International Antimony Association Comments

2019 draft Notice of Intended Change *Documentation for Antimony Trioxide*

31 May 2019

Introduction

The International Antimony Association, hereafter referred to as "i2a", welcomes the opportunity to comment upon the 2019 Notice of Intended Change (NIC) draft *Documentation for Antimony Trioxide.* i2a is a commodity association based in Brussels, Belgium that represents the collective interests of Antimony producing and importing companies worldwide. The membership of i2a consists of more than 30 companies located throughout Europe, North America, Middle-East and Asia. The mission of i2a is to conduct studies, and to disseminate information concerning the safe use and benefits of Antimony and Antimony compounds. This entails generating data, giving access to data, sharing and providing information on the interpretation of scientific studies, and promoting awareness of worldwide environmental, health and safety regulations that are relevant to Antimony substances.

i2a has reviewed ACGIH's NIC draft *Documentation for Antimony Trioxide* (2019). In most instances, the NIC relies upon the interpretation of insufficiently documented or supported older references, provides superficial reviews and background documentation on important endpoints such as genotoxicity, and infers (but does not display calculations for) concepts such as Human Equivalent Concentrations upon which animal to human extrapolation is based and which provide the basis for derivation of TLVs. Through calculations that are not presented in the NIC, rodent inhalation data for *respirable* particles are also used to calculate an *inhalable* exposure limit to limit human exposures in the workplace. These shortcomings prevent us from submitting a thorough and constructive assessment and comment on the proposed TLV. ***This submission therefore aims at bringing the most objective (though sometimes general) comments, pending the future publication of additional details necessary to the performance of a more complete comment on the proposed TLV.***

As regards the calculation of an *inhalable* TLV based on *respirable* exposure levels in particular, although i2a concurs with the indexing of TLV development to pneumonitis and understands the

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rationale for initiating TLV-development based upon the respirable fraction of aerosols used in rodent inhalation studies, no sound scientific rationale or transparent calculation is offered for the inhalable TLV value subsequently recommended. Key modeling parameters needed for predicting respiratory tract deposition using the MPPD are not presented, and the strategic rationale for the application of Assessment Factors integral for rodent to human extrapolation is never outlined. ***We respectfully wish to bring to your attention the fact that the absence of a clearly articulated scientific approach and rationale for the proposed TLV precludes meaningful review of the scientific merits of the draft NIC.***

These deficiencies are similar to those present in the 2017 NIC for diantimony trioxide and were commented upon extensively by i2a at that time. Unfortunately, ***deficiencies identified in the previous version of the NIC (2017) have not been addressed, and the present version does not provide the scientific transparency nor a compelling argument for significant downward revision of the Antimony Trioxide TLV.***

As also noted earlier, i2a has embarked upon a program of occupational exposure characterization, documenting the presence of respirable and inhalable aerosols in different antimony process environments. ***We wish to note that this i2a monitoring program is intended to replace outdated references of occupational exposure assessment.*** The exposure monitoring program is further assessing health surveillance data collected by its membership over many years - ***data analyzed to date and shared with ACGIH in 2017 already do not suggest significant health impacts from exposures at the current TLV, and do not demonstrate the health benefits that would result from a proposed downward revision of the TLV.***

It is from this perspective that i2a has reviewed the (2017 and) 2019 *Documentation for Antimony Trioxide* and propose a series of recommendations that would enhance the technical rigor and scientific transparency of the NIC, despite the very limited description and justification provided to document the TLV calculation.

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Recommendations

1. A paucity of information is provided by ACGIH concerning historical or contemporary occupational exposure levels to Antimony Trioxide. i2a provided historical and some current occupational exposure information in 2017, the inclusion of which was hoped to facilitate the interpretation of scientific publications and historical health data reviewed in the NIC. The monitoring program is ongoing, documenting both inhalable and respirable exposures to antimony compounds with first results expected after two annual campaigns (2019 and 2020), in 2021. ***We hereby wish to confirm that the results of this monitoring campaign will be made available to ACGIH and would permit updating of antimony exposure data to reflect modern production practices.***

2. A Threshold Limit Value (TLV) indexed to the *inhalable* particulate content of Antimony Trioxide occupational aerosols has been proposed. However, no **fundamental** context is supplied that relates this proposed inhalable TLV to the *respirable* exposure levels evaluated in rats and mice by NTP (2017). A study report evaluating the particle size distribution of occupational aerosols associated with Antimony Trioxide production and use was provided to ACGIH in 2017 to define probable relationships between *inhalable* and *respirable* exposure levels. This does not appear to have been factored into the current NIC proposal. ACGIH thus has proposed an inhalable TLV based upon the toxicity of respirable aerosols by rats and mice but the technical basis for extrapolating from one particle size fraction (inhalable) to another (respirable) is never discussed. ***We respectfully request that derivation of the inhalable TLV from respirable particle effects data should be presented by the NIC in sufficient detail to permit independent calculation and verification of the proposed TLV.***

3. The present *Documentation* contains no information regarding the ongoing development of medical surveillance procedures at Antimony Trioxide production facilities. These procedures were described in i2a's 2017 submission since they provide information on potential health impacts of Antimony Trioxide inhalation that are relevant to TLV derivation. The present NIC however, appropriately notes that the pneumonitis inducted by antimony trioxide is relatively benign and normally does not impact upon measures of pulmonary function. The documentation

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submitted by i2a in 2017 supports this conclusion. ***We respectfully request that more recognition is given to the recent workplace exposure practice and initiatives is given in the NIC.***

4. The overall medical surveillance framework under which a TLV is derived and enforced further bears upon the selection of appropriate assessment factors required to account for scientific uncertainty in TLV derivation. Appropriately designed surveillance programs can limit scientific uncertainty by identifying subpopulations with heightened sensitivity to antimony toxicity and/or validate the extrapolation of effects observed in animal studies to those anticipated to occur in humans. Exposure scenario characterization coupled to information on the presence or absence of health impacts thus increases the precision with which relationships between exposure intensity and health impacts can be defined for further investigation. The 2019 version of the NIC does not address the assessment factors that have been applied in the derivation of the current TLV proposal or sources of scientific uncertainty encountered. The application of assessment factors entails expert judgement decisions that (ideally) are presented in an open and transparent fashion. ***We respectfully request that the key decisions and assumptions made for purposes of TLV derivation are clearly identified and justified in the NIC.***

5. The *Documentation for Antimony Trioxide* proposes an inhalable TLV of 0.02 mg/m^3 based upon health impacts in rats and mice resulting from exposure to respirable particles. The current Antimony Trioxide TLV of 0.5 mg/m^3 inhalable particulate matter was adopted to reduce or prevent the incidence of pneumonitis in the workplace. Although i2a concurs with the health endpoint selected for TLV derivation (i.e. pneumonitis), the new proposed TLV is derived (without significant discussion) from a LOAEL of 3 mg/m^3 observed in recent inhalation studies conducted in rats by the National Toxicology Program of the United States (2017). Informed scientific evaluation of a TLV derived in what appears to be a rather arbitrary and cryptic fashion, is not possible, especially when available medical surveillance evidence does not identify any major or enhanced impact on workers' health when occupational exposures are maintained at or below the current TLV. At a minimum, ***we respectfully request that the animal study LOAEL is discussed in the NIC within the context of the combined available data from other animal studies, human occupational exposure data and other ancillary studies (often***

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mechanistic) that impact upon the Assessment Factors that are adopted in the derivation of the proposed TLV. The NIC alludes to the importance of such factors, but only offers a superficial review that does not permit a true weight of evidence evaluation. Only after the presentation of the critical data and assumptions relevant to TLV derivation can the scientific merits of a proposed TLV be properly critiqued.

6. The current NIC derives a human equivalent concentration (HEC) as the first step in extrapolating from the NTP LOAELs. Dosimetry modeling (MPPD v 2.1) was initially used to determine the antimony aerosol concentrations that would yield the same amount of deposition in rats and humans. Thus, a LOAEL of 3 mg/m^3 is said to be equivalent to a human exposure of 4.8 – 5.6 mg/m^3. However, the NIC provides little explanation of the rationale behind the derivation of the HEC. MPPD modeling is contingent upon the selection of substance- and species-specific inhalation parameters that influence particle deposition within the respiratory tract. Thus, MPPD model predictions are usually presented with clear definition of model input parameters (particle MMAD, patterns of breathing, levels of exertion etc.). The omission of this information prevents determination of whether the proposed HEC calculation is appropriate. The NIC further fails to specify the particle size distribution used as input to MPPD. Was modeling conducted based upon aerosols with characteristics similar to the NTP studies, or was the observational data of workplace aerosols provided by i2a used? HEC calculations are usually also indexed to calculations of the surface areas of different regions of the respiratory tract. In this fashion, species-specific predictions can be made that calculate the delivered dose of test substance per unit surface area of respiratory target tissue. Clearance half-times can also be generated (or observational data used) that can influence HEC calculations. The NIC does not present the key input parameters for fundamental to MPPD deposition modeling. As a result, i2a is unable to evaluate the validity of the HEC calculations that have been made. ***We respectfully request that key modeling assumptions are presented in the NIC, inclusive of all input variables used, in order to permit assessment of the HEC validity.***

7. *Occupational Exposure:* i2a recognizes that ACGIH prefers to place reliance upon information published in the peer-reviewed scientific literature. However, only limited published information is available on the levels of exposure to Antimony Trioxide in the workplace. i2a believes this is

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most likely due to the lack of health impacts, in particular following the adoption by ACGIH of exposure standards that seem to have eliminated the pneumonitis that was associated with excessive **historical** exposures to Antimony. Regulatory processes within the European Union have generated documentation that characterizes occupational exposures to Antimony Trioxide associated with a variety of workplace scenarios. For example, under the auspices of the Existing Substances Program of the European Chemicals Bureau, a formal risk assessment of Antimony Trioxide was undertaken by Sweden which included evaluation of levels of occupational exposure associated with multiple workplace scenarios (ECHA, 2008). ECHA risk assessment documents have been extensively reviewed by EU Member States and should be considered to have a peer-review status equivalent to that of a scientific publication known as a systematic review as described by Levels of Evidence guideline published by the Centre for Evidence Based Medicine (CEBM) at University of Oxford (Howick et al., 2011) .

The baseline years for the exposure assessments within the Swedish risk assessment were generally 2005 or earlier, and calculations were made of the median and upper 90th percentile inhalation exposure levels associated with different processes for the production and use of Antimony Trioxide. In general, the highest inhalation exposures observed were associated with the Antimony Trioxide production process of oxidative conversion (median and upper 90th exposures of 0.54 and 2.9 mg/m^3, respectively), refuming (0.23 mg/m^3 median and 0.94 mg/m^3 upper 90th), and packaging during final handling (0.79 mg/m^3 median and 2.1 mg/m^3 upper 90th). Use of respiratory protective equipment reduced the actual inhalation exposure levels experienced at some facilities. Past and no longer applicable exposures in the late 1990's for these same processes were noted to approach significantly higher levels of 10 mg/m^3 (Vandenbroele, 2003). Contrary to the statements of the NIC, the levels of exposure that characterized the industry in years past can and have been reconstructed, and have been previously communicated to ACGIH (as will be communicated the exposure levels that are being collected in the current monitoring). ***We respectfully request that citation of all relevant (historical) exposure data is made in the NIC.***

8. *Occupational aerosol particle size distribution:* Work commissioned from the Institute of Occupational Medicine (IOM) in Edinburgh by i2a for the EU Existing Substances Program characterized the occupational aerosols associated with Antimony Trioxide production

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(Hughson, 2005). The typical finished Antimony Trioxide commercial product had a mean diameter as small as 1 µm that, when aerosolized, would have a mass median aerodynamic diameter (MMAD) of approximately 2 µm. Given that the 90th percentile cut-off for respirable dust is 7 µm, it might at first appear that the majority of Antimony Trioxide in occupational aerosols would be of a respirable size range. Hughson (2005) characterized multiple Antimony Trioxide production sites and workplace scenarios using both cascade impactors and GRIMM aerosol spectrometers. Although significant variability was observed between sites and workplace scenarios, 60 – 80% of the Antimony Trioxide particles in occupational aerosols sampled by cascade impactors had MMADs greater than 7 µm, indicating that particle agglomeration occurred in occupational aerosols The relationship between respirable and inhalable dust measurements will likely be variable, but the available data indicates that inhalable dust measurements will be 2 – 5 times greater than respirable dust measurements. ***We respectfully request that ACGIH clarifies whether and how these studies have been taken into consideration in the NIC and/or if any conversion factors were applied to estimate the quantity of respirable material contained within an inhalable aerosol.*** The fashion in which an inhalable human TLV has been derived from rodent studies of respirable particles should be explicitly detailed.

9. *Medical surveillance programs:* The findings of the EU Antimony Trioxide Risk Assessment Report prompted i2a to commission voluntary health management guidelines for workers with occupational exposure to Antimony Trioxide (Hoet, 2009). These guidelines formalized medical surveillance, exposure assessment and respiratory protection procedures designed to monitor and protect the pulmonary function of workers exposed to Antimony Trioxide. These guidelines did not mark the initiation of medical surveillance among Antimony Trioxide workers – monitoring of health effects specific to Antimony Trioxide had, in some instances, been ongoing for 40 years or more. Nor were the guidelines mandatory. Instead, they were designed for voluntary implementation within the context of different national frameworks with access to medical information at times being limited by doctor-patient confidentiality regulations. Working towards, or below, an inhalable Antimony Trioxide TLV of 0.5 mg/m^3, the medical surveillance guidelines specified routine pulmonary function testing (spirometry and chest x-rays) for exposed workers, and monitoring of urinary Antimony excretion in an effort to identify workers whose inhalation

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exposure might exceed 0.5 mg/m^3. The urinary cut-off points utilized for such purposes varied among companies from the value of 49 µg/L recommended by Hoet (2009) to the lower value of 35 µg Sb/g creatinine recommended by Bailly *et al.* (1991) for identification of workers exposed to pentavalent Antimony at airborne concentration of 0.5 mg/m^3 or higher. Although specified for pentavalent Antimony (used in medical applications), the Bailly *et al.* (1991) urinary limit value had been judged by some companies to be appropriate for protection of the worker exposed to Antimony Trioxide.

Examples of medical surveillance data reported to i2a by its membership had been submitted earlier to ACGIH in 2017 and are reproduced in part below (Figure 1). This particular data set tracked the incidence of stibiose (Antimony pneumonitis before and after implementation of the ACGIH TLV recommendation of 0.5 mg/m^3): Data on the incidence of stibiose (Antimony pneumonitis) at an Antimony Trioxide production facility are displayed in the following figure:

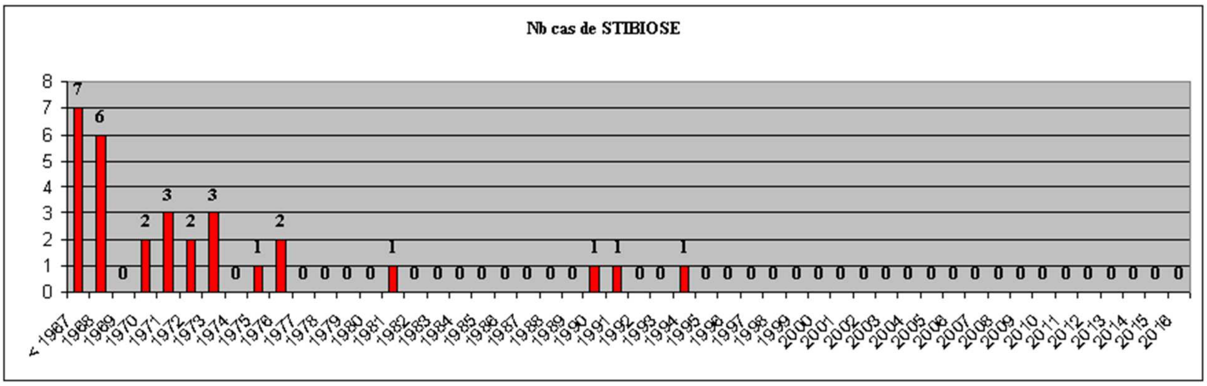

Figure 1. Incidence of Physician Diagnosed Antimony Pneumonitis at an Antimony Trioxide Production Facility (1967 – 2016)

These data are derived from a national jurisdiction where medical management of worker health is controlled by independent physicians who report to the company when the pulmonary health of a worker might be compromised by exposure to Antimony Trioxide. These diagnoses are made in accordance with professional physician judgment on the basis of x-ray and/or spirometry data. Such "self-reported" data must be regarded with appropriate caveats with respect to the different diagnostic criteria and monitoring equipment employed by different physicians, changing diagnostic criteria over time, and the completeness of data collection. Even given these limitations, the data indicate that although past exposure conditions in the industry created risk of Antimony pneumonitis, improvements in occupational hygiene practice and medical

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management (including the implementation of the current ACGIH TLV of 0.5 mg/m³) have dramatically reduced and probably almost limited the risk of pulmonary impairment. The data indicate that exposure conditions within this specific industrial facility have transitioned from multiple physician reported cases of pulmonary impairment per year to more than 20 years of exposure (1995 – 2016) without a single reported case of pulmonary impairment. ***We would like to request that the NIC explicitly acknowledges the markedly elevated historical, and now significantly improved, occupational exposure conditions in the industry.***

Additional detailed information regarding spirometry and chest x-ray medical surveillance data for Antimony Trioxide exposed workers were summarized in a report to i2a (2017) that was subsequently provided to ACGIH in 2017. The report suggests no impact of Antimony Trioxide upon lung capacity if the current TLV of 0.5 mg/m³ is not exceeded. Combined data from the two Antimony Trioxide facilities detailed findings on 60 workers for spirometry data (FVC, FEV1), chest x-rays and urinary Antimony values over the time period of 1999 to 2017. Despite a number of study limitations (e.g. data collection by different external services, lack of detail on equipment uses or specific protocols followed for spirometry data collection, lack of parallel data collection for personal air monitoring for Antimony Trioxide, lack of lung function data before 1999 for workers who have been employed since 1972, and limited access to raw data due to protection of personal data, etc.), initial analysis of the data has detected no significant relationships between lung function and seniority (a surrogate for past exposure to high levels of Antimony Trioxide). The relatively limited size of the cohort restricts study power and a small impact upon pulmonary function cannot be precluded – but cohort size was adequate to detect an impact of smoking upon pulmonary function.

Maximum urinary Antimony concentrations as high as 161 µg Sb/g creatinine were evident in the high exposure group, suggesting mainly **historical or specific task-related** inhalation exposures significantly in excess of 0.5 mg/m³ Antimony Trioxide, with no apparent subsequent lung impairment. Planned research expansion and more detailed analysis of the exposure database by i2a as part of its recently launched workplace exposure monitoring program will provide indications of whether adherence to the TLV of 0.5 mg/m³ is protective of lung function. ***We respectfully request the NIC to recognize the demonstrated effectiveness of the current TLV of 0.5 mg/m³, and to consider the upcoming occupational evidence.***

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10. *TLV Derivation:* The NIC proposes reduction of the TLV for Antimony Trioxide from 0.5 mg/m^3 (inhalable) to 0.02 mg/m^3 (inhalable) based upon the observation of pulmonary inflammation and impairment in rats and mice following exposure to respirable aerosols of 3 mg/m^3 of Antimony Trioxide in the studies conducted by the NTP (2017). Given the endpoint of concern (pneumonitis) and the respirable nature of the aerosols utilized in the NTP studies, the rationale for indexing a proposed TLV to inhalable Antimony Trioxide would be of significant interest but information required to evaluate the conversion from respirable to inhalable Antimony Trioxide limits is not provided. i2a concurs with the decision to focus upon pneumonitis (as opposed to neoplasia) for a LOAEL in the NTP studies, due to the extreme hypoxia and systemic stress induced by Antimony Trioxide exposure. However, no rationale is provided for the derivation of the TLV from the animal studies, and no attempt is made to align the NTP observations with either existing human data or other animal studies. One can presume that the step-wise application of Assessment Factors was involved in the derivation of the proposed TLV, but the nature and magnitude of assessment factors selected for use are not specified and their validity cannot be determined. In the absence of basic information on the assumptions made in extrapolating from observed effects in rodents to potential effects in humans, it is not possible to evaluate the scientific validity of the proposed TLV. ***We wish to restate that the NIC should be supplemented with a step-by-step description of the procedures and assumptions made in TLV derivation.***

i2a would like to offer the following supplemental observations regarding the derivation of the TLV proposed in the NIC:

- Parallel exposures to rats at similar Antimony Trioxide levels produced more pronounced systemic effects and body weight reductions that suggest exceedance of the MTD. Rats thus appear to be more susceptible to pulmonary toxicity from Antimony Trioxide than mice. The fashion in which species-specific toxicity differences was reflected in the selection of Assessment Factors cannot be determined based on information contained in the NIC.
- Although rats are seemingly more susceptible to toxicity from inhalation of Antimony Trioxide, the studies of Newton *et al.* (1994) cited in the NIC *Documentation* suggest a NOAEL of 0.5 mg/m^3 respirable Antimony Trioxide in the rat.

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- In modern workplace environments, an inhalable aerosol between 1.0 and 2.5 mg/m^3 would be required to yield a respirable aerosol concentration of 0.5 mg/m^3. Reduction of the TLV to 0.02 mg/m^3 (inhalable) would be expected to yield workplace aerosols with a respirable fraction of 0.004 mg/m^3 (20% of total). i2a believes that proper workplace monitoring should be attentive to both the inhalable and respirable fractions of occupational aerosols – with a preference for personal monitoring. The amount of material collected (particularly from respirable samplers) will be extremely limited and (depending upon the protocols followed and instrumentation available) near the limits of analytical detection. Promulgation of a new TLV should be accompanied by demonstrations and assurances that compliance with the TLV can be monitored with routine aerosol sampling technology. ***We respectfully request that ACGIH investigates and specifies the analytical procedures it expects will be required to monitor TLV compliance for the recent TLV proposal – ideally with indications of method feasibility and expectations for the limits of detection, analytical precision and accuracy.***
- Elevated inhalation exposure of humans to Antimony Trioxide is associated with pulmonary changes that validates the use of pneumonitis as an endpoint of concern – but observations of diminished pulmonary function are **historically** associated with inhalable exposures 20 times higher than those that likely had respirable fractions comparable in concentration to those producing effects in the recent inhalation studies of NTP.
- With the advent of lower occupational exposure standards (e.g. 0.5 mg/m^3, use of RPE and imposition of medical surveillance protocols) reports of pneumonitis have ceased.
- Medical surveillance program data, while **currently** not ideal in terms of the technical rigor of pulmonary function data acquisition, number of exposed workers, or inhalation exposure assessment, have detected no alterations in lung spirometry testing or radiographs in workers maintained below an inhalable Antimony Trioxide level of 0.5 mg/m^3. While not statistically significant, there are suggestions of effect in current workers **historically** exposed to markedly elevated inhalable Antimony Trioxide levels, and most probably specific workplace area and task-related exposures, significantly in excess of 0.5 mg/m^3.

We kindly ask ACGIH to (re-)consider the observations made by i2a and whether there is a scientifically demonstrated need for a TLV reduction to 0.02 mg/m^3 (inhalable).

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Meanwhile, i2a will keep ACGIH informed of expansion of its exposure monitoring program and more detailed analysis of the current and growing database aimed at demonstrating compliance with and adequacy of the current TLV of 0.5 mg/m³.

Citable Material

Bailly, R., Lauwerys, R., Buchet, J.P., Mahieu, P and Konings, J. (1991). Experimental and human studies on Antimony metabolism: their relevance for the biological monitoring of workers exposed to inorganic Antimony. Br. J. Ind. Med. 48: 93 – 97.

ECHA (2008). European Union Risk Assessment Report: DiAntimony Trioxide. Available at: https://echa.europa.eu/documents/10162/553c71a9-5b5c-488b-9666-adc3af5cdf5f.

Hoet, P. (2009). Management of the health risks related to chronic exposure to ATO in production workers. Report prepared for the International Antimony Association. **Attached as Annex C**.

Howick, J., Chalmers, I., Glasziou, P., Greenhalgh, T., Heneghan, C., Liberati,A., Moschetti, I., Phillips, B., and Thornton, H. "The 2011 Oxford CEBM Evidence Levels of Evidence (Introductory Document)". Oxford Centre for Evidence-Based Medicine. http://www.cebm.net/index.aspx?o=5653

Hughson, G. (2005). Assessment of dermal exposures and classification of workplace aerosols for antimony trioxide production. Institute of Occupational Medicine (Edinburgh) Report No. 602-00292. **Attached as Annex B.**

i2a (2017). Analysis of medical surveillance data at Antimony Trioxide production companies A and B. Report prepared for the International Antimony Association. **Attached as Annex A.**

i2a (2019). Takeaways of i2a Workplace Exposure Workshops 6 June 2018 and 21 February 2019. International Antimony Association. Brussels, Belgium. **Attached as Annexes E and F.**

i2a (2019). i2a Workplace Exposure Monitoring Guidance and data collection template. International Antimony Association. Brussels, Belgium. **Attached as Annexes G and H.**

Vandenbroele M., Van Sprang P. and Vangheluwe M. Diantimony Trioxide (DAT) exposure assessment: compilation and review of local exposure data. Revised Final Report 10 March 2003 by EURAS, Commissioned by International Antimony Oxide Industry Association (IAOIA). 2003; pp 1-130. **Attached as Annex D.**