Dr. Ruth Lunn
Director, Office of RoC
National Institutes of Health
Department of Health and Human Services
Telephone (919) 316–4637
lunn@niehs.nih.gov

Brussels, 30 October 2016

Dear Dr Lunn,

RE: Nominations to the National Toxicology Program for the Report on Carcinogens; Concept document for Antimony Trioxide

In follow-up of the information submitted on 11 October, and in preparation of the 15 December Board of Scientific Counselor Meeting (BSC), the International Antimony Association (i2a) would like to submit the following comments on the Draft Report on Carcinogens Concept for Antimony Trioxide (dated September 2016):

Pages 3 and 6 of the Concept state that "***Antimony is persistent in the environment***". We would like to clarify that because the persistence of a substance is determined by its potential to degrade, and a metal like antimony cannot degrade to CO2, water, and other elements, it would be incorrect to attribute persistence properties to Antimony.
The Globally Harmonized System of Classification and Labelling of Chemicals (United Nations, 2011) specifically stated that "*for inorganic compounds and metals, the concept of degradability as applied to organic compounds has limited or no meaning. Rather the substance may be transformed by normal environmental processes to either increase or decrease the bioavailability of the toxic species*" (p.222, 473). Typical transformation processes include complexation, speciation processes, precipitation, adsorption, and settling. Antimony and Antimony compounds released in the environment undergo such chemical processes, resulting in a partitioning over the different environmental compartments or media.
Physicochemical properties of these "media" affect the solubility of the metal ion, partitioning from the water column, and the species of metal ion that exists in the water column. In the water column, it is generally the *dissolved metal ions* which are of concern for toxicity. Interactions of Antimony with the media may either increase or decrease the level of ions, and hence the toxicity. It should be noted that changes in speciation/availability/toxicity are not necessarily permanent. In accordance with the principles of rapid removal (persistence) used for inorganic substances, the reduction of the soluble/toxic metal species by more than 70% in 28 days could be considered as an alternative criterion for assessing the removal (and persistence) of a metal from the aquatic compartment. A preliminary assessment on the behavior of Antimony in the water column indicated a 70% removal of dissolved Sb after 15 days (EUSES-model), suggesting that Sb is not persistent when the specific concepts for removal of inorganics are considered.

Section 2.3 of the Concept state that "***Based on a preliminary review of the literature, the mechanistic database is smaller and less established than for other metals, although antimony appears to be associated with some similar biological activities as other metals, such as oxidative damage.***" i2a would concur with this statement and is launching work to

complete the current database. A recent in-house assessment on the available genotoxicity and mutagenicity data on Antimony compounds indicates that the carcinogen mode of action (MoA) of Antimony and its inorganic compounds does not appear to be related to direct DNA reactive genotoxicity. It rather involves multiple MoAs that need to be distinguished and further elaborated in light of more recent information. In our view, understanding the range of key events in the carcinogenic process (whether it is related to an increased cell proliferation, cytotoxicity, or DNA repair inhibition) is an essential step for further evaluation of the MoA of Antimony.
To address this mechanistic data gap, i2a is initiating a tiered program of research to define the indirect mechanisms involved. The hypothesis beyond the proposed mechanistic approach is based on the positive association of the severe induction of lung chronic inflammatory in both exposed mice and rats after ATO exposure with the hypoxia developed in ATO-exposed rats (at 10 and 30 mg/m3) and mice (all exposed animals) with finally, the alteration of the Epidermal growth factor (Egfr) signaling pathway (identified as a key signaling pathway by NTP draft report on Antimony Trioxide). Indirect mechanisms entailing the induction of reactive oxygen species and/or inhibitory effects upon DNA repair are believed to mediate genotoxicity. As a result, nonlinear dose responses and potential thresholds for genotoxicity could be defined and would be expected to impart similar nonlinear dose response functions to carcinogenic responses.
The proposed studies would have merit and could contribute to refine the carcinogenicity and genotoxicity assessment of Antimony. We kindly ask you that you inform us on the best approach to share the outcomes of this upcoming work with the NTP, for consideration during the assessment of Antimony Trioxide.

Section 2.3 of the Concept furthermore notes that "***[…] the EU stated that the differences in toxicity between the two valence states is unclear because of few studies comparing the toxicity of both compounds under the same conditions.***" i2a would concur with this observation and is launching work to complete the current database (in addition to the one described above). We kindly ask you to inform us on the best approach to share the outcomes of this upcoming work with the NTP for consideration during the assessment of Antimony Trioxide.

Kind regards, and many thanks in advance for considering our future contributions,

Caroline Braibant
Secretary-General

Av. de Broqueville 12
B-1150 Brussels
T: +32 (0)2 779 00 49
F: +32 (0)2 762 82 29
M: +32 (0) 473 52 52 73
caroline.braibant@antimony.com
www.antimony.com

Geert Krekel
President of the Board

Nijverheidsstraat 2
B-2340 Beerse
T: +32 (0)14 60 15 07
F: +32 (0)14 60 15 74
M: +32 (0)473 96 02 18
geert.krekel@Campine.be
www.campine.be

Nathalie Branche
Chairwoman of the Assembly

Zone industrielle de la Vallée Verte
F-53940 Le Genest Saint-Isle
T: +33 (0)2 43 01 23 54
F: +33 (0)2 43 02 11 07
branche@pcdlucette.com
www.pcdlucette.com

Cc. Craig J. Boreiko, John A. Biesemeier