MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

INTEROFFICE COMMUNICATION

January 11, 2016

TO: Antimony Trioxide File (CAS#1309-64-4)

FROM: Mike Depa, Air Quality Division, Toxics Unit

SUBJECT: ITSL Derivation

Previously, the averaging time (AT) assigned to antimony trioxide was 24 hours, as per the default methodology (Rule 232(2)(b))(see attached memo from Margaret Sadoff dated June 17, 2004. The current file review concludes that the AT may appropriately be set at annual, based on the nature and duration of the key study and the ITSL value derivation, as allowed under Rule 229(2)(b). Therefore, the AT is set to annual.

Attached Memo from Margaret Sadoff dated June 17, 2004

MICHIGAN DEPARTMENT OF ENVIRONMENTAL QUALITY

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INTEROFFICE COMMUNICATION

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June 17, 2004

TO: File for Antimony Trioxide, Sb2O3 (CAS#1309-64-4)

FROM: Margaret M Sadoff

SUBJECT: Re-evaluation of Screening Level

The initial threshold screening level (ITSL) for antimony trioxide (Sb2O3) remains at 0.2ug/m3 based on EPA's derived Reference Concentration (RfC). An IRSL/SRSL for this compound cannot be established due to lack of data of sufficient quality.

PURPOSE

This is an update of the literature review for antimony trioxide with particular emphasis on new carcinogenicity data. The following databases were searched from 1995 forward as the EPA performed a thorough review of the literature pre-1995 when it set an RfC for Sb2O3: American Conference of Governmental Industrial Hygienists (ACGIH) Threshold Limit Values, National Institute for Occupational Safety and Health (NIOSH) Pocket Guide to Hazardous Chemicals, Integrated Risk Information System (IRIS), NIOSH's Registry of Toxic Effects of Chemical Substances (RTECS), Environmental Protection Bureau Library, International Agency for Research on Cancer (IARC) Monographs, CAS Online (1967 to December 2003), Hazardous Substance Data Bank (HSDB), National Library of Medicine/Toxline, Health Effects Assessment Summary Tables (HEAST), and National Toxicology Program (NTP) Study Database.

BACKGROUND

Antimony trioxide is used industrially as a component of pigments, paints, munitions primers, and in fire retardant materials (Patty's, 2001; Leonard & Gerber, 1996). In addition, antimony compounds have been used medicinally against a variety of tropical disease and even AIDS (Leonard & Gerber, 1996). Atmospheric concentrations of antimony have been estimated at 0.02 to 8.2 ug/m3 in urban areas of North America (Leonard & Gerber, 1996). Generally, and when compared to arsenic compounds, antimony is not very toxic though trivalent forms are usually more toxic than pentavalent forms. Stibene (SbH3) is a highly toxic gas that can be produced when hydrogen comes into contact with antimony metal in the presence of heat (e.g. welding, soldering, overcharged batteries, etc.)(Leonard & Gerber, 1996).

When the EPA derived its reference concentration of 0.2ug/m3 for Sb2O3 in 1995, there was insufficient data from which to estimate a quantitative risk estimate for cancer. During its investigation, EPA concluded that further testing of the oncogenic potential of Sb2O3 was

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warranted based on the fact that, though there was suggestive evidence from animal studies, these studies lacked reliability. In particular, EPA addressed concerns with two of the most often-cited studies by Watts et al. and Groth et al., both of whom reported positive results for lung cancer in female rats exposed via inhalation to Sb2O3 (EPA, 1983). (See "Evaluation of Carcinogenicity" section for study details and concerns addressed).

NIOSH has set occupational limits for antimony "compounds" as a group (0.5 mg/m3 TWA and 50 mg/m3 IDLH as Sb)(NIOSH Pocket Guide to Chemical Hazards, 2003). ACGIH has not set standards but has listed the *process* of antimony trioxide production as carcinogenic (ACGIH, 2001). It was emphasized that "the carcinogenic activity is associated with processes rather than a unique chemical form of the carcinogen." (Federal Register Proposed Rule 54 FR 35760, Dept of Labor, MSHA, Air Quality, Chemical Substances, and Respiratory Protection Standards).

ANIMAL EVIDENCE

Summary of Non-Cancer Endpoints

Evidence from animal studies has shown that inhalation exposure to Sb2O3 results in respiratory effects (Patty's 5th ed., 2001). Guinea pigs exposed to inhaled antimony trioxide at an average concentration of 45 mg/m3 for 33 to 609 hours exhibited signs of interstitial pneumonitis. Fatty degeneration of the liver was also exhibited in guinea pigs in this study. Rats and rabbits exposed to 90 to 125 mg/m3 of antimony trioxide in air for 100 hours/month for up to 14 months exhibited pneumonitis, lipoid pneumonia, fibrous thickening of alveolar walls and focal fibrosis with rabbits being more sensitive than rats in this study. Another study using female CDF rats and miniature swine were exposed to low (1.6 mg/m3) and high (4.2 mg/m3) doses of inhaled antimony trioxide for 6hr/day, 5 days/wk for one year showed pronounced morphological changes in rat lung but not in miniature pigs. Changes in rat lung were more pronounced in the high exposure group and included focal fibrosis, adenomatous and pneumonocytic hyperplasia, and cholesterol clefts (Patty's 5th ed, 2001).

Oral studies in experimental animals are less common but generally show that Sb203 in the diet is well tolerated. Rabbits fed up to 150 mg/kg daily for 4 weeks showed no pathologic changes (Patty's 5th ed., 2001). Rats fed 1 and 2% Sb203 for 24 weeks exhibited changes in some hematological parameters but overall toxicity was report as "generally slight" (HSDB).

Evaluation of Carcinogenicity

IARC has classified Sb2O3 as a possible human carcinogen (2B) based on suggestive evidence in animals but insufficient evidence in humans. As previously mentioned, the animal evidence on which this assertion is based is questionable. There are two major animal studies that have reported positive findings for carcinogenicity after exposure to inhaled antimony trioxide. Both of these studies were reviewed by EPA in 1995 prior to development of their RfC for Sb2O3 and were deemed to be of poor quality and insufficient from which to derive a cancer risk estimate for humans. These studies are summarized below.

Watts (1983) unpublished doctoral dissertation submitted for ToSCA review (as summarized in HSDB:

Groups of 49-51 female Fischer rats (CDF, Charles River), age 19 weeks, were exposed by inhalation to 0, 1.6±1.5, or 4.2±3.2 mg/m3 commercial grade Sb2O3 for 6 hrs/day, 5 days/wk for

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13 months. (Note the large standard deviations on exposure concentrations). Serial sacrifices and histopathologic examination were conducted after 3, 6, and 12 months of exposure. Lung tumors in the higher dose group were localized to the bronchioalveolar region as follows:

Adenomas	3/18
Scirrhous carcinomas	9/18
Squamous-cell carcinomas	2/18
Total Lung neoplasms	14/18

The authors reported additional findings of scirrhous carcinomas in the higher dose group that either died (5/7) or were sacrificed (1/9) during a two month period after the exposures. They also reported an incidence rate of 1/6 for bronchioalveolar adenoma among control rats during this same post-exposure period. It is interesting to note another series of unpublished ToSCA submissions for which abstracts were available but for which the author was not noted. The exposure groups, strain, number and sex of rats used, and the findings are identical to the findings of Watts as reported in HSDB. Therefore, it is likely that these abstracts can be attributed to Watts and can provide greater detail of the aforementioned study. Inhalation of Sb2O3 dust was evaluated for toxicity in female Charles River rats (50/group) and female Sinclair S-1 miniature swine (3/group). Exposure levels were 4.2, 1.6 and 0 mg/m3 for 6 hrs/day, 5 days/wk for one year. Rats were monitored for up to one year following the exposure period while swine were sacrificed immediately after the exposure period. Dose related lung pathology seen in treated rats included increased lung weights, pneumonitis, fibrosis, granuloma, adeonoma, and presence of dust particles. Swine lungs exhibited presence of dust particles, interstitial pneumonia and minimal fibrosis. Rats in the high dose group showed increased body weight throughout the exposure period and at 6 months post exposure. This difference was not significant at 1 year post exposure. Swine did not exhibit increased body weights. Increased blood urea nitrogen (BUN) values were seen in exposed rats and swine but were significantly higher only in high dose rats at 6 months post treatment. High dose rats showed both neoplastic and non-neoplastic response in the lungs while low dose rats showed only non-neoplastic effects. Primary lung neoplasms were classified as either scirrhous carcinomas, squamous cell carcinomas, or bronchioalveolar adenomas with evidence of local invasion but no metastasis. Non-neoplastic alterations were time and dose-related and included varying degrees of focal fibrosis, adenomatous hyperplasia, multi-nucleated giant cells, cholesterol clefts, pneumocyte hyperplasia, and pigmented macrophages. Microscopic examination of swine tissues revealed no treatment related alterations.

2. Groth DH, Stettler LE, & Burg JR. 1986. Carcinogenic effects of antimony trioxide and antimony ore concentrate in rats. Journal of Toxicology & Environmental Health, 18: 607-626.

A commercial grade of Sb2O3 was used in this study. Elemental analysis revealed contamination with many trace elements including arsenic, tin and lead. The target concentration for Sb2O3 and Sb ore was 50mg/m3 which was selected because it represented the mid-range of occupational exposures. Ninety male and 90 female Wistar-derived albino rats approximately 8 months of age were placed in each of two exposure groups plus a control group. Rats were exposed to 1) a mean daily TWA of 45 mg/m3 Sb2O3 (range=0 to 191mg/m3) or 2) a mean daily TWA of 36-40mg/m3 Sb ore (range=0-91mg/m3) or 3) filtered air (controls) for 7hrs/day, 5 days/wk for 52 weeks. The authors admitted considerable difficulty in establishing the target concentrations which would explain the wide range in the measured exposure concentrations. They also report that seven months into the exposure period, the aerosol neutralizer used in generating dusts was removed. This permitted higher

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concentrations of particulate to be attained in the chambers. (See Newton discussion on contribution of particle burden to toxicity presented later).

All animals were weighed one day prior to initiation of exposure, at weeks 1, 2, 3, and 4 and monthly thereafter. 5 male and 5 female rats were sacrificed for autopsy at 6, 9, and 12 months after initiation of exposure as were all animals that died or were sacrificed due to ill health during the study. The remaining animals were sacrificed and autopsied 18 to 20 weeks after termination of exposure. In addition, portions of liver, lungs, kidney, brain, spleen and blood samples were analyzed at serial sacrifices at 6, 9, and 12 months for determination of Sb and trace element concentrations. Mass median diameter of Sb2O3 particles was calculated to be 1.23um and mass median aerodynamic diameter was 2.8um.

Reporting of mortality is not very detailed. The authors include graphs of cumulative mortality and report that survival curves do not differ significantly between control and exposure groups. Females, overall, had greater survival rates than their male counterparts in their respective exposure groups. However, the graphs show that female mortality increased rather steadily throughout each 4-week interval while males begin to show a sharp increase in mortality after approximately 40 weeks. The differences in mortality rates during specific time intervals is not discussed.

Both females and males displayed statistically significant decreases in mean body weights as compared to controls between weeks 26 and 50, but maximum differences were no greater than 6% of the control weight. The concentration of Sb in the lungs of exposed male rats (38.3mg) was significantly greater than in exposed females (25.6mg). The lungs of both male and female exposed rats contained arsenic though male concentrations were significantly greater (0.213 vs 0.150 mg). In each group, all other female rat tissues contained higher arsenic concentrations than the corresponding tissue in males.

At 71-73 weeks after initiation of exposure (18-20 weeks after termination of exposure), all remaining animals were sacrificed and autopsied. At final sacrifice, the lungs of all exposed animals contained slightly elevated, confluent, white and yellow foci on the pleural surfaces of all lobes. No lung tumors were evident at gross pathology. Histopathology performed after the 6 month sacrifice revealed particles evenly scattered throughout the lobes of the lungs and in more than 90% of alveoli in female rats exposed to Sb2O3. Alveolar-wall thickening, consisting of interstitial fibrosis and alveolar-wall cell hypertrophy and hyperplasia appeared in about 50% of alveoloar duct regions and affected 5-10% of all alveoli. Protein aggregation was also noted around particles in alveoli. These lesions increased up through the 12 month sacrifice. The first lung neoplasms were seen at 12 months (1 bronchioalveolar adenoma, 1 squamous-cell carcinoma). At the 16-17 month sacrifice, particle density and protein accumulation in the alveoli had decreased, suggesting the activation of clearance mechanisms. Interstitial fibrosis, however, had increased, and in some rats, over 80% of alveoli were affected. The authors report that neoplasms occasionally arose from sites where scarring had appeared, presumably due to confluence of areas of interstitial fibrosis. However, no report was given as to the types of neoplasms observed or the number of animals affected. Incidence of various lung neoplasms in 19/50 surviving female rats exposed to Sb2O3 is presented in the table below. In some cases, individual rats had multiple tumor types and therefore the total number of tumors (25) exceeds the total incidence of tumors (19).

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Squamous-cell carcinomas	9/19
Scirrhous carcinomas	5/19
Bronchioalveolar adenomas and carcinomas	11/19

In male rats exposed to Sb2O3, the authors concluded that there was no significant difference in the extent and severity of interstitial fibrosis in males as compared to females exposed to Sb2O3. Other observations in male rat lung were similar to female but lesser in severity. Male rats appeared to have more mononuclear cells, lymphocytes and plasma cells present in interstitial spaces than did females, suggesting that higher immune functions in males might account for the differences in severity in male and female adverse effects in the lung. No lung tumors were seen in the control rats of either sex or in the male rats exposed to Sb2O3. Only females exposed to Sb2O3 developed lung neoplasms. This finding confirmed an earlier unpublished finding by Watts that there was a gender-specific difference in development of lung neoplasms in rats exposed to Sb2O3.

Critique of Watts and Groth Studies

Both the EPA and the researchers on whose work EPA based its 1995 RfC (Newton et al., 1994) were critical of the study design and findings of Watts and Groth. Newton et al. conducted a sub chronic and chronic inhalation toxicity study in rats (see next section) but could not repeat the results of Watts and Groth at similar or lower exposure concentrations. In Newton's discussion, he describes Groth's use of Wistar rats as "problematic" since this strain exhibits a high incidence of pituitary adenoma that may have accounted for the observed sex-related differences in the Groth study. Newton attributes the positive oncogenic results in female rats in both the Watts and Groth studies to particle-burden effects. Newton notes that "recent studies in rat have shown that at excessive lung burdens, insoluble particles have a reduced clearance rate. Under these conditions, even a relatively innocuous material can become neoplastic." This theory does not explain, however, why only the female rats in these studies were affected.

In addition, Groth noted some discrepancies in the Watt study. For example, Groth notes that the Watt study reported a much higher induction of lung neoplasms in female rats (62%) exposed to inhaled Sb2O3 at a much lower exposure level than was used in the Groth study. Groth also notes that the Watt study reports that Sb concentration in the lungs of male rats was significantly greater than in female rats, yet 27% of female rats developed neoplasms while male rats developed none. EPA made a similar comment.

Groth also notes the discrepancies in his own study. He reports that all females (including controls) contained higher concentrations of arsenic than males in all tissues EXCEPT for lung. He acknowledged that it is possible that systemic concentrations of arsenic, rather than lung concentrations, may be more critical in promoting a co-carcinogen effect with Sb2O3 exposure. He also discussed the possibility that higher systemic concentrations of arsenic in females may have led to immunosuppression in females.

Another confusing finding in the Groth study was the higher concentration of arsenic in the lungs of animals exposed to Sb2O3 as compared to Sb ore even though the Sb ore contained 20 times more arsenic than the Sb2O3 compound. These findings may be attributable to differences in clearance rates or solubility of arsenic in each of the test compounds but it also undermines confidence in the estimation of the actual Sb2O3 exposures.

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Groth et al. present additional conflicting remarks in their conclusion: They state that they have found interstitial fibrosis to be a frequent precursor to induction of lung cancer in rats with exposure to a variety of particulates but then later state that male rats exposed to Sb2O3 developed interstitial fibrosis but not lung cancer.

Watts and Groth used commercial grade test chemicals that were contaminated with other known carcinogens. In particular, arsenic could act as a co-carcinogen when antimony dusts and fumes are inhaled.

EPA's criticisms of both studies were reported in Newton et al. (1994). Newton quotes the USEPA finding that "…neither study is adequate to reasonably determine or predict the oncogenic risk to humans exposed to these substances. Use of only one sex in the Watt study, use of only one exposure level in the Groth study and lack of adequate control of exposure levels in both of these studies make their use as a basis for risk estimation difficult". The EPA then went on to state "Therefore, the EPA believes that further testing to characterize the oncogenic effects of exposure to Sb2O3 is warranted."

Newton PE, Bolte HF, Daly IW, Pillsbury BD, Terrill JB, Drew RT, Ben-Dyke R, Sheldon AW & Rubin LF (1994). Subchronic and chronic inhalation toxicity of antimony trioxide in the rat. Fundamental and Applied Toxicology 22: 561-576.

This study was used by EPA in deriving an RfC in 1995 for Sb2O3. Newton et al. were unable to duplicate the findings of Watts and Groth in this well-designed, properly controlled study.

65 male and 65 female Fischer 344 rats were exposed to 0, 0.06±0.04, 0.51±0.13 and 4.5±1.33 mg/m3 Sb2O3 (cum. means) via whole body inhalation for 6 hr/day, 5 days/wk for 52 weeks followed by a 12 month observation period. Though the usual exposure period in chronic bioassays for testing of carcinogenicity is 2 years, the authors were attempting to duplicate the findings of Watts and Groth who reported lung neoplasms in female rats after only one year of exposure. The authors assumed that they were not testing for *evidence* of carcinogenicity but rather for a dose-response relationship and for a sex-specific susceptibility to inhaled Sb2O3 in females. Animals were approximately 8 weeks of age and weighed 140-169 g (males) or 99-122 g (females).

A complete blood workup was conducted at 12, 18 and 24 months. Animals were observed for viability and overt signs of toxicity weekly during the first 13 weeks, monthly thereafter and at termination. Complete gross postmortem exams were performed on all animals. Tissues examined histopathologically included heart, nasal turbinates, larynx, trachea, lung, and peribronchial lymph nodes. Sb2O3 tissue levels were determined using the left lung, blood and feces samples.

Detailed clinical observations revealed a treatment-related increase in ocular opacities. There were no significant differences among groups in body weight gain. Absolute and relative lung weights were unaffected by Sb2O3 exposure at all concentrations. Results from clinical pathology (bloodwork) indicated no treatment-related effects. Chronic interstitial inflammation was observed in the lungs of numerous animals during both the exposure and observation periods. Interstitial fibrosis, granulomatous inflammation, and bronchiolar/alveolar hyperplasia of minimal to moderate severity were noted in a small number of animals during the observation period. Changes were most pronounced in the highest exposure group. Pulmonary carcinomas were reported in one male from the control group, one male from the 4.5mg/m3 group and one

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female in the 0.51 mg/m3 group. None of these carcinomas were considered to be treatment-related. The survival rate was 56% for males and 48% for females. Sb2O3 tissue level data show a lung-dependent effect on the Sb2O3 clearance rate.

Newton reports his results as "in conflict" with the Watt study which found neoplasms in 62% of animals at, reportedly, the same exposure level. Particle size data in both studies show similar size even though different measuring techniques were used. Newton concluded that "the higher prevalence of non-neoplastic changes and increased amounts of test material seen in the lungs in the Watt study as compared to the current study would suggest that the Watt exposure levels may have been above those reported." The EPA also stated similar concerns.

SUMMARY OF CARCINOGENIC AND NON-CARCINOGENIC EFFECTS REPORTED IN HUMANS

Short-term exposure to various antimony compounds in the workplace were reported to cause irritation of the skin, eyes and respiratory tract. Reported long-term workplace exposures have included effects such as dermatitis, lung disease, liver and kidney damage, and reproductive effects. Effects from workplace exposure are almost universally from inhalation exposure though dermal contact with airborne antimony has produced dermatosis and ocular irritation. Cardiac effects have been reported when patients were exposed to antimony via the intravascular route in therapeutic settings.

Reproductive & Developmental Effects

The often-cited Balyaera report noted an increase in the number of spontaneous abortions and menstrual cycle disturbances in female workers exposed to antimony-containing aerosols (dust containing metallic antimony, antimony trioxide, and antimony pentasulfide) during a two year period. However, a dose-response relationship could not be established because exposure concentrations were not specified. In addition, the study does not describe selection of controls nor exposure to other toxics in the workplace (HSDB, Patty's, 2001).

Carcinogenicity Studies in Humans

Unfortunately, much of the epidemiologic data of workers chronically exposed to antimony trioxide is confounded by simultaneous exposure to arsenic, silica dust or other workplace toxics that could account for the respiratory symptoms and pneumoconiosis-like syndromes reported in these studies. In addition, many of the older epidemiological studies of antimony workers did not report or control for smoking status of workers. Therefore the evidence for carcinogenicity of Sb2O3 in humans is currently qualitative in nature.

An epidemiological study comprised of 51 antimony smelting plant workers ages 31 to 54 were exposed to airborne dust containing up to 88% Sb2O3 and 12% antimony pentoxide for durations between 9 and 31 years (mean working years = 17.9). Pneumoconiotic changes were seen in the lung after 1 decade of employment. Respiratory symptoms including chronic coughing (60.8%), conjunctivitis (27.5%), antimony dermatosis (32/51), upper airway inflammation (35.3%), chronic bronchitis (37.3%), chronic emphysema (34.5%), and pleural adhesions (27.3%) were reported. Neither massive lung fibrosis nor malignant lesions were noted (HSDB).

Schnorr et al. (1995) conducted a mortality in a cohort of antimony smelter workers. The study consisted of 1,014 men employed between 1937 and 1971 in a Texas antimony smelter

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consisting primarily of workers of Spanish descent (928 men or 91.5% of the study group). No data on smoking history was collected but the authors state that Hispanics are known to smoke at much lower rates than non-Hispanics and their lung cancer and heart disease mortality is generally low. The authors found an increase in lung cancer mortality when ethnic specific mortality rates were used and a statistically significant increasing risk of lung cancer with increasing length of employment. It was noted that increases in mortality due to lung cancer could be due to simultaneous arsenic exposure at the smelter although no more than 0.6 excess lung cancer deaths would be expected at these arsenic exposure levels whereas 8 deaths were observed. Exposure to silica may also explain the elevated mortality due to pneumoconiosis. Another possible confounder includes the difficulty in identification of appropriate referent groups (white male data served as a control for Hispanic cohort).

Other Evidence

Studies on mutagenic, reproductive and teratogenic effects are weak and conflicting. There is some dispute over whether or not Sb2O3 is clastogenic, mutagenic, both or neither. One of the biggest hurdles with respect to *in vitro* testing of Sb2O3 is its insolubility. In a recent review of cobalt and antimony, *in vitro* and *in vivo* genotoxicity data for Sb2O3 gave conflicting results (DeBoeck et al., 2003). Overall, EPA and other experts do not consider antimony trioxide to be genotoxic in humans. EPA believe that evidence for mutagenicity, reproduction, and teratogenicity in mammals was weak and did not recommend further testing with regard to these effects.

CONCLUSION

Although the EPA recommended further investigation of the oncogenic potential of Sb2O3 in 1983 (EPA doc OPTS-42021), new animal and human data of sufficient quality from which to derive a risk estimate are lacking. The data that do exist are problematic primarily because 1) animal exposures were to commercial grade Sb2O3 containing traces of known carcinogens such as arsenic and 2) human exposures were limited to occupational exposures in antimony smelting operations or antimony ore mining. Both of these processes include exposures to arsenic and other metals in addition to silica dust and other unidentified workplace toxics. For these reasons, any positive results gleaned from these studies are difficult to interpret. Therefore, there is low confidence in the database.

Existing animal data on the carcinogenicity of antimony trioxide are inadequate. The two main positive studies which reported various lung tumors in female rats exposed to inhaled Sb2O3 are unreliable due to errors and/or uncertainty in experimental design and actual exposure concentrations. One properly controlled, well designed study reported herein by Newton et al. was unable to find evidence of carcinogenicity in rats via inhaled antimony trioxide at similar exposure concentrations previously reported.

The IRIS summary for Antimony and Compounds is in the process of being updated. The new assessment will characterize the chronic health hazards by the inhalation and oral routes of exposure and will include cancer and non-cancer endpoints. The projected completion date for this document is January 2005 (IRIS). Until this assessment is completed, or new data becomes available that provides further information on the carcinogenic potential of this compound, the current data are insufficient from which to make a qualitative or quantitative conclusion regarding cancer risk to humans from inhaled antimony trioxide. Therefore, the footnote associated with the carcinogenic potential of this chemical on the final screening levels list will be deleted.

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