Antimony trioxide; CASRN 1309-64-4

Human health assessment information on a chemical substance is included in the IRIS database only after a comprehensive review of toxicity data, as outlined in the IRIS assessment development process. Sections I (Health Hazard Assessments for Noncarcinogenic Effects) and II (Carcinogenicity Assessment for Lifetime Exposure) present the conclusions that were reached during the assessment development process. Supporting information and explanations of the methods used to derive the values given in IRIS are provided in the guidance documents located on the IRIS website.

STATUS OF DATA FOR Antimony trioxide

File First On-Line 09/01/1995

Category (section)	Assessment Available?	Last Revised
Oral RfD (I.A.)	not evaluated	
Inhalation RfC (I.B.)	yes	09/01/1995
Carcinogenicity Assessment (II.)	not evaluated	

I. Chronic Health Hazard Assessments for Noncarcinogenic Effects

I.A. Reference Dose for Chronic Oral Exposure (RfD)

Substance Name — Antimony trioxide
CASRN — 1309-64-4

Not available at this time.

I.B. Reference Concentration for Chronic Inhalation Exposure (RfC)

Substance Name — Antimony trioxide
CASRN — 1309-64-4
Last Revised — 09/01/1995

The inhalation Reference Concentration (RfC) is analogous to the oral RfD and is likewise based on the assumption that thresholds exist for certain toxic effects such as cellular necrosis. The inhalation RfC considers toxic effects for both the respiratory system (portal-of-entry) and for effects peripheral to the respiratory system (extrarespiratory effects). It is expressed in units of mg/cu.m. In general, the RfC is an estimate (with uncertainty spanning perhaps an order of magnitude) of a daily inhalation exposure of the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious effects during a lifetime. Inhalation RfCs were derived according to the Interim Methods for Development of Inhalation Reference Doses (EPA/600/8-88/066F August 1989) and subsequently, according to Methods for Derivation of Inhalation Reference Concentrations and Application of Inhalation Dosimetry (EPA/600/8-90/066F October 1994). RfCs can also be derived for the noncarcinogenic health effects of substances that are carcinogens. Therefore, it is essential to refer to other sources of information concerning the carcinogenicity of this substance. If the U.S. EPA has evaluated this substance for potential human carcinogenicity, a summary of that evaluation will be contained in Section II of this file.

NOTE: ****SEE BENCHMARK CONCENTRATION IN DISCUSSION. Discussion of the benchmark dose can be found in the Discussion of Principal and Supporting Studies Section.

I.B.1. Inhalation RfC Summary

Critical Effect	Exposures*	UF	MF	RfC
Pulmonary toxicity, chronic interstitial inflammation **Rat 1-Year Inhalation Toxicity Study** **Newton et al., 1994**	Benchmark Concentration: See Conversion Factors and Assumptions and Principal and Supporting Studies	300	1	2E-4 mg/cu.m

* Conversion Factors and Assumptions: MW = 169.8. BMC = 0.87 mg/cu.m. BMC(ADJ) = 0.87 +/- 6 hours/24 hours +/- 5 days/7 days = 0.16 mg/cu.m. The BMC10(HEC) was calculated for a

particle:respiratory effect in the thoracic region. The RDDR(TH) = 0.46 for MMAD = 3.7 microns and sigma g = 1.7, based on dosimetric modeling as described in U.S. EPA, 1994. BMC10(HEC) = BMC10(ADJ) x RDDR = 0.074 mg/cu.m.

I.B.2. Principal and Supporting Studies (Inhalation RfC)

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.

Newton et al. (1994) conducted a chronic study in which groups of 65 Fischer 344 rats/sex/group were exposed to target concentrations of 0, 0.05, 0.50, or 5.00 mg/cu.m (actual concentrations measured by atomic absorption were 0, 0.06, 0.51, or 4.50 mg/cu.m, respectively) antimony trioxide for 6 hours/day, 5 days/week for 1 year (duration-adjusted concentrations = 0, 0.01, 0.09, or 0.80 mg/cu.m, respectively). The article by Newton et al. (1994) is the published version of an earlier, more complete report (Bio/dynamics, 1990). In addition to the 1-year exposure, some animals were held for a 1-year recovery period. Interim sacrifices were conducted on 5 animals/sex/group at 6 and 12 months of exposure and at the end of the first 6 months of the 12-month postexposure recovery period. The remainder of the animals were sacrificed at the end of the 12-month recovery period. The antimony trioxide was determined to be 99.68% pure. The rats were exposed (whole body) in 6 cu.m stainless steel and glass chambers with a calculated air flow of 2,077- 2,280 L/min. The test atmosphere was generated with a Fluidized Bed Generator (TSI, Inc., Model 3400 or 9310). The test atmosphere was analyzed by atomic absorption spectrometry. Particle size distribution measurements were made once at the beginning of weeks 4, 8, and 13, and months 6 and 12 using a TSI Aerodynamic Particle Sizer. The particle size distribution at the high concentration also was analyzed using a Delron DCI-6 (Battelle) cascade impactor for comparative purposes. The MMAD was 3.7 microns, and sigma g was 1.7 for all concentrations. Body weights were measured weekly during the first 3 months of exposure and monthly thereafter; hematology analyses were conducted on 5 animals/sex/group at 12 and 18 months and on 10 rats/sex/group at 24 months. Gross and histopathological evaluations were performed on all animals. Microscopic examinations were performed on tissues of the larynx (1 section), lymph node [4 sections (peribronchial)], lungs (1 section from each lung and 1 from the main stem bronchi), trachea (1 section), nasal turbinates (4 sections), and heart for animals in all groups. The eyes, kidneys, liver, prostrate, spleen, and urinary bladder were examined in the control and high- exposure groups.

No difference between the control and exposed groups was noted in survival, although an unexplained increase in the number of deaths was noted in weeks 49-53. Body weight was not affected by exposure to antimony trioxide.

No significant changes in hematological parameters were observed that were concentration-related or consistent across time periods. However, an increase in mean corpuscular hemoglobin concentration was seen in both sexes exposed to the high concentration for 12 months. This effect was not noted at other exposure intervals.

An ophthalmoscopic examination was performed on all rats before the test and at 6, 12, 18, and 24 months. Mild, compound-related ocular irritation was noted at 6 months, but no indications of compound-related ocular disease were noted at 12 or 18 months. Examination of all surviving rats at 24 months revealed increases in the incidence of conjunctivitis (reported as chromodacryorrhea secondary to dental abnormality, infectious disease, or xerosis) and cataracts (females only; principally posterior subcapsular cataracts). Statistical analysis of the cataract response observed at 24 months was performed for both male and female rats (Allen and Chapman, 1993). Trend test and pairwise comparisons (Fishers Exact Test) revealed no concentration-response relationship for the male rats. Incidence in the females was 3/28, 8/21, 12/34, and 14/32 for the control and 0.06-, 0.51- and 4.50-mg/cu.m groups, respectively. Pairwise comparisons (Fishers Exact Test) suggest marginally significant increases over controls ($p < 0.05$) in the low- and mid-concentration groups (p values were between 0.03 and 0.04). When just those two concentration groups and the controls were included in a trend test analysis, the increases were determined not to be statistically significant (p value was 0.09). At the high concentration, however, a statistically significant increase in female cataracts was indicated by both the trend and pairwise tests ($p < 0.01$). Based on information provided by the principal investigators, this effect is not likely to be due to lack of cage rotation (resulting in unequal exposure to light among the groups). However, occupational studies that involved physical examinations and reported respiratory effects in workers exposed to antimony trioxide have not reported significant eye effects (Potkonjak and Pavlovich, 1983; Renes, 1953). There is a great deal of uncertainty and judgment involved in the designation of these lesions (Boorman, 1995). For this reason and because Newton et al. (1994) did not observe a dose response in either sex, and because the lesions attained statistical significance (trend test) only at the highest concentration in the female rats at 24 months (increasing the potential for confounding from spontaneous senile cataracts common among aging nocturnal albino rodents), these results can not be considered an adequate basis for a human risk assessment.

Microscopic lesions of the lungs revealed interstitial inflammation in control and exposure groups at the end of 6, 12, 18, and 24 months. Granulomatous inflammation and granulomas were observed in all exposure groups at 18 and 24 months. An increase in the number of alveolar and intraalveolar particle-laden macrophages was observed (at every exposure duration) in all but the control groups. There is no indication given in the report that the increases in particle-laden macrophages in the lungs of low- and mid- concentration group rats were anything but normal, compensatory responses. However, clearance half-times in the high-concentration groups were three times greater than in the low- and mid-concentration groups, indicating that

clearance mechanisms may be compromised severely at this level of exposure. It appears that this effect is largely due to the intrinsic toxicity of antimony trioxide and not a general "particle overload" phenomenon. The rate of clearance from lungs of deposited benign or slightly toxic insoluble particles has been reported to be reduced by 50% at a dust volume of about 1000 nL (Muhle et al., 1990). Newton et al. (1994) report a 50% decrease in clearance (or increase in half-time) at an antimony trioxide volume of about 270 nL in the high-exposure group. The disproportionate increase in antimony trioxide retention in the high-exposure group can be seen by comparing the exposure concentration ratios of 1:10:90 to the lung burden ratios of 1:11:138. Thus, the NOAEL for decreased rate of clearance is 0.51 mg/cu.m [NOAEL(HEC) = 0.042 mg/cu.m].

With respect to interstitial inflammation and granulomatous inflammation, statistical significance of incidence data was not reported in the study, but the raw data from the original unpublished report (Bio/dynamics, 1990) were evaluated using trend and pairwise (Fisher Exact) tests on the statistical significance of increases in severity grades and incidence (Allen and Chapman, 1993). An evaluation of male and female graded responses for interstitial and granulomatous inflammation using logistic regression techniques indicates no effect in females at any concentration level and marginally significant effects (for increased severity of interstitial inflammation) at the high- concentration level for males during the exposure period (first 12 months). However, in the second, follow-up year, significant ($p < 0.05$) increases in the incidence and severity of these responses were evident at the high- exposure level for both male and female rats that either died spontaneously or were sacrificed at 18 and 24 months (Bio/dynamics, 1990). When incidence alone was considered (regardless of severity), chronic interstitial inflammation in the female rats that were either sacrificed or died spontaneously was increased over controls in the mid-exposure group. However, overall incidence is not considered an appropriate response measure for this lesion due to the high rate (55%) of minimal to slight interstitial inflammation in female controls and the fact that this increase was not seen among sacrificed animals, but only among those female rats that died spontaneously before normal sacrifice. When severity of these lesions is taken into consideration, the analysis of Allen and Chapman (1993) indicates a LOAEL of 4.50 mg/cu.m and a NOAEL of 0.51 mg/cu.m [NOAEL(HEC) = 0.042 mg/cu.m].

DERIVATION OF A BENCHMARK CONCENTRATION (BMC): Incidence of chronic inflammation, granulomatous inflammation and fibrosis in male, female, and combined male and female rats observed during the 1-year period were analyzed for purposes of Benchmark Concentration (BMC) analysis. To minimize the confounding rate of background lesions, only chronic inflammation given a severity grade greater than 2 (slight) and granulomatous inflammation given a severity grade greater than 1 (minimal) were considered in the BMC evaluation. The concentrations associated with 1, 5, and 10% relative increases in the probability of response were estimated using both Weibull and linear models. Although limiting the

response to specific severity grades decreased the background rate, there was still enough of a response in the controls to cause a slight difference in the results of models that calculate relative (sometimes referred to as extra risk) vs. additional risk. A relative risk model was selected as most appropriate, based on the conservative assumption that the mechanisms causing the background response are independent of the mechanisms causing the treatment-related response.

Both the Weibull and linear models gave the same goodness of fit for male and female data. Although BMCs were not calculated and presented for all endpoints, as per standard operating procedures, the best curve fits and the lowest corresponding lower 95% confidence levels were obtained for chronic inflammation in female rats. A previous chronic exposure study (Groth et al., 1986) also determined female rats to be more sensitive to lung effects from antimony trioxide exposure. Further, Allen and Chapman (1993) also concluded, as a result of their analysis, that "males and females responded differently to antimony trioxide exposure for the subacute/chronic interstitial inflammation response, especially during the second, follow-up year." Because it is possible that there is a biological basis for these reported sex differences, the female data were evaluated separately. The studies by Faustman et al. (1994) and Allen et al. (1994) suggest that the 10% incidence level correlated with a NOAEL for one type of noncancer endpoint (quantal developmental effects). Consequently, a 10% relative increase was chosen as a benchmark response. The lower 95% confidence limit for the 10% relative increase in the probability of response among this subset was determined to be at 0.87 mg/cu.m. Although chronic inflammation can be considered a relatively mild, potentially compensatory effect, a similar BMC10 analysis for granulomatous inflammation and fibrosis (which can be considered to represent further progression of the inflammatory aggravation) gives BMC10 estimates of 1.21 and 2.85 mg/cu.m, respectively. Thus, more serious lesions do occur at only slightly higher concentrations. As stated earlier, when minimal and slight interstitial inflammation are included, the overall incidence of interstitial inflammation in female rats beyond the 12-month sacrifice was increased at the mid-concentration over controls. However, the high rate of minimal to slight inflammation in female controls and in animals that died prior to sacrifice suggests that the BMC10 analysis of higher severity grades is better representative of the true NOAEL. The BMC10 of 0.87 mg/cu.m was chosen for RfC derivation, and a human equivalent concentration [BMC(HEC)] of 0.074 mg/cu.m was calculated.

I.B.3. Uncertainty and Modifying Factors (Inhalation RfC)

UF — An uncertainty factor of 10 is used for the protection of sensitive human subpopulations. An uncertainty factor of 3 is used for interspecies extrapolation because the dosimetric adjustments account for part of this area of uncertainty. An uncertainty factor of 3 is applied for database inadequacies (principally, the lack of reproductive and developmental bioassays). Although epidemiologic studies were not considered adequate for use in a quantitative assessment, they provide qualitative support for the health endpoint selected as the basis for the

RfC and obviate the need for toxicity data in a second species. Studies addressed in the next section indicate the importance of exposure dose and duration on the dynamics of reaching and maintaining a steady-state concentration and lung clearance. There is no evidence that, at the lowest exposure level tested in the Newton et al. (1994) study, the levels of antimony in the rat lungs reached a steady- state concentration. Thus, an additional threefold uncertainty factor to account for a less-than-lifetime exposure duration is applied. This is less than the 10-fold uncertainty factor normally applied to adjust from subchronic (90-day) to chronic studies because exposures lasted for 1 full year.

MF — None

I.B.4. Additional Studies/Comments (Inhalation RfC)

As studies addressed in this section illustrate, the disposition of an antimony aerosol in the respiratory tract is dependent on the particle size, distribution, and solubility of the compound. In general, aerosols containing small particles (Felicetti et al., 1974a; Leffler et al., 1984; Thomas et al., 1973) composed of antimony compounds with low water solubility (Leffler et al., 1984) (e.g., particles of antimony oxides) are retained in the lungs for a longer period of time than those containing larger particles with high water solubility (e.g., particles of antimony tartrates). This is because particle size and distribution determine the initial deposition in the respiratory tract, and subsequent clearance depends on the deposition site, rate of absorption, dissolution, extent of metabolism, and tissue distribution. Retention reflects the difference between deposition and clearance. The toxic effects of antimony compounds also will vary according to these and other variables. Limited data on antimony trisulfide indicate that the critical effect associated with exposure to this compound is cardiotoxicity, and that effects may occur at similar, if not lower, exposure levels (Brieger et al., 1954). Hence, the antimony trioxide RfC is not representative of the entire class of antimony compounds and should not be used in this manner. Most atmospheric releases of antimony result from high-temperature industrial processes that produce antimony oxides. An RfC was derived separately for antimony trioxide because it is the primary form of antimony in the atmosphere (U.S. EPA, 1980), and because there are limited toxicologic data for other forms of antimony.

Chronic occupational exposure to antimony (generally antimony trioxide) is most commonly associated with "antimony pneumoconiosis" (Cooper et al., 1968; McCallum, 1967; Potkonjak and Pavlovich, 1983; Renes, 1953). This condition is characterized on X-rays by the presence of diffuse, densely distributed punctate opacities that are round, polygonal, or irregular in shape; have a diameter of usually <1 mm; and do not tend to conglomerate (Potkonjak and Pavlovich, 1983).

Renes (1953) studied 78 employees of a mining company involved in either antimony smelting operations or maintenance. The workers were exposed to an average of 4.69 and 11.81 mg/cu.m antimony in two different work areas, and 69 of these men reported illness within the first 5 months of operation. The smelter fume contained 35-68% antimony, 2-5% arsenic, 0.01-0.04% selenium, 0.04-0.30% lead, and 0.1-0.40% copper. Exposure to caustics (hydrogen sulfide and sodium hydroxide) also was possible. Chest X-rays taken of six men who were acutely ill revealed pneumonitis.

Cooper et al. (1968) examined 28 antimony smelter workers that had been exposed to antimony ore and antimony trioxide dust for 1-15 years. Antimony concentrations ranged from 0.08-138 mg/cu.m antimony, but particle size was not specified. Pulmonary function studies were carried out on 14 of these workers, and no consistent pattern of abnormalities was observed. However, 3/13 workers who underwent roentgenographic examination were found to have antimony pneumoconiosis and 5 more were suspected of having pneumoconiosis.

McCallum (1963) reported that pneumoconiosis in antimony smelter workers in the United Kingdom was generally benign (i.e., the workers were symptomless). He reported a correlation between the degree of radiographic abnormalities, amount of antimony retained in the lungs, and duration of exposure; changes often were noted after just a few years of employment (McCallum et al., 1971). Ambient antimony (as antimony trioxide) concentrations measured 37 mg/cu.m antimony during tapping operations, and averaged 5 mg/cu.m antimony in other areas; the particle size diameter was <1 micron. In a cross-sectional study of 274 antimony smelter workers in 1965- 1966, 26 new cases of pneumonoconiosis were found (McCallum, 1967).

Potkonjak and Pavlovich (1983) investigated 51 antimony smelter workers that had been employed for 9-31 years. The workers (aged 51-54 years) were examined (physical examination, laboratory analysis, chest X-ray, and pulmonary function studies) 2-5 times over the 25-year period. The airborne dust concentrations measured 17-86 mg/cu.m, and analysis of the dust revealed 0.82-4.72% free silica, 38.73-88.86% antimony trioxide, and 2.11-7.82% antimony pentoxide. Other agents present in the dust included 0.90-3.81% ferric trioxide and 0.21-6.48% arsenic oxide. More than 80% of the particles were <5 microns in diameter. X-ray findings considered positive were characterized by the presence of diffuse, densely distributed punctate opacities having a diameter <1 mm and concentrated in the mid-lung region and were found in many of the workers employed for over 9 years.

A subchronic study was performed (Newton et al., 1994; Bio/dynamics, 1985) in which groups of 50 Fischer 344 rats/sex were exposed to target concentrations of 0, 0.2, 1.0, 5.0, or 25.0 mg/cu.m antimony trioxide (actual concentrations were 0, 0.25, 1.08, 4.92, or 23.46 mg/cu.m, respectively) for 6 hours/day, 5 days/week for 13 weeks (duration-adjusted concentrations = 0, 0.05, 0.19, 0.88, or 4.20 mg/cu.m, respectively). The antimony trioxide was determined to be

99.93% pure. In addition, some animals were held for a 27- week recovery period. Interim sacrifices were conducted on 5 animals/sex/group at exposure weeks 1, 2, 4, 8, and 13 and at recovery weeks 1, 3, 10, 18, and 28. The protocol for exposure and the test atmosphere analysis were the same as described previously for the 1-year bioassay (Newton et al., 1994). The MMAD was 2.9, 3.9, 2.9, and 3.4 microns for the 0.25-, 1.08-, 4.92-, and 23.46-mg/cu.m levels, respectively, and sigma g was 1.6, 1.5, 1.6, and 1.5 for the four concentrations, respectively. Body weights were measured weekly during both exposure and recovery, and hematology and clinical chemistry analyses were conducted on five animals/sex/group at exposure weeks 1, 2, 4, 8, and 13 and at recovery weeks 1, 2, 4, 8, and 13. Complete gross and histopathological evaluations were conducted of all major organ tissues, including the lungs and heart, for all animals.

No exposure-related deaths occurred. Corneal irregularities and alopecia were observed in all groups (including controls) with higher incidence in the high-concentration group. Body weight was statistically significantly reduced at the two highest concentrations in both the males and the females during exposure and most of the recovery period. No significant changes in hematological parameters were observed that were concentration related or consistent across time periods. An exposure-related significant increase in aspartate transaminase was seen in the males exposed to the two highest concentrations of antimony trioxide during exposure. Mean and absolute lung weights were significantly increased in both males and females exposed to the two highest concentrations during exposure and the early part of the recovery period. Gross necropsy revealed lung discoloration in the 4.92- and 23.46- mg/cu.m groups during exposure and in the 23.46-mg/cu.m group during recovery. Microscopic lesions of the lungs observed in all animals exposed to antimony trioxide included particle-laden macrophages, degenerating macrophages, and cellular debris in the lumen of the alveoli. Multifocal pneumonocyte hyperplasia, nonsuppurative alveolitis, and focal alveolar wall thickening also were observed in both males and females exposed to 4.92 and 23.46 mg/cu.m. The macrophages, pneumonocyte hyperplasia, and alveolar wall thickening were still present after 27 weeks of recovery. No histopathologic findings were reported in any other tissues examined, including cardiac tissue. From these results, a NOAEL of 1.08 mg/cu.m [NOAEL(HEC) = 0.096 mg/cu.m], based on pulmonary effects from subchronic exposure, can be estimated.

Watt (1983) exposed groups of 50 female Wistar rats and 3 female Sinclair S-1 miniature swine to antimony trioxide for 6 hours/day, 5 days/week for 1 year. The exposure concentrations were 0, 1.9, and 5.0 mg/cu.m (duration- adjusted concentrations = 0, 0.3, and 0.9 mg/cu.m, respectively). The particle size (Ferret's diameter) was 0.44 and 0.40 microns for the low and high concentrations, respectively, and standard deviations were 2.23 and 2.13, respectively. No exposure-related effects on survival, hematology, or clinical chemistry were noted. The body weights of the exposed animals were consistently higher than the controls throughout the study. No consistent pattern of abnormalities were detected in electrocardiograms taken from swine at

preexposure, after 6 months of exposure, and at the end of exposure. Lung weight was increased in both species. Nonneoplastic pulmonary effects observed in all exposed animals included focal fibrosis, adenomatous hyperplasia, multinucleated giant cells, cholesterol clefts, pneumonocyte hyperplasia, and pigmented macrophages. The severity of these effects increased with concentration and duration of exposure. Postmortem findings that appeared to be treatment related included discoloration and increased pulmonary alveolar-intralveolar macrophages in the mid- and high-exposure groups and focal subacute-chronic interstitial inflammation and granulomatous inflammation in the high-exposure group. The incidence of lung tumors (scirrhous carcinomas, squamous cell carcinomas, and bronchoalveolar adenomas) was statistically significantly increased in the animals exposed to 5.0 mg/cu.m only. No other nonneoplastic or neoplastic lesions were observed in the exposed rats, and no microscopic, exposure-related changes were observed in the swine. Based on the occurrence of pulmonary effects in rats, a LOAEL of 1.9 mg/cu.m can be estimated from this study.

Cooper et al. (1968) exposed two groups of 10 Sprague-Dawley rats/sex to powdered antimony ore or antimony trioxide at a concentration of 1,700 mg/cu.m for 1 hour, 1-6 times every 2 months. This exposure regimen continued for 66- 311 days for the ore and 66-366 days for the antimony trioxide. No control animals were included in the study. The powdered ore induced mild and transient edema and lung congestion after the first exposure. Both the ore and the trioxide exposure resulted in a phagocytic response that became apparent 66 days after the first exposure and increased in intensity with continuing exposure. The authors noted that no signs of chronic pneumonitis were apparent at 311 days for the trioxide and 366 days for the ore. As the duration of exposure increased, scattered particles with moderate reticuloendothelial proliferation was noted in the spleen. No exposure- related effects were seen in the liver or kidney. No controls were used, and details regarding protocol (e.g., number of animals sacrificed at the end of the study) and results (e.g., incidence data) were lacking.

Guinea pigs (n = 24) were exposed to antimony trioxide at a concentration of 45.4 mg/cu.m (38.1 mg/cu.m antimony) for 2 hours/day, 7 days/week for 2 weeks, followed by 3 hours/day for the duration of the experiment (8-265 days). The particle size was assumed to be less than or equal to 1 micron (Dernehl et al., 1945). The authors assumed that lung retention of antimony was 50% and calculated a daily average retention of 1.6 mg. Interstitial pneumonitis was observed in all 24 guinea pigs, and, of the four deaths that occurred, two were from pneumonia. Increased lung weight was observed at necropsy, and subpleural petechial hemorrhages were observed in animals exposed for greater than or equal to 30 days. Increased liver weight, cloudy swelling of the liver, and fatty degeneration in 73% of the animals exposed for greater than or equal to 48 days were observed. Decreased white blood counts were reported in the exposed animals, and splenic hyperplasia and hypertrophy also were noted in half of the exposed animals. Electrocardiograms were taken of three guinea pigs, and no exposure-related abnormalities were noted.

In two separate studies, Gross et al. (1952, 1955) exposed 50 male Sprague-Dawley rats to antimony trioxide dust at a concentration of 100-125 mg/cu.m (84-105 mg/cu.m antimony) for 100 hours/month for up to 14.5 months. No experimental controls were included in the 1952 study, and animals exposed to 25 mg/cu.m dust containing 1% antimony trioxide (90% calcium phosphate) served as controls in the 1955 study. The authors determined by electron microscopy that the average particle size was 0.6 microns. Death due primarily to pneumonia occurred in many of the animals. On gross examination, the lungs appeared mottled, and swelling, proliferation, and desquamation of the alveolar macrophages were observed early in the experiment and were followed by fatty degeneration, necrosis, and cell death as the exposure duration increased. Alveolar fibrosis also was observed. The authors characterized these pulmonary changes as "endogenous lipid pneumonia." Rabbits administered the same levels of antimony trioxide, according to the same treatment regimen, exhibited similar pulmonary effects. However, the interstitial pneumonia was more pronounced in the rabbits, and the fibrosis was less diffuse (Gross et al., 1955). Considerable deposits of antimony trioxide were found in the lymph nodes, but there was no fibrosis. This prompted the authors to postulate that the lung damage observed was secondary to metabolic disturbances, fatty degeneration, and necrosis of alveolar macrophages, resulting in lipid deposits that, in turn, cause fibrosis (Gross et al., 1952, 1955).

In a study sponsored by NIOSH, groups of 90 male and female Wistar rats were exposed to dusts of antimony trioxide or antimony ore for 7 hours/day, 5 days/week for up to 52 weeks (Groth et al., 1986). The exposure concentrations were 45 mg/cu.m antimony trioxide (37.8 mg/cu.m antimony) and 36-40 mg/cu.m antimony ore (17.5 mg/cu.m antimony). Rats exposed to filtered air served as controls. The duration adjusted concentrations were 9.4 mg/cu.m and approximately 7.9 mg/cu.m antimony ore, respectively. The MMADs for the two test atmospheres were 2.80 (antimony trioxide) and 4.78 (antimony ore); the sigma g values were not reported. Interim sacrifices were performed on 5 animals/sex/group at 6, 9, and 12 months, and the remainder of the animals were held for an additional 20 weeks after the termination of exposure. Slight but statistically significant decreases in mean body weight were observed in both the males exposed to antimony trioxide (6.2%) and the females exposed to antimony ore (6.4%). Slightly elevated, confluent, white and yellow foci were grossly visible on the pleural surfaces of the lungs from all exposed animals. Histologically, interstitial fibrosis, alveolar-wall cell hypertrophy and hyperplasia, and cuboidal and columnar cell metaplasia of the lungs were observed in the exposed animals after 6 months of exposure. These effects increased with respect to the size of the area affected after 12 months of exposure, and the extent of fibrosis increased after 4-5 months of recovery. Cholesterol clefts also were seen in the lungs of the exposed animals. None of these effects were seen in the control animals, and no other exposure-related nonneoplastic effects were observed. An increase in the incidence of lung tumors (squamous-cell carcinomas, bronchoalveolar adenomas, bronchoalveolar carcinomas, and scirrhous carcinomas) was seen in 27% of the females exposed to antimony trioxide and 25% of the females exposed to antimony

ore. Based on the results of this study, a LOAEL(HEC) of 5 mg/cu.m (assumes a sigma g of 2) for antimony trioxide can be estimated for effects in the thoracic region of the respiratory tract.

Quantitative data regarding the disposition of inhaled antimony oxides in humans or laboratory animals are not available. However, antimony has been detected in the blood and urine of smelters, with and without lung changes, who were chronically exposed to antimony trioxide; urine levels of antimony often remained elevated for extended periods after exposure had terminated (Bailly et al., 1991; Brieger et al., 1954; Cooper et al., 1968; Ludersdorf et al., 1987; McCallum, 1963). This provides evidence that antimony oxides are absorbed by humans following inhalation exposure.

Data obtained from both live and deceased smelter workers indicate that antimony is retained in the lungs for long periods of time (Gerhardsson et al., 1982; McCallum, 1967; McCallum et al., 1971; Vanoeteren et al., 1986a,b,c). Gerhardsson et al. (1982) measured the antimony content of the lungs of 40 deceased smelter workers and found that the antimony levels in the exposed men (316 mg/kg) were 12-times greater ($p < 0.001$) than the levels of antimony measured in nonexposed referents. Furthermore, antimony concentration in the lungs did not tend to decrease with increasing period after cessation of exposure, which indicates that lung antimony has a long biological half-life. A series of studies conducted by Vanoeteren et al. (1986a,b,c) support the observation that antimony accumulates in lung and is retained for long periods of time.

The absorption and retention of antimony following inhalation exposure has been studied in laboratory animals, and the results support the observations made in humans that antimony can be retained in the lung (Newton et al., 1994; Felicetti et al., 1974a; Leffler et al., 1984; Thomas et al., 1973). These investigators have demonstrated that the extent of deposition and subsequent clearance and retention of antimony from the lung depends primarily on solubility (Leffler et al., 1984) and particle size (Felicetti et al., 1974a; Leffler et al., 1984; Thomas et al., 1973). Thomas et al. (1973) exposed mice to aerosols of radiolabeled trivalent antimony as a tartrate complex for 10 minutes. The aerosols were generated at three different temperatures (100, 500, and 1100 F) that yielded particle sizes (activity median aerodynamic diameter) of 1.6, 0.7, and 0.3 microns, respectively (with sigma g's of 1.9, 1.8, and 1.3, respectively). Whole-body scintillation counting was conducted immediately after exposure and at various intervals thereafter; serial sacrifices to determine tissue distribution were conducted at 0, 2, 4, 8, 16, and 32 days postexposure. The results of the serial whole-body counts revealed that antimony was cleared rapidly at first, and this initial, rapid phase was followed by a slower, steady decrease in antimony content. The aerosol generated at 100 F was more soluble than those generated at 500 and 1100 F; the more soluble material was cleared from the lung and absorbed into the systemic circulation at a higher rate (to be preferentially accumulated in the bone) than the aerosols generated at higher temperatures. Consequently, the less soluble and smaller particles that were generated at higher temperatures tended to be retained in the lung for long periods of time. Similar results were

obtained in dogs exposed to antimony aerosols generated at 100, 500, and 1100 F having particle sizes of 1.3, 1.0, and 0.3 microns, respectively (Felicetti et al., 1974a). The largest-sized particles demonstrated relatively rapid clearance from the upper respiratory tract, due in part, perhaps, to solubilization and absorption in the lung and rapid excretion via the urine. The smaller sized, less soluble particles were retained to a higher degree and for a longer duration in both the lungs and the whole body.

Leffler et al. (1984) reported that solubility had the greatest influence on the degree of lung retention of antimony in hamsters following intratracheal instillation. They treated hamsters with both copper smelter dust (volume median diameter of 5.0 microns with a sigma g of 2.1 microns), which contained 1.6% (by weight) antimony, or with pure antimony trioxide (volume median diameter of 7.0 microns with a sigma g of 2.2 microns). The results of these experiments were compared with experiments in which arsenic containing dust and pure arsenic trioxide were instilled intratracheally. Arsenic dust and arsenic trioxide are much more soluble than antimony dust or antimony trioxide. Lung clearance was characterized by two phases. In the initial phase, approximately 20% of the instilled pure antimony trioxide and approximately 35% of the instilled antimony dust were eliminated from the lungs during the first 20 hours (half-life of elimination was approximately equal to 40 hours for pure antimony and 30 hours for antimony dust). The second phase was slow, with half-lives of elimination of 20-40 days for both forms of antimony. The authors also instilled various particle sizes of antimony trioxide and found that, although there was a somewhat lower lung retention of antimony at larger particle sizes, the solubility of the particles was more influential in determining lung retention. The more soluble arsenic dust and arsenic trioxide were cleared much more quickly than antimony.

Antimony trioxide levels were measured in the chronic study conducted by Newton et al. (1994). The rate at which antimony trioxide was cleared by the lungs depended on the dose, with clearance half-times of 2.3, 3.6, and 9.5 months for the low-, mid-, and high-concentration groups. These results suggest that clearance is dependent on lung burden. Substantial amounts of antimony were found in the lungs of these animals after 1 year of exposure (10.6, 120, and 1460 micrograms/g lung tissue in the three exposure groups, respectively).

Data obtained from humans indicate that, as discussed above, inhaled antimony tends to accumulate in the lung, but is relatively rapidly cleared from other tissues. Gerhardsson et al. (1982) found no difference in antimony levels in either liver or kidney in deceased smelter workers, as compared with nonexposed referents.

Experiments in laboratory animals have shown that aerosols of trivalent antimony (tartrate) are distributed primarily to the lung, bone, liver, pelt, and thyroid following inhalation exposure and are excreted both in the feces and in the urine (Felicetti et al., 1974a; Thomas et al., 1973). Significant levels of antimony were found in the lungs and RBCs of animals inhaling antimony

trioxide (Newton et al., 1994). Felicetti et al. (1974b) compared the distribution of trivalent vs. pentavalent antimony inhaled as tartrate in hamsters. The liver accumulated more of the trivalent than the pentavalent form, whereas the opposite was true for the skeleton. Trivalent antimony in blood concentrated almost exclusively in the RBCs, whereas pentavalent antimony in blood was found to a greater extent in the plasma during the first 2 hours postexposure, after which, pentavalent antimony also concentrated in the RBCs. In an English abstract of a Russian study, Chekunova (1971) reported that high levels of antimony were found in blood and lungs, with the levels in liver, kidneys, spleen, and pancreas being similar following "chronic poisoning of rats by inhalation of antimony pentachloride and pentafluoride."

Bailly et al. (1991) studied the metabolism and excretion of antimony following parenteral administration of antimony trichloride to rats, in a woman who attempted suicide by ingesting antimony trisulfide, and in workers occupationally exposed to antimony pentoxide. No methylation of antimony was found in humans or animals. Antimony is excreted primarily in bile (conjugated to glutathione) and in urine. Urinary excretion of pentavalent antimony in exposed workers correlated with the level of exposure.

Gynecological examinations were performed on women (number not specified) occupationally exposed to dust containing metallic antimony, antimony trioxide, and antimony pentasulfide over a period of 2 years (Belyaeva, 1967). These women were compared with a group of control women, who, presumably, were not exposed. The level of exposure was not specified, and it is not known how the control group was selected, whether several important confounding variables were controlled for, or whether concurrent exposure to other potentially toxic substances occurred. A higher incidence of "various sexual disturbances" was reported in the exposed women as compared with controls (77.5% vs. 56.0%); these included disturbances of the menstrual cycle in 61.2% of the exposed women (as compared with 35.7% of the controls), inflammatory disease in 30.4% (as compared with 55.3% of the controls), and other ailments of the sexual organs in 8.4% of the exposed workers. Antimony was detected in the blood of the exposed workers at levels 10 times higher than in the controls. Antimony also was measured in the urine, breast milk, amniotic fluid, placental tissue, and umbilical cord blood of the exposed workers. The incidence of spontaneous abortions was 12.5% in the exposed women as compared with 4.1% in the controls, and the incidence of premature births was 3.4% (1.2% in the controls). The birth weights of children born to the exposed women were comparable to those of children born to the controls, but body weight of the children of exposed women began to lag considerably after 1 year.

Balyaeva (1967) also exposed female rats to antimony trioxide dust by inhalation for a total of 1.5-2.0 months at a concentration of 250 mg/cu.m (210 mg/cu.m antimony) for 4 hours/day. Exposure began 3-5 days before estrus and continued through mating and gestation until 3-5 days prior to delivery. Only 16/24 exposed rats became pregnant; 10/10 control rats were

pregnant. The average litter size was smaller in the exposed rats (6.2 vs. 8.3 in the controls). No teratogenic effects were seen in the fetuses of the exposed animals. No data were presented on the incidence of resorption or fetal deaths. In addition, no fetal abnormalities were seen in animals given a single dose of metallic antimony (50 mg/kg) 3-5 days prior to mating.

I.B.5. Confidence in the Inhalation RfC

Study — Medium
Database — Medium
RfC — Medium

Medium confidence is placed in the critical study because, although it used an adequate number of animals, adequately characterized the exposure atmosphere, and thoroughly examined the respiratory tract, it was not a chronic, lifetime study. Medium confidence is placed in the database because no adequate developmental or reproductive toxicity studies are available, although the human studies do suffice for toxicity data in a second species. A medium confidence in the RfC follows.

I.B.6. EPA Documentation and Review of the Inhalation RfC

Source Document — This assessment is not presented in any existing U.S. EPA document.

This assessment was peer reviewed by external scientists. This review was completed on August 31, 1993. Their comments have been carefully evaluated and considered in the revision and finalization of this IRIS Summary. A record of these comments is included in the IRIS documentation files.

Other EPA Documentation — U.S. EPA, 1980, 1985, 1987, 1989

Agency Work Group Review — 02/09/1993, 09/23/1993, 05/10/1995

Verification Date — 05/10/1995

Screening-Level Literature Review Findings — A screening-level review conducted by an EPA contractor of the more recent toxicology literature pertinent to the RfC for Antimony trioxide conducted in September 2002 did not identify any critical new studies. IRIS users who know of important new studies may provide that information to the IRIS Hotline at hotline.iris@epa.gov or (202)566-1676.

I.B.7. EPA Contacts (Inhalation RfC)

Please contact the IRIS Hotline for all questions concerning this assessment or IRIS, in general, at (202)566-1676 (phone), (202)566-1749 (FAX) or hotline.iris@epa.gov (internet address).

II. Carcinogenicity Assessment for Lifetime Exposure

Substance Name — Antimony trioxide
CASRN — 1309-64-4

This substance/agent has not undergone a complete evaluation and determination under US EPA's IRIS program for evidence of human carcinogenic potential.

III. [reserved]
IV. [reserved]
V. [reserved]

VI. Bibliography

Substance Name — Antimony trioxide
CASRN — 1309-64-4

VI.A. Oral RfD References

None

VI.B. Inhalation RfC References

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VI.C. Carcinogenicity Assessment References

None

VII. Revision History

Substance Name — Antimony trioxide
CASRN — 1309-64-4

Date	Section	Description
09/01/1995	I.B.	Inhalation RfC summary on-line
12/03/2002	I.B.6.	Screening-Level Literature Review Findings message has been added.

VIII. Synonyms

Substance Name — Antimony trioxide
CASRN — 1309-64-4
Last Revised — 03/01/1993

- 1309-64-4
- Antimony oxide
- Diantimony trioxide
- A 1530
- A 1582
- A 1588LP
- AMSPEC-KR
- Antimonious oxide
- Antimony peroxide
- Antimony sesquioxide
- Antimony trioxide
- ANTIMONY WHITE
- ANTIMONY(3+) OXIDE
- ANTOX
- ANZON-TMS

- AP 50
- BLUE STAR
- C.I. PIGMENT WHITE 11
- C.I. 77052
- CHEMETRON FIRE SHIELD
- CI PIGMENT WHITE 11
- CI 77052
- DECHLORANE A-O
- Exitelite
- Extrema
- FLOWERS of ANTIMONY
- HSDB 436
- NCI-C55152
- Nyacol A 1510LP
- NYACOL A 1530
- Senarmontite
- Thermoguard B
- Thermoguard S
- Timonox
- TWINKLING STAR
- Valentinite
- Weisspiessglanz [German]
- WHITE STAR