Brussels, January 30, 2017

Intervention by Dr Craig J. Boreiko at BSC meeting of 15 December 2016
On behalf of International Antimony Association

My name is Craig Boreiko, and I am appearing here today as a consultant to the International Antimony Association. I am grateful for the opportunity to make a few remarks regarding the current consideration of moving antimony trioxide onto the path for potential future listing in the Report on Carcinogens. The International Antimony Association has submitted written comments – my intent here today is to elaborate upon those comments.

First, I would like to briefly note that, in an apparent throwback to PBT criteria for prioritization of substances, persistence is noted as being of concern for antimony. Many regulatory processes have acknowledged the limited utility of applying persistence to prioritization of inorganic substances in risk or hazard based determinations. As has been clearly articulated in EPA's Metals Framework Directive and joint US-EU workshops on hazard classification, persistence adds little to the relative prioritization of inorganic substances.

However, the more important point I wish to address is the current convergence of regulatory processes in the US and the European Union. Antimony and its compounds will shortly be evaluated in the REACH process in the European Union – with the International Antimony Association embarking upon a program of research to address fundamental issues concerning hazard classification and risk assessment for antimony and its compounds. Efforts between now and 2018 will be generating new information pertinent to uncertainties associated with the carcinogenic and mutagenic properties of antimony and its compounds.

The profile of substances such as antimony trioxide may at first seem to be relatively simple and straight forward. Observations of lung cancer in two species after inhalation exposure, with some suggestions of systemic effects and genotoxicity, would seem to establish a clear path forward for considering the listing of antimony. Unfortunately, few things are as simple as they may at first seem:

- There are several reports of lung tumors after inhalation exposure of rats, with NTP recently finding some evidence for increased incidence of pulmonary neoplasms. However, impacts in the rat are difficult to interpret in light of evidence of the pulmonary overload known to occur in many studies. In the recent NTP inhalation studies, indications of pulmonary overload are acknowledged at the 10 and 30 mg/m3 exposure levels. Indeed, even at 3 mg/m3 clearance deviates from modelled predictions towards the end of the study in a fashion that one would expect under overload. Interpretation of lesions that develop under conditions of pulmonary overload is presently the subject of much debate and transcends the substance-specific effects of antimony. An increased incidence of pheochromocytomas was also observed in rats. There is a significant body

of evidence that such lesions are expected under conditions of pulmonary inflammation and hypoxia. They are a response to substance-induced pulmonary impacts and not a response to the substance itself, which is confirmed by the clinical observations that indicated that rats (at 10 and 30 mg/m³) and all exposed mice were suffering from abnormal breathing and thinness. Indeed, combined with significant body weight depression associated with inhalation exposure of rats and mice to antimony trioxide, these data suggest that the NTP study of rats was conducted at excessive airborne concentrations of antimony trioxide that inappropriately exceeded the maximum tolerated dose.

- The recent NTP studies of inhalation imparts in mice at first seem to provide solid evidence of carcinogenicity, but even this study is surrounded by a host of questions and uncertainties. If one adopts a critical eye, all exposure levels in this study produced significant pulmonary inflammation and sufficient impairment of pulmonary function to yield systemic hypoxia. Under the conditions of local pulmonary toxicity and systemic hypoxic stress, increases in neoplastic lesions, particularly those with high spontaneous incidence (such as B-cell lymphomas especially in female mice), must be interpreted with caution.

- As stressed above, any increase in B-cell lymphomas must be interpreted with caution. The histological work-up of these lesions by NTP was not informative and does not permit detailed diagnostic classification. Are these reactive lesions arising in response to pulmonary inflammation and hypoxia? Quite possibly so. Female B6C3F1N mice have a high background of spontaneously arising B cell lymphomas and increases are difficult to interpret. This is in contrast to T cell lymphomas that are most often chemically induced.

- Increased incidence of lung tumors in mice? A seemingly solid finding until one considers the high spontaneous incidence of lesions in the mouse lung and asks what might be expected under condition of severe inflammation and toxicity. Are the observed lesions chemically induced or are they, a response to altered conditions in the lung that permit enhanced clonal expansion of spontaneous lesions?

- The genotoxicity data do not help us answer this:
    - In vitro studies show responses at high concentrations that appear to entail indirect mechanisms such as induction of reactive oxygen species or inhibition of DNA repair.
    - NTP reported a very modest increase in erythrocyte micronuclei – but such increases are associated with perturbations in erythropoiesis similar to those we know occurred in mice.

- Positive Comet assay are reported by NTP, but such data needed to be adequately controlled for cytotoxicity and apoptosis. This is especially true given the conditions known to exist in the mouse lungs.
- Appearance of tumors with EGFR activated oncogenes? Past NTP studies have reported chemical specific fingerprints for the mutations seen in activated oncogenes, but oncogene activation via generic point mutations similar to spontaneous lesions are more difficult to interpret. The human experience tells us that patterns of oncogene activation in response to a single agent (cigarette smoke) vary as a function of time to tumor incidence, most likely as a function of selection for different tumor phenotypes. A small but growing body of evidence indicates that EGFR lesions confer a proliferative advantage to neoplasms growing under hypoxic conditions.
- When all is said and done – yes we know the tumors developed after inhalation exposure to antimony trioxide. We know that some are likely arising in response to the hypoxic effects created by exposure to antimony trioxide and not as a direct result of exposure to antimony trioxide per se. Others could be specifically induced by antimony trioxide, but at this point we do not know how or why.

Hazard-based classification could be attempted, but with the problem that we do not know how to make the translation to estimates of risk. Answers to such questions should be forthcoming in the next several years as a result of REACH and i2a research – leaving us with the fundamental question of whether parallel efforts in different regional jurisdictions can be aligned so as to work towards a common goal. Indeed, the European Chemical Authority's Directorate of Cooperation in international Relations is presently evaluating a request to pursue alignment of the ECHA and NTP classification and risk evaluation processes.