United States
Environmental Protection
Agency

EPA/690/R-08/004F
Final
8-5-2008

Provisional Peer Reviewed Toxicity Values for

Antimony Trioxide
(CASRN 1309-64-4)

Superfund Health Risk Technical Support Center
National Center for Environmental Assessment
Office of Research and Development
U.S. Environmental Protection Agency
Cincinnati, OH 45268

Acronyms and Abbreviations

bw	body weight
cc	cubic centimeters
CD	Caesarean Delivered
CERCLA	Comprehensive Environmental Response, Compensation and Liability Act of 1980
CNS	central nervous system
cu.m	cubic meter
DWEL	Drinking Water Equivalent Level
FEL	frank-effect level
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
g	grams
GI	gastrointestinal
HEC	human equivalent concentration
Hgb	hemoglobin
i.m.	intramuscular
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IUR	inhalation unit risk
i.v.	intravenous
kg	kilogram
L	liter
LEL	lowest-effect level
LOAEL	lowest-observed-adverse-effect level
LOAEL(ADJ)	LOAEL adjusted to continuous exposure duration
LOAEL(HEC)	LOAEL adjusted for dosimetric differences across species to a human
m	meter
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mg/kg	milligrams per kilogram
mg/L	milligrams per liter
MRL	minimal risk level
MTD	maximum tolerated dose
MTL	median threshold limit
NAAQS	National Ambient Air Quality Standards
NOAEL	no-observed-adverse-effect level
NOAEL(ADJ)	NOAEL adjusted to continuous exposure duration
NOAEL(HEC)	NOAEL adjusted for dosimetric differences across species to a human
NOEL	no-observed-effect level
OSF	oral slope factor
p-IUR	provisional inhalation unit risk
p-OSF	provisional oral slope factor
p-RfC	provisional inhalation reference concentration
p-RfD	provisional oral reference dose

PBPK	physiologically based pharmacokinetic
ppb	parts per billion
ppm	parts per million
PPRTV	Provisional Peer Reviewed Toxicity Value
RBC	red blood cell(s)
RCRA	Resource Conservation and Recovery Act
RDDR	Regional deposited dose ratio (for the indicated lung region)
REL	relative exposure level
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	Regional gas dose ratio (for the indicated lung region)
s.c.	subcutaneous
SCE	sister chromatid exchange
SDWA	Safe Drinking Water Act
sq.cm.	square centimeters
TSCA	Toxic Substances Control Act
UF	uncertainty factor
µg	microgram
µmol	micromoles
VOC	volatile organic compound

PROVISIONAL PEER REVIEWED TOXICITY VALUES FOR ANTIMONY TRIOXIDE (CASRN 1309-64-4)

Background

On December 5, 2003, the U.S. Environmental Protection Agency's (EPA's) Office of Superfund Remediation and Technology Innovation (OSRTI) revised its hierarchy of human health toxicity values for Superfund risk assessments, establishing the following three tiers as the new hierarchy:

1. EPA's Integrated Risk Information System (IRIS).

2. Provisional Peer-Reviewed Toxicity Values (PPRTV) used in EPA's Superfund Program.

3. Other (peer-reviewed) toxicity values, including:

   - Minimal Risk Levels produced by the Agency for Toxic Substances and Disease Registry (ATSDR),
   - California Environmental Protection Agency (CalEPA) values, and
   - EPA Health Effects Assessment Summary Table (HEAST) values.

A PPRTV is defined as a toxicity value derived for use in the Superfund Program when such a value is not available in EPA's Integrated Risk Information System (IRIS). PPRTVs are developed according to a Standard Operating Procedure (SOP) and are derived after a review of the relevant scientific literature using the same methods, sources of data, and Agency guidance for value derivation generally used by the EPA IRIS Program. All provisional toxicity values receive internal review by two EPA scientists and external peer review by three independently selected scientific experts. PPRTVs differ from IRIS values in that PPRTVs do not receive the multi-program consensus review provided for IRIS values. This is because IRIS values are generally intended to be used in all EPA programs, while PPRTVs are developed specifically for the Superfund Program.

Because new information becomes available and scientific methods improve over time, PPRTVs are reviewed on a five-year basis and updated into the active database. Once an IRIS value for a specific chemical becomes available for Agency review, the analogous PPRTV for that same chemical is retired. It should also be noted that some PPRTV manuscripts conclude that a PPRTV cannot be derived based on inadequate data.

Disclaimers

Users of this document should first check to see if any IRIS values exist for the chemical of concern before proceeding to use a PPRTV. If no IRIS value is available, staff in the regional Superfund and RCRA program offices are advised to carefully review the information provided in this document to ensure that the PPRTVs used are appropriate for the types of exposures and

circumstances at the Superfund site or RCRA facility in question. PPRTVs are periodically updated; therefore, users should ensure that the values contained in the PPRTV are current at the time of use.

It is important to remember that a provisional value alone tells very little about the adverse effects of a chemical or the quality of evidence on which the value is based. Therefore, users are strongly encouraged to read the entire PPRTV manuscript and understand the strengths and limitations of the derived provisional values. PPRTVs are developed by the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center for OSRTI. Other EPA programs or external parties who may choose of their own initiative to use these PPRTVs are advised that Superfund resources will not generally be used to respond to challenges of PPRTVs used in a context outside of the Superfund Program.

Questions Regarding PPRTVs

Questions regarding the contents of the PPRTVs and their appropriate use (e.g., on chemicals not covered, or whether chemicals have pending IRIS toxicity values) may be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300), or OSRTI.

INTRODUCTION

An oral RfD for antimony trioxide (CASRN 1309-64-4) is not available on IRIS (U.S. EPA, 2008). The HEAST (U.S. EPA, 1997) lists a chronic oral RfD of 4E-4 mg/kg-day for this compound, based on analogy to antimony (LOAEL of 0.35 mg/kg-day for reduced life span and serum chemistry changes in male and female rats exposed to potassium antimony tartrate in drinking water for 2 years by Schroeder et al., 1970 and a composite uncertainty factor of 1000 - uncertainty factors (UFs) of 10 each to account for the LOAEL to NOAEL conversion, interspecies extrapolation, and interindividual differences) by correcting for differences in molecular weight. The HEAST also adopted the chronic RfD as a conservative estimate of the subchronic RfD. A Health and Environmental Effects Profile (HEEP) for Antimony Oxides (U.S. EPA, 1985) and a Health Effects Assessment (HEA) for Antimony and Compounds (U.S. EPA, 1987) were cited as references for the RfD assessment in the HEAST.

A chronic inhalation RfC for antimony trioxide is available on IRIS (U.S. EPA, 2008). The RfC of 2E-4 mg/m^3 for antimony trioxide is based on a benchmark concentration of 0.87 mg/m^3 for a 10% increase in the incidence of chronic interstitial pulmonary inflammation (severity >2) in female rats exposed to antimony trioxide in the air for 1 year (and observed for an additional year) by Newton et al. (1994). A composite UF of 300 was used (UF of 10 for interindividual differences and factors of 3 each for interspecies extrapolation with a dosimetric adjustment, database uncertainties, and a less than lifetime exposure). No source documents were listed in IRIS for this assessment, which was verified on May 10, 1995. The HEAST lists a subchronic RfC of 2E-4 mg/m^3 for antimony trioxide and indicates that the chronic RfC on IRIS

was adopted as the subchronic RfC. CalEPA (2006) derived a chronic recommended exposure limit (REL) of 0.2 μg/m^3 (or 2E-4 mg/m^3) for antimony trioxide based on the IRIS RfC.

The Agency for Toxic Substances and Disease Registry (ATSDR) prepared a toxicological profile for antimony and compounds (ATSDR, 1992), but did not derive oral or inhalation MRL values for antimony trioxide. ATSDR concluded that the damage to the lungs and myocardium observed in several species of animals (Brieger et al. 1954; Bio/dynamics 1985, 1990; Gross et al. 1955; Groth et al. 1986; Watt 1983a,b) and in humans (Brieger et al. 1954; Potkonjak and Pavlovich, 1983) chronically exposed to airborne antimony (primarily antimony trioxide) showed serious adverse effects occurring at the lowest exposure levels tested. Thus, the data were considered inadequate for the derivation of MRL values. Among occupational-exposure standards and guidelines, the American Conference for Governmental Industrial Hygienists (ACGIH), the National Institute for Occupational Safety and Health (NIOSH) and the Occupational Safety and Health Administration (OSHA), respectively, recommend a threshold limit value-time weighted average (TLV-TWA), REL and permissible exposure limit (PEL) of 0.5 mg/m^3 for antimony and compounds (as Sb) (OSHA, 2007; ACGIH, 2006; NIOSH, 2005) based on skin and upper respiratory tract irritation.

A cancer assessment for antimony trioxide is not available on IRIS (U.S. EPA, 2008) or in the HEAST (U.S. EPA, 1997). The HEEP for Antimony Oxides (U.S. EPA, 1985) and HEA for Antimony and Compounds (U.S. EPA, 1987) acknowledged there was suggestive evidence of lung cancer in female rats exposed to antimony trioxide by inhalation, but declined to perform quantitative carcinogenicity assessments. In both cases, the decision was based on EPA's Federal Register response to an Interagency Testing Committee (ITC) recommendation for carcinogenicity testing of antimony (U.S. EPA, 1983a) in which the data available at the time were characterized as inadequate to reasonably predict oncogenic risk of antimony in exposed humans. U.S. EPA (1992) assigned antimony in drinking water to weight-of-evidence Group D (not classifiable as to human carcinogenicity) based on the reasoning that evidence of lung cancer following inhalation exposure is of uncertain relevance to oral drinking water exposure. Antimony is classified in cancer weight-of-evidence Group D in the Drinking Water Standard and Health Advisories List (U.S. EPA, 2006). The International Agency for Research on Cancer (IARC) (1989) concluded that antimony trioxide is possibly carcinogenic to humans (Group 2B), based on sufficient evidence in animals and inadequate evidence in humans. ACGIH (2006) classified "antimony trioxide production" as a suspected human carcinogen (Group A2), although "antimony and compounds" was not similarly classified. In the time since these assessments were performed, additional studies in both humans and animals have entered the literature. The available data regarding the carcinogenicity of antimony are reviewed below.

Computer searches of TOXLINE (1990-1997), CANCERLINE (1990-1997), DART (1989-1996), ETICBACK (1989-1996), TSCATS, CCRIS, EMIC and EMICBACK were conducted in June 1996 and May 1997 for antimony (Sb) and compounds. Update literature searches were performed in January 1999 for the 1996 to 1999 time period in HSDB, RTECS, MEDLINE and TOXLINE (and its subfiles) databases. A recent update literature search was performed in January 2006 for the time period of 1999 to present in TOXLINE, MEDLINE (plus PubMed cancer subset), BIOSIS and DART/ETICBACK. Databases searched without date limitations included TSCATS, RTECS, GENETOX, HSDB and CCRIS. Search of Current

Contents encompassed July 2005 to January 2006. The literature search was updated to July 2008.

REVIEW OF PERTINENT DATA

Human Studies

Oral Exposure

No data were located regarding the oral toxicity or carcinogenicity of antimony trioxide in humans.

Inhalation Exposure

Several occupational exposure studies have examined the toxicity of antimony trioxide. The most frequently reported health effect in workers exposed to antimony trioxide is pneumoconiosis (Potkonjak and Pavlovich, 1983; Cooper et al., 1968; Renes, 1953). Immune alterations were suggested to play a role in the dermal and pulmonary effects of occupational antimony trioxide exposure (Kim et al., 1999).

Kim et al. (1999) evaluated serum cytokine and immunoglobulin levels in antimony workers at a factory in Korea that produced antimony trioxide as a major product. The study subjects consisted of antimony-exposed workers that frequently complained of dermatitis (n=12), workers at the same factory not exposed to sources of antimony (n=22) and healthy volunteers recruited as visitors from a nearby hospital (n=33). The geometric mean air concentration of antimony in the manufacturing area was 0.766 mg/m^3. Urinary concentrations of antimony were highest in workers with dermatitis (410.8 µg/g creatinine), as compared to other factory workers (112.5 µg/g creatinine), and healthy volunteers (27.8 µg/g creatinine). Total IgG levels did not differ among subject groups; however, the distribution of IgG subclasses was slightly altered, with lower levels of IgG1 present in serum of highly exposed workers. The serum concentration of IgE was also lower in these workers. No significant correlation was observed between the urinary concentration of antimony and the serum concentrations of IgG1, IgG2, IgG3 or IgE within each subject group; however, a significant correlation was seen between IgG4 levels and urinary antimony concentration among the 12 subjects in the highest exposure group. Interleukin-2 concentrations did not differ among exposure groups in this study. Serum interferon concentrations were lower in the two worker groups as compared to controls, but did not appear related to the level of antimony exposure.

Potkonjak and Pavlovich (1983) examined 51 workers with definitive signs of pneumoconiosis employed in an antimony smelting plant for 9-31 years (mean 17.91). The workers were examined 2-5 times over a 25-year period. The dust concentration ranged from 17-86 mg/m^3 and more than 80% of the dust particles were <5 µm in diameter. The dust was primarily composed of antimony (38.73-88.86% antimony trioxide and 2.11-7.82% antimony pentoxide) and smaller percentages of free silica (0.82-4.72%), arsenic trioxide (0.21-6.48%) and ferric trioxide (0.9-3.8%). X-ray findings considered indicative of pneumoconiosis included the presence of diffuse, densely distributed punctate opacities with a diameter of <1 mm and

concentrated in the mid-lung region. Pneumoconiosis was not observed in workers exposed to antimony oxide dust for less than 9 years. The most common symptom reported by the workers was chronic coughing (60.8% of workers). No consistent alterations in pulmonary function tests were observed. Dermatosis was observed in 32 of the 51 workers. The dermatosis was characterized as vesicular or occasionally pustular and the incidence was higher in the summer and in workers working near the furnace.

Cooper et al. (1968) examined 28 workers exposed to airborne antimony trioxide or antimony ore for 1-15 years. Airborne antimony levels were measured at numerous locations, the range being 0.081-138 mg/m^3; particle size distribution was not reported. Roentgenographic examinations were conducted in 13 of the workers. Based on this examination, 3 of the workers were diagnosed as having antimony pneumoconiosis and 5 others were suspected of having pneumoconiosis. No consistent pattern of functional lung abnormalities was observed, although lung function changes were observed in some of the workers. Abnormal electrocardiogram (EKG) readings, indicative of slight bradycardia, were observed in 1 of the 7 tested subjects.

Renes (1953) examined 78 workers employed at a smelter and exposed to an average of 4.69 and 11.81 mg/m^3 antimony trioxide dust in two different work areas. The smelter fumes contained 35-68% antimony, 2-5% arsenic, 0.01-0.4% selenium, 0.04-0.30% lead and 0.1-0.4% copper. The workers also may have been exposed to hydrogen sulfide and sodium hydroxide. Several of the symptoms reported by the workers (soreness and bleeding of the nose, nasal septal perforations, laryngitis and erosion or ulceration of vocal cords) may have been due to exposure to caustic agents, rather than antimony trioxide. Pneumonitis was observed in six acutely ill workers who all received chest x-rays. Dermatitis and nodular ulcerative lesions in sweaty friction areas were reported during a brief period of high exposure to fumes. Altered EKG readings, indicative of bradycardia, were observed in about 14% of the exposed workers.

Belyaeva (1967) examined the reproductive toxicity of antimony in women (number of individuals not reported) working at an antimony metallurgical plant who were exposed to a mixture of antimony trioxide, antimony pentasulfide and metallic antimony. The workers were examined over a 2-year period. A control group was also examined; however, a description of the control group was not provided in the report. The level of airborne antimony and the presence or absence of other compounds were not reported. Disturbances of menstrual cycle, inflammation and other ailments of sexual organs were reported in 77.5% of the workers, as compared to 56% in the control group. Disturbances of menstrual cycle were the most frequently reported problem. No details or description of the effects were reported. Increased number of spontaneous abortions (12.5%) was observed in the workers as compared to controls (4.1%). Because it is not known if the controls had comparable jobs to the exposed group or what type of work the exposed group did, it is difficult to determine if these effects were exposure related. No difference in birth weight was observed among infants born to women exposed during pregnancy. Starting at 6 months of age, body weight gain of infants from exposed mothers was lower than in the control group.

The mortality experience of antimony smelter workers in England was studied by Jones (1994). The study population included all workers employed at an antimony smelter in northeast England on January 1, 1961 and all workers hired after that date (n=2508). The current analysis

was limited to male workers with at least 3 months of employment (n=1452). The population was divided into four groups based on occupation: antimony workers, maintenance workers, zircon workers and others. Antimony workers are those who worked in the antimony plant for at least 3 months. The antimony plant produced antimony metal, antimony alloys and antimony oxide from antimony ore (production of antimony metal and alloy ceased in 1973). Different ores were used over the years, but the primary ore used in the 30 years leading up to the study was a South African sulfide ore containing approximately 60% antimony and up to 0.5% arsenic. In some years during alloy production, supplemental arsenic metal and arsenic trioxide were brought in to assist production of arsenical antimony alloys. Workers in the antimony plant are expected to have had variable exposure to metallic antimony, antimony trioxide, metallic arsenic, arsenic trioxide, lead, combustion products [including polycyclic aromatic hydrocarbons (PAHs)] and sulfur dioxide. Workers never employed in the antimony plant were assigned as maintenance workers, zircon workers or other workers depending on their latest occupation. Maintenance workers would have had exposure to antimony plant chemicals when working in the plant during times of equipment breakdowns (exposures may have been unusually high). Zircon workers were employed in the milling of zircon sand, a purely physical process and the only substantial non-antimony activity at the site. These workers were not exposed to the chemicals at the antimony plant. They were similar to the antimony plant workers, however, in that both operations employed primarily unskilled manual laborers and paid similar wages. The group of other workers included office workers and management staff, who were not exposed to antimony plant chemicals.

Mortality experience was followed through December 31, 1992; 32 of the 1452 subjects (3%) were lost to follow-up, leaving a study population of 1420 workers. Among these, there were 357 known deaths (mortality information was not pursued for 29 emigrants in this group). Expected death rates were calculated based on national rates for England and Wales and local rates in Tyne and Wear. Comparisons reported below are based on local rates. There was an excess of neoplasms in the antimony workers (69 vs. 54.7, $p=0.07$) due to a significant excess of lung cancer (37 vs. 23.9, $p=0.016$). Maintenance workers also had a significant excess of lung cancer (15 vs. 8.1, $p=0.038$). The incidence of lung cancer was not elevated in the zircon workers or the other workers. The cohort was divided into workers present on January 1, 1961 and those added subsequently. There was a two-fold excess of lung cancer in antimony workers (32 vs. 14.7, $p<0.001$) and maintenance workers (12 vs. 5.3, $p=0.016$) employed on January 1, 1961. These workers accounted for 70% (44/63) of all observed lung cancer deaths in the study population. They also accounted for over 60% of all expected lung cancer mortality in the study population, a reflection of the fact that these groups contributed most of the man-years at risk in the study. There was no excess of lung cancer in the zircon workers or other workers employed on January 1, 1961 and no excess in any group among workers added to the study after January 1, 1961.

Subsequent analysis of the lung cancer deaths in antimony workers showed that people who started work before 1940 and in 5-year blocks from 1941 up to 1960 all showed excess lung cancer mortality, while those who started in 5-year blocks from 1961 to 1990 did not (expected values were very low after 1970, however). When antimony workers were grouped by number of years since first exposure, it was found that there was no excess of lung cancer in workers with less than 20 years since first exposure, but that a significant excess did occur in workers

with more than 20 years since first exposure. This suggests a latency period of approximately 20 years for lung cancer associated with antimony production. Analysis by duration of exposure did not show evidence of increased risk with longer duration, but interpretation is hindered by the small number of expected tumors in the 5-year groupings used.

Jones (1994) concluded that there was an excess of lung cancer in antimony smelter and maintenance workers hired before January 1, 1961 that did not, however, become evident until 20 years after first exposure. Because very few employees from the group hired after January 1, 1961 had their first exposure more than 20 years before this study, this study was inconclusive as to whether the carcinogenic effect persisted beyond 1960. This study was also inconclusive as to identification of the carcinogenic agent. Antimony workers were exposed to arsenic and arsenic trioxide, which are known to cause lung cancer (U.S. EPA, 2006), in addition to antimony and antimony trioxide (albeit at much lower concentrations). Antimony workers would also have been exposed to unknown quantities of PAHs, some of which are carcinogenic (U.S. EPA, 2006). In addition, the prevalence of smoking among smelter workers in 1961 was very high (72%). However, the absence of excess lung cancer among zircon workers, who were drawn from the same population as the antimony workers, suggests that smoking alone is not likely to be responsible for the observed excess of lung cancer in antimony workers. It should be noted that the results of this study from analysis of the workers employed on January 1, 1961 are subject to survivor bias; workers from the years before 1961 who left employment before January 1, 1961 (e.g., for health reasons) are not included in the study. This means the risks associated with employment in the antimony plant before 1961 may have been underestimated in the current analysis.

Schnorr et al. (1995) studied the mortality experience of antimony smelter workers at a plant in southern Texas. The plant, which was built in 1930 and continued to operate unchanged until closing in 1979, was used to recover antimony metal and antimony oxide from ore mined in Central and South America. The ore consisted primarily of antimony oxide and antimony sulfide (32-60%), but also contained arsenic (0.05-0.13%), sulfur (0.44-18.5%) and lead (0.11-0.40%). Industrial hygiene surveys at the plant in 1975 and 1976 found airborne antimony levels ranging from 50-6200 $\mu g/m^3$. The geometric mean concentrations for different departments ranged from 140-1498 $\mu g/m^3$; the geometric mean concentration for the entire plant was 551 $\mu g/m^3$ in 1975 (n=12 8-hr area samples) and 747 $\mu g/m^3$ in 1976 (n=50 8-hr breathing zone samples). Arsenic concentrations ranged from 1-47 $\mu g/m^3$, with departmental geometric means of 1-19 $\mu g/m^3$ and plant-wide geometric means of 2 $\mu g/m^3$ in 1975 and 5 $\mu g/m^3$ in 1976. The study population included 1014 male workers hired between January 1, 1937 and January 1, 1971 and employed in the plant for a minimum of 3 months. Vital status was determined up to December 31, 1989. Expected deaths were calculated based on national statistics for white males and Texas statistics for males with Spanish surnames. A total of 928 of the 1014 workers in this study (91.5%) had Spanish surnames. The researchers cited this fact and studies showing markedly lower rates of lung and heart disease and cigarette smoking in Hispanic males compared with non-Hispanic white males as motivation for calculating expected deaths based on Texas statistics for males with Spanish surnames.

When compared with expected cancer rates based on national statistics for white males, the rates observed in the antimony smelter workers were reduced for mortality due to lung cancer

(30 observed vs. 40 expected), as well as colon cancer (2 observed vs. 16 expected) and heart disease (154 observed vs. 263 expected). These findings were expected for this predominantly Hispanic population. Of the 30 lung cancers observed in the antimony workers, 28 (93%) occurred 20 years or more after first employment, suggesting a latency period of approximately 20 years for lung cancer in antimony smelter workers. Although the lung cancer rate was lower among antimony workers as a whole than would be expected based on national statistics in white males, the lung cancer rate among antimony workers with the longest time since first exposure (>20 yrs) and the longest duration of employment (>10 yrs) was elevated (albeit not to a statistically significant degree), even when compared with national statistics for white males (SMR=1.55 based on 9 observed and 5.8 expected; 90% CI: 0.86-2.60). When expected mortality was calculated using national statistics for white males for the white antimony workers and the rates for Texans with Spanish surnames for the antimony workers with Spanish surnames, the lung cancer rate was found to be elevated in the antimony workers (SMR=1.39; 90% CI: 1.01-1.88). Segregation of workers into groups based on duration of employment showed that the increase in lung cancer occurred in workers with 5-10 years exposure (SMR=2.24 based on 8 observed) and >10 years exposure (SMR=2.73 based on 9 observed). There was no increase in workers with <5 years exposure (SMR=0.83 based on 11 observed). The trend for increased lung cancer mortality with increasing exposure duration of antimony workers was statistically significant ($p<0.005$). Smelter workers were not segregated according to job title or exposure level, so no dose-response analysis was performed.

The researchers concluded that this study demonstrated increased lung cancer mortality in antimony smelter workers by using ethnic-specific state mortality rates and that the risk of lung cancer in these workers increased with duration of exposure. The researchers attributed the excess lung cancer mortality in these workers to antimony exposure. They acknowledged arsenic as a potential confounding exposure in the exposed population, but estimated that only 0.6 of the 8 excess lung cancer deaths in this population could be attributed to the low-level arsenic exposure experienced by these workers [based on an assumed average arsenic exposure of 5 $\mu g/m^3$ for 1014 workers exposed an average of 6.8 years and the OSHA risk assessment model for arsenic (NIOSH, 2005)].

Antimony (as antimony trioxide) is one of numerous chemicals to which workers in the glass industry may be exposed. Studies of glass workers have frequently found excess risk of lung cancer in the workers investigated; cancers of the brain, colon, stomach, larynx and pharynx have also been found in excess in various studies (Wingren and Englander, 1990; Wingren and Axelson, 1993). Wingren and Axelson (1993) attempted to associate the cancer findings in glass workers with specific chemical exposures. They related semi-quantitative data on the use (none/low/high) of 10 different metals (including antimony) at 7 different glassworks to case-referent evaluations of lung, stomach and colon cancer among workers at these plants. They found that there was a clear increasing trend for risk of colon cancer with increasing use of antimony. The odds ratio (95% CI) for colon cancer increased from 1.4 (0.6-3.3) with no antimony exposure to 1.8 (0.8-13.8) with low antimony exposure and 5.0 (2.6-9.6) with high antimony exposure. Exposure to lead, which was strongly correlated with exposure to antimony in glass workers ($r=0.76$), is a possible confounding exposure in this analysis. Stomach and lung cancer in glass workers was not obviously related to antimony use in this analysis. The data

relating antimony exposure to colon cancer in glass workers in this study is suggestive, but is not by itself conclusive proof of a causal relationship.

Animal Studies

Oral Exposure

Omura et al. (2002)

The testicular toxicity of antimony trioxide was evaluated in Crj:Wistar rats (7-8/group) and Cjr:CD-1 mice (8-10/group) (Omura et al., 2002). Antimony trioxide (purity >99.9%) (12 or 1200 mg/kg-day) was administered by oral gavage to rats (3 days/week for 4 weeks) and mice (5 days/week for 4 weeks). Animals were sacrificed by carbon dioxide inhalation 24 hours after the final gavage dose was administered. The testes, epididymides, ventral prostate and seminal vesicle (without fluid) were removed and weighed. Histopathological changes were evaluated in the testes and the number, motility and morphology of sperm from the cauda epididymides were assessed. Three mice (1 control, 2 given 1200 mg/kg-day) died due to gavage error. No significant effect on body weight or organ weight of reproductive tissues was observed. Sperm parameters were not affected by antimony trioxide treatment and histopathology results were essentially negative. A NOAEL value of 1200 mg/kg-day was derived for male reproductive effects of antimony trioxide in this study; a LOAEL value was not determined (no effects were seen at the highest dose tested).

Hext et al. (1999)

A 90-day dietary study of antimony trioxide was conducted in male and female Wistar rats (Alpk:APSD strain) (Hext et al., 1999). Rats (12/sex/group) were fed diets containing 0, 1000, 5000 or 20,000 ppm antimony trioxide (99% purity). Food consumption was measured continuously and calculated as a weekly mean. Body weights were measured weekly. Doses were calculated for each week, based on feed consumption and body weight. Cage-side observations were made daily and detailed clinical observations were made weekly. During the last week of the study, control and high-dose rats received an eye examination using an indirect ophthalmoscope and a mydriatic substance to dilate the pupil. Urine samples were collected (16 hour collection) from rats housed in metabolic cages during the last week of the study. Urine volume was measured and samples were analyzed for appearance, specific gravity, pH, glucose, ketones, bilirubin, protein and blood. Urine was centrifuged and the sediment was stained and examined. Blood samples were obtained for hematology and clinical chemistry by cardiac puncture following sacrifice by halothane overdose. Hematology parameters included red cell count, hematocrit, hemoglobin, mean cell volume, total and differential white cell count and platelet count. Plasma was used for clinical chemistry measurements of urea, glucose, total protein, albumin, cholesterol, triglycerides, total bilirubin, creatinine, sodium, potassium, chloride, calcium and phosphate. Plasma enzyme activities that were measured included alkaline phosphatase, alanine aminotransferase, γ-glutamyl transferase, creatinine kinase and aspartate aminotransferase. Adrenal glands, brain, kidneys, liver, epididymides and testes were removed, weighed and prepared for histopathological examination. All tissues from the control and high-dose rats were examined, as well as any abnormal tissue from the intermediate dose groups.

Food consumption and body weight gain were similar to controls for all treatment groups. The study authors calculated mean daily antimony trioxide doses of 0, 84, 421 or 1686 mg/kg-day for male rats and 0, 97, 494 or 1879 mg/kg-day for female rats. No significant clinical signs or ocular changes were associated with exposure to antimony trioxide. In high-dose female rats, urine volume was increased (+79%) and specific gravity was decreased (-1%). Urinary pH was increased in male rats given 1000 ppm (+5%) or 20,000 ppm (+5%), but was similar to the control value in the 5000 ppm group. Changes in urinary parameters were not dose-related and were considered by the study authors to be incidental. Minor changes were noted in some hematological parameters, with an elevated red cell count in high-dose male rats (+4%) and a decreased mean cell volume in high-dose female rats (-2%). The study authors considered the hematological changes to be too small to be of toxicological significance. Triglyceride content was increased (+30%) and alkaline phosphatase activity was decreased (-12%) in high-dose male rats. High-dose female rats exhibited an increase in plasma cholesterol (+13%), a decrease in alkaline phosphatase activity (-36%) and an increase in aspartate aminotransferase activity (+52%). Alkaline phosphatase activity was also decreased (-23%) in female rats given 5000 ppm of antimony trioxide in the diet. No other treatment related changes in plasma biochemistry were observed. Absolute and relative liver weights were increased by approximately 10% in female rats fed 20,000 ppm antimony trioxide.

No gross findings indicative of toxicity were seen at necropsy. The incidence of pituitary cysts was higher in the 20,000 ppm dose groups of both male and female rats (4/12 treated males, 3/12 treated females, 1/12 control males and females). The study authors considered pituitary cysts to be a common spontaneous lesion with reported incidence values within the historical control range (i.e., not treatment-related). Three male rats in the high dose group had slight to moderate plasma cell infiltration in the cervical lymph node. This change has also been previously seen in historical controls from the same laboratory and was therefore not considered treatment related. No other histopathological lesions were observed. The high dose in female rats, 1879 mg/kg-day, can be considered a minimal LOAEL based on small increases in liver weight and serum aspartate aminotransferase, as well as decreased alkaline phosphatase activity in female rats, in the absence of histopathological changes. A NOAEL value of 494 mg/kg-day antimony trioxide was derived from female rats in this study.

Ainsworth et al. (1991)

Ainsworth et al. (1991) exposed groups of short-tailed voles (8-10/group, sex not reported) to 500 mg Sb/kg-day (administered as antimony trioxide) in the diet for 30, 40, 50 or 60 days. An additional group of 6 voles was exposed to 20,000 mg Sb/g-day in the diet for 12 days. The study was primarily designed to measure levels of antimony in various tissues. Organ concentrations of antimony were highest in the liver, followed by the kidney and lung. During the 60-day experiment, voles exposed to 500 mg Sb/kg-day appeared healthy. No gross lesions were identified at necropsy and wet and dry organ weights for the liver, kidney, and lung were similar to control. No clinical signs of toxicity were observed in voles fed 20,000 mg Sb/kg-day for 12 days. No histological alterations were observed in the liver or kidney sections examined by electron microscopy.

Sunagawa et al. (1981)

In a subchronic study conducted by Sunagawa et al. (1981), groups of 5 Wistar rats were exposed to 0, 0.5, 1.0 or 2.0% metallic antimony in the diet (estimated doses of 0, 500, 1000 and 2000 mg/kg-day) or 0, 1.0 or 2.0% antimony trioxide in the diet (0, 1000 or 2000 mg/kg-day) for 24 weeks. The description of this study from the Japanese literature is taken from the English language abstract. In the rats exposed to metallic antimony, significant adverse effects included dose-related decreases in body-weight gain, decreases in hematocrit and hemoglobin levels in the high-dose group and slight cloudy swelling in hepatic cords in the mid- and high-dose groups. Decreased erythrocyte levels and slight cloudy swelling of hepatic cords were observed in both groups of rats exposed to antimony trioxide. The English abstract provided no further details on this study.

Inhalation Exposure

Subchronic and chronic animal studies have evaluated inhalation exposure to antimony trioxide (Newton et al., 1994; Groth et al., 1986; Watt, 1983a,b; Gross et al., 1955). Groth et al. (1986) also characterized effects in rats that were exposed to antimony ore (46% antimony trisulfide). A nose-only inhalation developmental toxicity study using antimony trioxide was also conducted in rats (IAOIA, 2004, abstract only). Pulmonary toxicity, characterized by chronic interstitial inflammation, granulomatous inflammation and interstitial fibrosis, is the primary health effect seen after inhalation exposure to antimony trioxide (Newton et al., 1994; Groth et al., 1986; Watt, 1983a,b; Gross et al., 1955). Pulmonary tumors have also been noted in some studies (Groth et al., 1986; Watt 1980, 1983a,b).

Newton et al. (1994); Bio/dynamics (1985, 1990)

In a subchronic study conducted by Newton et al. (1994; Bio/dynamics, 1985), groups of 50 male and 50 female Fischer 344 rats were exposed to 0, 0.25, 1.08, 4.92 or 23.46 mg/m^3 antimony trioxide (99.68% purity) for 6 hours/day, 5 days/week for up to 13 weeks. Groups of 5 animals per sex were killed after 1, 2, 4, 8 and 13 weeks of antimony trioxide exposure and 1, 3, 9, 18 and 27 weeks post exposure. The mean particle size, measured with a TSI Aerodynamic Particle Sizer during weeks 1-4, 8 and 13, was 3.05 μm with a geometric standard deviation (sigma g) of 1.57. Daily observations, body weight measurements, hematological and serum clinical chemistry indices (hemoglobin, hematocrit, erythrocyte, leukocyte-total and differential, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, BUN, fasting glucose, total protein and electrolyte levels evaluated after 1, 2, 4, 8 and 13 weeks of exposure), lung weight measurements and gross and histopathology of major organs and tissues (including nasal turbinates, trachea and lungs) were used to assess toxicity.

No antimony-trioxide related deaths were observed. In-life observations performed weekly revealed the occurrence of corneal irregularities at a higher incidence in treated male rats (maximum of 22-44% in the different dose groups, but not in a dose-related order) than controls (maximum of 9%) starting in the second week of exposure and continuing through the rest of the exposure period and most of the recovery period. Corneal irregularities occurred at rates similar to treated males in both treated (maximum of 37-49%) and control (maximum of 43%) females. Histological observations of sacrificed animals revealed incidences of 1/25, 2/25, 3/25, 5/25 and 3/25 for corneal irregularities in male rats exposed to 0, 0.25, 1.08, 4.92 or 23.46 mg/m^3

antimony trioxide for 13 weeks, and 0/25, 5/25, 4/25, 6/25 and 2/25, respectively, in male rats sacrificed during the 27-week recovery period. In females, the incidences were 5/25, 6/25, 11/25, 5/25 and 7/25 for those sacrificed during exposure and 2/25, 6/25, 11/25, 8/25 and 3/25 for those sacrificed during the recovery period.

A small (6%), but statistically significant, decrease in body weight gain was observed in the male rats exposed to 23.46 mg/m^3. No significant alterations in body weight gain were observed in the other groups of male rats or in the female rats. No exposure-related effects on hematological or clinical chemistry indices were observed. Absolute lung weights were significantly increased in the male and female rats exposed to 4.92 or 23.46 mg/m^3; in the 23.46 mg/m^3 group, the lung weights were still elevated 27 weeks post exposure.

Histological alterations related to treatment were limited to the lungs and peribronchial lymph nodes. Dose-related increases were observed in the incidence and severity of alveolar/intraalveolar macrophages in the lungs of male and female rats. Both incidence and severity of this effect were greater during the post exposure period as compared to the exposure period. The respective incidences for animals with increased alveolar/intraalveolar macrophages in the 0, 0.25, 1.08, 4.92 and 23.46 mg/m^3 groups were 3/25, 1/25, 5/25, 11/25, and 9/25 for males sacrificed during the exposure period; 6/25, 10/25, 5/25, 21/25 and 24/25 for males sacrificed during the recovery period; 2/25, 0/25, 4/25, 10/25 and 11/25 for females sacrificed during the exposure period; and 1/25, 3/25, 11/25, 21/25 and 25/25 for females sacrificed during the recovery period. Using the recovery period incidences, the differences from control were statistically significant at $\geq$4.92 mg/m^3 in males and $\geq$1.08 mg/m^3 in females (Fisher Exact test performed for this review). Severity ranged from minimal to moderate, generally increasing with dose. The number of macrophages containing small particles of foreign material (presumably antimony trioxide) in the lungs and peribronchial lymph nodes were also increased accordingly.

The incidences of chronic interstitial inflammation and granulomatous inflammation (minimal to moderate severity) were similar in control and treated rats sacrificed during the exposure period. However, rats sacrificed during the recovery period showed increases in both lesions in the highest dose group. Incidences of chronic interstitial inflammation in the 0, 0.25, 1.08, 4.92 and 23.46 mg/m^3 recovery groups were 15/25, 13/25, 17/25, 17/25 and 25/25 for males and 9/25, 14/25, 12/25, 16/25 and 25/25 for females. The increases were statistically significant at 23.46 mg/m^3 in both sexes. Incidences of granulomatous inflammation in the 0, 0.25, 1.08, 4.92 and 23.46 mg/m^3 recovery groups were 2/25, 0/25, 4/25, 1/25 and 6/25 for males and 1/25, 0/25, 0/25, 5/25 and 7/25 for females. The increase was statistically significant only for females at 23.46 mg/m^3.

The subchronic Newton et al. (1994) study identified a NOAEL of 0.25 mg/m^3 and a LOAEL of 1.08 mg/m^3 antimony trioxide based on increased incidence of female rats with alveolar/intraalveolar macrophages. Other pulmonary effects (increased lung weights, as well as interstitial inflammation and granulomatous inflammation) were seen at higher concentrations.

In a one-year study conducted by Newton et al. (1994; Bio/dynamics, 1990), groups of 65 male and 65 female Fischer 344 rats were exposed to 0, 0.06, 0.51 or 4.5 mg/m^3 antimony

trioxide (99.68% purity) for 6 hours/day, 5 days/week for 52 weeks. Groups of 5 rats per sex were killed after 6 and 12 months of exposure and 6 months post-exposure. The remaining animals were killed 12 months post-exposure. The mass median aerodynamic diameter (MMAD) for the three concentrations of antimony trioxide was 3.76 μm and the sigma g was 1.79; the particle size distribution was measured every three months using a TSI Aerodynamic Particle Sizer. The following parameters were used to assess toxicity: daily observations, body weight, hematological and serum clinical chemistry indices (hemoglobin, hematocrit, erythrocyte, leukocyte-total and differential, aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, BUN, fasting glucose, total protein and electrolyte levels measured at exposure termination and 6 and 12 months post exposure), lung weight measurements and gross and histopathology of major tissues and organs (including nasal turbinates, trachea and lungs). Lung and blood samples were collected and analyzed for antimony content.

Ophthalmoscopic evaluation of surviving rats at 24 months revealed an apparently dose-related increase in the incidence of ocular opacities (including posterior polar cataracts, posterior subcapsular cataracts and complete cataracts) in both male and female rats (incidences of 11%, 15%, 21% and 18% in males and 13%, 40%, 36% and 47% in females at 0, 0.06, 0.51 and 4.5 mg/m^3, respectively). Chromodacryorrhea (conjunctivitis) was also observed in the treated rats, but may have been secondary to dental abnormalities. No statistically or toxicologically significant alterations in survival, body weight gain, absolute and relative lung weights, or hematology and clinical chemistry parameters were observed. Pulmonary concentrations of antimony trioxide at the end of the 12-month exposure period were 0, 11.5, 132 and 1420 μg/g in control, low-, mid- and high-exposure males and 0, 9.6, 107 and 1500 μg/g in control, low-, mid- and high-exposure females. Although not specified, these concentrations were apparently based on fresh (wet) lung weights (FW). Pulmonary clearance was found to be burden-dependent and the half-times were 2.3, 3.6 and 9.5 months in the 0.06, 0.51 and 4.5 mg/m^3 groups, respectively. The authors (Newton et al., 1994) noted that the decreased pulmonary clearance was not likely due to particle overload phenomena but rather to the intrinsic toxicity of the antimony trioxide. By comparing exposure concentration ratios (1:10:90) to lung burden ratios (1:11:138), U.S. EPA (2006) concluded that the decrease in pulmonary clearance observed in the 4.5 mg/m^3 group was an adverse effect.

As with the 13-week study, histological alterations were limited to the lung and surrounding lymph tissue. Increased incidence and severity of chronic interstitial inflammation and granulomatous inflammation were observed (statistical analysis performed by U.S. EPA, 2008). During the 12-month exposure period, no significant alterations in interstitial inflammation were observed in the female rats; in the males, the severity of interstitial inflammation was significantly increased at 4.5 mg/m^3. In the post exposure period, the severity of interstitial inflammation was significantly increased at 4.5 mg/m^3 (to minimize the confounding high background rate of this effect, animals with minimal or slight inflammation were not considered). Thus, the 1-year study found a NOAEL and LOAEL of 0.51 and 4.5 mg/m^3 antimony trioxide for lung effects.

Survival in treated groups did not differ significantly from controls and was adequate in all groups for evaluation of late-developing tumors (56-58% in males, 40-66% in females at

study termination). Pulmonary carcinomas were seen in only 3 animals - 2 males (1 control, 1 high-exposure) and 1 female (mid-exposure); they were not considered by the researchers to be related to antimony trioxide exposure. No other neoplasms were observed in this study.

Groth et al. (1986); Wong et al. (1979)

In a study sponsored by NIOSH (Groth et al., 1986; Wong et al., 1979), groups of 90 male and 90 female Wistar rats were exposed to target concentrations of 0 or 50 mg/m^3 antimony trioxide (80% pure) or 0 or 50 mg/m^3 antimony ore (46% antimony trisulfide) for 7 hours/day, 5 days/week for 52 weeks. Two exposure chambers were used for each exposure group, with equal numbers of male and female rats in each chamber. The mean TWA concentrations of antimony trioxide in the two exposure chambers were 45.0 and 46.0 mg/m^3; the MMAD was 2.80 μm (geometric standard deviation of particle distribution was not reported). For the antimony ore, the mean daily TWA concentrations were 36.0 and 40.1 mg/m^3 and the MMAD was 4.78 μm (geometric standard deviation not reported). Due to problems generating the dusts, exposure concentrations of both substances were well below the target level for the first 5 months of the study. Rats were examined twice daily for mortality and weighed periodically throughout the study. Interim sacrifices (5 rats/sex/group) were performed after 6, 9 and 12 months of exposure. Remaining animals were sacrificed 18-20 weeks after the end of exposure. All animals sacrificed or found dead during the study were necropsied. All organs were examined grossly and selected tissues were collected and processed for histopathological examination. Samples from the lungs and several other organs were also analyzed for their concentrations of antimony and other trace elements.

Concentrations of antimony in the lungs (measured after 9 months of exposure) were approximately 5 times higher for antimony trioxide exposure [38,300 μg/g dry weight (DW) for males, 25,600 μg/g DW for females] than for antimony ore exposure (7140 μg/g DW for males, 4520 μg/g DW for females). Pulmonary antimony concentrations were 9-10 μg/g DW in control males and females. Pulmonary arsenic concentrations were also higher in rats exposed to antimony trioxide (213 μg/g DW for males, 150 μg/g DW for females) than those exposed to antimony ore (10 μg/g DW for males, 14 μg/g DW for females) or controls (6.5 μg/g DW for males, 18.5 μg/g DW for females). Arsenic concentrations in other body tissues were also higher in trioxide-exposed rats than in ore-exposed rats, usually by about a 2-fold difference. For both compounds, females had 2-fold higher arsenic concentrations than males in tissues other than the lung.

No significant alterations in survival were observed in rats exposed to antimony trioxide. A slight, but statistically significant decrease in body weight gain was observed in the antimony trioxide-exposed rats from week 26 to 50; these rats weighed 6.2% less than the controls. Increased number of particle-laden alveolar macrophages, increased amount of alveolar protein, interstitial fibrosis and alveolar wall cell hypertrophy and hyperplasia were observed in the male and female rats after 6 and 12 months of exposure to antimony trioxide. In animals sacrificed 4-5 months post-exposure, the extent of interstitial fibrosis was increased compared to animals killed at the end of the exposure period. This study identifies a LOAEL of 45.5 mg/m^3 antimony trioxide (average of two TWA concentrations) for pulmonary effects in male and female rats.

No significant alterations in survival were observed in the antimony ore-exposed rats. From week 26 to 50, significant decreases in body weight gain were observed in the female rats exposed to antimony ore; however, the differences in body weight were slight, the antimony ore-exposed rats weighed ≤6.4% of controls. Increased number of particle-laden alveolar macrophages, increased amount of alveolar protein and interstitial fibrosis were observed in rats exposed to antimony ore for 6 or 12 months and in rats killed 4-5 months post-exposure. The LOAEL is 38 mg/m^3 antimony ore (average of two TWA concentrations) for pulmonary effects in male and female rats.

Although no lung tumors were clearly identified at gross necropsy, histological examination revealed that both antimony trioxide and antimony ore produced lung tumors in the female rats. Overall incidence was 19/89 (21%) in the trioxide-exposed females and 17/87 (20%) in the ore-exposed females (0/89 in controls). If rats that died or were sacrificed prior to appearance of the first tumor (53 weeks in the trioxide group and 41 weeks in the ore group) are excluded, the incidence was 19/70 (27%) in the trioxide group and 17/68 (25%) in the ore group (0/69 in controls). Tumor types included squamous-cell carcinomas, bronchioalveolar adenomas, bronchioalveolar carcinomas and scirrhous carcinomas. The incidence of the individual tumor types was similar in the trioxide- and ore-exposed females. Tumor diameter averaged 0.43 cm in the trioxide group and 0.25 cm in the ore group (the difference was not statistically significant). No lung tumors were found in male rats or controls in this study. The incidence of other tumors in exposed rats did not differ from controls. Sex-related differences found in both control and treated rats were a 3-fold higher incidence of thyroid tumors in males and a 3-fold higher incidence of pituitary tumors in females.

In summary, lung tumors were found in female, but not male Wistar rats, aged 8 months at the start of the study, exposed to 45.5 mg/m^3 antimony trioxide (MMAD=2.8 μm) or 38 mg/m^3 antimony ore concentrate (MMAD=4.8 μm) for 1 year and observed for an additional 20 weeks. These exposures produced high lung antimony loadings in both males and females (4500-38,300 μg/g DW). The absence of a response in male rats could not be attributed to lower lung loadings of antimony (males had higher loadings for both test substances) or arsenic (males had higher loadings after antimony trioxide exposure). Female rats exposed to both forms of antimony did have 2-fold higher concentrations of arsenic in blood and other non-pulmonary tissues than males. The researchers suggested that a systemic effect of arsenic on the immune system may have made the female rats more susceptible to antimony-induced lung tumors. The researchers also raised the possibility that the high incidence of tumors in the pituitary, a critical organ controlling endocrine function, in the female rats may have played a role in the sex-relatedness of the tumor response. This study was limited by failure to include lower exposure levels and by problems generating the test atmospheres.

Watt (1980, 1983a,b)

Watt (1980, 1983a,b) exposed groups of 50 female Charles River CDF rats and 2-3 female Sinclair S-1 miniature swine to 0, 1.6 or 4.2 mg/m^3 antimony trioxide (99.4% pure, 0.02% arsenic) for 6 hours/day, 5 days/week for 1 year. The rats and swine were exposed to antimony trioxide in the same exposure chamber. The particle size (Ferret's diameter) was 0.44 and 0.40 μm for the 1.6 and 4.2 mg/m^3 concentrations, respectively, and the standard deviations were 2.23 and 2.13. Based on these data, Newton et al. (1994) estimated that the MMAD of the

exposure aerosol was 5.06 μm in the high-exposure chamber and 6.9 μm in the low-exposure chamber. Groups of rats were killed after 3, 6, 9 or 12 months of exposure and 2 months and 1 year post-exposure; the swine were killed at the end of the 12-month exposure period. Body weight measurements, hematological and serum clinical chemistry indices (hemoglobin, hematocrit, erythrocyte, leukocyte-total and differential, total protein, albumin, globulin, creatinine, bilirubin, BUN, glucose, cholesterol, sodium, potassium, alkaline phosphatase, aspartate aminotransferase, alanine aminotransferase, lactate dehydrogenase, CPK and HBD levels), organ weight measurements and gross and histopathology were used to assess toxicity in the rats and swine. Electrocardiograms (taken pre-exposure and after 3, 6 and 12 months of exposure) and roentograms (taken pre-exposure and after 6 and 12 months of exposure) also were used to assess toxicity in the swine.

In the rats, no significant alterations in hematological and serum chemistry indices were observed. Increases in body weight gain and absolute lung weight were observed in the antimony trioxide-exposed rats. Pneumonia was observed in the rats killed prior to exposure, but was not observed in the control or antimony trioxide-exposed rats after 3 months of exposure. Effects on survival were not reported. Histological alterations in the lungs included focal fibrosis, adenomatous hyperplasia, multinucleated giant cells, cholesterol clefts, pneumocyte hyperplasia and pigmented macrophages. The severity of the pulmonary effects increased with increasing concentration and exposure duration. The high exposure concentration produced lung tumors in the rats (4.2 mg/m^3, MMAD=5 μm). The incidence was 21/34 (62%) in rats examined at the end of the exposure period or later, with most responders being in the group held for an extra year of observation prior to sacrifice. Tumor types, all in the bronchioalveolar region, included scirrhous carcinoma, squamous cell carcinoma and adenoma. Only one rat each from the low-exposure and control groups had a lung tumor in this study (both bronchioalveolar adenomas). No exposure-related tumors were found in other tissues. A LOAEL of 1.6 mg/m^3 antimony trioxide for pulmonary effects in female rats can be identified from this study. In the pigs, body weight gain, hematological and serum chemistry indices, EKGs, roentgenograms and histological examination did not reveal any exposure related effects; thus, the NOAEL in swine is 4.2 mg/m^3 antimony trioxide.

The finding of lung tumors in female Fischer rats exposed to 4.2 mg/m^3 antimony trioxide (MMAD=5 μm) for one year and observed for an additional year (Watt et al., 1980, 1983a,b) conflicts with the results of Newton et al. (1994), who found no exposure-related lung tumors in male or female Fischer 344 rats exposed to 0, 0.06, 0.51 or 4.5 mg/m^3 antimony trioxide (MMAD=3.8 μm) for 1 year and observed for an additional year. One potential explanation proposed by Newton et al. (1994) is that exposure levels in the Watt study may have been higher than reported. There is some evidence to support this view: a pathologist who reviewed slides from all 3 studies found that exposed rats had more damage and appeared to have considerably more test material in the lungs in the Watt study compared with the Newton study (Newton et al., 1994). Watt (1980, 1983a,b) did not report lung antimony loadings. However, Groth et al. (1986) reported that examination of the histopathology slides from the Watt study found less than 10% of the amount of particulate in the lungs compared with the Groth study. The lung loading in the Groth study was 25,600-38,300 μg/g DW following antimony trioxide exposure. This suggests the loading in the Watt study might have been in the range 2500-3800 μg/g DW. This is lower than the lung loading in the high-exposure group in

the Newton study (approximately 12,500 µg Sb/g DW, reported by the researchers as 1500 µg Sb_2O_3/g FW).

Gross et al. (1955)

Gross et al. (1955) exposed groups of 50 male Sprague-Dawley rats to 100-125 mg/m^3 antimony trioxide dusts for 100 hours/month for 14.5 months. The mean particle size was 0.6 µm, as determined by electron microscopy. A group of 50 rats exposed to 25 mg/m^3 calcium halophosphate phosphors containing 1% antimony trioxide served as the control group. Mottling of the lung surface was observed after 9 months or more of exposure; the severity was duration-related. Fatty degeneration and necrosis of alveolar macrophages and lipoid crystals within alveolar walls and interstitial tissue were observed in the rats exposed to antimony trioxide.

Gross et al. (1955) also exposed groups of 31 rabbits exposed to 89 mg/m^3 antimony trioxide, 100 hours/month for 10 months. There was a high incidence of mortality among the antimony trioxide-exposed rabbits (85%) and the primary cause of death was pneumonia. Interstitial pneumonia and pneumonitis, secondary to accumulation of lipids, were observed. The authors noted that the rabbits appeared to be more sensitive to the pulmonary toxicity of antimony trioxide than the rats.

IAOIA (2004)

Antimony trioxide was administered at concentrations of 0, 2.6, 4.4 or 6.3 mg/m^3 to pregnant female rats (26/group) in a nose-only inhalation chamber for 6 hours/day from days 0 to 19 of gestation (IAOIA, 2004, abstract only). No clinical signs of toxicity were observed in pregnant dams and gestational body weight gain and food consumption were unaffected by treatment. Gross maternal and fetal examination, uterine implantation data, fetal sex ratios, fetal body weights, crown-rump distance and skeletal and visceral examination of fetal tissues revealed no effects of antimony treatment. Maternal lung weight was increased 24, 31 and 39% for the 2.6, 4.4 and 6.3 mg/m^3 exposure groups, respectively, as compared to controls. Pulmonary histopathology revealed diffuse accumulation of pigmented alveolar macrophages, suggesting phagocytosis and accumulation of particulate matter in the lung. A free-standing LOAEL for maternal toxicity in this study was 2.6 mg/m^3 based on increased lung weight in dams. No developmental effects of exposure were noted in this study. The NOAEL for fetal effects was 6.3 mg/m^3.

In summary, animal studies suggest that the lung is the primary target organ affected by inhalation exposure to antimony trioxide. Pulmonary toxicity, characterized by chronic interstitial inflammation, granulomatous inflammation and interstitial fibrosis, has been demonstrated in several inhalation studies (Newton et al., 1994; Groth et al., 1986; Watt et al., 1983a,b; Gross et al., 1955). Antimony (in the form of antimony trioxide and antimony ore concentrate) has been shown to produce lung tumors in female rats by inhalation exposure (Groth et al., 1986; Watt et al., 1983a,b). Although study design flaws and apparently inconsistent results between studies limit the interpretation of the results, these studies have established that antimony trioxide and antimony ore concentrate can produce lung tumors following inhalation exposure. The low level arsenic exposure in these studies is not likely to be responsible for the observed tumors. Arsenic, although an established human carcinogen, has repeatedly tested negative for carcinogenicity in laboratory animals (U.S. EPA, 2006).

Other Studies

Genotoxicity Studies

Antimony trioxide did not produce reverse mutation in *Salmonella typhimurium* (Kanematsu et al., 1980; Kuroda et al., 1991; Zeiger et al., 1992; Elliott et al., 1998) and *Escherichia coli* (Kanematsu et al., 1980). Antimony trioxide was positive in the rec assay for differential killing in DNA repair-proficient and DNA repair-deficient strains of *Bacillus subtilis* (Kanematsu et al., 1980; Kuroda et al., 1991). This compound, although only slightly water soluble, gave strong positive results at very low concentrations (as low as 0.3 μg/disk) in the rec assay conducted by Kuroda et al. (1991). Antimony trioxide was negative in the L5178Y mutation assay, but did produce chromosome aberrations and induce micronucleus formation in isolated human peripheral lymphocytes (Migliore et al., 1999; Elliott et al., 1998). Antimony trioxide also increased SCE in V79 Chinese hamster cells *in vitro* (Kuroda et al., 1991). A prospective molecular epidemiology study in atherosclerotic patients (Izzotti et al., 2007) provided evidence for the crucial impact of oxidative stress and certain gene polymorphisms on clinical and biochemical patterns as well as survival of patients. Oxidative DNA damage, as measured by the enzyme-modified COMET assay, was observed in workers exposed to antimony trioxide (Cavallo et al., 2002). Lymphocyte micronuclei formation and sister chromatid exchange (SCE) were similar to unexposed control workers. Gurnani et al. (1992, 1993, 1994) reported that antimony trioxide produced chromosomal aberrations in mouse bone marrow *in vivo*; however, Elliott et al. (1998) reported that antimony trioxide was non-clastogenic in the *in vivo* mouse bone marrow micronucleus assay and produced negative findings in the *in vivo* rat liver DNA repair assay. DeBoek et al. (2003), while summarizing data concerning genotoxicity and carcinogenicity of cobalt and antimony, reported equivocal assessments of *in vivo* potential of antimony trioxide to induce chromosomal aberrations. The authors concluded that human carcinogenicity data is difficult to evaluate given the frequent coexposure to arsenic. In a 14-21 day oral dosing study Kirland et al. (2007) reported lack of genotoxicity in rat bone marrow exposed at doses equivalent to maximum tolerated dose (MTD).

DERIVATION OF A PROVISIONAL SUBCHRONIC RfD FOR ANTIMONY TRIOXIDE

Repeated-dose oral exposure studies in animals have been conducted using antimony trioxide (Omura et al., 2002; Hext et al., 1999; Ainsworth et al., 1991; Sunagawa et al., 1981). These studies generally reported only minimal liver changes or no significant effects as compared to control animals. Omura et al. (2002) evaluated the testicular toxicity of antimony trioxide; however, no significant changes from control were observed for body weight, organ weight and histopathology of reproductive tissues, or sperm parameters (NOAEL of 1200 mg/kg-day). No significant effects were seen in short-tailed voles exposed to 500 mg Sb/kg-day for 60 days or 20,000 mg Sb/kg-day for 12 days as antimony trioxide (Ainsworth et al., 1991). Sunagawa et al. (1981) reported minor changes (decreased erythrocytes, slight cloudy swelling in the liver) in rats treated with 1000 or 2000 mg/kg-day of antimony trioxide for 24 weeks; however, no further details were provided in the English language abstract for this study.

Hext et al. (1999) performed a 90-day dietary study in male and female rats. This was considered the critical study for evaluation of the oral effects of antimony trioxide, because multiple dose groups were used and subchronic toxicity was adequately described (i.e., the study included assessment of survival, body weight change, hematology, clinical chemistry, gross lesions, and histopathological evaluation of several tissues). Some minor changes were noted in clinical chemistry values for high dose male (30% increase in triglyceride content, 12% decrease in alkaline phosphatase activity) and female rats (13% increase in plasma cholesterol, 36% decrease in alkaline phosphatase activity, 52% increase in aspartate aminotransferase activity). Absolute and relative liver weights were also increased by approximately 10% in high-dose female rats. No histopathological lesions were observed in the liver of male or female rats. A minimal LOAEL value of 1879 mg/kg-day for this study was based on small increases in liver weight and serum aspartate aminotransferase in high-dose female rats, in the absence of histopathological changes. A NOAEL value of 494 mg/kg-day antimony trioxide was derived from female rats in this study.

The **subchronic p-RfD of 0.5 mg/kg-day for antimony trioxide** is based on minimal liver effects seen in the 90-day dietary study of antimony trioxide (Hext et al., 1999). This study was chosen as the critical study because multiple dose groups were used and subchronic toxicity was adequately described. The subchronic p-RfD is derived by dividing the NOAEL of 494 mg/kg-day by a composite UF of 1000, as follows:

Subchronic p-RfD	=	NOAEL / UF
	=	494 mg/kg-day /1000
	=	0.5 mg/kg-day

A composite UF of 1000 was used based on individual factors of 10 for interindividual differences, animal-to-human extrapolation and database deficiencies.

The UF of 10 is used to account for variation in sensitivity within human populations because there is limited information on the degree to which humans of varying gender, age, health status or genetic makeup might vary in the disposition of, or response to antimony trioxide.

The interspecies UF of 10 is used to account for potential pharmacokinetic and pharmacodynamic differences across species.

A UF of 10 for database deficiencies is selected due to the lack of oral subchronic and chronic studies demonstrating clearly adverse toxicological effects, developmental toxicity studies, and multigeneration reproductive toxicity studies.

Confidence in the critical study is medium. The principal study (Hext et al., 1999) included adequate numbers of dose levels and animals, and assessed hematology, clinical chemistry and histopathology. However, only minor changes were seen in high-dose rats. Confidence in the database is low. The database does not provide oral subchronic or chronic toxicity studies that demonstrate clearly adverse toxic effects. In addition, the database lacks developmental toxicity studies and a multigeneration reproductive toxicity study for antimony

trioxide. Overall, confidence in the subchronic p-RfD is low for antimony trioxide: The subchronic provisional RfD value for antimony trioxide (based on molecular weight of the salt, not the metal content) is appropriate for antimony tetroxide (CASRN 1332-81-6) and antimony pentoxide (CASRN 1314-60-9), when adjusted for the molecular weight difference of the compounds, i.e. RfD for tetroxide = RfD for trioxide x MW Tetroxide/MW Trioxide, etc.

DERIVATION OF A PROVISIONAL CHRONIC RfD FOR ANTIMONY TRIOXIDE

The subchronic provisional RfD of 0.5 mg/kg-day was based on a composite uncertainty factor of 1000 that covers three areas of uncertainties. In the absence of chronic toxicity data for antimony trioxide, the subchronic study (Hext et al., 1999) can be used with an additional UF of 10 for duration for the derivation of a chronic p-RfD; thus resulting in a composite UF (10,000), which would exceed the maximum allowed uncertainty factor of 3000. Because of such higher uncertainties, a provisional chronic RfD was not derived for antimony trioxide.

DERIVATION OF A PROVISIONAL SUBCHRONIC RfC FOR ANTIMONY TRIOXIDE

Occupational and animal studies demonstrate that lung effects are the primary changes observed following inhalation exposure to antimony trioxide. Pneumoconiosis (characterized on x-rays as diffuse, densely distributed punctate opacities) without impaired lung function has been observed in several groups of workers (Potkonjak and Pavlovich, 1983; Cooper et al., 1968; Renes, 1953). Study limitations (e.g., exposure to a wide range of antimony trioxide concentrations, lack of data on particle size distribution) preclude establishing a concentration-response relationship from the human data. In rats exposed to antimony trioxide for 13 weeks to 1 year, increases in the incidence and/or severity of chronic interstitial inflammation, granulomatous inflammation, and interstitial fibrosis have been observed (Newton et al., 1994; Groth et al., 1986; Watt et al., 1983a,b; Gross et al., 1955). The animal data suggest that these effects are concentration and duration-related. In the 13-week study by Newton et al. (1994), significant increases in the incidences of interstitial inflammation and granulomatous inflammation were observed at 23.46 mg/m^3 in animals sacrificed during the recovery period. The incidences in the 4.92 mg/m^3 and lower dose groups were not statistically different from the controls. When the rats were exposed to antimony trioxide for one year, the severity of interstitial inflammation was higher in the 4.5 mg/m^3 group and similar to controls in the 0.51 mg/m^3 group. The most sensitive effect observed in the 13-week study (Newton et al., 1994) was an increase in the incidence of rats with alveolar and intraalveolar macrophages (seen at concentrations of $\geq$1.08 mg/m^3 in female rats). Other pulmonary effects (increased lung weights, interstitial inflammation, and granulomatous inflammation) were seen at higher concentrations.

As reviewed by U.S. EPA (2008), antimony is very slowly cleared from the lungs of humans and animals. The Newton et al. (1994) 1-year study found that antimony clearance from the lung was lung burden dependent; in the rats exposed to 4.5 mg/m^3 antimony trioxide, the clearance half-time was 9.5 months, which was substantially longer than the half-times at the two

lower concentrations (0.51 and 0.06 mg/m^3 with half-times of 3.6 and 2.3 months, respectively). It is likely that pulmonary toxicity will increase with increasing retention times. Data comparing pulmonary clearance times for different antimony compounds are limited. The available data suggest that solubility and particle size are the primary determinants of lung retention time.

The Newton et al. (1994) 13-week study was selected as the principal study for derivation of the RfC. This study was well conducted and included four treatment groups. Other available studies possessed significant limitations, including the use of only one concentration level and problems with generation of the antimony atmosphere within the inhalation chamber (Groth et al., 1986; Watt et al., 1983a,b; Gross et al., 1955). Microscopic findings related to antimony trioxide exposure in the Newton et al. (1994) study (observed during the 27-week recovery period) included chronic interstitial inflammation, interstitial fibrosis, granulomatous inflammation, and an increase in the number of alveolar and intraalveolar macrophages. The pulmonary effect occurring at the lowest dose level was the increased incidence of rats with alveolar and intraalveolar macrophages (NOAEL of 0.25 mg/m^3 and a LOAEL of 1.08 mg/m^3 antimony trioxide). Pulmonary toxicity was also indicated by a large increase in the incidence of rats with interstitial inflammation at high concentrations (25/25 at 23.46 mg/m^3 antimony trioxide). Data from the Newton et al. (1994) study, as well as other studies, provide evidence that female rats are more sensitive to the pulmonary toxicity of antimony trioxide than male rats; thus, data for the female rats were used to calculate a provisional subchronic RfC.

U.S. EPA (2002) recommends that benchmark dose analysis (BMD) should be used to derive reference values whenever possible, and that derivation of a reference value should consider all relevant and appropriate endpoints of toxicity. In this case, incidence data for two indicators of pulmonary toxicity (alveolar and intraalveolar macrophages and interstitial inflammation) were evaluated using BMD modeling. The point of departure values (PODs) for each pulmonary effect were compared to determine the critical effect used for derivation of the provisional subchronic RfC.

All dichotomous models in the EPA Benchmark Dose Modeling Software (BMDS; Version 1.3.2) were fit to the incidence data for interstitial inflammation and increased alveolar and intraalveolar macrophages in female rats (see Table 1). For each model, a benchmark response (BMR) of 10% extra risk (as recommended by U.S. EPA, 2000) was used to calculate a BMD and its lower 95% confidence limit (BMDL). Tables 2 and 3 show the modeling results for interstitial inflammation and increased alveolar and intraalveolar macrophages, respectively. All models provided acceptable global goodness-of-fit (chi square p-value $\geq$0.1) to the incidence data for interstitial inflammation (Table 2). Most models, with the exception of the quantal quadratic and logistic models, provided acceptable global goodness-of-fit (chi square p-value $\geq$0.1) to the incidence data for increased alveolar and intraalveolar macrophages (Table 3).

As recommended by U.S. EPA (2000), the model with the lowest AIC value was selected as the best fitting model for each data set. The quantal quadratic model was the best fitting model for interstitial inflammation and yielded a BMD of 2.51 mg/m^3 and a BMDL of 1.64 mg/m^3. A plot of the observed and expected incidence of pulmonary interstitial inflammation in female rats versus exposure concentration from the results of the quantal quadratic model is

Table 1. Incidence of Pulmonary Interstitial Inflammation and Increased Alveolar/Intraalveolar Macrophages in Female F344 Rats Exposed to Antimony Trioxide for 6 Hours/Day, 5 Days/Week for 13 Weeks and Observed During the 27 Week Post Exposure Period from Newton et al. (1994)

Antimony Trioxide Concentration (mg/m^3)	Incidence of Interstitial Inflammation	Incidence of Increased Alveolar/Intraalveolar Macrophages
0	9/25[a]	1/25 [a]
0.25	14/25	3/25
1.08	12/25	11/25 [b]
4.92	16/25	21/25[b]
23.46	25/25[b]	25/25[b]

[a] $p<0.05$ Cochran-Armitage trend test (performed for this assessment)
[b] $p<0.05$ Fisher's Exact test (performed for this assessment)

Table 2. BMD Modeling Results for Incidence of Interstitial Inflammation in Female F344 rats from Newton et al. (1994)

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit p-Value	AIC	BMD_{10} (mg/m^3)	$BMDL_{10}$ (mg/m^3)
Quantal Quadratic	3	2.01	0.57	140.28	2.51	1.64
Probit	3	2.05	0.56	140.39	1.15	0.72
Logistic	3	2.33	0.51	140.79	1.07	0.68
Multistage (degree=1)[a]	3	3.04	0.38	141.77	0.74	0.44
Quantal Linear	3	3.04	0.38	141.77	0.74	0.44
Weibull (power $\geq$1)	2	2.01	0.37	142.28	2.47	0.52
Gamma (power $\geq$1)	2	2.03	0.36	142.31	3.29	0.52
Log-logistic (slope $\geq$1)	2	2.04	0.36	142.31	4.32	1.28
Log-probit (slope $\geq$1)	2	2.04	0.36	142.31	3.93	1.22

[a] Degree of polynomial initially set to (n-1) where n= number of dose groups including control; model selected is lowest degree model providing adequate fit. Betas restricted to $\geq$0.

Table 3. BMD Modeling Results for Incidence of Increased Alveolar/Intraalveolar Macrophages in Female F344 rats from Newton et al. (1994)

Model	Degrees of Freedom	χ^2	χ^2 Goodness of Fit p-Value	AIC	BMD_{10} (mg/m^3)	$BMDL_{10}$ (mg/m^3)
Gamma (power $\geq$1)	3	0.60	0.90	87.61	0.26	0.19
Multistage (degree=1)[a]	3	0.60	0.90	87.61	0.26	0.19
Quantal Linear	3	0.60	0.90	87.61	0.26	0.19
Weibull (power $\geq$1)	3	0.60	0.90	87.61	0.26	0.19
Log-probit (slope $\geq$1)	3	1.14	0.77	88.19	0.42	0.30
Log-logistic (slope $\geq$1)	2	0.58	0.75	89.98	0.31	0.13
Probit	3	6.23	0.10	93.44	0.75	0.58
Logistic	3	6.41	0.09	93.72	0.77	0.57
Quantal Quadratic	3	9.61	0.02	96.37	1.14	0.91

[a] Degree of polynomial initially set to (n-1) where n=number of dose groups including control; model selected is lowest degree model providing adequate fit. Betas restricted to $\geq$0.

shown in Figure 1. Four models exhibited the lowest AIC values for the increased incidence of alveolar and intraalvelor macrophages (gamma, multistage, quantal linear, weibull). Each of these models gave a BMD of 0.26 mg/m^3 and a BMDL of 0.19 mg/m^3. A plot of the observed and expected incidence of alveolar and intraalveolar macrophages in female rats versus exposure concentration from the results of the gamma model (as an example) is shown in Figure 2. A comparison of model outputs suggests that the increase in the incidence of female rats with alveolar and intraalveolar macrophages is a more sensitive indicator of pulmonary toxicity than interstitial inflammation. The BMDL of 0.19 mg/m^3 serves as the point of departure for the provisional subchronic RfC for antimony trioxide. The BMDL was adjusted for duration of exposure as follows:

$$\begin{aligned} BMDL_{[ADJ]} &= \text{BMDL x 6 hours/24 hours x 5 days/7 days} \\ &= 0.19\ mg/m^3 * 6/24 * 5/7 \\ &= 0.034\ mg/m^3 \end{aligned}$$

The human equivalent concentration ($BMDL_{[HEC]}$) was calculated by multiplying the duration-adjusted concentration ($BMDL_{[ADJ]}$) by the regional deposited dose ratio of particles for the thoracic region ($RDDR_{TH}$). The $RDDR_{TH}$ for MMAD of 3.05 μm and sigma g of 1.57 is 0.567 based on dosimetric modeling, as described in U.S. EPA (1994).

$$\begin{aligned} BMDL_{[HEC]} &= BMDL_{[ADJ]} \text{ x } RDDR_{TH} \\ &= 0.034\ mg/m^3 \text{ x } 0.567 \\ &= 0.019\ mg/m^3 \end{aligned}$$

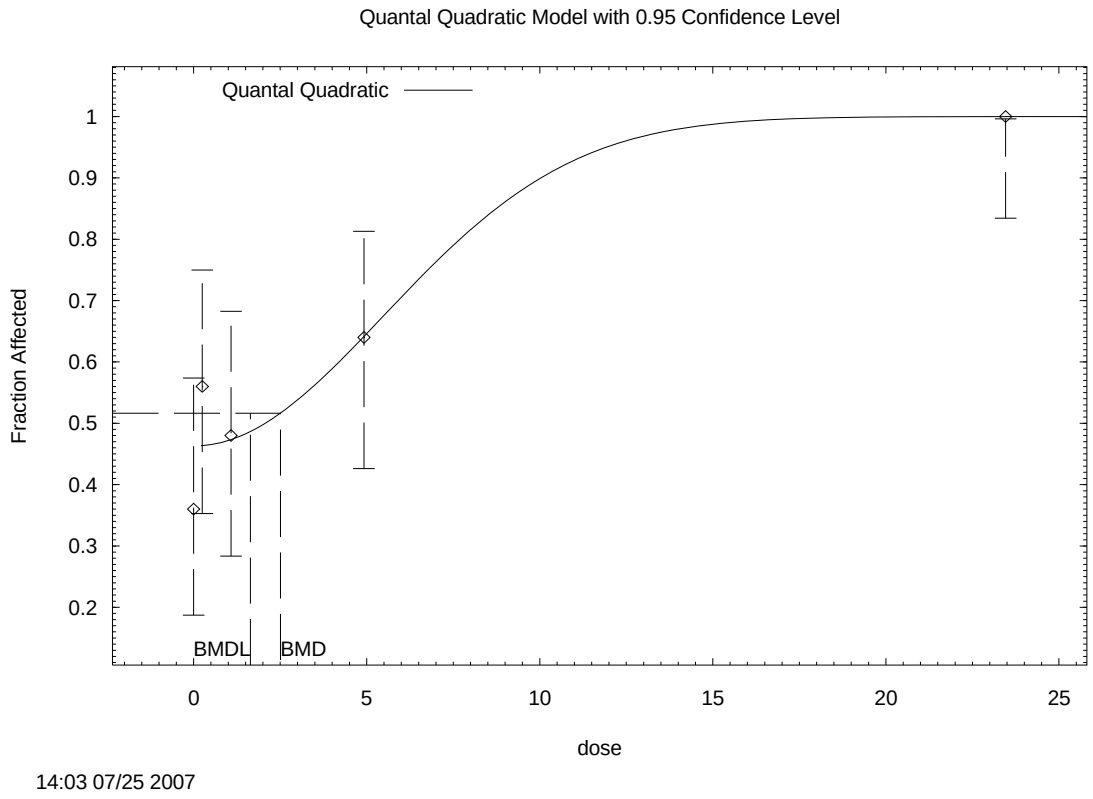

Figure 1. Dose response modeling of incidence data for pulmonary interstitial inflammation of F344 female rats exposed to antimony trioxide for 6 hours/day, 5 days/week for 13 weeks and observed during a 27 week post exposure period. Dose in units of mg/m^3 antimony trioxide

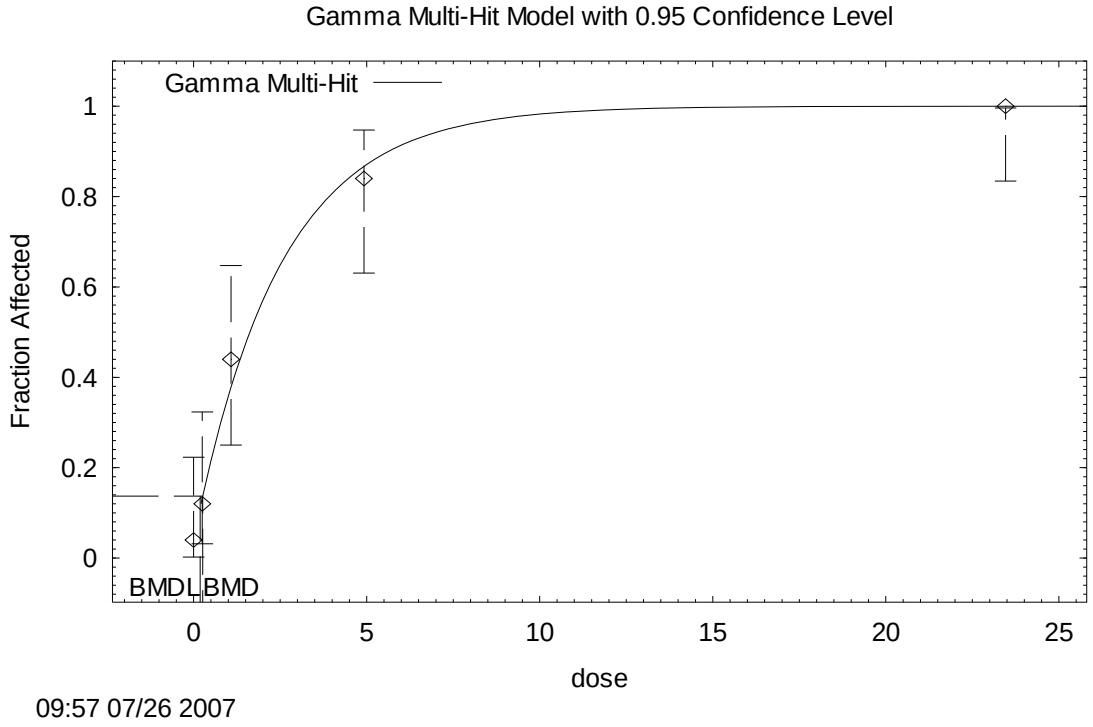

Figure 2. Dose response modeling of incidence data for increased alveolar and intraalveolar macrophages in F344 female rats exposed to antimony trioxide for 6 hours/day, 5 days/week for 13 weeks and observed during a 27 week post exposure period. Dose in units of mg/m^3 antimony trioxide

The **subchronic p-RfC of 2E-4 mg/m^3** for antimony trioxide is derived by dividing the $BMDL_{[HEC]}$ of 0.019 mg/m^3 by a composite UF of 100, as shown below. This p-RfC value is identical to the chronic RfC value on IRIS, based on granulomatous inflammation in rats exposed to antimony trioxide by inhalation for one year (U.S. EPA, 2008).

$$\begin{aligned} \text{Subchronic p-RfC} &= BMDL_{[HEC]} / UF \\ &= 0.019 \text{ mg/m}^3 / 100 \\ &= 0.00019 \text{ mg/m}^3 \text{ or } 2E\text{-}4 \text{ mg/m}^3 \end{aligned}$$

The composite UF includes a factor of 3 for animal-to-human extrapolation using dosimetric adjustment, 10 for interindividual variability and 3 for database deficiencies.

The interspecies UF of 3 reflects a factor of 1 for pharmacokinetic differences across species (reduced from 3 due to application of the dosimetric equations) and a factor of 3 for pharmacodynamic considerations.

The UF of 10 is used to account for variation in sensitivity within human populations because there is limited information on the degree to which humans of varying gender, age, health status or genetic makeup might vary in the disposition of, or response to, antimony trioxide.

The partial UF of 3 for database deficiencies is selected due to the lack of a multigeneration reproductive toxicity study and a developmental toxicity study in a second animal species (the developmental study in rats was presented as an abstract only; IAOIA, 2004).

Confidence in the principal study is medium to high. The Newton et al. (1994) study is a well designed study using an adequate number of animals and examining appropriate endpoints. Confidence in this study is decreased because of the small number of animals (n=5) examined at the end of the exposure period. Confidence in the database for antimony trioxide is medium. A number of human and animal studies are available; however significant limitations were noted in several of the supporting studies, including the use of only one concentration level and problems with generation of the antimony atmosphere within the inhalation chamber. In addition, the database is lacking reliable studies on the developmental and reproductive toxicity of inhaled antimony trioxide. Reflecting the medium confidence in the database, confidence in the provisional subchronic RfC is medium.

This subchronic p-RfC applies only to antimony trioxide.

PROVISIONAL CARCINOGENICITY ASSESSMENT FOR ANTIMONY TRIOXIDE

Weight-of-Evidence Descriptor

Under the *Guidelines for Carcinogen Risk Assessment* (U.S. EPA, 2005), there is "suggestive evidence of the carcinogenic potential" of antimony trioxide by the inhalation route

of exposure. There is "inadequate information to assess carcinogenic potential" by the oral route of exposure. This weight-of-evidence conclusion is based on limited data in both humans and animals.

The studies by Jones (1994) and Schnorr et al. (1995) demonstrated excess lung cancer in antimony smelter workers. The study by Schnorr et al. (1995) also demonstrated that the risk of lung cancer in antimony smelter workers increased with duration of exposure. In both studies, workers were exposed to arsenic, and possibly PAHs, in addition to antimony. Jones (1994) did not present any quantitative exposure information, but Schnorr et al. (1995) reported measurements for both antimony (551-747 $\mu g/m^3$) and arsenic (2-5 $\mu g/m^3$) (plant-wide geometric means in 1975-1976). Jones (1994) was inconclusive as to whether the observed excess of lung cancer in the smelter workers was due to antimony or confounding exposure to arsenic or PAHs. Schnorr et al. (1995), however, used the quantitative data on arsenic concentrations in the smelter and the OSHA risk assessment model for arsenic to conclude that the low-level arsenic exposure experienced by these workers accounted for only 0.6 of the 8 excess lung cancer deaths in their worker population. These researchers attributed the excess lung cancer mortality in smelter workers to antimony exposure. These studies constitute only limited evidence of antimony carcinogenicity due to the existence of potential confounding exposures and lack of information regarding the smoking habits of the exposed workers.

The animal studies by Groth et al. (1986) demonstrated that antimony (as antimony trioxide or antimony ore concentrate) can produce lung tumors in female rats by inhalation exposure. However, these studies constitute only limited evidence for antimony trioxide carcinogenicity because of a study design limitation (one exposure concentration in the Groth study). The negative data reported in the Newton et al. (1994) study, as well as the poor documentation of control exposures, results in further uncertainties related to cancer incidence.

Mode of Action Discussion

There is limited information available regarding key events that may be involved in a potential mode of action for antimony trioxide carcinogenicity. Some studies suggest that antimony trioxide may be clastogenic; however both positive and negative findings were reported for chromosome aberrations and micronucleus formation in mammalian cells and for *in vivo* studies of micronucleus formation in mice. Antimony trioxide was generally negative in bacterial and mammalian cell mutagenicity assays, although some positive findings were reported in the *Bacillus subtilis* rec assay (see *Genotoxicity Studies* above).

Quantitative Estimates of Carcinogenic Risk

Oral Exposure

There are no human or animal oral data on which to base an oral cancer assessment for antimony.

Inhalation Exposure

The data are insufficient for derivation of an inhalation unit risk for antimony trioxide. The study of antimony smelter workers by Schnorr et al. (1995) included quantitative measurements of antimony concentrations in the plant, but the workers were not categorized according to exposure level or job title, so that no dose-response information was obtained. The study of smelter workers by Jones (1994) did not include measurement of antimony concentrations. The study of rats by Groth et al. (1986) included only a single high-dose level. The study of rats by Watt (1980, 1983a,b) included two dose levels, but questions have been raised regarding the uncertainty factors and the accuracy of the stated exposure levels (Newton et al., 1994; U.S. EPA, 1983a,b). Although these studies together provide sufficient qualitative evidence to categorize antimony as having "suggestive evidence of carcinogenic potential" by the inhalation route of exposure according to U.S. EPA (2005) guidelines, exposure-response data are inadequate to serve as the basis for quantitative risk assessment.

REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). 2006. 2006 Threshold Limit Values for Chemical Substances and Physical Agents and Biological Exposure Indices. ACGIH, Cincinnati, OH.

Ainsworth, N., J.A. Cooke and M.S. Johnson. 1991. Behavior and toxicity of antimony in the short-tailed field vole (*Microtus agrestis*). Ecotoxicol. Env. Saf. 21:165-170.

ATSDR (Agency for Toxic Substances and Disease Registry). 1992. Toxicological Profile for Antimony. Review Draft. U.S. Public Health Service. Atlanta, GA. TP-91/02.

Belyaeva, A.P. 1967. The effect of antimony on reproduction. Gig. Truda. Prof. Zabol. 11(1):32-37. (Russian)

Bio/dynamics. 1985. A three-month inhalation toxicity study of antimony trioxide in the rat followed by a recovery period. Prepared by Bio/dynamics, East Millstone NJ, prepared for Antimony Oxide Industry Association. Submitted to U.S. EPA, OTS0511116, Section 4.

Bio/dynamics. 1990. A one year inhalation toxicity study of antimony trioxide in the rat (with a one year recovery period). Prepared by Bio/dynamics, East Millstone NJ, prepared for Antimony Oxide Industry Association. Submitted to U.S. EPA, OTS0526425, Section 4.

Brieger, H., C.W. Semish III, J. Stasney and D.A. Piatnek. 1954. Industrial antimony poisoning. Ind. Med. Surg. 23:521-523.

CalEPA (California Environmental Protection Agency). 2006. Air – chronic RELs. California Office of Environmental Health Hazard Assessment. Available at http://www.oehha.ca.gov/air/chronic_rels/AllChrels.html.

Cavallo, D., I. Iavicoli, A. Setini et al. 2002. Genotoxic risk and oxidative DNA damage in workers exposed to antimony trioxide. Environ. Mol. Mutag. 40:184-189.

Cooper, D.A., E.P. Pendergrass, A.J. Vorwald, et al. 1968. Pneumoconiosis among workers in an antimony industry. Am. J. Roetgenol. Radium Ther. Nucl. Med. 103:495-508.

DeBoeck, M., M. Kirsch-Volders and D. Lisbon. 2003. Cobalt and antimony: Genotoxicity and carcinogencity. Mutat. Res. 533:135-152.

Elliott, B.M., J.M. MacKay, P. Clay and J. Ashby. 1998. An assessment of the genetic toxicology of antimony trioxide. Mutat. Res. 415:109-117.

Gebel, T., P. Birkenkamp, S. Luther and H. Dunkelberg. 1998. Arsenic (III), but not antimony (III), induces DNA-protein crosslinks. Anticanc. Res. 18:4253-4258.

Gross, P., M.L. Westrick, J.H.U. Brown, R.P. Srsic, H.H. Schrenk and T.F. Hatch. 1955. Toxicologic study of calcium halophosphate phosphors and antimony trioxide. Arch. Ind. Health. 11:479-486.

Groth, D.H., L.E. Stettler, J.R. Burg, W.M. Busey, G.C. Grant and L. Wong. 1986. Carcinogenic effects of antimony trioxide and antimony ore concentrate in rats. J. Toxicol. Environ. Health. 18:607-626.

Gurnani, N., A. Sharma and G. Talukder. 1992. Comparison of the clastogenic effects of antimony trioxide on mice *in vivo* following acute and chronic exposure. Biometals. 5:47-50.

Gurnani, N., A. Sharma and G. Talukder. 1993. Comparison of clastogenic effects of antimony and bismuth as trioxides on mice *in vivo*. Biol. Trace Elem. Res. 37:281-292.

Gurnani, N., A. Sharma and G. Talukder. 1994. Comparison of the clastogenic effects of antimony trioxide on mice in vivo following acute and chronic exposure. Biometals 5:47-50.

Hext, P.M., P.J. Pinto and B.A. Rimmel. 1999. Subchronic feeding study of antimony trioxide in rats. J. Appl. Toxicol. 19:205-209.

IAOIA. 2004. TSCA Section 8(e) Notification on Antimony Trioxide (CASRN 1309-64-4). International Antimony Oxide Industry Association. February 27, 2004.

IARC (International Agency for Research on Cancer). 1989. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Vol 47, Some Organic Solvents, Resin Monomers and Related Compounds, Pigments and Occupational Exposures in Paint Manufacture and Painting. IARC, World Health Organization, Lyon, France.

Izzoti, A., A. Pianna, G. Minniti, M. Vercelli, L. Perrone and S. DeFlora. 2007. Survival of atherosclerotic patients related to oxidative stress and polymorphisms. Mutat. Res. 621:119-128.

Jones, R.D. 1994. Survey of antimony workers: Mortality 1961-1992. Occup. Environ. Med. 51:772-776.

Kanematsu, N., M. Hara and T. Kada. 1980. Rec assay and mutagenicity studies on metal compounds. Mutat. Res. 77:109-116.

Kanisawa, M. and H.A. Schroeder. 1969. Life term studies on the effect of trace elements on spontaneous tumors in mice and rats. Cancer Res. 29:892-895.

Kim, H-A., Y. Heo, S-Y. Oh et al. 1999. Altered serum cytokine and immunoglobulin levels in the workers exposed to antimony. Hum. Exp. Toxicol. 18:607-613.

Kuroda, K., G. Endo, A. Okamoto, Y.S. Yoo and S. Horiguchi. 1991. Genotoxicity of beryllium, gallium and antimony in short-term assays. Mutat. Res. 264:163-170.

Kirkland, D., J. Whitewell, J. Deyo and T. Sorex. 2007. Failure of antimony trioxide to induce micronuclei or chromosomal aberrations in rat bone marrow after subchronic oral dosing. Mutat. Res. 627:119-128.

Migliore, L., L. Cocchi, C. Nesti and E. Sabbioni. 1999. Micronuclei assay and FISH analysis in human lymphocytes treated with six metal salts. Environ. Mol. Mutag. 34:279-284.

Newton, P.E., H.F. Bolte, I.W. Daly et al. 1994. Subchronic and chronic inhalation toxicity of antimony trioxide in the rat. Fund. Appl. Toxicol. 22:561-576.

NIOSH (National Institute for Occupational Safety and Health). 2005. Online NIOSH Pocket Guide to Chemical Hazards. Available at http://www.cdc.gov/niosh/npg/npgdcas.html.http://www.cdc.gov/niosh/npg

Omura, M., A. Tanaka, M. Hirata and N. Inoue. 2002. Testicular toxicity evaluation of two antimony compounds, antimony trioxide and antimony potassium tartrate, in rats and mice. Environ. Health Prev. Med. 7:15-18.

OSHA (Occupational Safety and Health Administration). 2007. OSHA Standard 1910.1000 Table Z-1. Part Z, Toxic and Hazardous Substances. Available at http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992

Potkonjak, V. and M. Pavlovich. 1983. Antimoniasis: A particular form of pneumoconiosis. Int. Arch. Environ. Health. 51:199-207.

Renes, L.E. 1953. Antimony poisoning in industry. Arch. Ind. Hyg. Occup. Med. 7:99-108. (Cited in ATSDR, 1992 and U.S. EPA, 2006).

Schnorr, T.M., K. Steenland, M.J. Thun and R.A. Rinskey. 1995. Mortality in a cohort of antimony smelter workers. Am. J. Ind. Med. 27:759-770.

Sunagawa, S. 1981. Experimental studies on antimony poisoning. Igaku Kenkyu. 51:129-142. [Japanese].

U.S. EPA. 1983a. Antimony Metal, Antimony Trioxide and Antimony Sulfide: Response to the Interagency Testing Committee. Federal Register. 48:717.

U.S. EPA. 1983b. Antimony Metal, Antimony Trioxide and Antimony Sulfide: Decision to Accept Negotiated Testing Program. Federal Register. 48:39979.

U.S. EPA. 1985. Health and Environmental Effects Profile for Antimony Oxides. Prepared by the Environmental Criteria and Assessment Office, Office of Health and Environmental Assessment, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EPA/600/X-85/271.

U.S. EPA. 1987. Health Effects Assessment for Antimony (and Compounds). Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste and Emergency Response, Washington, DC. EPA/600/8-88/018.

U.S. EPA. 1992. Drinking Water Criteria Document for Antimony. Prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati OH for the Office of Drinking Water, Washington DC. PB92-173293.

U.S. EPA. 1994. Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry. Prepared by the Office of Health and Environmental Assessment, Research Triangle Park, NC. EPA/600/8-90/066F.

U.S. EPA. 1997. Health Effects Assessment Summary Tables. Annual FY 1997. Office of Solid Waste and Emergency Response, Office of Emergency and Remedial Response, Washington, DC.

U.S. EPA. 2000. Benchmark Dose Technical Guidance Document. Risk Assessment Forum, Washington, DC. External Review Draft. EPA/630/R-00/001.

U.S. EPA. 2002. A Review of the Reference Dose and Reference Concentration Processes. Risk Assessment Forum, Washington, DC. Final Report. EPA/630/P-02/002F.

U.S. EPA. 2005. Guidelines for carcinogen risk assessment. Risk Assessment Forum, Washington, DC; EPA/630/P-03/001F. Federal Register 70(66):17765--17817. Available online at http://www.epa.gov/raf.

U.S. EPA. 2006. 2006 Edition of the Drinking Water Standards and Health Advisories. Office of Water, Washington, DC. EPA 822-R-06-013.

U.S. EPA. 2008. Integrated Risk Information System (IRIS). Online. Available at http://www.epa.gov/iris

Watt, W.D. 1980. Chronic inhalation toxicity of antimony trioxide: validation of the TLV-progress report - summary of results. OTS206195.

Watt, W.D. 1983a. Chronic inhalation toxicity of antimony trioxide: validation of the threshold limit value. Diss. Abstr. Int. B 44:739-740.

Watt, W.D. 1983b. Chronic inhalation toxicity of antimony trioxide: Validation of the threshold limit value. Ph.D. Dissertation. Wayne State Univ.

Wyllie, S. and A.H. Fairlamb. 2006. Differential toxicity of antimonial compounds and their effects on glutathione homeostasis in a human leukaemia monocyte cell line. Biochem. Pharmacol. 71:257-267.

Wingren, G. and O. Axelson. 1993. Epidemiologic studies of occupational cancer as related to complex mixtures of trace elements in the art glass industry. Scand. J. Work Environ. Health 1993 (suppl 1):95-100.

Wingren, G. and V. Englander. 1990. Mortality and cancer morbidity in a cohort of Swedish glassworkers. Int. Arch. Occup. Environ. Health 62:253-258.

Wong, L.C.K., J.M. Winston, J. Hagensen, K. Smith and C.B. Hong. 1979. Study of carcinogenicity and toxicity of inhaled antimony trioxide, antimony ore concentrate and thallic oxide in rats. Prepared by Midwest Research Institute, Kansas City MO for National Institute for Occupational Safety and Health, Cincinnati OH. EPA/OTS05116065 and EPA/OTS0511066, Section 4.

Zeiger, E., B. Anderson, S. Haworth, T. Lawlor and K. Mortelmans. 1992. Salmonella mutagenicity tests: V. Results from the testing of 311 chemicals. Environ. Mol. Mutagen. 19 (Supp 21):2-141.