International Antimony Association

International Antimony Association Comments
2017 draft NIC *Documentation for Antimony Trioxide*
31 May 2017

Executive Summary

The International Antimony Association (i2a) has reviewed the NIC draft *Documentation for Antimony Trioxide* and has recommendations that would both enhance the technical rigor and scientific transparency of the NIC. Specific recommendations include the addition of supplemental occupational exposure data, review of probable relationships between inhalable and respirable fractions of Antimony Trioxide occupational aerosols, and description of medical surveillance and exposure assessment protocols presently used and undergoing further refinement by industry.

Although i2a concurs with the indexing of TLV development to pneumonitis and understands the rationale for recommending a TLV based upon the respirable fraction of occupational aerosols, no sound scientific basis is offered for the TLV value subsequently recommended. The absence of a clearly articulated rationale for the proposed TLV precludes meaningful review of the scientific merits of the draft NIC by our experts, and does not make a compelling argument for significant downward revision of the Antimony Trioxide TLV.

i2a is presently analyzing expanded workplace and health surveillance data collected by its membership over many years, and data analyzed to date do not suggest significant health impacts from exposures at the current TLV, and do not support the proposed downward revision of the TLV. i2a is further evaluating the feasibility of harmonizing and expanding existing surveillance programs so as to permit more rigorous scientific evaluation of occupational exposure standards that are protective of worker health.

Introduction and List of Recommended Actions

The International Antimony Association, hereafter referred to as "i2a", welcomes the opportunity to comment upon the 2017 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 37 companies located throughout Europe,

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North America 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 may be relevant to Antimony compounds. It is from this perspective that i2a has reviewed the *Documentation for Antimony Trioxide* and developed a series of recommendations that include the following:

1. A paucity of information is provided by ACGIH concerning historical or contemporary occupational exposure levels to Antimony Trioxide. i2a is thus providing occupational exposure information (Annex A), the inclusion of which should facilitate the interpretation of scientific studies and historical health data reviewed in the Notice of Intended Change.
2. A Threshold Limit Value (TLV) indexed to the respirable particulate content of Antimony Trioxide occupational aerosols has been proposed. However, no **fundamental** context is supplied that relates this proposed TLV to the more commonly applied measurements of inhalable particulate aerosols of Antimony Trioxide. A study evaluating the particle size distribution of occupational aerosols associated with Antimony Trioxide has thus been provided (Annex B) to permit comparison of the proposed TLV to the more widely applied measure of occupational exposure to inhalable aerosols.
3. The present *Documentation* contains no information regarding the ongoing development of medical surveillance procedures at Antimony Trioxide production facilities. These procedures (Annex C) are described herein since they provide information on potential health impacts of Antimony Trioxide inhalation that are relevant to TLV derivation. The overall medical surveillance framework under which a TLV is enforced further bears upon the selection of appropriate assessment factors required to account for scientific uncertainty in TLV derivation, since surveillance programs can limit scientific uncertainty regarding susceptible subpopulations and/or extrapolation of effects from animals to humans. Exposure scenarios need to be considered with due consideration of medical surveillance results in order to understand the relation between measured exposure and workers' health.
4. The *Documentation for Antimony Trioxide* proposes a TLV indexed to respirable Antimony Trioxide particulate matter intended to reduce or prevent the incidence of pneumonitis in the workplace. Although i2a concurs with the health endpoint selected for TLV derivation, the proposed TLV of 0.03 mg/m^3 is derived, without meaningful discussion, from a LOAEL of 3

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mg/m^3 observed in recent inhalation studies conducted in mice by the National Toxicology Program of the United States. Scientific review of a TLV derived in such an arbitrary fashion is not possible, especially when available medical surveillance evidence does not point towards any major or enhanced impact on workers' health with the current TLV is implemented. At a minimum, the significance of the LOAEL should be interpreted within the context of the available data from other animal studies, human occupational exposure data and other mechanistic or ancillary data that impact upon the Assessment Factors that are to be applied in derivation of the proposed TLV from an animal inhalation LOAEL. Only after the inclusion of such critical information can the scientific merits of a proposed TLV be meaningfully evaluated.

Rationale

Occupational Exposure Levels: 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 most likely due to the lack of health impacts, in particular following the adoption of currently implemented exposure standards to eliminate pneumonitis, associated with excessive **historical** exposures to Antimony Trioxide, which seem to be disregarded by ACGIH. **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 was undertaken by Sweden of Antimony Trioxide which included evaluation of levels of occupational exposure associated with multiple workplace scenarios (ECHA, 2008). The baseline years for these exposure assessments 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

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facilities. Recent past exposures in the late 1990's for these same processes were noted to approach levels of 10 mg/m^3 (Vandenbroele, 2003; cf. Annex D).

Occupational aerosol particle size distribution: Work commissioned from the Institute of Occupational Medicine in Edinburgh by i2a for the EU Existing Substances Program characterized the occupational aerosols associated with Antimony Trioxide production (Hughson, 2005 – attached in Annex). The typical finished Antimony Trioxide commercial product has 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 could be presumed that the majority of Antimony Trioxide in occupational aerosols would be respirable. 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. Somewhat greater fractions of respirable dust were collected by GRIMM aerosol spectrometers, a finding consistent with the known limited efficiency with which the GRIMM collects coarse aerosol particles. The Hughson (2005) work indicated that a TLV indexed to a respirable Antimony Trioxide aerosol fraction will be associated with a significantly higher measurement of total or inhalable aerosol. 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. Acknowledgment of this agglomeration effect will greatly facilitate comparison of any new respirable standard to the existing data base on inhalable dust levels collected by industrial facilities over the past several decades. Facilities would be further alerted to the need for new characterizations of occupational aerosols prior to the implementation of engineering controls or RPE that might be needed to meet any new TLV. **The relevance of a respirable TLV of 0.03 mg/m^3 as proposed by ACGIH should be assessed in light of the phenomenon of likely particle agglomeration in order to arrive at a meaningful and measurable value applicable to real workplace conditions.**

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,

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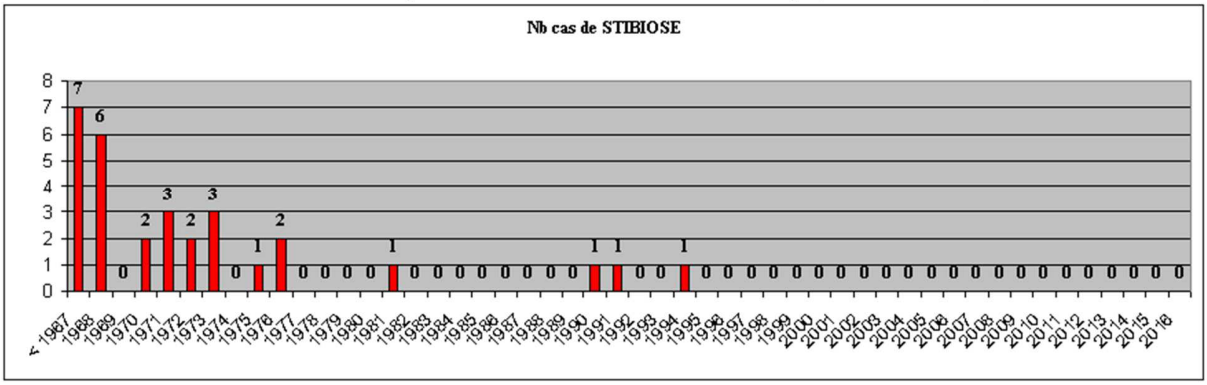
exposure assessment and respiratory protection procedures designed to monitor and protect the pulmonary function of workers exposed to Antimony Trioxide. These guidelines did not mark the initiation of medical surveillance among Antimony Trioxide workers – monitoring of health effects specific to Antimony Trioxide had, in some instances, actually been ongoing for 40 years. Nor were the guidelines mandatory. Instead, they were designed for voluntary implementation within the context of different national frameworks governed by doctor-patient confidentiality. The intent of the guidelines was harmonization of medical surveillance procedures for the Antimony Trioxide exposed worker so as to permit the compilation of industry statistics by i2a and the ultimate development of industry wide "best practice" protocols. Working towards, or below, an inhalable Antimony Trioxide TLV of 0.5 mg/m^3, the 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 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, **as a proactive move towards advancing the safety of workers involved in the production of Antimony Trioxide**.

Examples of medical surveillance data reported to i2a by its membership are included in this submission. Data on the incidence of stibiose (Antimony pneumonitis) at an Antimony Trioxide production facility are displayed in the following figure:

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



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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 thus 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 management dramatically reduced the risk of pulmonary impairment.** Although measurements of exposure (e.g. urinary Antimony or airborne Antimony Trioxide levels) may have been collected and would be informative with respect to risk of pulmonary impairment, such exposure data were not made available by the reporting physicians for reasons of patient confidentiality, among other reasons. None-the-less the data indicate that **exposure conditions within this 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**. Much of this time was associated with adherence to a TLV of 0.5 mg/m^3 or higher for Antimony Trioxide.

Absence of clinical Antimony pneumonitis does not, of course, preclude the incidence of preclinical changes in pulmonary function in response.

More detailed information regarding spirometry and chest x-ray medical surveillance data for Antimony Trioxide exposed workers has recently been summarized in a report to i2a (2017) and suggests no impact of Antimony Trioxide upon lung capacity if the current TLV of 0.5 mg/m^3 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, especially in

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workers exposed prior to 1999) or average urinary Antimony concentration. 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.

Since the use of average urinary Antimony concentration as an exposure metric could mask early elevated urinary Antimony levels with more recent low values (urinary Antimony values is not necessarily a predictor of current and actual **workplace** exposure, but is used as a indicative measure of potential overall exposure), the exposure cohort was divided into those workers with one or more urinary Antimony value above 35 µg Sb/g creatinine (and thus past and task-specific Antimony Trioxide inhalation exposure likely in excess of 0.5 mg/m^3) and a so-called low exposure cohort that had never exceeded this level. After this stratification, a decline in FEV1% and Tiffeneau index was observed in the high but not the low exposure group as a function of average urinary Antimony concentration. However, the difference did not achieve statistical significance. This finding, although not statistically significant, is potentially consistent with pulmonary impairment as a result of airborne exposures in excess of 0.5 mg/m^3. Indeed, maximum urinary Antimony concentrations as high as 161 µg Sb/g creatinine in the high exposure group suggests mainly **historical or specifically task-related** inhalation exposures significantly in excess of 0.5 mg/m^3 Antimony Trioxide, with no apparent lung impairment however. **Planned expansion and more detailed analysis of this data base by i2a is expected to affirm that adherence to the TLV of 0.5 mg/m^3 is protective of lung function.**

TLV Derivation: The NIC proposes reduction of the TLV for Antimony Trioxide from 0.5 mg/m^3 (inhalable) to 0.03 mg/m^3 (respirable) based upon the observation of pulmonary inflammation and impairment in mice following exposure to respirable aerosols of 3 mg/m^3 of Antimony Trioxide in studies conducted by the NTP. 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 respirable Antimony Trioxide can be inferred; however, it should be more clearly articulated and (as judged feasible) related to probable inhalable aerosol concentrations. i2a further concurs with the decision to focus upon pneumonitis as opposed to neoplasia in the NTP studies, due to the extreme hypoxia and systemic stress induced by higher levels of 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 application of Assessment Factors was involved in the derivation of the proposed TLV, but the nature and magnitude

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of assessment factors selected for use are not specified. **In the absence of such basic information, it is not possible to evaluate the scientific basis for the proposed TLV.** With respect to the proposed TLV of 0.03 mg/m^3 (respirable) i2a would like to offer the following initial technical observations:

- ACGIH has elected to utilize a LOAEL based upon pulmonary changes observed in mice during the NTP studies.
- 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.
- 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.
- 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.
- 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 up to 10 mg/m^3 or higher 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 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 inhalable Antimony Trioxide levels, and most probably specific workplace area and task-related, significantly in excess of 0.5 mg/m^3.
- **The preceding observations are not consistent with the need for a TLV reduction to 0.03 mg/m^3 (respirable).**

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- i2a will keep ACGIH informed of planned expansion and more detailed analysis of the current and growing data base aimed at demonstrating compliance with and adequacy of the current TLV of 0.5 mg/m³.

Citable Material

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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**.

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.**

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.**

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