International Antimony Association

i2a observations on the October 2019 ATSDR Toxicological Profile for Antimony and Antimony Compounds

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The final version of the United States Agency for Toxic Substances and Disease Registry (ATSDR) new Toxicological Profile for Antimony and Antimony Compounds was released in October of 2019. The Profile is impressive from the standpoint of the encyclopedic citation of scientific studies dating back 60 or more years.

Unfortunately, the breadth of the literature reviewed is not matched by a critical evaluation of toxicological data. The following deficiencies were noted by i2a staff.

- There is minimal critical evaluation of cited studies – no formal assessments of study quality were made or factored into weight of evidence evaluations. As a result, comparable reliance is placed upon GLP studies from the past decade and studies with low technical rigor from the 1940's through the 1990's.
- The review of published studies often does not provide definition of Sb valence state in the evaluation of effects. Although the document acknowledges that Sb(V) compounds are likely less toxic then Sb(III) compounds, the evaluation of data from different studies frequently does not consider the valence state of the compounds under study. This deficiency is evident to varying extents throughout the document.
- The review of the scientific literature also pays Inadequate attention to chemical speciation. The dosimetry for the impacts of Sb upon numerous health endpoints is evaluated based upon the Sb content of the compounds evaluated. Thus, compounds such as stibene (a highly toxic gaseous Sb compound) are included in evaluations of impacts associated with exposure to much less toxic and/or inert forms of Sb.
- Particle size is noted to be an important determinant of pulmonary deposition patterns after inhalation exposure but known differences in particle size distribution are not considered in the comparison of studies that generate discordant or conflicting results. Different deposition patterns may explain some of the discordant impacts seen in rodent cancer bioassays.

In addition to the general observations noted above, the following specific observations were made:

- Minimal risk levels (MRLs) of 0.3 – 1.0 □g/m^3 are calculated for human inhalation exposure to antimony compounds and similar low values are derived for oral exposures. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified duration of exposure and is the ATSDR equivalent to the derivation of a DNEL. These MRLs are much lower than the DNELs that have been derived by i2a.
- The ATSDR MRLs were derived by calculation of the lower 10% bound of benchmark dose estimates of effect (a probability estimate of no effect similar to a NOAEL) and the application of combined assessment factors of 30 for extrapolation from animals to humans.
- For assessments of inhalation exposure, the calculation of a Human Equivalent Concentrations (HECs) was also used to extrapolate from effects in rodents to predicted impacts in humans. The HECs appear to be based upon comparative estimates of deposition patterns within the respiratory tract of rodents and humans but the HEC derivations are described in vague terms that do not permit their evaluation. In addition, the health endpoint used for the calculation of an acute inhalation MRL (squamous metaplasia of the epiglottis in mice) is influenced by high upper airway deposition related to rodents being obligate nose breathers (and/or swallowing of deposited material). Such

factors combine with species-specific anatomical features to enhance the sensitivity of the rodent epiglottis to damage during inhalation studies and complicate efforts to extrapolate effects upon the epiglottis in mice and rats to humans.

- Evaluations are made of reproductive and developmental effects but no distinctions are made of the known potency differences between Sb(III) and Sb(V) compounds. Moreover, stibine gas is discussed as if the effects it produced were representative of effects from other Sb compounds. The dose-response for stibene-induced effects should not be equated with that for other Sb compounds.
- Effects associated with extremely high historical occupational exposures in the older literature (e.g. EKG alterations) are reviewed as if they were applicable to modern occupational exposures. Future evaluation of potential health effects associated with past high historical exposures by i2a may be required.
- The evaluation of genotoxicity after *in vivo* or *in vitro* exposure is at best superficial and does not factor study quality into weight of evidence deliberations. For example, the technically deficient positive chromosome aberration studies of Gurnani et al. seem to be given equal weight to the similar, but higher quality, studies by Kirkland et al. Moreover, two studies by Gurnani et al (1992 and 1993) are cited without seeming recognition that the 1993 paper is merely republication of work published in 1992. Deficiencies such as this make it seem as if the original scientific publications were not read in during the preparation of the Profile.
- The section on genotoxicity largely consists of tabular presentation of published results with conclusions being drawn based upon the prevalence of positive and negative results in the tables. There is no apparent recognition that assays which are true indicators of mutagenic events should be given higher weight then the results obtained from indicator assays. Sweeping generalizations are also made regarding the impact of valence state upon genotoxicity without apparent recognition of the valence state of some of the compounds tested. As with other critical sections of the document, this cannot be considered a true weight of evidence evaluation.
- The upper cut-off size range for respirable aerosols is indicated to be 5 microns. This is supportive of the i2a petition that the NTP Report on Carcinogens should restrict its conclusions on cancer to the respirable fraction of diantimony trioxide occupational aerosols with an upper respirable cut off of 4 microns. Unfortunately, numerous aspects of Sb toxicokinetics are provided superficial treatment. The transport systems for uptake from the GI tract or into cells have been identified but are not cited. Statements are also made that Sb is not subject to metabolism, ignoring recent evidence indicating that bacteria mediated methylation occurs under anaerobic conditions and that methylated forms of Sb can be present in food crops. Methylation is now thought to occur in humans as well and the enzyme systems responsible for this have been identified.
- A summation is provided of airborne and soil Sb levels at shooting ranges. Some aerosols measured at indoor ranges are reported to have up to 216 mg/m^3 Sb in air concentrations that would be problematic if airborne exposure limits of 500 mg/m^{3}were to be significantly decreased.

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