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i2a's assessment of NTP's long-term carcinogenicity studies on antimony trioxide (ATO)

1. Background

Antimony trioxide (ATO) was nominated by the U.S. Consumer Products Safety Commission due to substantial human exposure in occupational settings concomitant with lack of adequate 2-year carcinogenicity studies. The NTP draft report on ATO (NTP TR 590) was made available in January 2016 and went through peer-review on February 16, 2016.

The 2-year carcinogenicity studies on ATO were designed in compliance with established guidelines for cancer bioassays. The groups of 60 male and 60 female Wistar Han [Crl:WI (Han)] rats and B6C3F1/N mice were exposed to ATO aerosols by whole body inhalation at chamber concentrations of 0, 3, 10, or 30 mg/m^3 for 6 hours/day, 5 days/week for up to 2 years. The exposure concentrations for the 2-year ATO studies were selected based on the findings of 2-week studies in the Wistar Han rats and B6C3F1/N mice. A 12-month interim evaluation was included for comparison to previous 1-year exposure studies. In accompanying tissue burden studies, the groups of 25 female rats and 25 female mice were exposed to the same concentrations of ATO for up to 79 weeks. It is worth noting that the current 2-year inhalation study on ATO is one of a few studies performed by the NTP with the Wistar Han rat strain; hence, only very limited historical control data exist, which should be factored into any conclusions, and particularly those related to effects observed at low incidences.

ATO particle size distribution employed in the NTP studies was in a range of Mass Median Aerodynamic Diameter (MMAD) between 0.9 and 1.5 µm with a Geometric Standard Deviation (GSD) between 1.8 and 2.1. Compared with previous studies on ATO (Watt, 1983; and Groth *et al.*, 1986; Newton *et al*., 1990), the particles were characterized by likely finer size. The smaller particle size distribution (PSD) would be expected to result in higher rates of alveolar deposition from experimental aerosols. Greater alveolar deposition would then result in higher local adverse effect, which was demonstrated in the current NTP study, by the strong chronic active induction of inflammatory responses in both species.

2. ATO Carcinogenicity profile

2.1. Main NTP studies outcome

According to the NTP draft study report, the study yielded **some evidence** of carcinogenic activity of ATO for rat respiratory tissue. However, elevation of pulmonary neoplasms (alveolar/bronchiolar (A/B) adenomas and carcinomas) failed to achieve statistical significance. No genotoxic toxicity was observed. The histopathological findings indicated a time- and dose-dependent increase in inflammatory changes.

For development of lung tumors from particle overload in rats, inflammation has to be severe enough to cause fibrosis. Thus, lung tumor formation, even in rats, is a high-dose effect. If clearance mechanisms are not overwhelmed and inflammation is prevented, lung cancer risk will not be increased. The mechanisms leading to an oxidative and inflammatory pulmonary environment are considered as clearly threshold-related (Morfeld *et al.*, 2015).

In ATO-exposed mice, **clear evidence** of carcinogenic activity, with dose-dependent elevations of neoplastic and pre-neoplastic lesions in respiratory tissues in males, and dose-dependent elevation

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of lymphoma incidence in female mice, were observed. The induction of pulmonary neoplasms in exposed female mice failed to exhibit dose dependency, and early mortality from pulmonary neoplasms and pulmonary toxicity was significant in both exposure and chamber controls. The link between the incidence of neoplasms and genotoxic effects was suggested by Comet assay studies of pulmonary tissue and micronucleus induction in circulating erythrocytes.

In the NTP studies, A/B adenomas and carcinomas represent the most frequently developed chemically-induced tumors in the lungs of rats and mice, with hyperplasia and inflammation being the most common non-neoplastic changes in both species (Dixion *et al.*, 2008). Although the A/B tumor incidence in female B6C3F1/N mice generally represents a consistently lower baseline than that in males, greater response above baseline to the effects of lung carcinogens were observed in female B6C3F1/N mice in the NTP studies. It was concluded by Moore *et al.* (2013) that female mice may have a limited capacity for tumor defense or repair, and a greater susceptibility to environmental stressors, and that their tumor response may be age-dependent. Therefore, due to the sensitivity of female mice, there is a potential for this endpoint to over-predict a carcinogenic response in humans (Moore *et al.*, 2013).

2.2. Lung overload occurrence in NTP studies on ATO

In the NTP studies on ATO, significantly increased incidences of foreign body, presumed to be the test ATO, occurred in the lungs of all exposed rats and mice at the 12-month interim evaluation and in the 2-year studies. The foreign particles were present in alveolar macrophages in both species, and often extracellularly in the proteinaceous fluid of the alveoli in rats, or in the alveolar spaces in mice. As with the rat data, the impacts of ATO in mice are suggestive of pulmonary overload. Indeed, lung overload occurred in rats and mice at exposure concentrations of 10 and 30 mg/m^3, but was not reached at 3 mg/m^3 in either species. Higher concentrations of ATO seem to inhibit the clearance of particles and the spectrum of inflammatory changes observed in mice are qualitatively similar to those seen in rats. The sites of impact and cell targets for toxicity and neoplasia in mice, are further similar to those impacted in the rat. In contrast to animal data, results obtained from humans indicate that inhaled antimony tends to accumulate in the lung (Garg *et al.*, 2003), but is relatively rapidly cleared from other tissues. Gerhardsson *et al.* (1982) found no difference in antimony levels in either liver or kidney in deceased smelter workers, as compared with non-exposed referents (IRIS, US EPA).

Overall, it seems appropriate to assume that the ATO inhaled by rodents or humans will be subject to particle-size dependent deposition in the respiratory tract. Also, for all ATO workplaces, fractional deposition can be predicted with the aid of the MPPD model both for rodents and humans. However, epidemiological findings contrast with the results of experimental studies on rats/mice, in which at higher exposure levels, an excess of lung tumors were detected. Thus, the interpretation and relevance of animal data for human health remains unclear.

2.3. Inflammatory responses developed in ATO-exposed mice and rats

Chronic active inflammation, bronchiole, alveolar epithelium hyperplasia and infiltration of cellular lymphocytes were significantly developed in all ATO-exposed rats and mice. In general, the severities of these non-neoplastic lesions increased with increasing exposure concentrations in both tested species.

In humans, chronic occupational exposure to antimony (generally antimony trioxide) is most commonly associated with "antimony pneumoconiosis" (McCallum, 1967; IRIS US EPA, Cooper *et al.*, 1968;; Potkonjak and Pavlovich, 1983). However, antimony workers are also exposed to a variety of other compounds like arsenic oxide, iron oxide, hydrogen sulfide, and sodium hydroxide (Cooper *et al.*, 1968; Potkonjak and Pavlovich, 1983). Therefore, the co-exposure of antimony with other

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metals is a main drawback hampering causal attribution based on available epidemiological data. In addition to the above, most of the data on ATO toxicity in occupational workplaces dates from an earlier era where there was no adequate protection equipment in place (Sundar and Chakravarty, 2010).

2.4. Analysis of *Kras* and *Egfr* mutations in rat and mouse alveolar/bronchiolar tumors

Mutation analyses of selected genes (*Kras, Egfr*) in observed A/B neoplasms revealed increased frequencies of point mutations within the *Egfr* gene, providing evidence of a possible involvement of *Egfr* signaling in the pulmonary carcinogenesis. It is interesting to note that in mice, mutations of *Kras* were observed in both spontaneously and ATO-induced A/B tumors. In both cases, the majority of mutations occurring in codon 12 were G→A transitions. Since G→T transitions in *Kras* codon 12 appear to correlate with 8-hydroxydeoxyguanine adducts that result from oxidative stress, the contribution of oxidative stress in the ATO-mediated lung carcinogenesis appears unlikely.

The increase of lung cancer tumors in humans correlates with the occurrence of some disease syndromes, e.g. chronic obstructive pulmonary disease (COPD), which impairs lung function and leads to hypoxic conditions. Inflammation is a well-established tumor promoter contributing to cancer growth and progression by modulating proliferation and survival of malignant cells, promoting angiogenesis and metastasis, and decreasing adaptive immunity (Karoor *et al.*, 2012). In addition, signaling pathways involving *Egfr* appear to play a role in the growth of such tumors under hypoxic conditions (Karoor *et al.*, 2012). The alteration of *Egfr* signaling is linked to the ability of cancer cells to survive in hypoxic microenvironments (Murakami *et al.*, 2014). Thus, the prevalence of *Egfr* alterations in ATO- exposed animals may be a result of selection for tumors capable of undergoing rapid clonal expansion under the hypoxic conditions associated with the pulmonary toxicity produced by ATO.

2.5. Evidence of hypoxia development in ATO-exposed mice and rats

The clinical findings of ATO-exposed rats (at 10 and 30 mg/m^3) and mice (all exposed animals) included abnormal breathing and thinness in male and female rats and mice, and cyanosis in both genders of rats. In rats, the hyperplastic marrow in animals exposed to ATO often exhibited a shift in the myeloid/erythroid ratio, with a distinguishable increase in the erythroid precursors. In contrast, hyperplasia in chamber control animals often occurred with inflammatory lesions, in which the bone marrow generally maintained a normal myeloid to erythroid ratio, or tended towards an increase in myeloid precursors.

The clinical findings strongly suggest systemic hypoxia conditions that developed in ATO-exposed rats and in particular ATO-exposed mice. Incidences of bone marrow hyperplasia and significant increases in the percentage of reticulocytes were observed in blood in ATO-exposed female and male mice, suggesting a stimulation of bone marrow erythropoiesis. Furthermore, the NTP draft report indicated that the bone marrow hyperplasia was predominantly of myeloid cell type, and may have been secondary to inflammation in the lung.

Overall, the clinical and physiological findings after ATO exposure to rats (at 10 and 30 mg/m^3, pulmonary overload conditions) and mice (all exposed animals) strongly suggest a systemic hypoxia that developed *due to decreased capacity of the lungs and an increase of inflammatory responses*.

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2.6. Pheochromocytoma in rats and its link with hypoxic conditions

In the NTP study on ATO, hyperplasia in the adrenal medulla occurred with a positive trend in both male and female rats, reaching only statistical significance at the highest concentration of 30 mg/m^3. Also, in the 30 mg/m^3 exposed male and female rats, the incidences of benign pheochromocytoma were significantly increased compared to those in the chamber control groups. One malignant pheochromocytoma was found in a 30 mg/m^3 female. Significant formation of pheochromocytoma in ATO-exposed mice did not occur.

A possible correlation between marked hypoxic conditions in the lungs (lung tumors, inflammation, and fibrosis) and occurrence of pheochromocytoma has been suggested previously. Also, there is no indication of the involvement of genotoxic mechanisms in the induction of pheochromocytoma by chemicals in animals. In rats, a series of non-genotoxic mechanisms may be involved in the proliferation of chromaffin cells: uncoupling of oxidative phosphorylation, hypoxia, disturbance in calcium homoeostasis, and disturbance of the hypothalamic endocrine axis (Ozaki *et al.*, 2002; Greim *et al.*, 2009).

2.7. Lymphomas in mice

Lymphomas are common and naturally occurring tumors in mice. The incidence of lymphomas in control mice varies by strain, stock, gender and age. According to the NTP database, there are two patterns of induction of lymphomas in mice: early induction associated with increased mortality and decreased survival (often thymic T-cell lymphomas), and increased incidence of lymphomas (typical naturally occurring B-cell lymphomas from spleen, Peyer's patches or mesenteric lymph node) at the end of the 2-year bioassay. In the NTP studies on ATO, the incidences of malignant lymphomas occurred at the end of the 2-year carcinogenicity study, and were predominantly B-cell in nature. The lymphomas increased in an exposure concentration-related manner and exceeded the historical control ranges in 10 and 30 mg/m^3 (lung overloading condition) tested female mice. In the 3 mg/m^3 exposed females, the neoplasms appeared at the upper end of the historical control ranges for inhalation studies, and for all routes of administration.

The interpretation of lymphomas is a great challenge especially regarding distinguishing whether lymphoid hyperplasia results from a natural age-related process, or is a consequence of targeting the immune system by a test chemical (Ward, 2005). The follicular/pleomorphic lymphoma is an often naturally occurring type and most commonly arises in spleen, mesenteric lymph node and/or Peyer's patches of small intestine. Follicular lymphoma is mainly composed of variable populations of centroblasts and centrocytes in various proportions (Ward, 2005). In ATO-exposed mice, lymphoma occurred in both the spleen and the lung. In many animals thymus, bronchial lymph nodes and/or mediastinal lymph nodes were also observed. The histopathological evaluation of spleen lymphomas developed in ATO-exposed mice, mirrors the follicular/pleomorphic lymphoma, i.e. the naturally occurring and age- related type of lymphoma characteristic of this particular mouse strain.

2.8. Species differences and lung tumor development

It is well known that anatomy, cellular component and cell type location in the lung varies by species (Dixon *et al*., 2008). In addition, mice and rats exhibit strain-specific differences in their susceptibility to specific cancers (Bauer *et al*., 2001; Dragani, 2003). Therefore, the genetic background of the strain can influence the outcome and the interpretation of the results. Mouse lung tumors often display a distinctive location in the terminal bronchiolar region of the lung and a distinctive cuboidal cellular morphology characteristic of either type II pneumocytes or club cells. In contrast, human lung tumors tend to originate centrally in bronchi, are of basal or bronchial cell origin, and show a very strong association with smoking (80-85%). In addition, the role of stimulated alveolar macrophage (AMs) and polymorphonuclear leukocytes *(*PMNs) was strongly suggested, as lung tumors have

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never been reported in rats when pulmonary inflammation was absent. There are species differences in cell size, composition, localization, and function between the different AM subsets, which might well account for some of the observed differences in responses to inhaled ATO particles.

Overall, the increased incidences of extra-pulmonary neoplasms observed in ATO-exposed rats and mice seem to be species and gender dependent.

3. ATO Genotoxicity and mutagenicity profile

3.1. Background

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. Indirect mechanisms entailing the induction of reactive oxygen species and/or inhibitory effects upon DNA repair are believed to mediate genotoxicity of antimony compounds (Takahashi *et al*., 2002, Grosskopf *et al*., 2010). 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 (Kirkland *et al*., 2015).

Considering the results obtained in previous *in vivo* genotoxicity studies, their individual quality and reliability, it was concluded by weight-of-evidence that ATO does not induce gene mutations *in vitro*. Whereas ATO has some potential to induce structural chromosome aberrations in mammalian cells *in vitro*, the relevance of *in vitro* genotoxicity to the *in vivo* situation remains uncertain.

The high µM concentration of antimony compounds required to induce effects *in vitro* appear to be far higher than antimony concentrations that can be achieved via intensive dosing *in vivo*. Also, such elevated µM concentrations are much higher than the nM systemic concentrations observed by Kirkland *et al.* (2007) after oral administration of antimony in rats but may be relevant to high lung tissue burdens that are associated with direct deposition upon lung tissue after inhalation exposure of experimental animals in studies such as those conducted by NTP (2016) or Groth *et al*. (1986).

3.2. Micronucleus (MN) Test analysis

In the NTP study on ATO, there were no signs of increased Micronucleus (MN) frequencies in normochromatic erythrocytes (NCEs) in the peripheral blood of male or female rats. However, in mice, MN frequencies in mature erythrocytes (NCEs) of male and female mice exposed to all four concentrations of ATO (0, 3, 10, or 30 mg/m³) showed a dose-dependent increase.

The positive dose-response relationship and a MN-NCE frequency above the historical control range indicates a potential of antimony trioxide to induce clastogenic or aneugenic mutations in the bone marrow of male B6C3F1/N mice. However, the overall increase of MN is weak and only present in the highest tested concentration. Moreover, in light of a complete absence of *in vivo* MN effects in two species for ATO when administered via gavage up to the limit dose of 1000 mg/kg bw/day (Elliot *et al.*, 1998; Whitwell, 2006, Kirkland *et al.*, 2007), coupled with toxicokinetic evidence that oral exposure leads to appreciable Sb concentrations in bone marrow, the positive findings in the NTP inhalation study appear somewhat questionable. It seems more plausible that the dose-dependent increase of the MN frequency is a direct result of the increased erythropoiesis through severe inflammatory effects in the lung.

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3.3. Comet Assay analysis

In the NTP study on ATO, lung tissues from a separate cohort of rats and mice exposed to ATO for 12 months were analyzed for DNA damage by a Comet assay. No DNA damage in blood leukocytes or lung cell samples was observed in exposed rats, while positive assay responses were reported for cells within mouse lung tissue. Although the draft document does not attribute great significance to the positive Comet assay results, it must be noted that the protocols employed to conduct the Comet assay in this study do not meet minimal quality standards. Application of the Comet assay to intact tissues must carefully control for natural process that can produce DNA fragmentation and false positive assay outcomes. Cytotoxicity, apoptosis, oxidative stress and terminal differentiation must all be carefully assessed for their impact upon assay outcomes.

Overall, understanding the range of key events in the carcinogenic process (whether related to an increased cell proliferation, cytotoxicity, or DNA repair inhibition) is an essential step for further evaluation of the MoA of antimony compounds.

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 changes in both mice and rats after ATO exposure with attendant hypoxia developed in ATO-exposed rats (at 10 and 30 mg/m^3) and mice (all exposed animals), and finally, the alteration of the Epidermal growth factor (*Egfr*) signaling pathway (identified as a key signaling pathway by NTP draft report on Antimony Trioxide). The proposed studies would have merit and could contribute to refining the carcinogenicity and genotoxicity assessment of antimony compounds.

4. Systemic vs local exposure to ATO

Given that trivalent antimony ions in blood seem to be initially bound within the erythrocyte (ATSDR, 1992; Ogra, 2009), the concentration of antimony ions available for distribution to the soft tissues may be quite low. As a result, WHO concluded that there was no evidence that antimony causes adverse health effects in humans from exposure through drinking water (WHO, 2003).

Whereas systemic impacts might be unlikely, local exposures associated with inhalation and particle deposition in the deep lung may be significantly higher. The increased incidence of lung tumors in rats and mice following inhalation exposure to high levels of antimony trioxide (NTP, 2016) provides suggestive evidence that high local exposures associated with inhalation can enhance the carcinogenic process but efforts to associate this effect with genotoxicity have produced only weak associations and equivocal results.

5. ATO safety – general conclusions

In all ATO-exposed animals, substantial lung toxicity and impaired lung function were observed. The occurrence of B-cell lymphoma is similar to a high-incidence spontaneous neoplasm in female mice, and may have developed following an adaptive response in the spleen to the chronic inflammation and hypoxic conditions. Importantly, the species differences in sensitivity of the respiratory system to ATO, differences in lung anatomy, cell content and cell type location, strongly suggest that the carcinogenic effects observed in rats and especially female B6C3F1/N mice are of less relevance for human risk assessment.

In addition, the extrapolation of high, cytotoxic and pro-inflammatory ATO concentrations applied to laboratory rodents by inhalation is problematic for human risk assessment due to the low ATO

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exposures of workers in modern workplaces employing personal protective equipment (PPE), and therefore not displaying tissue irritation, cellular damage or pulmonary inflammation.

The NTP findings on ATO anyhow confirm that there is a need for precautionary measures to avoid ATO dust inhalation in occupational settings.

For downstream applications of ATO, where inhalation of fine dust is prevented (*e.g*. because ATO is present in a granulated master batch, or dissolved in a paste, or moisturized with plasticizers), the exposure assessed in the study does not take place, and consequently, neither does the risk for a carcinogenic effect.

For the end user / consumer, ATO is processed into a polymeric finished product, fixed into a matrix out of which it can (nearly) not migrate.

Where there is no inhalation exposure, i.e. in modern, well-controlled personal protective equipped (PPE) workplaces, or in purposefully designed products, there is no risk of carcinogenicity.

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