28 november 2018

EHS topics update

1	Evaluation	

	1.1 Substance Evaluation	In the context of the Substance Evaluation, i2a continues to share with BAuA the progress of the research program aiming to tackle the remaining knowledge gaps around the toxicology of Sb substances.
		An update of the strategy developed under COLLA will be sent to BAuA by end of the year. It will list all the actions i2a has already taken:
		- Set up of the in vivo reproductive toxicity study plan
		- Set up of the tests for the lung toxicity assessment:
		  o Validation of the method for determination of the total antimony dissolved and antimony V and III in simulated physiological media
		  o Bio-elution testing on the 10 antimony substances in simulated gastric fluid and simulated gastric fluid + proteins
		  o In vitro inhalation study on alveolar cells (see in vitro inhalation test section)
		- Set up of genotoxicity testings:
		  o Tox tracker assay on 12 antimony substances
		  o Assay to interpret micronucleus observed in vivo in the NTP study
		- Set up of a workplace monitoring campaign aiming to generate workplace air exposure data.
		- Contacting the Belgian Federal Police to collect exposure data from indoor shooting ranges.
		
		BAuA will be able to comment the strategy but will not issue an official document to agree or disagree on i2a's plan.
		
		A Toxicologists Task Force and a Monitoring Task Force have been set up to enable more in-depth discussions on the reprotoxicity study, in vitro inhalation study and workplace monitoring program among scientific experts of i2a members . Conference calls, webinars or meetings are scheduled every 6/8 weeks on these specific topics. EHS participants are invited to notify i2a their interest to be included in these two TF.
		
		Registrants of the trivalent substances are expecting the formal Draft SEv decision from ECHA in April 2019.
		
		i2a's COLLA/SEv plan is also being used to satisfy i2a's commitment to the Metals and Inorganics Sectorial Approach (MISA). MISA aims to facilitate a more systematic improvement of Registration Dossiers by asking associations to inform ECHA about their internal update plans. By submitting i2a's dossier update work plan through MISA, i2a's planned SEv work becomes visible to the broader ECHA structure and other Member States, thereby decreasing the risk that Sb substances are picked up in parallel REACH or CLP processes.

	1.2 REACH dossiers submission	The 2018 dossier updates for SHHA, SAA and APO have been submitted. All of i2a reach Dossiers have now been updated during the current year and reflect now the new health assessment triggered by the results of the 2017 NTP carcinogenicity study.

International Antimony Association (VZW)
Avenue de Broqueville 12, 1150 Brussels, Belgium//Phone : +32 (0) 32 2 762 30 93 / Fax : +32 (2) 762 82 29
www.antimony.com

2	**Classification**	
	2.1 eSDS review	Following the review of all the eSDS, and the collection of translation needs among i2a Members, translated versions are now finalized. All members will receive in the coming week the specific language versions they have requested in the original survey. The new German OEL of 0.006 mg Sb/m³ respirable applicable to ATO and ATS has been included in the ATS eSDS and will be included in the ATO eSDS which were prepared before the German OEL became public.
	2.2 Transport Classification	The plan is still to submit a new transport classification proposal after the REACH Evaluation.
3	**EHS strategy**	
	3.1 Status of scientific publications	- The tox tracker report *"Genotoxic properties assessed by ToxTracker*" is finalized (Annex 1). 12 substances have been now tested (the 10 i2a substances having a Reach dossier and 2 additional substances typically reported in reference literature: antimony triacetate and antimony potassium tartrate). None of the tested antimony compounds showed genotoxic properties in the ToxTracker assay in absence or presence of a metabolizing system. Significant levels of oxidative stress were observed for most of the compounds, but there was no indication that oxidative stress led to indirect genotoxicity. Activation of the unfolded protein response was also observed for most tested compounds. There was no indication for any of the tested antimony compounds that their toxicity was increased due to metabolism by the liver. R. Cortvrindt will now start the drafting of the article analyzing these results through a publication. i2a will need to revert on the identification of the scientist journal to publish. - The second genotoxicity article on "Analysis and synthesis of genotoxicity data on antimony substances" will be drafted by C. Boreiko as main author in 2019. - No new action has been taken on the article on: "The presence of Sb in consumer products". The Sb Day however revealed that information could be collected with Br and PVC producers and users, who have generated leaching data. - The potential article on the reprotoxicity study plan will be placed on the agenda when the planned reprotox study will be finalized (mid-2019).
	3.2 In vitro Inhalation Study	Following the last Tox TF call on the in vitro inhalation study with Matthew Boyles from IOM, i2a has organized a face to face meeting to discuss in details the strategy of the study. For recall, the main objectives of the study are: - Assessing the solubility and lung cytotoxicity potential of the various Sb substances

International Antimony Association (VZW)
Avenue de Broqueville 12, 1150 Brussels, Belgium//Phone : +32 (0) 32 2 762 30 93 / Fax : +32 (2) 762 82 29
www.antimony.com

		- Filling knowledge gaps, especially on Sb (V) - Avoiding a grouped harmonized Classification Carc 1B with no specified exposure route following Substance Evaluation During the meeting, it has been agreed to first identify the characteristics of the substances to be tested. Identification of the physical form, particle size, surface area, stability will be assessed for each antimony substance and at all stage of the life cycle, from the production to the placing on the market. This will allow to select the relevant substances for lung toxicity, and the physical form/size in which they should be tested. Therefore a request for proposal for characterization of the particle size and surface area for all substances will be sent to different labs. Depending of the output of the analysis, the way to prepare the samples will be defined (milled/grounded). The substances to be tested will be selected and their surface charge and endotoxin contamination will be also characterized before testing. Then, IOM will proceed in an in vitro screening on alveolar cells (macrophage and epithelial cells) from cells lines of rat, mice and human species. It will enable to highlight the cytotoxicity, cell viability, oxidative potential and cytokine release (marker of inflammation) and to compare the effects of different substances in different species. Those Sb substances yielding a positive effect (i.e. high solubility and cytotoxicity) will be screened again in a second phase to attempt to determine the mode of action of the oxidative stress and the DNA damage which will enable to refine the Mode of Action (MoA) hypothesis and strengthen the read across. The initial proposal from IOM will be updated by end of the year and will be shared with the EHS group for final discussion and approval.
	3.3 Reprotoxicity study	As discussed at the last tox TF a Combined Repeated Dose Toxicity Study with the Reproduction/Developmental Toxicity Screening (OECD 422) has been designed to generate information concerning the effects of antimony substances orally administrated on male and female rats reproductive performance such as gonadal function, mating behaviour, conception, development of the conceptus and parturition. It has been designed to clarify two questions of specific relevance to Sb substances: the link between the observed foetus toxicity and the maternal toxicity, and the effect of Sb and possible reversibility of the delayed ossification observed in previous studies. This study is coordinated by Lindsay Aveyard, expert in reprotoxicology and will be performed by Envigo. The study will last 28 days + 3 weeks to observe the effects on offspring reared to weaning and selected offspring treated at least from weaning is planned to be; The proposal has been sent for review and comments and is now accepted. The contract with ENVIGO will be signed by the end of November, formalities and laboratory capacity secured in December, and the study will be performed in Q1 2019.

International Antimony Association (VZW)
Avenue de Broqueville 12, 1150 Brussels, Belgium//Phone : +32 (0) 32 2 762 30 93 / Fax : +32 (2) 762 82 29
www.antimony.com

	3.4 Bioelution test	ECTX has received from the lead registrants the 10 substances to be tested in the 2 simulated gastric fluids (with and without proteins). The protocol will follow the SOP procedure developed by Eurometaux and ECVAM. The study plan with a timeline and a quote will be addressed to i2a beginning of December and will be shared at the next EHS call. The plan is to collect the bioelution samples 1st half of January and to measure them at Vito site 2nd half of January. These results will allow to inform the choice of the test item for the reproductive toxicity study, and refine the read-across justification for the oral chronic endpoints. The potential need to test on other biofluids (e.g. alveolar, lysosomal or interstitial) is still under assessment. Identification of the relevant proteins for the inhalation route, and the validation of the Sb determinations from these fluids will be needed before these follow-up bioelution tests are launched.
	3.5 Quantification and speciation method	VITO has finalized the report on the validation of the method for the determination of Sb in several bioelution fluids (Annex 2). The bioelution samples in gastric fluids will be now analyzed through these methods. The Total dissolved antimony will be measured through the ICP-MS method whereas the antimony III and V will be measured through the more complex method, HPLC ICP-MS, able to distinguish both species, antimony III and antimony V. However, it has been shown that the method to identify antimony V in the simulated gastric fluid with proteins was not fully reliable. i2a is investigating what are the implications in the interpretation of the future measurements of this species.
	3.6 Workplace air exposure monitoring	Following the i2a communication, through the Task Force and the recent antimony days, i2a received a lot of interest in the workplace air exposure monitoring campaign. IOM, selected partner of the program, has presented the different steps of the projects during the antimony days (Annex 3) - Development of the monitoring guidance document for collection of inhalation and respirable samples and supporting contextual information - Collection of respirable and inhalable personal samples and measure particle size distribution (PSD) at producer and DU sites - Development and population of an exposure database - Appropriate agreed statistical analysis of the collected exposure measurement data and reporting At its recent conf call, the Monitoring TF was invited to comment the second draft version of the Monitoring Guidance and companies were invited to come forward and express their interest to participate in the Campaign. First confirmed companies will have the possibility to exchange with IOM to define their specific monitoring strategy and budget requirements, and may also be able to loan the monitoring equipment from IOM, instead of purchasing it. A minimum of two producers and two users of each main use of Sb substances (not only

International Antimony Association (VZW)
Avenue de Broqueville 12, 1150 Brussels, Belgium//Phone : +32 (0) 32 2 762 30 93 / Fax : +32 (2) 762 82 29
www.antimony.com

		ATO) needs to be identified before the 21 Feb 2019 kick-off workshop. Ideally, three or more of each producer or users should participate.
4	**Next meetings/calls and AOB**	
	4.1 AOB	- T25 analysis for ATO has been calculated. The assessment of the applicability of the method is in the hands of Eurometaux and the Cobalt institute. i2a's input and the input of other sectors has been used to obtain recognition that the T25 approach may not be applicable to metals. A dedicated Work Group is being set up by ECHA to further discuss what the best solution would be. - A PSLT workshop (Poorly Soluble Low toxicity particles) will be organized by Paul J.A. Borm and Kevin E. Driscoll on the next 1 and 2 April, 2019. This WS has been initiated in the context of the proposed classification of titanium dioxide (a PSLT) as a Carc Cat 2. Indeed, a paradigm stating that the rat tumours caused by PSLTs are not relevant for humans, has been developed by these two scientists. i2a has been invited and has accepted to join the initiative as we know that the antimony effects after inhalation exposure also result in a particle overload in rat lung. i2a has been invited to sponsor the event with up to 2000 €. It is i2a's Secretariat recommendation that this should be provided as this discussion around carcinogenicity effects caused by PSLT is directly relevant for the expected classification discussions on Sb substances.
	4.2 Next meetings/calls	The next call is planned on 13 December at 2:00 PM (CET) The date for the 2019 EHS calls will be sent by end of the year with a 2 months occurrence. A dashboard to visualize/monitor the progress of the many projects managed under the EHS Group umbrella will be proposed at the next call. Relevant EHS events include: - i2a Workplace Exposure Monitoring Workshop: 21 February 2019 in Brussels (Belgium) - PSLT Workshop: 1-2 April 2019 in Edinburgh (UK)

Annex 1: Tox Tracker final report
Annex 2: Validation of a method for determination of total dissolved antimony, and antimony III and V
Annex 3: IOM presentation on the Workplace monitoring program
Annex 4: Summary of the PSLT survey
Annex 5: PSLT Work Shop agenda – 1 and 2 April 2019

International Antimony Association (VZW)
Avenue de Broqueville 12, 1150 Brussels, Belgium//Phone : +32 (0) 32 2 762 30 93 / Fax : +32 (2) 762 82 29
www.antimony.com