injection, tends to partition to blood plasma and the spleen whereas Sb 3+ is preferentially found with the erythrocyte and the liver (Edel et al., 1983; Poon et al., 1998; Coelho et al., 2014). Sb ions cross the placenta, but there is no comparative data that documents the impact of valency state upon placental transfer. The half-life of systemic Sb appears to be in the order of 10 days.	Conversion of 23% of Sb 5+ to Sb 3+ has been documented in studies of substances administered via intramuscular injection to humans (Vasquez et al., 2006). This conversion appears to be thiol mediated (Ferreira et al., 2003) and not enzymatically controlled. Whereas metabolism of Sb 3+ was not thought to occur, recent studies have documented di and tri-methyl Sb 5+ metabolite formation from Sb 3+ (He et al., 2019). Initially documented in plants, bacteria and fungi, in crops, methylation varies as a function of cultivar and section of the plant that is sampled (Ji et al., 2018). Human populations residing in Sb contaminated areas excrete methylated Sb in their urine, a probable reflection of ingestion of methylated Sb (Li et al., 2018) whereas inorganic Sb in urine is associated with occupational exposure. Some level of Sb methylation is suspected to occur in the liver, with subsequent accumulation of methylated Sb within the erythrocyte (Wu et al., 2018). The mechanism for this metabolism has yet to be determined but appears to result in the conversion of Sb 3+ to di- and tri-methyl Sb 5+ compounds. This metabolism is thought to be a detoxification mechanism that facilitates excretion and reduces the systemic burden of more toxic Sb 3+ moieties.	The impact of valency, and changes in valency, of systemic Sb once taken up into mammalian systems has not been well characterized but appears to influence Sb distribution within the body and subsequent excretion. Valency does affect excretion routes with Sb 5+ exhibiting urinary excretion while fecal metabolism predominates for Sb 3+.

The information above shows that Sb 3+ and Sb 5+:

- Have a comparable limited gastrointestinal absorption of around 1%;
- Will follow different distribution paths after absorption, with Sb 3+ found mainly in erythrocyte and the liver, while Sb 5+ found in blood plasma and the spleen;
- Will convert (from Sb 5+ to Sb 3+), especially where they are soluble (insoluble forms will remain unchanged); and be subject to methylation that converts Sb 3+ to di- and tri-methyl Sb 5+;
- Will follow different excretion paths, with Sb 3+ being excreted via feces and Sb 5+ via urine.

Two valency states of Sb ions can be released by Sb substances: Sb 3+ and Sb 5+ forms. Although sharing a number of properties, differences are evident in toxicokinetics, potential metabolism and, possibly also, toxicity of the two valency states. The significance of these differences will vary as a function of possible

valency state interconversion such that exposure to Sb 5+ may result in the formation of Sb 3+, and Sb 3+ may undergo conversion to methylated forms of Sb 5+. Although methylation of Sb is generally regarded as a detoxification pathway, the toxicity of methylated Sb has not been well characterized. The extent of methylation in plants is highly variable and contributes to methylated Sb in the diet (Ji et al., 2018). In vivo methylation in mammals may occur as a result of gastrointestinal flora activity or within organs such as the liver (Wu et al., 2018). The extent of methylation appears to be low (e.g. 1 – 2%) but requires further study.

For metals under homeostatic control, uptake is regulated and bioavailability can be of secondary importance. For others, such as Sb, uptake is not necessary a linear function of dose since sites of uptake (carrier systems) can saturate. The actual uptake of Sb ions/oxyanions from the gastrointestinal tract appears to be mediated by saturable carrier protein transport systems and will occur with low (<1 %) efficiency (ATSDR, 2017). Actual systemic exposure will hence be limited by this very low absorption for any Sb substance.

As regards the species that is released to become available for exposure, as explained in section 3.1 above, Sb 3+ compounds will normally hydrolyze to release an electrophilic Sb ion $Sb(OH)_3$. The behavior of Sb 3+ compounds in solution is likely to be complex and involve the sequential formation of Sb oxide chloride (SbOCl), Sb oxide hydroxide (SbO(OH)) and ultimately the formation of Sb trioxide (Sb_2O_3) (Hashimoto et al., 2003). The pentavalent Sb pentachloride is similarly an electrophilic oxidizing agent which, as a function of pH, will also undergo a series of hydrolytic transformations to oxychlorides and oxide hydroxides that result in the formation of Sb_2O_5 (Zheng, Zhi and Chen, 2006). Although the precise nature of the chemical moiety released in both cases remains unknown, the bio-accessibility data indicates that Sb 3+ substances will likely release Sb 3+ ions, whereas Sb 5+ substances (except Sb pentoxide which does not release at all) will release Sb 5+ ions.

Considering bioavailability as a conservative approach in the assessment of Sb uptake and hazard, and using bio-accessibility results as a worst-case prediction of bioavailability potential, ***for the purpose of read-across, the following subgroups can be established on the basis of bio-accessibility data:***

- ***Subgroup 3+: Show limited release of Sb 3+ in bio-elution tests***
- ***Subgroup 5+ except Sb pentoxide: Show higher release of Sb 5+ in bio-elution tests***
- ***Subgroup Sb pentoxide: Does not release any Sb in bio-elution tests***

3.4 Consistency of the reproductive toxicity information for Sb substances

The assessment of the reproductive toxicity dataset on Sb substances is made in Section 2.4 above and concludes the following:

- The available data (none of which is an OECD 421 study) support the conclusion that Sb substances are not considered to impact fertility.
- The available developmental evidence allows to provisionally conclude that the ossification retardation effects observed are considered not to constitute severe and irreversible reproductive toxicity, and that Sb substances do not have a direct adverse effect on the development of the conceptus.
- In light of this, no reproductive toxicity classification is warranted.

There is some indication of consistency that neither Sb 3+ compounds, nor Sb 5+ compounds (including Sb pentoxide) have reproductive toxicity effects, except those resulting from maternal toxicity or from a possible influence on the Ca metabolism. 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 reproductive toxicity 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 reproductive toxicity 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 Sb 3+:** Source substances: Any Sb 3+ substance releasing Sb 3+ ion and having moieties or impurities which do not have a more toxic systemic toxicity profile than Sb 3+. Target substances: Other Sb 3+ substances releasing Sb 3+ ion and having moieties or impurities which do not have a more systemic toxicity profile than Sb 3+. **Subgroup Sb 5+:** Source substances: Any Sb 5+ substance (except Sb pentoxide) releasing Sb 5+ ion and having moieties or impurities which do not have a more toxic systemic toxicity profile than Sb 5+. Target substances: Other Sb 5+ substances (except Sb pentoxide) releasing Sb 5+ ion and having moieties or impurities which do not have a more systemic toxicity profile than Sb 5+. **Subgroup Sb pentoxide:** Source/Target substance: Sb pentoxide as described in Table 5. Cf. Table 5 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 Sb 3+:** All substances in the category have in common that they have one or more Sb 3+ atoms bond through ionic or covalent bonding with moieties, many of which are essential nutrients or Essential Trace Elements (ETEs), with none or negligible reproductive toxicity, or normal metabolites (NM), which are expected to be rapidly metabolized. **Subgroup Sb 5+:** All substances in the category have in common that they have one or more Sb 5+ atoms bond through ionic or covalent bonding with moieties, many of which are essential nutrients or Essential Trace Elements (ETEs), with none or negligible reproductive toxicity, or normal metabolites (NM), which are expected to be rapidly metabolized. **Subgroup Sb pentoxide:** The only substance in the category is Sb pentoxide. Cf. Table 5 for more detailed identification and characterization information.
Structural differences that are allowed within the category are specified	**Subgroup Sb 3+:** 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, i.e. Sb 3+, remains comparable. **Subgroup Sb 5+:** 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, i.e. Sb 5+, remains comparable. **Subgroup Sb pentoxide:** The only substance in the category is Sb pentoxide. Cf. Table 5 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 Sb 3+:** All substances in the category have in common that they release a common Sb (oxyan)ion 3+ form in vivo. This Sb 3+ form can be considered as a common transformation product.

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Assessment Element/Details	Supporting evidence
	Systemic exposure will be to this common transformation product, no matter the original form of the substance originally present and/or administered. Low level metabolism to methylated Sb 5+ forms may occur, but is believed to be a detoxification pathway. **Subgroup Sb 5+:** All substances in the category have in common that they release a common Sb (oxyan)ion 5+ (which may partially convert into a Sb 3+ form in vivo). The Sb 5+ form can be considered as a common transformation product. Systemic exposure will be to this common transformation product, no matter the original form of the substance originally present and/or administered. Some conversion to Sb 3+ may occur. **Subgroup Sb pentoxide:** The only substance in the category is Sb pentoxide. Cf. Section 3.3 for more information on transformation products.
Degradation, bioaccumulation and impact of non-common compounds	**Subgroup Sb 3+, Sb 5+ or Sb pentoxide:** The moieties of the various Sb substances of the group will be absorbed for essential functions in the body or metabolized as any other normal metabolite. Cf. Section 3.2 for more information.
Impact of impurities on the prediction	
The identified impurities have an impact on the prediction	**Subgroup Sb 3+, Sb 5+ or Sb pentoxide:** 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 5 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 Sb 3+:** The reproductive toxicity dataset available for Sb 3+ substances contains only one endpoint for which comparable studies are available on more than one Sb 3+ substance: Prenatal Developmental Test. Overall there is test data for three Sb 3+ substances (Sb metal, Sb trioxide and Sb trichloride). The results are globally the same: delayed ossification possibly mediated by maternal toxicity. **Subgroup Sb 5+:** The reproductive toxicity dataset available for Sb 5+ substances is limited to information on Sodium hexahydroxoantimonate. The results are the same as for the Sb 3+ substances: delayed ossification possibly mediated by maternal toxicity. **Subgroup Sb pentoxide:** There is no reproductive toxicity data for Sb pentoxide. 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 reproductive toxicity 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 read-across approach for Sb substances.

Name	CAS #	Reproductive toxicity classification	Further testing needs
Subgroup Sb 3+:			• Array of 2-week dose-range finding/tolerance studies; • OECD 422 in vivo Combined Repeat Dose Screening Reproductive studies; • OECD 414 in vivo Prenatal Developmental Toxicity studies, if necessary; • Additional higher tier oral study, if necessary.
Sb –powder	7440-36-0	Not classified	
Sb – massive	7440-36-0	Not classified	
Diantimony trioxide	1309-64-4	Not classified	
Antimony sulfide	1345-04-6	Not classified	
Antimony tris (ethylene glycolate)	29736-75-2	Not classified	
Subgroup Sb 5+ (except Sb pentoxide):			
Antimony trichloride	10025-91-9	Not classified	
Sodium hexahydroxoantimonate	33908-66-6	Not classified	
Sodium antimonate	15432-85-6	Not classified	
Antimony pentachloride	7647-18-9	Not classified	
Potassium hexahydroxoantimonate	12208-13-8	Not classified	
Subgroup Sb pentoxide			
Antimony pentoxide	1314-60-9	Not classified	

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4. References

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