International Antimony Association

To : Mr. Ryan Peltier
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Concerning: Additional scientific information for 'Antimony trioxide' and 'Antimony and compounds' TLVs

Brussels, 26 May 2014

Dear Mr Peltier,

Following your correspondence of May 13, 2014 we are submitting this letter on behalf of the members of the International Antimony Association (i2a). We are an international non-profit association whose mission is to gather, study and disseminate information on the safe use of antimony and antimony compounds, especially with regard to the relevant environmental, health and safety regulations.

We would like to inform you about some recent scientific developments that might be of interest for the evaluation and interpretation of the inhalation carcinogenicity potential of antimony trioxide ('ATO', CAS 1309-64-4) and 'antimony and compounds' currently listed on the TLV for Chemical Substances (TLV-CS) Committee Under Study list for 2014:

- on 20th January 2014, ECETOC (*European Centre for Ecotoxicology and Toxicology Of Chemicals*) released their Technical Report 122 '*Poorly Soluble Particles / Lung Overload*'. This publication aims to '*examine the current scientific understanding of the "lung overload" hypothesis with regard to the anticipated sensitivity and specificity of the rat lung responses, its implications for hazard identification and human risk assessment*', and is available at http://www.ecetoc.org/index.php?mact=MCSoap,cntnt01,details,0&cntnt01by_category=22&cntnt01order_by=date%20Desc&cntnt01template=display_list_v2&cntnt01display_template=display_details_v2&cntnt01document_id=8386&cntnt01returnid=59

- in the DNEL (*Derived No Effect Level*) derivation for the purpose of the EU REACH registration of ATO, i2a recently applied the following approach:
  (i) based on the Newton et al (1994) study (for lack of a qualitatively more adequate study), the LOEL from this study as a point-of-departure was modified using a state-of-the-art extrapolation from laboratory animal (rats) to humans by deriving a so-called human equivalent concentration ('*HEC*'), and
  (ii) by considering substantial differences between animal laboratory conditions and the occupational setting, based on a combination of laboratory simulations and actual workplace particle size distribution monitoring, this HEC was recalculated to realistic workplace conditions.

The thus derived DNEL of 0.7 mg/m³ confirms the current OEL of 0.5 mg/m³ (as used by eg ACGIH and NIOSH) as a conservative value.

- the toxicokinetic data for poorly soluble trivalent Sb substances (including ATO) have been extensively revised to reflect absorption rates at doses that are typically used for toxicity testing. From this exercise, following values were derived:
  - °Bioaccumulation potential: no bioaccumulation potential
  - °Absorption rate - oral: 0.05-0.3%
  - °Absorption rate - dermal: 0.01-0.1%
  - °Absorption rate - inhalation: <<1%

These data are included in the relevant EU-REACH dossiers, substantiating the low bioavailability of ATO at 'relevant' doses; as such, these conclusions update and revise the conservative values derived under the EU Risk Assessment and OECD-SIAP for ATO (2008).

- i2a has sponsored a 2-year postdoctoral research program at the University of Copenhagen examining the effects of poorly soluble ATO particles (in comparison with the readily soluble antimony trichloride) on the viability and functionality of rat macrophages, using human monocytes as a model for comparative purposes. First results indicate that rat macrophages effectively and rapidly phagocytose ATO up to the limit of their viability, but without any quantitatively relevant intracellular dissolution, thus supporting the overload hypothesis. Final reporting is expected Q2 of 2014. Scientific publication will follow soon after.

Please do not hesitate to contact us for further details on the above topics, should any of these perhaps be of interest for your current work.

Best regards,

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