III. BIOLOGIC EFFECTS OF EXPOSURE

Extent of Exposure

Antimony (Sb) is a metal obtained chiefly as a byproduct or coproduct of base metal and silver ores, and is used in a variety of industries [1]. At standard temperature and pressure, antimony and most of its compounds are solid; hence, they are usually encountered as dusts in the industrial environment. Most occupational exposures are to antimony trioxide, a soft, flowing powder. Antimony pentachloride is the only compound occurring as a liquid at standard temperature and pressure. The antimony halides, unlike the oxides and sulfides, can severely burn the skin, eyes, and mucous membranes. Table XII-1 lists physical and chemical properties of antimony and some common antimony compounds.

Antimony is brittle and hard with a Mohs rating of 3-3.5. It alloys readily with many metals. When alloyed with antimony, lead is harder and more resistant to chemical corrosion than when unalloyed [1]. Until recently, the major use of antimonial lead has been for production of grids and terminals for storage batteries. This use is now declining because the automotive battery industry is adopting calcium-tin and low antimony alloys [2].

The specific heat and electrical resistance of antimony make it useful in electronic semiconductors and thermoelectric devices [1,3]. The peculiar light-transmitting qualities of antimony trioxide and the various colors of antimony compounds make them outstanding pigments for ceramics, glass, metalware, and enamels. Plastics and flame-retardant chemicals are also major end-products. Tables XII-2 and XII-3 show additional uses, originating forms, and production tonnages of antimony.

About 25 countries throughout the world are involved in antimony production [1]. In 1976, the US imported almost 24,000 tons of antimony metal, oxide, and ore for consumption; predominant sources were the Republic of South Africa, Bolivia, the United Kingdom, and France. US production totaled almost 35,000 tons, of which 42% (over 14,900 tons) came from primary sources (283 tons from ore, 14,618 tons from primary smelters), and 58% (almost 20,000 tons) was secondary (recycled) metal [2]. Secondary antimony is recovered chiefly from battery scrap.

Domestic mine production totaled 283 tons during 1976, down 68% from 1975, the result of a long strike at one mine and the continued development of another. The two mining operations producing antimony metal in the US are in Idaho and Montana. A new smelter is expected to open in Texas [2].

Domestic consumption of primary antimony in 1976 was up over 1975 consumption despite a loss of tonnage in metal products; the loss was more than offset by gains in nonmetal and flame retardant applications. Antimony trioxide, often referred to as antimony oxide, is in increasing demand as a fire retardant, and represents the largest class of primary antimony material produced in the US (about 10,600 out of 14,900 tons). In 1976, there were five major producers of antimony trioxide [2]. Most other antimony compounds are derived from the trioxide. Of these, antimony pentoxide, antimony tri- and pentasulfide, antimony tri- and pentachloride, and antimony potassium

tartrate (tartar emetic) are materials of commercial significance in the United States. Table XII-3 shows the end uses of these materials.

NIOSH estimates that 1.4 million US workers are potentially exposed to antimony in their occupational environment. Exposures are largely to metal alloys and to the metal oxide and sulfide. Table XII-5 lists occupations that have the potential for antimony exposure.

Health problems associated with occupational exposure to antimony have been reported from textile dyeing [4]; antimony mining, smelting, and refining [5-14]; the abrasives industries [15]; and glass manufacturing [16]. Exposure problems associated with minor uses of the metal, such as in the chemical industry, in metal polishing and decorating, and in the pharmaceutical industry, have not been reported. Antimonial drugs are not known to be manufactured in the US at this time.

Historical Reports

Antimony was probably first used industrially by the Chaldeans around 4000 BC to manufacture vases and vessels, according to a comment by Bradley and Fredrick [17]. Reference to the use of the element as an eye cosmetic can be found in the Bible, and both Dioscorides and Pliny discussed its use as a medicine [18]. The Romans knew of antimony's emetic properties. When they allowed wine to stand in goblets made of antimony-rich alloys, sufficient antimony leached from the cup to induce vomiting [19].

(a) Occupational Exposures

The first known accounts of occupational hazards ascribed to antimony were written in 1713 by Ramazzini [20]. In his description of diseases of chemists, Ramazzini recorded the case of a chemist who had inhaled fumes of antimony and sulfur after an accident that occurred while he was making a preparation. For 4 weeks after the accident, the chemist was described as being tormented by a cough and could think of no reason other than the acid fumes that had roughened his respiratory organs. Ramazzini [20] also reported that workmen who pulverized stibium (Sb_2S_3) to make glass suffered from vertigo and that their lungs were affected. Wright's translation of Ramazzini's account of the maladies occurring in glass workers is vivid:

> But a far worse fate awaits those who make colored glass for bracelets and other ornaments for women of the lower class and for other uses. In order to color the crystal, they use calcinated borax, antimony, and a certain amount of gold; these they pound together to an impalpable powder and mix it with glass to make the paste needed for this process, and however much they cover and avert their faces while they do this they cannot help breathing in the noxious fumes. Hence it often happens that some of them fall senseless, and sometimes they are suffocated; or in the course of time they suffer from ulcers in the mouth, oesophagus, and trachea. In the end they join the ranks of consumptives, since their lungs become ulcerated, as has been clearly shown by the dissection of their corpses.

Ramazzini pointed out that such symptoms were not observed among glass workers in a factory that did not make colored glass [20].

In 1910, McWalter [21] suggested that many of the obscure and characteristic disorders of printers were due to antimony rather than lead. He reported observing a number of printers with a form of neuritis similar to arsenic neuritis. He described the disorder as being nonfatal, characterized by languor, intense depression, pallor, a tremor-like writer's palsy but more painful and confined to the ulnar side of the hand, pain in the region of the bladder and urethra, temporary impotence, dyspnea without physical signs of lung disease, irritable hyperactivity of the heart, and gastric irritation. The author [21] recognized that many of the symptoms described could be produced by arsenic, a contaminant of the type metal. Lead was also thought to be a possible cause of some of the symptoms, although McWalter [21] noted that the men had few if any of the classic signs of plumbism.

Schrumpf and Zabel [22], also in 1910, described a chronic malady, similar to that observed by McWalter [21], occurring among 15-20% of young typesetters. In addition, Schrumph and Zabel noted a somewhat lower blood pressure, and found antimony in the feces. The arsenic content of the feces was not given although trace amounts of arsenic were stated to have been found in the metallic antimony used to make the type metal. The authors [22] did not explain what "traces of arsenic" meant. Examination of the workers' blood samples showed leukopenia with concomitant eosinophilia. The symptoms disappeared after suspension of work for 2-3 weeks. The results of experiments with rabbits, though poorly controlled, led Schrumph and Zabel to conclude that antimony, and to some extent arsenic, caused the illnesses in the workers. The authors [22] were convinced that lead did not cause the observed symptoms.

In 1913, Rambousek [23] expressed doubt that industrial poisoning was traceable to antimony or its compounds and that arsenic, usually present as a contaminant, was more likely the cause. No supporting data or information were presented.

Seitz, in 1923 [24] and again in 1924 [25], reported that workers in a type foundry were found to have abnormal blood profiles. The factory workers were exposed to metallic dusts containing lead and antimony and to vapors that contained, according to Seitz, antimony in barely measurable concentrations. The method of analysis was not given. The most consistent blood changes among the workers included more than a 50% reduction in the normal thrombocyte (platelet) count and a 50% increase over the normal eosinophil count. A slight lymphocytosis was also reported. Seitz [24,25] related the results of experimental studies in cats, rabbits, and guinea pigs that tended to suggest that antimony and not lead was responsible for the blood changes observed in the foundry workers.

Shirley [26] suggested in 1927 that antimony pentasulfide, present in rubber-compounding ingredients, was responsible for skin irritation leading to eczema or dermatitis, irritation of mucous membranes, ulcerations around the mouth, and a variety of gastrointestinal disturbances including anorexia, cramps, and diarrhea. The author [26] thought it doubtful that absorption of antimony caused any central nervous system disorders.

In a reply to Shirley's article, Shirk [27] refuted the charges against antimony and stated that he knew of no cases of antimonial poisoning among 25-50 workmen engaged over a 12-year period in the manufacture of about 15 million pounds of precipitated antimony sulfide (pentasulfide). Furthermore, no case had come to his attention from six other plants producing antimony sulfide, nor from rubber factories using the product. Shirk, however, did not refer to any medical reports to back up his assertion that the workers suffered no symptoms.

In 1928, Selisky [4] reported 200 cases of skin lesions ascribed to solutions containing antimony potassium tartrate that were being used as mordants in cloth dyeing operations. He described the condition as a pustular necrotic dermatitis commencing as a folliculitis and eventually resulting in atrophic scarring. Acid intermediate products, resulting from the addition of priming colors to the dye solutions, were thought responsible for the dermatitis. The addition of chalk as a neutralizer drastically reduced the number of cases [4].

In 1939, Feil [28] described adverse dermal and mucous membrane effects among workers engaged in the production of antimony metal, antimony trioxide, and crude or pure antimony sulfide. The antimony ore used in the foundry was reported to contain only small amounts of arsenic; the maximum concentration in the ore was 10 mg/kg (0.001%). Of 15 foundry workers studied, 14 had skin eruptions or histories of eruptions. At the time of examination, seven cases of active rash were noted. The eruptions, described as being itchy and resembling chickenpox or smallpox, were usually found on the neck, forearms, and lower extremities. Feil noted that the lesions disappeared with time (about 3 weeks), especially if the workers quit their jobs. Heat, perspiration, and scratching maintained the rash, according to the author. The rash was more prevalent in the summer. Other frequent diagnoses among the 15 workers included conjunctivitis (7) and tracheitis, pharyngitis, and headache (5). Six anemias were also reported but details were not provided. Three workers had a decrease in sexual potency which seemed to be associated with high exposures at the foundry's furnaces.

Feil [28] also related that workers engaged in the production of yellow sulfur and antimony vermillion (antimony oxysulfide) had no signs of antimony toxicity even though they were "absolutely" covered with powder. The powders were described as amorphous antimony sulfides formed either by the reaction of antimony chloride and a hyposulfite or by the decomposition of a sulfoantimonate by an acid. The sulfides produced ranged from golden yellow to deep violet and were used as coloring agents or in the vulcanization of rubber [28].

(b) Therapeutic Use

The therapeutic use of antimony became widespread after it was discovered in 1906 that antimony, combined with an organic molecule, could be administered intravenously (iv) in doses much larger than those tolerated orally. This represented a significant advance in the treatment of tropical diseases [29]. Organic antimonial compounds became, and in many cases remain, the drugs of choice for the treatment of the different forms of schistosomiasis or bilharziasis (caused by parasitic flukes of the genus Schistosoma) and leishmaniasis (caused by parasitic protozoa of the genus Leishmania) [30]. The trivalent antimonial compounds generally have been most

effective against schistosomiasis; the pentavalent drugs have been used primarily against leishmaniasis and as drugs of second choice against schistosomiasis [18,30]. The effects of antimonial drugs are discussed in the subsection on therapeutic exposures under Effects on Humans.

Effects on Humans

Most information on the biologic effects of antimony on humans is derived from clinical studies in which organic forms of antimony were used therapeutically and administered parenterally. Occupational exposures occur primarily by inhalation and skin contact with inorganic forms of antimony (metallic, inorganic salts, and hydrides). Though caution must be exercised in drawing strict parallels between occupational and therapeutic data, the latter may be valuable in assessing the occupational hazards of antimony. For this reason, information from therapeutic and from accidental exposures is reviewed in this document.

(a) Nonoccupational Exposures

(1) Accidental

Acute poisoning following the ingestion of antimony is characterized by a burning sensation in the stomach or other abdominal pain, nausea, intense vomiting, diarrhea, and possibly collapse [31,32]. Dunn [33] and Monier-Williams [31] recounted a 1928 incident of accidental antimony posioning at a company picnic. Lemonade made from fruit crystals was prepared in new white enamelware buckets for the firm's employees and was allowed to stand overnight. Approximately 70 of the 500 employees drank the lemonade, and practically all of these people became rapidly ill. Fifty-six employees were hospitalized for burning stomach pains, colic, nausea and vomiting, and collapse. Diarrhea was not observed. The severity of illness seemed to vary with intake, though in some cases hysteria may have added to the degree of distress and period of incapacity. Most patients returned to work within 3 hours and some were able to eat dinner shortly after the incident. Two of the patients remained in the hospital overnight but were released without sequelae the next morning [31].

Analysis of the bucket enamel that had not been touched by the lemonade indicated 2.88% antimony trioxide [33]. The acid lemonade solution had dissolved the antimony from the enamel, and analysis found the lemonade to contain 0.013% metallic antimony. Each person who consumed a 300-ml tumblerful of the solution would have ingested 36 mg of antimony, or if expressed as tartar emetic, 100 mg of the drug. The British Pharmacopoeia listed the emetic dose of tartar emetic as 30-65 mg [33].

Werrin [32] recounted a similar incident that occurred in 1959. About 150 children became ill at a church picnic after drinking pink lemonade. The drink had been prepared the preceding day, and antimony had leached from the agate lining of the pot. Each child had probably consumed 7.5 mg of antimony, equivalent to 20 mg of tartar emetic. The principal symptoms were nausea, intense vomiting, abdominal pain, and some diarrhea. Most children recovered within a few hours [32].

Although antimonial compounds, usually tartar emetic, have reportedly been used as agents for suicide or homicide, the emetic properties of the tartrate generally make its use for these purposes of questionable effectiveness. A number of such cases were summarized by Polson and Tattersall [34].

Chronic antimony toxicity of nonoccupational origin is not commonly reported. In a discussion of clinical toxicology, Polson and Tattersall [34] described chronic antimony intoxication as resembling natural illness, with nausea, vomiting, loss of appetite, thirst, and diarrhea. Muscular cramps, sometimes severe, were considered to be an outstanding feature. Death was reported to follow chronic antimony intoxication [34], but no details were given.

(2) Therapeutic

(A) Effects on the Heart

The sudden death of a patient during a routine course of therapy for schistosomiasis was described by Khalil [35] in 1931. The patient had collapsed and died while seemingly well, 6 hours after an injection of antimony potassium tartrate. Death was ascribed to sudden heart failure although an autopsy was not performed. The death was typical of other cases Khalil had observed that rarely occurred before the sixth dose and usually a few hours after the injection [35]. Khalil suggested that the drug exerted a toxic effect on the heart and that strenuous muscular effort contributed to the deaths.

Mainzer and Krause [36] reported in 1940 that 9 of 12 bilharziac patients receiving routine therapeutic administration of antimony potassium tartrate had altered electrocardiograms (ECG's). The ECG changes were primarily in the T wave. Of the nine ECG's showing changes, three were considered pathological, four suspicious, and two were judged insignificant. Bradycardia, which the authors [36] considered significant and related to cardiotoxic effects of antimony, was also noted.

Numerous authors using many antimonial drugs have attempted to elucidate the action of antimony on the heart. A complete description of the ECG changes seen following antimonial therapy was provided by Honey [37] in 1960. Although Honey's patients had received antimony sodium tartrate, the effects observed have been seen regularly after administration of antimony potassium tartrate [36,38-40], antimony sodium gluconate [41-43], antimony dimercaptosuccinate [41,44-49], stibophen [38,39,41,50], and antimonate of n-methyl glucamine [41]. Not all drugs produced the full range of effects described by Honey [37].

In all but one of Honey's 59 patients, ECG changes were seen toward the end of the course of therapy [37]. In the single case, the changes were seen very early. Changes varied from very slight (within normal limits) to severe changes that, in the absence of a history of antimony sodium tartrate administration, would have been interpreted as indicating severe myocardial disease [37].

ECG leads consisted of three standard and three augmented unipolar limb leads and the precordial leads V1 to V6. The following changes were considered to be characteristic. The P wave became tall and broad in some

leads, while R wave voltage became significantly lowered. In some patients, minor changes in the QRS axis were noted. No changes in PR or QRS intervals were found. The QT interval increased in most cases [37].

The most characteristic abnormalities seen were in the ST segment and T waves. The earliest change was a reduction in amplitude of the T wave in all leads. As this progressed, the T waves in the left precordial leads became unmistakably abnormal with decreased voltage; both the upstroke and downstroke became more gradual and prolonged. This accounted for much of the QT prolongation. Later on in therapy, the T wave became flat or diphasic in the three standard bipolar limb leads, and, in V5 and V6, the outermost precordial leads. At this time, the ST segment became straight, especially in the precordial leads V2 to V4, located over the heart. Characteristically, the terminal portion of the T wave dipped progressively further below the isoelectric line. This terminal negative phase of the T wave was accentuated by a prominent upright U wave in some instances. Later, in severely affected cases, the T wave became completely inverted, sometimes very deeply, especially in V2 and V4. Inversion of the T wave tended to appear later in V5 and V6. In many patients, the U wave became exaggerated, either interrupting the downslope of a broad low T or following an inverted T or the terminal portion of a diphasic T. No consistent change in pulse rate was seen, though there was one case of serious ventricular arrhythmia. Honey [37] theorized that the longest intervals were associated with sinus arrest or sinoatrial block.

The ECG changes described above have been associated with both trivalent and pentavalent antimonial therapy, though more commonly with the more widely used trivalent compounds, especially those given iv [38,39,51]. Unfortunately, the most effective drugs in the treatment of schistosomiasis also cause the greatest disturbance to the heart. The percentage of patients having altered ECG's has often approached 100% after iv administration of the trivalent antimony potassium or sodium tartrate [37-39]. The percentage of patients with altered ECG's usually has been less than 80% for those receiving trivalent antimonials intramuscularly (im), probably because im administration allows more dilution of the antimony compound in the blood before the drug reaches the heart (DK Detweiller, written communication, May 1978).

ECG changes following treatment with pentavalent compounds have been infrequently observed. Germiniani et al [41] studied the ECG's of 30 patients under treatment for schistosomiasis or leishmaniasis. Both trivalent and pentavalent antimonials were used; however, only five patients received the pentavalent compound. Administration of trivalent and pentavalent drugs both resulted in flattened T waves, anomalous QT intervals, and myocardial ischemia of the subepicardial layer [41].

In contrast, Lopez and da Cunha [52] failed to see ECG alterations in patients treated with the pentavalent drug despite the much larger doses given of pentavalent than trivalent antimony in a study comparing the two drugs. The total dose of pentavalent antimony ranged from 4.95 to 19.35 g given iv over 5-10 days, whereas the total dose of trivalent antimony ranged from 214 to 510 mg given iv over 2-9 days. All patients given trivalent antimony sodium gluconate showed diffuse alterations in ventricular repolarization, seen primarily in the T wave, accompanied by a sinus tachycardia in one case. In the group receiving the pentavalent drug n-methyl glucamine antimoniate,

only one patient showed ECG changes; the authors [52] attributed the arrhythmia to the patient's advanced case of kala-azar.

Tarr [39] was similarly unable to find ECG alterations in three patients treated with the pentavalent drugs ethylstibamine or glucostibamine sodium. However, he did find the typical changes in the T wave of patients given either of two trivalent compounds, antimony potassium tartrate or stibophen.

The mechanism of myocardial toxicity due to antimonial drugs is not completely understood. According to one opinion, antimony becomes fixed to the cardiac cellular membrane and interferes with sodium permeability, thus slowing repolarization and causing ECG alteration until the antimony is excreted (DK Detweiller, written communication, May 1978). Pentavalent antimony compounds are generally excreted more quickly than trivalent, a fact which may help explain the apparent differences in myocardial toxicity between the two valence forms. Excretion is discussed further in this section under Distribution and Fate.

Honey [37] noted that the action of antimony on the myocardium appeared to be cumulative on an individual basis; ECG changes became progressively more severe during the course of therapy. However, taking the group of patients as a whole, there was no relation between total dose per unit of body weight and the degree of ECG change. Individual patient susceptibility apparently played a great part in the observed ECG changes. Honey believed that Asians and Africans (from Nigeria, Ghana, Sudan, Uganda, Mauritius, Iraq, and Kuwait) were more susceptible than Europeans to the cardiotoxic effects of antimony. Of 15 African or Asian patients, 11 had severe ECG changes; 7 of 45 European patients had changes classified as severe [37].

Others have noted that women may be more susceptible than men to the cardiotoxic effects of antimonial drugs [44,53,54]. Huang et al [53] reported that among Chinese, severe cardiac arrhythmia was more frequently encountered in female patients, especially during menstruation or lactation. The authors [53] were, however, not aware of any severe arrhythmia episodes occurring in pregnant women receiving antimony therapy. Lu and Liu [54] referred to a government report of the People's Republic of China which stated that the female death rate due to antimonial drug intoxication was much higher than the male death rate. Neither group of investigators presented specific data.

Waye et al [44] noted that although only about 25% of their 38 US patients receiving antimony dimercaptosuccinate were women, the 3 patients who showed severe ECG changes were all women. No explanations were offered.

The cardiotoxic effects of antimony therapy occasionally have been severe enough to elicit the Stokes-Adams syndrome (periodic weakness, dizziness, or loss of consciousness from lack of cerebral blood flow due to recurring atrioventricular heart block). Dancaster et al [42], in 1966, reported such a case in a 26-year-old female bilharziac patient receiving antimony sodium gluconate. Twenty-four hours after her fourth daily injection (totaling 760 mg of the drug), the woman suddenly lost consciousness. There was no pulse and her blood pressure could not be recorded. She stopped breathing temporarily and became cyanotic but recovered after external cardiac massage. During the next 24 hours, she lost consciousness six times, about 90 seconds in each case, all preceded by a ringing in the ears and blurring of vision. The first ECG taken showed changes compatible with hypokalemia, with

flattening of the T wave, and a prominent U wave. An ECG taken 24 hours later showed changes suggesting an inferior myocardial infarction. The authors [42] thought that the myocardial injury, possibly including patchy necrosis or infarction, could be due either to a direct effect of antimony on the myocardium or to coronary spasm caused by the antimony. The woman's ECG gradually returned to normal in 6 weeks. Similar case histories with other organic antimonial drugs and drug regimens have been reported [43-45,50].

Khalil [55], in 1936, estimated 0.2% mortality following antimony potassium tartrate administration in Egypt. This estimate probably involved under-reporting [55]. Huang et al [53] indicated that mortality following antimony therapy in China had dropped from 0.4% in 1950 to 0.005% in 1958 due to improved methods of treatment.

According to Lu and Liu [54], cardiac intoxication caused 70-97% of reported antimony drug-related deaths, followed by hepatic or acute generalized intoxication, though no data were given. An autopsy on a person who died after 12 injections of antimony sodium tartrate, totaling 1.5 g of the drug, showed cardiac edema and fragmentation of myocardial fibrillar structures [37]. The heart gave appearances of a very recent moderate-sized myocardial infarction. Analyses for antimony showed: blood, 0.017 mg/100 g; liver, 0.020 mg/100 g; skeletal muscle, 0.30 mg/100 g; and heart muscle, 0.20 mg/100 g. The apparent affinity of antimony for muscle tissue was not discussed.

In 1947, Tarr [39] looked for trends in heart rate in the records of 181 courses of antimony therapy. The investigation revealed an increase averaging 10-15 beats/minute (range, 6-30) in 48 courses, a decrease in rate averaging 10-15 beats/minute in 77 cases, and no change in the remaining 56. Tarr [39] was unable to draw any relationship between the T wave and heart rate changes. Other investigators [37,38,40,44,46] generally have failed to observe significant changes in heart rate in their patients receiving antimonial drugs.

(B) Effects on Blood

Hematologic disorders associated with antimony therapy have only rarely been reported and then only with the treatment of schistosomiasis [56-59]. The blood conditions observed could have been caused or contributed to by factors other than antimony, particularly the cases of hemolytic anemia and eosinophilia.

De Torregrosa et al [56] described two cases of hemolytic anemia and referred to six others, all of which occurred in schistosomiasis patients receiving stibophen. Five of the eight patients died of hemolytic reactions with anaphylactic shock. The authors [56], however, were not convinced that antimony had caused the reactions. They suggested that the anemias may have resulted from an immunological response to the organic portion of the stibophen molecule.

Eosinophilia in 24 of 36 patients receiving antimony dimercaptosuccinate was reported by Spingarn et al [57] in 1963. In six of these patients, the percentage of eosinophils rose to 55-60%. The authors [57] reported that the eosinophilia was usually noted at the completion of therapy, implying that the

eosinophilia was a response to the antimony drug, but it is also possible that histamine release in tissues damaged by the parasites caused the condition [60].

Kahn and Brod [58], in 1961, described a case of thrombocytopenic purpura that occurred in a 55-year-old woman being treated with stibophen for schistosomiasis. Both ecchymoses and petechiae were present. Ecchymoses were noted on the left buttock at the injection site and on the left shoulder. Petechiae were present on the face, all extremities, the back, the buccal mucosa, the hard palate, and the bulbar conjunctiva of both eyes. One retinal hemorrhage was noted. Initial laboratory findings were virtually normal except for a very low platelet count of 34,000/cu mm. The plasma prothrombin and whole blood clotting times were normal. Following several in vitro and in vivo challenge studies, Kahn and Brod [58] concluded that the stibophen-related thrombocytopenic purpura was an immunologic phenomenon involving antibodies and complement.

Rivera et al [59] reported another case of immune thrombocytopenic purpura due to stibophen in a 33-year-old man. Following the fourth injection of the third course of treatment, numerous petechiae and ecchymoses developed over the patient's entire body. Extensive subconjunctival hemorrhages were present, but the retinas were normal. There was marked periorbital swelling and purple discoloration. Submucosal ecchymoses were present in the oral cavity, fauces, tonsils, and vocal cords. All laboratory and clinical tests, including an ECG, were normal. Administration of plasma from this patient to another who also received stibophen produced thrombocytopenia without purpura. It was postulated that this case of thrombocytopenic purpura was due to the occurrence of a drug-antibody complex capable of destroying or agglutinating platelets and depressing megakaryocyte activity [59].

(C) Hepatic and Renal Effects

The therapeutic use of antimony has been associated with hepatic damage. O'Brien [50] stated in 1959 that acute fatal liver necrosis had occurred among a small proportion of West African soldiers treated during World War II with antimony potassium tartrate for schistosomiasis. The number treated and proportion affected were not given.

Elevated serum transaminase levels, indicative of cardiotoxic or hepatotoxic effects, have been reported following the administration of several antimonial compounds [44,57,61,62]. The enzyme glutamic-oxalacetic transaminase, found in various tissues, primarily the heart and liver, is released into the serum as the result of tissue damage; hence, serum glutamic-oxalacetic transaminase (SGOT) levels may increase following heart or liver damage. A value of 4-44 units is normal. Glutamic-pyruvic transaminase is another enzyme found in the serum (SGPT) that concentrates in the liver. A normal blood value is 3-36 units. Hepatic disease, such as parasitic infection, or insult, such as the toxic action of a drug, can result in increased concentrations of both enzymes in the blood.

Abdalla et at [61] determined SGOT and SGPT levels in 55 Egyptians before, during, and after antimony potassium tartrate therapy. Increases in SGOT and SGPT before treatment were seen in all cases, though the increases were moderate and more pronounced in hepatosplenic infections than in urinary or intestinal ones. SGOT and SGPT levels in all patients rose throughout

treatment and reached 182 units/ml for SGOT and 178 units/ml for SGPT in the hepatosplenic group, which had consistently higher values than the urinary or intestinal groups. Fifteen days after treatment ended, serum levels of both enzymes had declined gradually in cases of urinary and intestinal schistosomiasis, but were still high in hepatosplenic cases [61].

Asshauer [62] found that rises in SGOT and SGPT occurred simultaneously in 38 patients given antimony potassium tartrate or stibophen for schistosomiasis. SGOT was normal in all cases before antimony therapy. Following treatment, 59% of the cases had abnormally high values, the highest being 510 units. No relation to dose was found. SGPT was elevated in one case prior to treatment and in 57% of the cases after treatment. The maximum level found was 349 units. The increase in SGPT level also was not related to dose [62].

Waye et al [44], however, found a somewhat positive correlation between SGOT elevation and total dose of antimony dimercaptosuccinate. The highest value, 320 units, was found in a patient who had received 65 mg of the drug/kg. Waye et al believed that SGOT could not be used as an index of cardiotoxicity during antimony therapy. Forty percent of their patients without significant ECG changes had SGOT elevations, but only one of three patients with severe ECG changes had a rise in SGOT. They [44] concluded that SGOT was a measure of hepatic, not cardiac, necrosis during antimony treatment. The authors [44] admitted, however, that more frequent SGOT determinations might have revealed a greater incidence of elevated levels in patients with altered ECG's.

Spingarn et al [57] noted considerable SGOT elevations in 17 of 23 patients receiving antimony dimercaptosuccinate. Three patients had high levels (up to 86 units) before therapy, indicating that some heart or liver damage could have occurred due to the parasitic disease. Following antimony therapy, increases of up to 360 units over pretreatment values were seen. SGOT elevation was generally proportional to the dose administered. Of the 17 patients with abnormal SGOT levels, 12 also had abnormal ECG's. These studies [44,57,61,62] indicate that antimony therapy was the major cause of the reported SGOT and SGPT elevations, but whether they indicated hepatic or cardiac intoxication is unclear.

Renal complications following antimonial therapy have been reported. Charlas and Benabadji [63] reported in 1962 that a 4-year-old girl being treated for kala-azar had developed azotemic nephritis 1 week after a second course of therapy with n-methyl glucamine antimoniate, a pentavalent compound. The nephritis, not known to be a complication of kala-azar, suggested metal poisoning to the authors [63] because it was characterized by an initial anuria followed by a polyuria. Based on the nature of the azotemic nephritis, the recent antimony therapy, and the lack of any other evident cause, the authors [63] concluded that the nephritis was caused by the antimonial drug.

Two cases of lupus erythematosus aggravated by the therapeutic use of anthiolimine, a trivalent antimonial drug, were described by Rollier et al [64]. In one case the drug was thought to be responsible for transforming edematous lupus erythematosus into severe systemic lupus erythematosus. The authors [64] viewed this response as exceptional since several patients had previously received anthiolimine without aggravation of their lupus.

(D) Other Effects

The most common side effects of antimony therapy have been mentioned in articles that emphasized other, more severe, effects. More or less in passing, it was stated [35,37,43,47,56,58] that some patients experience some or all of the following symptoms: nausea, anorexia, vomiting, dizziness, joint or muscle pains, headache, diarrhea, fever, and coughing. Reports have generally not given estimates of how widespread these effects are among patients. Khalil [35] found that the numbers of affected patients differed according to the drug administered. He estimated that in patients receiving antimony potassium tartrate, 10% experienced coughing in varying degrees of intensity. Nausea without vomiting occurred in about 1.6% of the cases, and with vomiting in 3.8%. After administration of stibophen, no cases of coughing occurred, nor was there nausea without vomiting. Vomiting was reported in 0.36% of these patients, and dizziness in 0.018%. The percentages were based on at least 2,000 patients [35].

An association between antimony therapy and the occurrence of herpes zoster infections has been noted by several investigators [64-66]. Aslamazov et al [65] observed herpes zoster (shingles) in 2 of 28 bilharzic patients under treatment with antimony sodium tartrate and in 1 of 42 patients treated with stibophen. Most et al [66] reported that herpes zoster infections had developed in 6 of 600 patients being treated with tartar emetic or stibophen. Rollier et al [64] reported shingles in the same patient whose lupus erythematosus had become systemic after treatment with anthiolimine.

(b) Distribution and Fate

Distribution and excretion profiles for man have been determined largely from therapeutic studies. In general, the studies show that trivalent antimony has a greater affinity for red blood cells [67] and is eliminated more slowly than are pentavalent compounds [68]. Antimony is primarily eliminated via the urine following parenteral administration.

Boyd and Roy [68] investigated excretion of a pentavalent compound, ethylstibamine, and compared it with a trivalent compound, antimony sodium tartrate. Estimates of antimony in the urine were made by the Gutzeit method of Sanger and Reigel [69].

Two patients each received a single 300-mg iv dose of ethylstibamine containing 123 mg of pentavalent antimony [68]. Antimony in the urine was determined at frequent intervals for the first 3 days and then every 24 hours for several days. The authors [68] reported that about 19% of the antimony injected was excreted in the first 2.5 hours, 41% during the first 24 hours, 6% during the second 24 hours, and 1.25% during the third 24 hours. Thereafter, daily excretion remained low (1% or less) and was measureable for as long as the two patients were followed (11 and 13 days). An average of 49% of the antimony was excreted in the first 3 days. Reducing the dose to 150 mg did not alter the excretion rate.

A trivalent compound, antimony sodium tartrate, was given in single iv doses of 50 or 60 mg to two patients [68]. These doses represented about 20 and 24 mg of trivalent antimony. The resulting excretion pattern was distinctly different from that observed with the pentavalent compound. The data showed that about 2.5% of the antimony was excreted during the first 24

hours and 2% in the second 24 hours; it decreased very gradually to about 1% or less during the next 24 hours. Total excretion after 3 days was estimated to be about 5% (see Table III-1). Concentrations in the blood were not reported.

TABLE III-1

URINARY EXCRETION OF TRIVALENT AND PENTAVALENT ANTIMONIAL DRUGS

Compound	Ref. No.	Total Dose of Sb (mg)	Route	Excretion, Cumulative Percent Days 1	2	3
		Trivalent Compounds				
Antimony potassium tartrate (Tartar emetic)	[70]	19-120	iv	12	17	20*
Antimony sodium tartrate	[68]	20-24	iv	2.5	3.5	4.3
Lithium antimony thiomalate	[67]	34.5	im	11.4		
Sodium antimony dimercaptosuccinate (Astiban)	[71]	75-125	im	25**		
		320-619	im	36	38	
Monosodium antimony thioglycollate	[67]	31	im	8.1		
		Pentavalent Compounds				
Ethylstibamine (Neostibosan)	[68]	123	iv	41	47	49
		123	im	34	37	38
		61.5	iv	39	43	44
	[67]	127.5	iv	19		
Antimony sodium gluconate	[67]	195	iv	43		
Urea stibamine	[72]		iv	35	41	

*31% after 1 week; 73% after 4 weeks
**50% after 2 weeks

Following the same experimental design, a single dose of 300 mg of ethylstibamine was administered im to two patients [68]. Averaging the

results from the patients, 34% of the antimony was excreted during the first 24 hours, 3% during the second 24 hours, and 1.5% during the third 24 hours. Thereafter, daily excretion rates were low (1% or less) and constant.

The work by Boyd and Roy [68] indicated that dose and route of administration of antimony drugs exerted little effect on the rate of excretion. Intramuscular administration produced a slightly slower excretion rate, a predictable finding in view of the slower absorption expected from im administration. The excretion patterns of a trivalent drug and a pentavalent drug were found to be different.

Otto et al [67] also compared the distribution and excretion patterns of trivalent and pentavalent compounds in a 1947 report. A total of 497 determinations for antimony were made by Maren's colorimetric method on blood cells, blood plasma, feces, and urine of 14 patients being treated with antimony compounds. Two trivalent compounds, anthiolimine and monosodium antimony thioglycollate, and two pentavalent compounds, antimony sodium gluconate and ethylstibamine, were studied.

Distribution of the trivalent compounds in blood was characterized by rapid movement of antimony to the blood cells and continued higher concentrations in blood cells than in surrounding plasma. On the other hand, pentavalent antimony showed little or no affinity for blood cells, but concentrations in plasma were high (see Table III-2).

TABLE III-2

AVERAGE 24-HOUR ANTIMONY LEVELS IN ERYTHROCYTES, PLASMA, AND URINE AFTER INTRAMUSCULAR INJECTIONS OF TRIVALENT AND PENTAVALENT ANTIMONIALS

		Concentration of Antimony			
	Average Dose of Sb given (mg)	Cells (μg/g)	Plasma (μg/g)	Ratio Cells/Plasma	Sb Excreted (% dose)
Trivalent Compounds					
Anthiolimine	34.5	0.15	0.03	5.0	11.4
Monosodium antimony thioglycollate	31	0.35	0.07	5.0	8.1
Pentavalent Compounds					
Antimony sodium gluconate	195	0.6	0.32	1.9	43.0
Ethylstibamine	127.5	0.25	0.8	0.31	17.0

Adapted from Otto et al [67]

Even after repeated heavy doses of the pentavalent drugs, the amounts of antimony recovered from blood cells were scarcely more than could be accounted for in light of known contamination of the cell fraction with plasma [67]. The high plasma concentration of pentavalent antimony and its corresponding low affinity for blood cells apparently enabled quick excretion. Trivalent antimony, on the other hand, became bound to blood cells and remained in circulation for a considerable time.

Some variation in excretion rates was seen by Otto et al with the two pentavalent compounds they studied. They theorized that rate of excretion may to some extent be inversely proportional to the toxicity of the compound [67]. Valency seems to be the primary determinant of excretion rate, but the configuration of the organic molecule also seems to play a role.

Khalil [35], in 1931, reported on the analysis of urine, feces, sweat, milk, and sputum as potential routes of antimony excretion. The subjects were undergoing routine treatment with antimony potassium tartrate or stibophen. Antimony was reported to be excreted only in the feces following im or iv administration of either drug. During the 45 days of observation, 45-50% of administered antimony was excreted in the urine and 3.5% was excreted in the feces.

Baseline values of antimony concentrations in blood, urine, and feces of normal healthy Japanese city dwellers were measured by Hirayama [73] in 1959. The study participants had no known history of occupational or therapeutic exposure to antimony. Analysis for antimony was performed by a procedure that combined the microcolorometric methods of McChesney [74] and Elkind et al [75].

Antimony concentrations in the whole blood of 104 subjects (79 men and 25 women) ranged from undetectable to 13.5 μg of antimony/100 g of whole blood [73]. The overall median value was 2.4 μg/100 g. Medians for men and women were 2.5 and 2.1 μg/100 g, respectively. Twenty-four-hour urine values were determined for 80 men and 55 women. Urine values ranged from undetectable to 18.5 μg/day. The overall median value was 5.3 μg/day; for men and women the medians were 5.4 and 5.1, respectively. Antimony excreted in the feces of 85 men and 41 women ranged from a trace to 56 μg/day. Half of all the cases measured were 13 μg/day or less, and 95% were 35 μg/day or less. There were no statistically significant differences due to sex in blood, urine, or fecal concentrations of antimony.

Hirayama [73] speculated that the baseline levels were probably common to industrial cities, resulting from factory soot containing antimony and factory waste fluid that had emptied into river and irrigation water. Ingestion of various plants and animals containing antimony had probably occurred, which could explain the high antimony concentrations in the feces. The author [73] thought it unlikely that enamel on eating utensils was a source of antimony. The influence of cultural factors, including diet, in affecting biologic antimony levels is not known.

The concentration and distribution of antimony in the human lung and other organs were studied by Molokhia and Smith [76] in 1967. Radioactive analysis of 45 samples of lung tissue obtained from men and women 40-70 years of age who were killed in accidents in Glasgow, Scotland, showed a mean wet-weight

antimony concentration of 0.095 ppm, a range of 0.007-0.45 ppm, and a median concentration of 0.056 ppm.

Results of distribution studies from 15 lung pairs are shown in Table III-3; distribution of antimony was log-normal [76]. Antimony concentrations were more than twice as high at the apex of each lung than at the base, which led the authors [76] to conclude that the source of the accumulated antimony was airborne dust. No information was provided about occupations, smokizg habits, places of residence, or disease states of the victims.

TABLE III-3

DISTRIBUTION OF ANTIMONY IN LUNG AND OTHER TISSUES*

Tissue	Mean Concentration (ppm Wet Weight)
Right lung, Apex	0.084
Middle	0.038
Base	0.033
Left lung, Apex	0.087
Base	0.035
Lymph glands	0.258
Right paratracheal hilar	0.429
Left paratracheal hilar	0.339
Visceral pleura	0.037
Trachea	0.007
Pulmonary artery	0.006
Pulmonary vein	0.007
Tongue	0.007

*Data determined from 15 lung pairs

Adapted from Molokhia and Smith [76]

(c) Occupational Exposures

Numerous authors [4-9,15,16,77-80] have stated that antimony causes occupational health problems. This has been questioned by several other authors [18,81,82], some of whom have noted that many of the reported symptoms and signs of occupational "antimony toxicity" are similar to those of arsenic. Arsenic is a common contaminant of antimony ore and is often found with industrial grades of antimony [83]. Arsenic lies just above antimony in the periodic table [84], and its chemical, physical, and toxicologic properties are similar in several respects to those of antimony [5,85,86]. Arsenic, like antimony, is caustic to skin and mucous membranes and can cause eczema and other forms of dermatitis [87,88], congestion of the upper respiratory tract, and cardiovascular changes [87-93]. These similarities have caused

considerable doubt in some investigators about the actual cause of the occupational toxicity ascribed to antimony, especially that related to mucous membrane and skin effects [77,81].

(1) Effects on the Heart

Reports of altered ECG's in workers occupationally exposed to antimony trioxide and trisulfide have been made by Brieger et al [15] and Klucik and Ulrich [11]. Brieger et al found altered ECG's in 37 of 75 workers exposed to antimony trisulfide who were engaged in the manufacture of resinoid grinding wheels. Klucik and Ulrich found T wave depression, borderline normal QT waves, a prolonged atrio-ventricular transmission, prolonged QRS complexes, and ST segment changes in metal workers exposed to antimony trisulfide and trioxide. Details of these key studies are presented in this chapter under Epidemiologic Studies. They [11,15] are the only reports of altered ECG's in workers, and the only reports implicating inorganic antimony.

(2) Skin and Mucous Membrane Effects

Skin irritation and rashes resulting from occupational exposure to antimony compounds, which often contain arsenic as a contaminant, have been well documented [4-6,10,12,77,78]. These effects have most often been observed following exposure to antimony trioxide [5,77,81] and have been usually associated with hot environments such as might occur during smelting operations or in the summer months [5,12,77,81]. Antimony oxychloride, pentachloride, and trisulfide have not been reported to cause dermatitis.

Rothman [94] suggested in 1943 that antimony salts, as with salts of other heavy metals, form compounds with fatty acid radicals of the sebum and other fats of the skin surface and are absorbed in these forms. No data were presented.

Stevenson [78] gave a different opinion in 1965 on the cause of "antimony spots." After finding dermatitis in 23 of 150 workers exposed to antimony trioxide at the antimony works at Newcastle-upon-Tyne, England, Stevenson noted that all affected workers were exposed to hot environments; 17 worked at the furnaces. Workers in cooler but equally dusty parts of the factory had no spots. The antecubital area, where sweat and flexing occurred, was most often involved. The dermatitis subsided in 3-14 days when the worker was transferred to a cooler part of the factory. Microscopic examination of the lesions showed epidermal cellular necrosis with associated acute dermal inflammatory cellular reaction. The lesions were found close to sweat ducts. A questionnaire survey disclosed that 6 men who bathed relatively infrequently did not have more severe or extensive lesions than the remaining 17. There were no positive reactions in patch tests conducted with dry antimony trioxide or with antimony trioxide suspended in water. Stevenson noted that antimony trioxide is soluble in lactic acid, which is present in sweat in increased amounts following heavy exercise. From these findings, Stevenson concluded that the lesions arose from the irritant properties of antimony trioxide on the dermis after dissolving in sweat and penetrating the sweat ducts [78].

Dermatitis in a worker engaged in the manufacture of fireproof packing material was reported by Paschoud [77] in 1964. A series of cutaneous contact tests of materials going into the final product gave negative results except with antimony trioxide. A positive test for arsenic was noted even though

arsenic was not one of the ingredients in the mixture. Paschoud indicated that other workers exposed to antimony in the same plant also showed positive reactions to both antimony and arsenic. On the other hand, eczemas caused by arsenic in other workers showed negative tests for antimony. The author [77] concluded that the antimony trioxide powder contained impurities of arsenic and that sensitization to both occurred. Double sensitization was thought to be a more plausible explanation than cross-sensitization. Though the process was considered allergic, friction was emphasized as a causative factor [77].

Dermatitis, occurring in two workers producing an antimony trioxide-based powder for treating internal parasites in chickens, was reported by Thivolet et al [81] in 1971. The dermatitis was periodic, usually appearing in the warmer months and disappearing over holidays and during the winter. The lesions were in areas of friction and sweating, such as inside of elbows, popliteal hollows, inguinal folds, and scrotum, and were described as itchy varioliform or necrotic papular pustules.

Chemical analysis of the powder by an undefined method failed to show any traces of arsenic trioxide, and the concentration of the antimony trioxide was not given [81]. A series of skin tests with and without scarification was conducted on the two workers with the commerical antimony trioxide powder and its constituents to determine the cause of the rash. Pure antimony trioxide, pure arsenic trioxide, and Fowler's solution (a solution containing 1% arsenic anhydride) were also tested. Fourteen controls had the same tests. The concentrations used were not reported.

Results of the patch tests without scarification were negative with pure antimony trioxide in 10 controls and in both workers. The results were positive with pure arsenic trioxide in 9 of 10 control subjects and in 1 of 2 workers, and were positive with Fowler's solution in 6 of 10 controls and in the same worker who had responded to arsenic trioxide [81].

With scarification, patch test results were positive with the commerical antimony trioxide powder and arsenic trioxide in both workers, and were positive with pure arsenic anhydride or the commercial antimony trioxide powder in four control subjects [81].

Thivolet et al concluded that the antimony trioxide in industrial or commercial preparations does not appear to play any role in the observed dermatitides, and that an arsenic contaminant was the causative agent. They [81] also concluded that the dermatitides were not due to an allergic process but were caused by the irritant properties of arsenic, the severity of which depended on the degree of individual perspiration.

Linch and Sigmund [82] reported in 1976 the results of laboratory patch tests on 45 women and 7 men who ranged from 17 to 35 years old. A blend of powdered antimony trioxide containing 0.29% arsenic was used. Adhesive patches with moistened gauze centers covered with test material were applied nine times, 24 hours each, over 3 weeks. This series was followed 2 weeks later by a single challenge patch to detect skin sensitization. Because no skin reaction was noted in any subject, the authors [82] did not consider the test material a primary skin irritant or a skin sensitizer. The effects of friction, heat, and sweating as contributing factors to irritation were not studied.

Antimony pentachloride, leaking from a reactor (undefined), was cited by Cordasco [95] as the agent responsible for respiratory distress in a man acutely exposed to an undetermined concentration of the chemical. The patient had received second and third degree burns over most of his body as a result of the accident. The temperature of the material and the worker's protective clothing and equipment were not reported. Almost immediately following exposure, severe coughing, wheezing, dyspnea, and chest tightness developed. Moist rales were found in both base and midlung fields. Pulmonary edema developed which was treated successfully. Antimony pentachloride was also cited by the author [95] as the cause of two fatalities, but no details were provided.

(3) Effects on the Lungs

Exposure by inhalation to dusts and fumes of antimony or antimony compounds has resulted in respiratory illnesses, including pneumoconiosis [5-7,12,95,96]. The amount of functional impairment resulting from most of these exposures in unclear. These reports will be discussed under Epidemiologic Studies.

(4) Effects on Blood

Occupational exposure to antimony has been linked to blood profile alterations, although reported changes have not been frequent. Seitz [24], in 1923, reported thrombocytopenia and relative lymphocytosis in type foundry workers. Anisocytosis was reported by Oliver [10] in 1933 in one of six antimony oxide workers he studied, but he stated that differential white cell counts were generally average, and that the men appeared healthy and apparently had lost little if any time at work because of illness. Gallina and Luvoni [16] found blood profile alterations in workers exposed to antimony pentasulfide (see Epidemiologic Studies).

The most severe cases of blood changes following occupational exposure to an antimony compound were described by Nau et al [97] in 1944. Three metal refinery workers were poisoned by a gaseous mixture containing stibine, arsine, and hydrogen sulfide. The workers suffered severe hemolysis as evidenced by bloody urine and blackened vomitus. Blood bilirubin was elevated. Blood transfusions and fluid replacements were required. These severe symptoms have not been reported following exposure to other antimony compounds.

(5) Other Effects

To elucidate a relationship between induction of chromosome abnormalities and carcinogenesis, Paton and Allison [85] investigated effects of a variety of metal compounds on chromosomes in vitro. Human leukocytes were treated with 2.3 nM concentration of antimony sodium tartrate. One hundred metaphases were examined; 12% of the cells displayed chromatid breaks. This amount of chromosome damage in human cells was reported to be significant at the 0.05 level; controls were not discussed, however. Only salts of antimony, arsenic, and tellurium produced chromosome damage. Although this type of work is used as a screen for mutagenic agents, the results offer limited information and cannot be regarded as conclusive. Nishioka [98] reported no indication of mutagenic activity for antimony tri- and pentachloride in recombination assay experiments using bacterial strains.

Epidemiologic Studies

In 1954, Brieger et al [15] recounted an unexplained increase in the number of sudden deaths among factory workers engaged in the manufacture of resinoid grinding wheels. The workers involved were all from one department and worked in air-conditioned rooms where machines mixed, molded, and pressed materials together. Following the replacement of lead with antimony trisulfide for safety reasons, six sudden deaths and two deaths due to chronic heart disease occurred among 125 workers exposed for 8-24 months. Four of the dead persons were less than 45 years old. In the 16 years before the switch to antimony trisulfide, only one death, from coronary thrombosis, had occurred among the workers in that department. Brieger et al reported that heart disease was suspected in all but one of the sudden deaths. Since autopsies were not performed, confirmation of the suspected heart disease was not possible. An occupational hazard was suspected, which led to a survey of the plant.

Antimony trisulfide in concentrations usually exceeding 3.0 mg/cu m (range, 0.58-5.5 mg/cu m) was found in the air [15]. Phenol formaldehyde resin was also used in the process, but concentrations of this compound in the workroom environment were not reported.

A clinical survey of the employees of that department revealed ECG changes in 37 of 75 workers examined. Alteration of the ECG's was mainly of the T wave. Brieger et al [15] did not define qualitatively or quantitatively the T wave changes but indicated that a cardiologist considered the alterations significant. Apparently, no control ECG's for the 75 workmen studied were available. Alterations in rate and rhythm were not observed. Following cessation of the use of antimony trisulfide in the process, presumably after 2 years, no additional deaths or abnormal cardiac effects were noted. Reexamination of 56 of the workers showed that altered ECG's persisted in 12. Duration of followup was not specified, but it was probably several years.

Of the 113 men examined in the survey, 14 had blood pressures exceeding 150/90 mm and 24 had pressures under 110/70 mm. The ages and weights of these men were not given. X-ray examination revealed that 7 of 111 (63 per 1,000) workers had gastrointestinal ulcers; there were 59 known cases of ulcer in the total plant population of 3,912 (15 per 1,000). These figures are not comparable; more cases of ulcer in the total plant population could have been detected if X-ray screening had been conducted. Irritation of the skin, mucous membranes, and respiratory tract was not found [15].

Urine samples collected at random from the workers contained 0.8-9.6 mg antimony/liter [15]. Antimony content of the urine was analyzed according to a modification of the colorimetric method of Fredrick [99]. Brieger et al [15] did not mention smoking, drinking, or medical histories of the workers. Experiments on rats, rabbits, and dogs conducted by these researchers (discussed under Animal Toxicity) tended to corroborate their occupational findings.

In 1960, Klucik and Ulrich [11] studied 42 metal workers exposed to antimony trisulfide and trioxide at concentrations ranging from 1.3 to 237 g/cu m of inhaled air (sic). The concentrations reported could possibly be 1000-fold in error and may actually have been 1.3-237 mg/cu m. The workers were often reassigned within the plant, making it difficult to establish

exposure groups. Instead, the workers were divided according to the intensity and kind of complaints they expressed. Fourteen had frequent complaints that the authors [11] considered to be related to the heart, including hard breathing, weakness, sweating, stabbing pains or pressure in the chest, and a nonproductive cough. ECG's of these workers were compared with ECG's of the 28 workers who had fewer subjective complaints that might be related to heart problems.

Abnormal ECG's were found in 8 of the 14 workers with frequent subjective complaints. T wave depression, borderline normal QT waves, a prolonged atrioventricular transmission, prolonged QRS complexes, and changes in the ST segment were noted [11]. In three workers, the positive ECG findings were unequivocal; in five, symptoms of disturbance were only probable and judged positive in light of the subjective complaints. Three QRS complex changes were noted in the group of 28 workers who complained less, but were thought equivocal. The average age of both groups was in the middle to late 40's.

Klucik and Ulrich's attempt to correlate antimony exposure and heart problems raises some doubts. The authors [11] admitted that some other factor, particularly arsenic, could have caused or contributed to the observed ECG changes. Second, their evaluation of the ECG's does not seem to have been made independently of the workers' complaints. Thus, ECG abnormalities and subjective complaints were positively correlated, but antimony was not proven to be the cause.

The ECG's of a number of workers taken before and after their workshifts were also examined. No significant changes were reported. The ECG of an individual experimentally exposed to the plant dust at 35 mg/cu m remained unchanged for an observation period totaling 26.5 hours. Procedures used to expose the individual were not given.

Renes [5] in 1953 reported a survey, conducted with the plant physician, of employees of a company engaged in mining, concentrating, and smelting antimony sulfide ore. Illnesses had been reported among the workers in the smelting operations and among maintenance workers who spent a substantial part of their time in the smelter building. According to Renes, the illnesses had begun soon after the initial operation of the smelter and had continued for more than 1.5 years.

During the first 5 months of operation, 69 of the 78 workers employed longer than 2 weeks made a total of 218 visits to the plant physician. Dermatitis and mucous membrane irritation were among the most common complaints, but most cases of dermatitis were seen during a 1-week period of heavy exposure. The dermatitis was usually found in sweaty, hairy friction areas such as the axillae, groin, and back of the neck. The lesions were described as nodular and ulcerative. More than 70% of the workers had experienced soreness or bleeding from the nose. In those complaining of laryngitis, erosions or ulcerations of the vocal cords were always observed. An unspecified number of workers complained of shortness of breath. Chest X-rays of six men acutely ill from "heavy" exposure to smelter fumes showed definite pneumonitis extending like a fan from each hilus. However, no evidence of peripheral parenchymal pulmonary damage was found. Table III-4 summarizes the illnesses reported by Renes [5].

TABLE III-4

EFFECTS OF OCCUPATIONAL EXPOSURE TO ANTIMONY TRIOXIDE

Diagnoses	% Workers*
Dermatitis	20
Rhinitis	20
Laryngitis	11
Tracheitis	10
Pharyngitis	8
Bronchitis	7
Pneumonitis	5.5
Conjunctivitis	4
Septal perforations	3.5
Secondary sinusitis	1.5

*From a total of 69 examined

Adapted from Renes [5]

Undefined "heavy" exposure to smelter fumes was also said to have caused systemic effects such as abdominal cramps, diarrhea, vomiting, dizziness, nerve tingling, severe headaches, and prostration [5]. Antimony concentrations in the urine of seven of the nine heavily exposed men ranged from traces to 60 mg/100 ml. It is assumed that these were spot samples although no information was given. The urine containing 60 mg/100 ml was described as heavily discolored with albumin and was obtained from a worker who was severely ill. Another patient had an unspecified amount of arsenic in the urine. According to Renes [5], symptomatic treatment and removal from exposure for several days provided relief. Antimony or arsenic levels in the urine of the other workers were not reported.

The percentage concentrations of the hygienically important constituents present in the materials handled and produced by the workers are shown in Table III-5.

A study of the smelter environment 6 months after the operation began showed gross contamination of the air with dusts and fumes [5]. Renes divided the smelter into two zones for comparison: the electric furnace area, and the cupel area. Breathing zone and general air samples for antimony and arsenic were taken from each area. Table III-6 shows the results.

An average antimony content of about 11 mg/cu m and an average arsenic content of about 0.73 mg/cu m were found in the overall smelter environment. At the cupel operation that used caustic soda to refine the antimony metal, 12, 60, and 64 mg of sodium hydroxide/cu m of air were also found. Microscopic examination showed most of the particulate material to be less than 1 μm.

One year later, according to Renes [5], engineering controls had lowered the average content of the air to approximately 6.8 mg antimony/cu m and 0.54

mg arsenic/cu m. Table III-7 shows concentrations by area on the second survey. Renes noted that work-related illnesses were still occurring even though engineering controls had been installed.

TABLE III-5

METAL CONSTITUENTS OF HYGIENIC SIGNIFICANCE IN SMELTER MATERIALS

Material or Substance	Concentration of Constituent Elements (%)						
	Antimony	Arsenic	Selenium	Tellurium	Lead	Beryllium	Copper
Dross, iron refining cupel	67.6	4.1	0.04	0	0.28	0	0.4
Dross, arsenic refining cupel	56.9	2.1	0.03	0	0.30	0	0.4
Ore concentrate	21.5	3.6	0.01	0	0.04	0	0.1
Settled fume	35.1	5.3	0.02	0	0.15	0	0.2

Adapted from Renes [5]

TABLE III-6

ANTIMONY AND ARSENIC CONCENTRATIONS IN SMELTER BUILDING (FIRST SURVEY)

Type of Sample	Antimony (mg/cu m)			Arsenic (mg/cu m)		
	No. of Samples	Concentration Range	Average	No. of Samples	Concentration Range	Average
Electric Furnace Area						
Breathing zone	12	0.92-70.7	10.07	12	0.04-4.66	1.10
General room	4	0.40-3.43		3	0.13-1.93	
Cupel Area						
Breathing zone	7	1.19-42.40	11.81	7	0.05-1.45	0.36
General room	8	0.91-22.90		8	0.02-1.59	

Adapted from Renes [5]

TABLE III-7

ANTIMONY AND ARSENIC CONCENTRATIONS IN SMELTER BUILDING (SECOND SURVEY)

	Antimony (mg/cu m)			Arsenic (mg/cu m)		
Type of Sample	No. of Samples	Concentration Range	Average	No. of Samples	Concentration Range	Average
Electric Furnace Area						
Breathing zone	2	5.0-16.90	4.96	2	1.20-2.90	0.76
General room	4	0.29-3.90		4	0.01-0.33	
Cupel Area						
Breathing zone	3	3.30-17.60	8.23	3	0.08-8.10*	0.39
General room	6	0.23-37.00		6	0.01-2.10	

*The value of 8.10 was not included in the zone average because it resulted from an unusual and noncontinuous step in the process.

Adapted from Renes [5]

Renes recognized that the symptoms observed among the workers were characteristic of both antimony and arsenic intoxication. However, antimony concentrations greatly exceeded the arsenic concentrations both in individual and average values (see Table III-8). The author [5] thought it significant that none of the most common early signs of arsenic intoxication, such as increased pigmentation of certain skin areas, keratoses of the palms and soles, loss of hair and nails, garlic-like odor of the breath and perspiration, or swelling of ankles, were reported among these workers. In addition, higher arsenic exposures, found in the electric furnace area, were not reflected by more intense or larger numbers of illnesses in that area. Therefore, Renes concluded that antimony trioxide, the predominant air contaminant, was responsible for the illnesses [5].

TABLE III-8

PERCENT DISTRIBUTION OF ANTIMONY AND ARSENIC CONCENTRATIONS IN SMELTER AIR

Substance	Concentration Range (mg/cu m of air)		
	0.01-0.49	0.5-4.9	5.0 and above
Antimony	7%	54%	39%
Arsenic	71%	27%	2%

Adapted from Renes [5]

Belyaeva's [13] 1967 report is the only recent investigation into the effects of antimony on reproduction. She noted that Feil [28] had earlier found reduced sexual potency among some men workers in an antimony foundry (discussed under Historical Reports).

Belyaeva compared the reproductive experience of women working in an antimony metallurgical plant, located in the USSR, with that of a group of similar working women not exposed to antimony [13]. Conditions and jobs were not defined. Workers in the metallurgical plant were exposed to unspecified concentrations of metallic antimony dust, antimony trioxide, and antimony pentasulfide. Belyaeva conducted extensive gynecologic examinations twice each year from 1962 through 1964 and reported that the exposed group had higher incidences than the control group of late-occurring spontaneous abortions (12.5% vs 4.1%), premature births (3.4% vs 1.2%), and gynecologic problems (77.5% vs 56%). Gynecologic problems included menstrual cycle disorders (61.2% vs 35.7%), inflammatory disease (30.4% vs 55.3%), and other diseases of the reproductive apparatus (8.4% of antimony-exposed women). No percentage was reported for controls in this last category. The author [13] also observed that the weights of children born to antimony-exposed women were not different at birth from those of control babies, but began to lag behind the controls at 3 months and were significantly less at 1 year of age. Table III-9 gives additional details.

TABLE III-9

WEIGHT OF NEWBORN INFANTS AND DEVELOPMENT OF CHILDREN UP TO 1 YEAR OLD

	No. of Children	Weight of Children (g)			
		At Birth	At 3 months	At 6 Months	At 1 Year
Experimental	70	3,360 ±60	6,300 ±110	7,460 ±120	8,960 ±155
Control	20	3,350 ±7	6,410 ±100	7,950 ±80	10,050 ±90

Modified from Belyaeva [13]

Antimony concentrations in the blood of exposed workers were more than 10 times greater than in the control group. Average urine levels of antimony for exposed workers ranged from 2.1 to 2.9 mg/100 ml. The highest value found was 18.2 mg/100 ml, and the lowest, 0.5 mg/100 ml. Low levels of antimony were found in the urine of several persons in the control group, according to the report [13], but concentrations were not given (see Table III-10).

Analysis of the antimony workers' biologic fluids by an undefined method detected antimony in breast milk (3.3 ±2 mg/liter), in placental tissue (3.2-12.6 mg/100 ml), in amniotic fluid (6.2 ±2.8 mg/100 ml), and in umbilical cord blood (6.3 ±3 mg/100 ml). Belyaeva [13] also conducted a study of the reproductive effects of antimony on rats (discussed under Animal Toxicity).

Oliver [10] was the first of several investigators to study the health and working conditions of antimony workers at the antimony processing plant at Newcastle-upon-Tyne, England. At the time of Oliver's study (1933), six men were engaged in oxide manufacture, four of whom had worked at this for 13 years, but had been antimony smelters for many years before oxide production began [10]. The two other men had worked with antimony for 2 and 3 years, although they had been with the company for many years.

Observation within the smelter indicated that no special hygienic precautions were taken, and according to Oliver, none appeared necessary. Respirators were provided for workers packing the final product, antimony trioxide, but they were not regularly worn. Despite considerable skin exposure, only a few cases of mild skin irritation were observed. Microscopic examination of the blood showed slight anisocytosis in one man. Differential white cell counts were average except for slightly elevated eosinophils. Chemical examination of the urine (method unspecified) did not detect antimony.

TABLE III-10

LEVELS OF ANTIMONY IN BLOOD AND URINE OF ANTIMONY METALLURGICAL WORKERS

Group of Subjects	Sb in Blood (mg/100 ml)				Sb in Urine (mg/100 ml)			
	No. Sub-jects	Min	Max	Mean ±SE*	No. Sub-jects	Min	Max	Mean ±SE*
Workers in dustiest shops (melting, pentasulfide, beneficiation plant)	161	0.5	20.0	5.3 ±0.6	133	0.5	18.2	2.9 ±0.5
Workers in less dusty shops (chemical laboratory, quality control)	157	0.5	18.2	4.0 ±0.5	139	0.5	16.2	2.1 ±0.4
Control group	115	0	3.3	0.3 ±0.06	-	-	-	-

*Author did not state that these values were standard errors of the mean.

Adapted from Belyaeva [13]

Examination of the feces by an undefined method indicated that intake of antimony had occurred. Levels of antimony in the feces ranged from 10.3 to 97.8 mg, but these amounts were not given per unit weight of feces. Because antimony was excreted in feces rather than in urine, Oliver concluded that antimony was poorly absorbed from the gut [10].

A subsequent examination comparing fecal antimony content before and after more strict enforcement of hygienic work practices was conducted in three of the six men. The average fecal antimony level was 76 mg without strict hygienic supervision, and ranged from 5.1 to 35.7 mg with strict supervision [10].

Oliver [10] stated that the men in the study appeared to have blood pressures below average for their ages, a situation he considered unusual among men engaged in heavy work. Weights of the six men ranged from 112 to 159 pounds. Only one man was over 136 pounds. Three men were less than 63 inches tall. Oliver concluded that the men were healthy and lost very little working time because of illness. He did not consider antimony to be a hazardous substance, but a nuisance to the occasional worker who suffered dermatitis.

In 1963, McCallum [12] reported the results of a survey of the same antimony processing plant at Newcastle-upon-Tyne. Air samples taken at various locations and over several weeks showed that antimony concentrations in the work environment generally exceeded 0.5 mg/cu m. The trioxide powder averaged less than 1 μm in diameter. The concentrations of antimony were particularly high during the relatively short periods when tapping operations (pouring molten metal) at the furnace were underway; the mean value at these times was estimated to be about 37 mg/cu m. Other parts of the factory had concentrations up to 5 mg/cu m.

Clinical and radiographic examinations of the workers (number not specified) revealed dermatitis and pneumoconiosis. McCallum [12] found situations of severe discomfort due to skin irritation in warm weather and occasional loss of work due to itching and subsequent secondary infections. The rashes consisted of papules and pustules around sweat and sebaceous glands and resembled lesions associated with chickenpox or smallpox. The rashes were found particularly on the forearms and thighs and the flexures where chafing from clothing was likely. Rashes were not observed on the face, hands, or feet. The "antimony spots" were reported to be transient, disappearing over a weekend or holiday and reappearing upon return to work. The author [12] noted that men with the cleanest personal habits were less likely to develop severe dermatitis, if at all.

Pneumoconiosis, resembling that of coal workers (classified by an international group [100] as a simple pneumoconiosis), was diagnosed by radiographic examination in an unreported number of the antimony process workers [12]. The lung changes appeared to be symptomless in nearly all cases. Two of the men subsequently developed tuberculosis which responded to chemotherapy and a third worker, the only one with respiratory symptoms, had chronic bronchitis and respiratory obstruction. Pulmonary function tests suggested that the latter subject had emphysema but no pulmonary fibrosis.

Spot samples of urine taken from three of the antimony process workers with pneumoconiosis had antimony concentrations of 425, 480, and 680 μg/liter [12]. The case of a retired furnace worker suggested that antimony excretion may continue for some time after exposure ceases. In this subject, urinary antimony concentrations were 55 μg/liter after 7 months of retirement and 28 μg/liter after 4 years. Information on urinary levels while working, blood levels, and other possible exposure sources was not given. Even after 4 years of retirement, the furnace worker's urine antimony level was still higher than

the peak background level found by Hirayama [73] among unexposed Japanese (discussed under Effects on Humans).

McCallum [79] reported in 1967 that improved radiological techniques had led to discovery of 26 cases of antimony pneumoconiosis. Eighteen cases were already under clinical observation following the 1963 study [12]. All told, 44 of 262 men employed at the Newcastle-upon-Tyne antimony works had pneumoconiosis ascribed to antimony. Another form of radiologically-discovered pneumoconiosis due to zirconium (processed in an adjacent factory) was present in eight men; eight others had shadows thought to result from mixed dusts. All pneumoconioses were of the simple type. Preliminary results of a new method [8] enabled improved distinction of different dusts in the lung.

Results of microscopic examination of a lung section from an antimony worker who had died from carcinoma of the lung also were reported [79]. Accumulations of dust particles and dust-laden macrophages lying in alveolar septa and in perivascular tissues were described. No fibrosis or inflammation was seen, suggesting that there was little or no reaction to antimony dust in the lung [79].

McCallum et al [8], in 1971, described the method for the detection and measurement of inhaled antimony trioxide dust retained in workers' intact lungs. The method depended on the dust absorbing monochromatic X-rays having two alternative wavelengths which lie on either side of the k critical wavelength of antimony. The antimony content of the lung was deduced from the differential attenuation of these two beams, using a scintillation counter as the detector.

One hundred and thirteen antimony process workers were screened by this method [8]. Most workers had been employed at the Newcastle-upon-Tyne factory for less than 20 years and had worked at different operations for varying periods. The amount of antimony in the lungs of these men ranged from undetectable levels to just over 11 mg/sq cm of lung area. The method of measuring lung area was not described. Although individual lungs varied a great deal, the authors [8] felt that an association could be made, particularly if only the first 20 years of employment were considered. An increase in radiographic category [100] of pneumoconiosis was associated with a rise in the mean period of employment [8]. The man with the highest level of antimony in his lungs (11.2 mg/sq cm) was employed at the factory for 35 years, 16 of which he packed antimony trioxide. Higher median concentrations of an unspecified type of antimony were found in the lungs of the foremen and baghouse workers than in furnace workers; laborers and other workers had the least antimony in their lungs [8].

A continuing investigation into reports of lung cancer deaths among antimony process workers was reviewed in 1973 in a two-page abstract-type statement by Davies [14], then Chief Medical Advisor for the Employment Medical Advisory Service of England. The study was begun in 1962 after it was learned that a man engaged in the processing of antimony had died of lung cancer. Retrospective study found seven other deaths from lung cancer among antimony workers in the previous 8 years. Four of these men had worked at the antimony works at Newcastle-upon-Tyne, which had been studied by Oliver [10] in 1933 and by McCallum in 1963 [12] and 1971 [8]. The other three men had worked in an antimony processing plant that had discontinued operations.

For the period of 1961-1971, 1,081 men and women employees who had been working or had subsequently joined the workforce after 1961 were studied. At the end of 1971, 937 people were known to be alive and living in England, 20 had emigrated and were lost to the study, 56 had died, and 68 were still being traced. Of the 56 deaths, 10 were ascribed to lung cancer. According to Davies [14], the number of lung cancer deaths in persons of all ages was higher among the antimony factory employees than might be expected according to the local community statistics (10 vs 8.0). Nine of the ten had worked solely at antimony smelting and related activities. Among this group of workers, the expected number of deaths from lung cancer was 5.7. It was also observed that 8 of 9 lung cancer deaths were from the 45-64 age group, where the expected rate was 4.5. Deaths from all causes among the antimony factory workers (including office personnel and others not exposed to antimony) were less than expected, 56 vs 65.8. Smoking habits were not reported nor was information on the exact procedures used for computing the reported death rates.

Additional data (KP Duncan, written communication, June 1978) followed the trends seen in the 1973 data, but also did not supply the needed information. Deaths from all causes remained lower than expected for the whole factory (95 vs 108.11) and for the subgroup working in smelting and related activities (64 vs 74.30). The number of deaths from all cancers was slightly greater than expected for the whole factory (31 vs 29.11) and for the smelter subgroup (25 vs 19.93). There was a disparity between observed and expected deaths due to lung cancer for the whole factory (21 vs 14.03), but most of the excess occurred in the smelter subgroup (18 vs 10.25). The disparity was especially prominent in the 45-64 age group (13 vs 7.22). This recent communication, like the earlier report, was brief. Essential information was absent, including control (community) and factory population descriptions, data analysis, medical data, and environmental, blood, and urine antimony concentrations.

In 1958, Karajovic [6] reported on the working conditions and clinical status of 101 men employed at an antimony smelter in Yugoslavia. Common complaints included shortness of breath, muscle pains, mild cough, dyspepsia, diarrhea, and a feeling of tiredness at work. Of the 101 men examined, 51 had catarrhal symptoms of the upper respiratory tract, 12 had conjunctivitis, and 16 had ulcerated nasal septa. Roentgenography of the lung was performed on 62 workers and revealed 31 cases without pathological findings, 17 cases designated only as type X, and 14 cases of simple pneumoconiosis. Emphysema with bronchitis was found in 22 workers, 8 of whom were less than 40 years old. There were four cases of tuberculosis. Karajovic [6] noted that there were no symptoms of damage to the gastrointestinal tract, liver, cardiovascular system, and central and peripheral nervous systems.

Sixteen cases of dermatitis were found among the workers studied, 13 of whom worked at blast furnaces. The skin rashes and itch were reported to have been most prevalent during the summer. The dermatitis was described as vesicular, varioliform, and efflorescent. The efflorescence underwent necrosis in the center and left scars that were hyperpigmented [6].

Roentgenographic examinations of 20 selected workers, 20-50 years old who had worked 3-15 years at the smelter, yielded 8 cases of simple pneumoconiosis, all among men who had spent most of their working hours at the blast furnaces and in the filtering plants. Tests of the workers with

pneumoconiosis showed ventilatory function to be normal in three cases and slightly reduced in four. It was not tested in the remaining individual. Karajovic [6] also reported that blood pressure values were somewhat lower in five of the eight workers with pneumoconiosis, although no data were given. ECG's and hepatograms were normal. Data on the blood pressure determinations and ECG's for the other 12 workers were not provided.

Analysis of blood and urine with Gutzeit's test did not detect antimony [6]. A polarographic method detected 25 μg antimony/liter of urine in three unidentified workers. Antimony was not reported to have been determined in feces.

A survey of the work environment showed that clouds of production dust were often visible. Gravimetric analysis showed dust loads to be 16-248 mg/cu m consisting of 2,150-12,800 particles/cu m. The vast majority of the particles were <0.5 μm in diameter, according to Karajovic [6]. The mixed dust to which the workers were exposed contained antimony trioxide (36-90%), antimony pentoxide (1-6%), arsenic trioxide (0.3-9.0%), ferric oxide (2-4%), and total silica 1-12%, in addition to 1-7% free silicon dioxide [6] (the crystalline form of silica, which, unlike amorphous silica, can cause silicosis).

Karajovic did not doubt that the lung changes observed were contracted as a result of working in the antimony smelter; some workers with lung changes had no other work experience. There was some doubt, however, about whether the changes were attributable to antimony, silica, or both. The author [6] stated that radiographic changes in the lungs of miners with mixed silicosis differed from the changes seen among the smelter workers, a finding that implicated antimony oxides. The influence of arsenic trioxide in causing the observed effects was similarly unclear.

Cooper et al [9] presented data in 1968 on 28 persons who had worked at antimony smelting or ore processing operations for 1-15 years. Pneumoconiosis, determined roentgenographically, was demonstrated positively in three cases and was regarded as suspicious in five others. Cooper et al noted that the 28 employees had lost little if any worktime because of sickness.

Pulmonary function tests were conducted on 14 of the subjects [9]. The tests included vital capacity, lung volume, maximum midexpiratory flowrate, forced 1-second expiratory volume, minute ventilation, mixing efficiency as measured by closed helium circuit technique, tidal volume, maximum breathing capacity, and diffusing capacity. The authors [9] did not present specific data, but they reported that some isolated findings formed no consistent pattern of functional deficit. There were, however, several radiographic changes. One worker had definite small opacities, one had very early unspecified changes, and two had negative chest roentgenograms. Three remaining subjects with either suspicious or definite roentgenographic abnormalities had normal pulmonary function tests.

Cooper et al [9] had monitored the smelter environment in 1966 and found that air concentrations of antimony ranged from 0.081 to 138 mg/cu m. The highest concentration was associated with the bagging operation. Only in that operation did antimony concentrations exceed 75 mg/cu m. In the majority of

cases, concentrations did not exceed 10 mg/cu m. Particle diameters were not given.

ECG's from seven of the workers, three of whom had pneumoconiosis, showed six with normal tracings and one with a slight bradycardia. No other data were provided [9].

The antimony concentrations in urine of these workers were determined in 1962, 1965, and 1968 [9]. The number of subjects sampled varied. The antimony levels in the urine ranged from 7 to 1,020 μg/liter, with most between 70 and 800 μg/liter. No correlations between urine antimony levels, roentgenographic abnormalities, and pulmonary function tests could be established. Cooper et al [9] also conducted a limited experimental study of the effects of antimony on animals, which is described under Animal Toxicity.

Le Gall [7] reported in 1969 that pnemoconiosis was diagnosed in 10 of 40 workers who operated or worked near furnaces used to produce antimony oxide. Though the cases were labeled as silicosis, Le Gall believed that the pneumoconiosis was caused by antimony. Concentrations of antimony trioxide in the factory ranged from 0.3 to 14.7 mg/cu m, and most particles were reported to be smaller than 3 μm in diameter. The extent of exposure to silica is unclear; the article stated that the presence of silica in dust of the foundry could not be proved, but at another point, it stated that the ore being used contained 1-20% silica. Sulfur dioxide was also found in the air [7].

Urine samples from a few workers did not show the presence of antimony [7]. The workers had been employed at the foundry for 6-40 years, and, except in one case, the pneumoconiosis could not have resulted from other occupations. One affected worker had no work experience except his present job at the oxide furnace, where antimony exposure could be assumed to be relatively high, and silica exposure low or nonexistent. Clinical signs included shortness of breath, coughing, some expectoration, prolonged expiration, and sparse adventitious sounds. The tests used were not specified. The radiographs were described as showing moderate, dense reticulonodular formations scattered through the pulmonary fields. There was no overt illness.

Gallina and Luvoni [16] reported in 1958 on their investigation into a series of illnesses among six workers in a Milan glass manufacturing plant. The affected workers were engaged in preparing a mixture used to produce yellow glass. The disturbances began 15-20 days after the introduction of a new mixture that was intended to produce a more satisfactory color than the old mixture [16]. The previous mixture contained carbon, sulfur, and sodium sulfate. In addition to these ingredients, analysis of the new mixture showed 1.04-1.74% antimony pentasulfide. The affected men were reported to have been exposed to unspecified large amounts of dust when they filled the mixer by shoveling and emptied it by pouring the mixture into trolleys. A worker's only respiratory protection was a single handkerchief applied over the mouth [16].

Case histories indicated that the workers began to feel ill 1-2 hours after their workshifts began. Vomiting was a usual occurrence. Malaise, nausea, abundant salivation, a pasty metallic taste, and diarrhea were common. Most workers felt better after vomiting [16].

Clinical examination of the men yielded evidence of systemic toxicity [16]. Analysis of the urine samples showed that antimony had reached the circulation. Urinary levels of antimony (determined by the colorimetric method of Maren [101]) ranged from 3 to 21 μg/100 ml and were virtually unchanged 8 days later [16]. Exactly when the dust exposures were first determined was not stated.

In all the men they studied, Gallina and Luvoni [16] found metamyelocytes in the blood. Metamyelocytes constituted 2-6% of the total white cell count. Monocyte counts tended to be elevated, in one case to 15%. Hemoglobin values were generally found to be 90-100% of normal except for two cases that were 66% and 82%. A decreased percentage of lymphocytes was seen in cases 5 and 6, although case 5 had 14,000 total leukocytes/ml of blood. Gallina and Luvoni suggested that these changes indicated a slight modification in the secondary leukopoiesis under the toxic stimulus of antimony.

The investigators [16] also reported rapid and very evident hepatic involvement. Clinical examination of the six employees exposed to antimony pentasulfide revealed enlarged livers with rounded edges that were painful upon palpation in several cases. Urobilinuria was present in all cases. Hepatic function tests were apparently not conducted, and no evidence of any renal involvement was observed.

Upper respiratory tract irritation was reported in 1966 by Taylor [96] following the exposure of seven men to antimony trichloride fume. Antimony trichloride as a 98% solution in concentrated hydrochloric acid was being used as a chemical catalyst in an unexplained enclosed process in which it was circulated at a high temperature (100 C) and pressure (about 7-14 atmospheres). Such a corrosive mixture occasionally produced leaks in the two nickel alloy reciprocating pumps. The men had complete protective clothing (neoprene suits, boots, gloves, and plastic eye shields or airline helmets), but six of the exposed men had removed the helmets or did not wear respirators, and the seventh had taken no precautions at all. Exposure to the fume ranged from several minutes to 8 hours. Three men were exposed briefly to both fume and spray. Environmental measurements suggested that the workmen were exposed to air containing up to 146 mg/cu m of hydrochloric acid and 73 mg/cu m of antimony. Taylor suggested that the transient (1-2 days) irritation of the upper respiratory tract were due primarily to the HCl vapor. Dyspnea and nasal ulceration were not seen in these workers.

Taylor [96] also noted slightly delayed gastrointestinal symptoms experienced by five of the seven men exposed to the antimony trichloride. Nausea, abdominal pain, and anorexia were the most common complaints; vomiting also occurred. The symptoms were somewhat delayed, usually occurring toward the latter part of the workday or on the following day. Anorexia persisted in one case for 10 days. Because antimony was found in excess of 1.0 mg/liter in the urine of five workers, Taylor concluded that the gastrointestinal symptoms were due to systemic action of antimony, not to local action as a result of ingestion.

Linch and Sigmund [82] attempted in 1976 to measure the health status of workers in a plant that manufactured antimony trioxide. Personal samples taken between 1971 and 1975 indicated antimony dust concentrations in the range of 0.3-56 mg/cu m. Of 61 samples, 59 exceeded 0.5 mg/cu m of antimony.

In the breathing zone samples, 25-40% of the dust was respirable as measured by a cyclone separator.

No acute reactions (ie, dermatitis, eye irritation, or pulmonary, gastrointestinal, or upper respiratory tract effects) were reported in the 37 permanent workers then employed, or in any of the 499 workers employed since the plant began operations 24 years earlier [82]. However, information was not available regarding cause of death or the current health status of most of the 499 former employees. Further, no information was available from medical examinations performed before employment or after it ended. The limited medical records available (140 X-rays and reports for 52 workers) disclosed two cases of arteriosclerotic changes, one case of pericardial calcification, one lung cancer, two heart cases (undefined), and a death from cirrhosis of the liver. The authors [82] did not consider the observed medical episodes unusual in a total work population of that size.

Animal Toxicity

Short- and long-term animal exposures to antimony or antimony compounds have been reported to cause lung damage [9,102-105], myocardial damage [15,17,106,107], liver degeneration [17,102,103], splenic damage [102], and changes in the blood [17,102]. Skin effects following cutaneous contact were not observed in the animals studied [104,108]. LD50's of antimony compounds following oral, intraperitoneal (ip) and subcutaneous (sc) administration are listed in Table III-11.

TABLE III-11

LD50's OF ANTIMONY AND COMPOUNDS

Compound	Species	Route	LD50 mg/kg	Ref. No.
Tartar emetic	Rat	oral	300	[17]
"	"	ip	11	[17]
Antimony trifluoride	Mouse	oral	804	[17]
"	"	sc	22.9	[106]
Antimony	Rat	ip	100	[17]
"	Guinea pig	"	150	[17]
Antimony trisulfide	Rat	"	1,000	[17]
Antimony pentasulfide	"	"	1,500	[17]
Antimony trioxide	"	"	2,250	[17]
Antimony pentoxide	"	"	4,000	[17]

Bradley and Fredrick [17] conducted chronic feeding studies in rats in addition to LD50 tests. The animals were fed daily doses of antimony potassium tartrate and antimony metal up to 100 mg/kg and 1000 mg/kg, respectively, for up to 12 months. No tolerance was found to antimony at any dose level. Antimony potassium tartrate produced consistent and reproducible

injury to the heart, indicated by what was described as an increase in the connective and fibrous tissues of the myocardium. There was a marked variation in the staining of myocardial fibers. These changes were similar to the cardiomyopathies observed in the hearts of the animals surviving the acute tests, which are described later in this section.

Levina and Chekunova [103] investigated the acute and chronic toxic effects of antimony trifluoride. Parallel experiments were conducted with other antimony compounds including antimony trioxide, trisulfide, and pentasulfide. To assess the toxic influence of the fluoride, experiments with sodium fluoride were conducted simultaneously with the antimony studies.

The LD50 for antimony trifluoride following a single sc injection in mice was found to be 22.9 mg/kg [103]. Subcutaneous administration of antimony trioxide, trisulfide, and pentasulfide at 50 mg Sb/kg did not kill the animals or cause any significant toxic effects during the 10-30 days of observation. Doses of 500 mg/kg of antimony trioxide or 100 mg/kg of sodium flouride killed all the animals.

Levina and Chekunova [103] also reported that single intratracheal administrations to rats of antimony trifluoride, ranging from 2.5 to 20 mg, always resulted in death accompanied by labored breathing and convulsions attributed to asphyxia. Rats survived doses of 1.0-1.5 mg and appeared to be normal again after a severe loss of weight. Introduction of 20 mg of antimony trioxide or trisulfide produced an unspecified weight loss in the treated animals; no other signs of toxicity were reported. Rats survived administration of 5 mg of sodium fluoride in the trachea but not 10 mg. The authors [103] did not give the volume or acidity of the solutions used in these experiments. They noted that antimony trifluoride readily hydrolyzes, producing hydrogen fluoride. The marked local action of antimony trifluoride on lungs (described below) was believed to be due to the formation of the irritant hydrogen fluoride.

Levina and Chekunova also described the results of a 1-month study in which 25 sc injections of antimony trifluoride or trioxide were given to rats, in each case at a dose of 89 μg Sb/kg. Antimony trifluoride produced a severe local reaction that limited the study to 1 month. Compared with controls, antimony trifluoride produced a significant reduction of weight and, near the end of the month, a tendency toward hyperglycemia. Average blood sugar values expressed in mg/100 ml were 141 $\pm$29 for antimony trifluoride, 115 $\pm$16 for antimony trioxide, and 92 $\pm$4 for controls. No differences were found in oxygen consumption or central nervous system integration, though the tests used were not explained. At the end of the study, the rats were killed and various organs were taken for examination. Weights of the lungs, adrenals, and kidneys as compared with those of controls were signicantly increased in the antimony trifluoride-treated animals. Less severe changes were observed in the antimony trioxide-treated animals, described only as vascular distensions and small hemorrhages in parenchymatous organs [103].

Gross et al [108] reviewed their findings in 1955 on the effects of antimony trioxide in rats by several routes of administration. A single oral administration of 2.5 g of antimony trioxide, approximately 16 g/kg of body weight, produced no ill effects. No deviation from controls was observed in growth rate or food consumption during 30 days after oral antimony administration. A single intraperitoneal injection of 200 mg of antimony

trioxide produced some peritoneal adhesions seen at examination 2 months later in all three rats tested. The dust deposits were attached to the peritoneal wall as capsules, confined by a thin connective tissue. One year after the injection, no adhesions and only very small foci of dust deposition were found. No significant alterations were observed in the liver, kidney, spleen, or intestinal walls.

No abnormalities were noted in the organs of rabbits receiving one iv 20-mg dose of antimony trioxide nor in rabbits receiving repeated iv injections totaling 200 mg (53 mg/kg) at 2-day intervals. The animals were observed for up to 1 year. In an extended study, 2% antimony trioxide added to a basal diet caused animals to gain weight at a slower rate than controls. No gross or microscopic abnormalities of organs or tissues were noted after 7.5 months at the end of the feeding experiment [108].

Felicetti et al [109] studied clearance of inhaled trivalent and pentavalent radio-labeled antimony aerosols. In a tartrate complex, 124Sb was used as the tracer. Twenty hamsters were exposed to the trivalent and 34 to the pentavalent aerosols. The median aerodynamic diameters determined from radioactive distribution of both aerosols was 1.6 μm; therefore, differences observed in the biologic behavior of the aerosols were attributed to valence state.

Whole-body clearance of both aerosols occurred in two phases; the initial clearance, which was rapid, eliminated 90% of the day 1 body burden by the 7th day after exposure. The average body burden on the first day after exposure for the trivalent and pentavalent aerosols was 65% and 60%, respectively, of that found in animals killed on the day of exposure. This indication of rapid 24-hour clearance was followed by a slower clearance phase during which the remaining antimony was eliminated with a biologic half-life of about 16 days. No statistically significant differences in excretion patterns were observed between the two aerosol groups [109].

Distribution of blood antimony between red blood cells (RBC), and plasma differed with the two valence states. Uptake of trivalent antimony by the RBC was more rapid than with pentavalent antimony, but at 24 hours the ratios of antimony in the RBC to the serum were similar regardless of the valence [109].

Tissue concentration and retention data, corrected for physical decay, indicated the solubility of both aerosols by their rapid loss from the lungs [109]. Two hours after exposure, when the first animals were killed, less than 1% of the body burden of either aerosol remained in the lungs. High gastrointestinal tract content in animals killed early in the experiment probably resulted from considerable upper respiratory tract clearance. Tissue deposition patterns in the two aerosol groups were similar, with greatest antimony concentrations in the liver, skeleton, and pelt. However, a significant difference was the greater deposition of trivalent antimony in the liver. This indicated to the authors [109] that extensive reduction of pentavalent to trivalent antimony had not occurred. Apparently, deposition in the heart did not differ from that in other muscle tissue, because the heart was not discussed. Trivalent antimony was consistently found in higher concentrations in muscle than was pentavalent, but these concentrations were not among the higher levels found.

The degree of uptake of inhaled antimony probably depends on particle size and solubility [104,110]. According to Thomas et al [111], both of these factors can be influenced by the temperature at which antimony aerosols are generated. They [111] found that particles formed at 100 C were more soluble and had a greater aerodynamic diameter (1.6 μm) than particles generated at 500 C (0.7 μm) and at 1,000 C (0.3 μm). It was speculated that the tartrate became an oxide at the two higher temperatures. Larger particles resulted in greater deposition in the upper respiratory tracts of dogs and mice and were cleared more rapidly from the lungs [111].

(a) Effects on the Heart

Death was attributed to myocardial failure in experiments conducted by Bradley and Fredrick [17], reviewed in part earlier (Table III-11). Rats dying a few days after injection showed labored breathing, weight loss, general weakness, hair loss, and evidence of myocardial insufficiency. Myocardial congestion with engorgement of cardiac blood vessels and dilation of the right heart were noted. Experiments with guinea pigs showed similar changes [17].

Microscopic changes in the hearts of animals surviving the LD50 tests were also found by Bradley and Fredrick. They [17] observed a marked variation in the staining of myocardial fibers. Intensely red staining cells showed indistinct fibrillar structures. The changes appeared more numerous in the subendocardial and epicardial zones. A fine stippling of dark staining pigment was present within numerous muscle fibers and was more noticeable in animals receiving antimony metal. In the hearts of the group receiving antimony potassium tartrate there was an increase in "connective and fibrous tissues of the myocardium" [17].

Brieger et al [15], in 1954, exposed rats, rabbits, and dogs to dusts containing concentrations of antimony trisulfide ranging from 3.07 to 5.6 mg/cu m for 7 hours/day, 5 days/week for at least 6 weeks. Most inhaled particles measured 2 μm or less. Parenchymatous degeneration of the myocardium was found in rats and rabbits. Definite and consistent functional disorders of the heart were manifested by ECG changes, primarily a flattened T wave.

Bromberger-Barnea and Stephens [106] reported in 1965 that antimony sodium and potassium tartrates produced a progressive decrease in myocardial contractile force when injected as a single dose of 10-15 mg/kg body weight into the coronary circulation of isolated canine hearts. This decrease was not reversible. The same dose injected iv was fatal in intact open-chested dogs; death resulted within 120 minutes. ST segment changes were seen in the ECG's of both isolated and intact hearts.

(b) Effects on the Lungs

In 1945, Dernehl et al [102] reported pathologic changes produced in guinea pigs that inhaled antimony trioxide at concentrations averaging 45.4 mg/cu m. Exposures were for 2 hours daily, 7 days/week for the first 3 weeks, and then increased to 3 hours daily. The total hours of exposure ranged from 33 to 609. The authors [102] assumed that the maximal retention was 50%, from which they estimated a theoretical daily retention of 1.6 mg. Of 24 guinea

pigs retaining amounts varying from 13 to 424 mg, all showed extensive pneumonitis; all those retaining 50 mg or more showed scattered subpleural hemorrhages [102].

Lipoid pneumonia developed in rats after inhalation of antimony trioxide for 25 hours/week over 14.5 months, according to a 1952 report by Gross et al [105]. Fifty rats were exposed at 100-125 mg/cu m; particles averaged 0.5 μm. Antimony trioxide induced cellular proliferation, swelling, and desquamation of alveolar lining cells. Fatty degeneration became increasingly evident in the alveolar macrophages and led to subsequent necrosis and rupture of the cells. Lipids from these cells were demonstrable as sudanophilic droplets and crystals, were soluble in fat solvents, and gave a positive reaction for steroid. The authors [105] stated that pulmonary fibrosis appeared to be secondary to the irritant action of the liberated lipids. The absence of fibrosis in lymph nodes, where antimony was heavily deposited, was considered evidence that antimony did not directly cause pulmonary fibrosis. Similar but less severe lesions were produced after intratracheal injection [105].

Gross et al [104] further studied the effects of antimony trioxide on the lungs and reported the results in 1955. Fifty rats were exposed at concentrations ranging from 100 to 125 mg/cu m for 25 hours/week over 14.5 months. Twenty rabbits were exposed at 89 mg/cu m, 25 hours/week for 10 months. There were numerous spontaneous deaths due to pneumonia, especially among the rabbits. Of the experimental animals, 85% of the rabbits and 18% of the rats died. The difference between species was thought to be due to unlike clearance mechanisms, greater sensitivity of rabbit lung tissue, and the occurrence of more bacterial infections among rabbits. Microscopically, lungs of both species resembled the 1952 findings except there was a more pronounced interstitial pneumonia in rabbits, and less diffuse fibrosis. Lymph node deposits of antimony in rabbits were small and few. Despite considerable antimony trioxide in rat lymph nodes, there was no indication of fibrosis, a finding that Gross et al thought remarkable. Both species exhibited the pneumonitis considered secondary to lipid accumulation [104].

Cooper et al [9], in 1968, presented the results of exposure studies of rats to powdered antimony ore or antimony trioxide at an aerosol concentration of 1,700 mg/cu m. The exposed animals consisted of two groups, each composed of 10 male and 10 female Sprague-Dawley albino rats. Use of control groups was not reported. Animals received from one to six exposures, 1 hour each, every 2 months, for 66 to 311 days with the trioxide and for 66 to 366 days for the powdered ore. Some animals from each group were killed and examined periodically during the experiment. Immediately after exposure to antimony ore, the lungs of some rats exhibited a generalized pulmonary congestion with mild edema, which the investigators [9] thought was the result of an acute chemical pneumonitis. This was predominantly a transitory response and was not seen in the group exposed to the trioxide. Exposure to the trioxide or the ore produced similar effects except for the acute response to the ore. At 66 days after exposure to either antimony compound, dust-laden phagocytes were seen lying free within the alveolar spaces or intermingled with cells of the septa. In some rats there was a tendency for the cells to form small focalized deposits throughout the lung. With subsequent exposures, these focalized deposits became increasingly prominent. The phagocytic response persisted 311 days after trioxide exposure and 366 days after exposure to antimony ore without any appreciable chronic pneumonitis [9].

Levina and Chekunova [103] reported in 1964 that a single dose of 2.5-20 mg of antimony trifluoride in the rat trachea invariably proved to be fatal, with labored breathing and convulsions attributed to asphyxia. Post-mortem examination revealed acute serous or serohemorrhagic edema; the lungs were about three times their normal weight. Only with doses of 1.0-1.5 mg did the rats survive. Pulmonary edema apparently had occurred in the latter rats also, but it was reported that their lung weights had returned to normal after a month. Cellular infiltrations of interalveolar septa, areas of atelectasis, and areas where the bronchial epithelium had separated were evident. It is not clear whether the effects seen in these rats were due to antimony or to fluoride, or were agonal.

The only overt change produced by the introduction of 20 mg of antimony trioxide, trisulfide, or pentasulfide into the trachea was a reduction in animal weight for a few days. At inspection a month after the compounds were given, the lungs exhibited signs of macrophage reaction, collections of lymphoid elements around vessels and bronchi, and atelectatic areas showing accumulations of epithelioid cells [103].

(c) Effects on Blood

Dernehl et al [102] recorded blood changes in six guinea pigs that had inhaled antimony trioxide at concentrations averaging 45.4 mg/cu m. The affected guinea pigs had probably retained at least 293 mg of antimony trioxide in their lungs. White cell counts of the treated animals were lower than in controls. A decrease in polymorphonuclear leukocytes and a relative increase in lymphocytes were the most outstanding feature of the differential cell counts. Red blood cell counts and hemoglobin values remained normal.

The blood of Bradley and Fredrick's [17] rats showed eosinophilia after LD50 doses of all compounds tested but was apparently otherwise normal.

(d) Effects on the Liver, Kidneys, Spleen, and Adrenal Glands

Dernehl et al [102] found that 11 of 15 rats retaining at least 77 mg of antimony trioxide in their lungs had fatty degeneration of the liver. Hyperplasia of the lymph follicles of the spleen was also observed, as were phagocytes filled with antimony trioxide. Fifty percent of the spleens examined showed decreased numbers of polymorphonuclear leukocytes. There was also an abnormal amount of blood pigment in 62% of the spleens examined [102].

During their determinations of ip LD50's of antimony compounds, Bradley and Fredrick [17] found that the livers of nearly all experimental rats showed moderate periportal congestion and in some instances pigmentation by blood. A mild hepatotoxemia was seen, characterized by functional hypertrophy with many of the hepatic cells appearing cloudy with finely reticulated cytoplasm. Numerous plasma cells were found in the liver. In animals given antimony potassium tartrate, there was slight periportal connective tissue increase with capillary congestion and infiltration of a few lymphocytes into the livers. Antimony oxides produced no changes in the spleen, but in animals that received antimony metal or tartrate, there was a slight congestion and a moderate diffuse hyperplasia. Glomerular congestion with coagulated material in the tubules was seen in the kidneys of the animals given antimony metal or tartrate.

Levina and Chekunova [103] found that 25 sc injections (each 15 mg/kg over a 1-month period) of antimony trifluoride produced liver and kidney changes in rats. The liver showed a moderate degree of cloudy swelling, fatty infiltration, and areas of edema. The most marked degenerative changes were seen in the kidneys, including cloudy swelling of the epithelial cells lining the convoluted tubules, nuclear pyknosis, karyolysis and desquamation of epithelium, hemorrhages, protein masses in the lumina of tubules, accumulations of cell elements between tubules, and occasional shriveled glomeruli [103].

Minkina et al [107] investigated the effects of antimony trioxide and lead acetate on the adrenals and on biologic amines in rats and reported the results in 1973. Antimony trioxide was administered sc five times a week for 3 months, for a total dose of 165 mg (1/20 the LD50). No changes were observed after four injections of the antimony compound, but, after 20 injections, a broadening of the cortical layer was found, due primarily to growth of the fascicular and retriculate zones. The cell size in these zones was increased, as were the nucleus diameter and monoamine oxidase activity. The authors [107] indicated that these were signs of increased adrenocortical functional activity, which virtually disappeared after 35 injections and were completely gone after 47 injections. Minkina et al considered this finding an example of what was translated as habituation to a toxin but did not explain the phenomenon.

(e) Effects on Skin and Eyes

Gross et al [108] described the irritant properties of antimony trioxide on rabbits and rats in a 1955 report. Acute tests of the eye and skin were performed, and an extended study investigated the effect of antimony trioxide on the healing of open wounds. The antimony trioxide used in these experiments had an average particle size of 1.3 μm and contained up to 0.2% arsenic as a contaminant.

The eye irritation tests were conducted by Gross et al in three groups of 10 rabbits each according to the method of Carpenter and Smyth [112]. A 1-ml aqueous suspension, containing 1.50 mg of the dust, was instilled in the right eye of each animal; the left eye served as a control. Examination of the eyes at 1, 2, and 7 days showed no irritative effects of the conjunctiva or the cornea [108].

Cutaneous toxicity tests were conducted in three groups of eight rabbits each [108]. Antimony trioxide dust (2.6 g) was incorporated into an aqueous methyl cellulose paste and applied lightly to about two-thirds of the torso which had been carefully clipped 24 hours earlier. The treated area was covered, and the material held in contact with the skin for 1 week. Gross et al [108] reported no significant local reactions from the single application. Signs of systemic toxicity were not observed, indicating to the authors [108] that absorption through the skin had not taken place. No data on antimony in the blood or excretion of antimony were given.

The effect of antimony trioxide on wound-healing was also investigated [108], though the rationale for this type of experiment was not given. One gram of dry antimony trioxide powder was packed into a 2.5-cm incision on the shaved back of each of 10 rats. A duplicate incision made on the opposite

side that was left undisturbed served as a control. Although the dust-filled wounds tended to heal somewhat slowly, Gross et al believed that the delay was within the limits that could be expected with any nonspecific foreign body.

In another type of wound-healing experiment, Gross et al [108] excised circular areas 1 cm in diameter by electrocautery from the shaved backs of rabbits and rats. Five wounds were made on each animal. The wounds were dusted with 100 mg of antimony trioxide and then covered by a membrane that was cemented to the surrounding skin. The lesions were inspected periodically, and some were totally excised for microscopic examination after 1 week, 2 weeks, or 1 month. According to the authors [108], the wounds healed cleanly and rapidly.

(f) Carcinogenicity, Mutagenicity, Teratogenicity, and Reproductive Effects

Several reports suggestive of potential carcinogenic, mutagenic, or reproductive effects in animals following exposure to antimony have been published. The report of most concern in this section is the 1967 paper by Belyaeva [13], which is the only evidence of adverse effects on reproduction due to antimony exposure.

Animal studies were undertaken following Belyaeva's observations of reproductive disorders among women working at an antimony metallurgical plant (discussed under Epidemiologic Studies). Rats were given single and multiple exposures extending over 60 days to antimony, and their reproductive function, litter size, and weight of offspring were studied.

In the acute experiment, Belyaeva [13] injected antimony metal dust (diameters up to 5 μm) in a single ip dose of 50 mg/kg to each of 30 female rats. The animals were mated while in estrus, 3-5 days after treatment. Fifteen became pregnant; 8 at the first mating, 5 at the second mating (1 month after treatment), and 2 only after the third mating. Of the 15 rats that failed to conceive, 6 were mated once, 7 twice, and 2 were mated three times. In the control group, only one rat failed to conceive after mating once. The experimental animals that became pregnant produced fewer offspring per animal than controls (5.7 vs 7.8) (see Table III-12).

In the second experiment [13], 24 female rats repeatedly inhaled antimony trioxide dust 4 hours daily for 1.5-2 months, at a concentration of 250 mg/cu m. Procedures for mating were like those used in the acute experiment except that dust exposure continued after mating until 3-5 days before delivery, when the rats were moved to individual cages. Sixteen of the 24 exposed rats conceived. The ten control females all became pregnant.

Table III-12 shows that the number of pups born to antimony-exposed dams was less than that of controls (6.2 vs 8.3). No other differences were noted.

Microscopic studies of 23 rats (from both the single and repeated exposure groups) showed uterine and ovarian changes which, Belyaeva suggested, would tend to interfere with the process of maturation and development of egg cells. The ovarian follicles either lacked ova or contained uncharacteristic ova. Cortical hyperemia of the ovaries and follicular cysts were common, as was metaplasia of the uterus. In some animals, the tubes also showed metaplasia. These effects on the reproductive organs were most clearly seen in the animals

treated ip with metallic antimony. In the rats exposed by inhalation to antimony trioxide, the most notable changes were in the lungs, liver, kidneys, and pancreas; changes in reproductive organs were not as clearly expressed [13].

TABLE III-12

EFFECTS OF ACUTE AND CHRONIC EXPOSURES TO ANTIMONY ON THE LITTER SIZES AND WEIGHTS OF NEWBORN RATS

Exposure	No. of Females	Mean Weight of Dams (g)	Mean Litter Size	Weight of Infants at Birth (g)	Weight of Infants After 3 Weeks (g)
		Single ip Metallic Antimony			
Exposed	30	190.0 ±5.2	5.4 ±0.2	5.5 ±1.1	32 ±9.2
Control	12	188.5 ±2.5	7.8 ±0.5	5.4 ±0.5	28.1 ±0.4
		Repeated Inhalation Antimony Trioxide			
Exposed	24	195.5 ±7.2	6.2 ±1.0	5.6 ±1.2	25.2 ±2.8
Control	10	197.8 ±14.0	8.3 ±0.2	5.5 ±1.6	23.5 ±3.4

Modified from Belyaeva [13]

The reproductive organs of the treated rats that became pregnant were found to be normal except for some changes among the acutely treated rats. Uterine metaplasia and follicles without egg cells were observed in a few cases. Gross inspection of the placentas and newborns, and microscopic examination of several fetuses showed no morphological changes [13]. Belyaeva concluded from these findings that antimony may adversely influence the condition and function of the reproductive apparatus. The report cannot be regarded as conclusive, however. There was no discussion of vaginal smears; it is unclear how the author [13] determined that mating had occurred. Rates of resorption and fetal death among the experimental and control groups were likewise not discussed. A definitive interpretation of Belyaeva's [13] work is not possible without further evidence.

Casals [113], in a 1972 report, administered a solution of antimony dextran glycoside containing 125 or 250 mg Sb/kg to pregnant rats on five occasions between the 8th and 14th day of gestation. No fetal abnormalities were observed nor could the drug be detected in the six fetuses examined.

Andronikashvili et al [114] investigated the concentration of some heavy metals in nucleic acids in the process of neoplastic growth. In 1974, they [114] reported that RNA and DNA isolated from tumor tissues in rat livers (Sarcoma M-1 and Walker-256 carcinosarcoma) contained considerably greater

amounts of a number of trace elements including antimony than those found in DNA and RNA isolated from the livers of control rats. The role of metals in nucleic acids during normal and neoplastic growth has not been explained, making interpretation of these results difficult [114].

In 1972, Trifonova [115] reported on the distribution of antimony in tumorous rats. Ten rats received grafts of sarcoma-45 tumors; 10 others were controls. All animals received five ip injections of metallic antimony totaling 300 mg/kg suspended in peach oil [115]. Antimony was found to have accumulated in greater concentrations in the lungs of the tumorous rats than in controls. Antimony concentrations in muscles and skin of tumorous rats were also greater than in controls. The spleens and livers of both groups showed small concentrations of antimony. The author [115] did not speculate on the meaning of these results.

The carcinogen 3,4 benzo(a)pyrene, injected simultaneously with antimony into rats, was taken up by the lungs in greater amounts (21%) than in animals treated with benzo(a)pyrene alone, according to Erusalimski and Suspa [116].

Kanisawa and Schroeder [117] reported in 1969 that 76 mice given 5 μg of antimony potassium tartrate/ml of drinking water throughout their lifetimes showed no increased incidence of tumors or other indications of carcinogenesis. There were 71 control mice.

Correlation of Exposure and Effect

Exposure to antimony and its compounds in the occupational setting has been associated with numerous health problems, including dermatitis and mucous membrane irritation, pneumoconiosis, ECG alterations, hepatic involvement, and hematologic changes. Many of these symptoms have also been described following occupational exposure to arsenic, a common contaminant of antimony ores and antimony compounds used in industry. Confounding exposures have made it difficult to evaluate cause-and-effect relationships. Studies of the effects of therapeutic administration of antimonial drugs are relevant because the antimony given has been considered responsible for heart, hematologic, hepatic, and renal abnormalities in the absence of arsenic contamination.

(a) Effects on the Heart

Two epidemiologic studies have implicated antimony in heart disease and ECG alterations among workers [11,15]. Brieger et al [15] noted eight deaths, attributed to heart disease, following occupational exposure to antimony trisulfide at relatively low airborne concentrations (0.58-5.5 mg/cu m). According to the report, most samples were over 3.0 mg/cu m; however, no information on frequency and duration of sampling was given. In the department where the deaths occurred, 37 of 75 workers showed ECG changes, primarily of the T wave. There was only one death in 16 years preceding the use of antimony trisulfide, and there were no further deaths reported after the use of antimony trisulfide was discontinued.

Following the deaths, Brieger et al [15] exposed rats, rabbits, and dogs to the same dust present in the work environment. Rats and rabbits exposed at 3.07 and 5.6 mg/cu m, respectively, 6 hours/day, 5 days/week for 6 weeks appeared to be normal but showed definite and consistent ECG changes. The T

waves were especially affected. Dogs were exposed at 5.5 mg/cu m 7 hours/day, 5 days/week for 10 weeks; their ECG's were reported to suggest some myocardial injury, but the changes were not specified.

Klucik and Ulrich [11] found abnormal ECG's in workers exposed to antimony trisulfide and trioxide in a metallurgical plant. The ECG changes consisted of T wave depression, borderline normal QT waves, prolongation of atrioventricular and QRS transmission, and changes in the ST segment. All workers with ECG alterations also had symptoms that the authors [11] considered to be indicative of heart problems. The concentrations reported (1.3-237 g Sb/cu m) could have been a result of editorial error, sampling error, or may actually have been accurate measurements of extremely high concentrations. There was also known arsenic contamination.

These two studies [11,15], implicating antimony trisulfide and a mixture of antimony trisulfide and trioxide, are the only evidence of adverse effects on the heart in workers. Cooper et al [9] found no ECG changes in seven workers exposed to antimony trisulfide ore and antimony trioxide, although one case of slight bradycardia was noted. Karajovic [6] did not find ECG alterations among workers exposed to antimony trioxide and pentoxide dust that contained 0.3-0.9% arsenic trioxide. Investigators of other antimony compounds have not reported the measurement of worker ECG's [5,7,10,12,13,16]. In rats, Bradley and Fredrick [17] reported myocardial damage following exposure to antimony metal, antimony potassium tartrate, antimony tri- and pentasulfide, and antimony tri- and pentoxide. Bromberger-Barnea and Stephens [106] reported a progressive decrease in myocardial contractile force in open-chest preparation dogs that ended in death following a single 10-15 mg/kg iv dose of antimony sodium or potassium tartrate.

The evidence needed to characterize the effects of various antimony compounds on the heart is far from complete. A primary problem in these determinations is identifying what, if any, influence is exerted by arsenic. Industrial antimony compounds are generally contaminated with small amounts of arsenic, a substance also associated with myocardial damage and ECG changes [89-93]; thus, it is difficult to ascribe observed ECG changes in antimony workers to antimony itself.

Pharmaceutical grades of antimony, however, contain no significant amounts of arsenic; therefore, effects due to arsenic should not occur following exposure to these compounds. Unfortunately, no data are available on antimony exposures in pharmaceutical workers. However, it is highly significant that patients who received arsenic-free antimony drugs in treatment against parasitic infections [36-45,49-50] showed essentially the same ECG changes as those observed among the antimony workers [11,15], and in animals exposed to antimony compounds [15,17]. The common denominator in all of these situations was antimony.

(b) Effects on the Lungs

Both Renes [5] and Karajovic [6] reported respiratory illnesses accompanying dermatitis and mucous membrane irritation in the worker populations they studied. Renes stated that pneumonitis and bronchitis occurred in workers exposed to antimony trioxide at 0.40-70.7 mg/cu m. Karajovic reported that of 101 men working at an antimony smelter exposed to concentrations of mixed dust totaling 16-248 mg/cu m that included silica with

antimony oxides, 4 had tuberculosis and 22 had emphysema with bronchitis. These symptoms were probably more related to silica than to antimony exposure.

Karajovic conducted X-ray examinations of 62 of the workers, which revealed 14 cases of pneumoconiosis, all without fibrosis. Ventilatory function was normal in three workers, slightly reduced in four, and not tested in the remaining individuals. Antimony oxides, representing the bulk of the dust load, most likely caused the pneumoconiosis, but the cause of the slightly reduced ventilatory function is not clear.

McCallum [12,79] reported 44 cases of pneumoconiosis in 262 workers exposed to antimony trioxide and metal dusts at concentrations reported to exceed 0.5 mg/cu m. The pneumoconiotic workers seemed to be free of symptoms. Microscopic examination of a lung section from a deceased antimony worker showed an accumulation of dust and dust-laden macrophages lying in alveolar septa and perivascular tissues, but there was no fibrosis or inflammation [79]. This finding might be expected in most work situations where large amounts of dust are generated and inhaled.

Cooper et al [9] reported 3 definite and 5 suspicious cases of pneumonconiosis from a group of 28 workers exposed to antimony ore and antimony trioxide in concentrations ranging from 0.08 to 138 mg/cu m, with most exposures under 10 mg/cu m. Unspecified decrements in pulmonary function were observed in 4 of 14 workers tested, which presumably included the workers with pneumoconiosis.

Le Gall [7] reported pneumoconiosis in 10 of 40 workers exposed to 0.3-14.7 mg/cu m containing antimony metal and trioxide. Airborne silica and sulfur dioxide were also present. X-ray examinations showed moderate, dense reticulo-nodular formations scattered throughout the pulmonary fields. Shortness of breath, coughing, some expectoration, prolonged expiration, and sparse adventitious sounds were noted. Antimony dust was probably responsible for the pneumoconioses, though silica cannot be disregarded. One affected employee had worked only at the oxide furnace, where antimony exposure could be assumed to be high and silica exposure low or nonexistent [7].

Animal experiments have resulted in lung changes similar to those described in workers. Dernehl et al [102] found pneumonitis in guinea pigs exposed to antimony trioxide at concentrations averaging 45 mg/cu m for 33-609 hours. In addition, subpleural hemorrhages were seen with the heavier exposures. Lipoid pneumonia and pulmonary fibrosis were reported by Gross et al [105] in rats repeatedly exposed to antimony trioxide at 100-125 mg/cu m. Fibrosis has not been reported in humans following levels of exposure common to the occupational environment.

In describing the effects of high (1,700 mg/cu m) intermittent exposure to antimony trioxide or antimony ore on the lungs of rats, Cooper et al [9] noted dust-laden phagocytes lying free within the alveolar spaces or intermingled with cells of the septa. In some rats, the phagocytes formed focalized deposits throughout the lungs. These observations are similar to those of McCallum [79], who described the lungs of a deceased antimony worker. Macrophage reaction in rats was also noted by Levina and Chekunova [103] following intratracheal administration of 20 mg of antimony trioxide, trisulfide, or pentasulfide. Animal studies have not addressed the issue of

pulmonary function impairment, but the decrements noted in humans by several investigators [6,7,9] may suggest functional impairment of the lungs as a result of antimony exposure.

(c) Skin and Mucous Membrane Effects

Dermatitis and mucous membrane irritation are two prevalent complaints of antimony workers; arsenic, however, produces the same effects [87-89]. One author [81] considered arsenic wholly responsible for the observed skin condition. Opinions have differed as to whether the dermatitis was an allergic response [77] or due to local irritation [78,81].

Renes [5] recorded the full range of skin and mucous membrane effects among smelter workers exposed to antimony (0.40-70.7 mg/cu m) with concomitant exposure to arsenic (0.02-4.66 mg/cu m). Twenty percent of the workers had dermatitis, which was usually found in sweaty, hairy, friction areas of the body. Most cases occurred during a 1-week period of heavy exposure (LE Renes, written communication, March 1978). Numerous cases of irritation of the conjunctival, nasal, and respiratory mucous membranes, and ulceration of the nasal septum and larynx were also seen. Renes noted that many common early signs of arsenic intoxication were not present in these workers [5].

Karajovic [6], like Renes, described respiratory tract irritation, conjunctivitis, ulcerated nasal septa, and dermatitis in antimony smelter workers. The dermatitis was more prevalent during the summer months. Of 16 workers with skin problems, 13 worked at the blast furnaces in hot temperatures with resulting perspiration.

Stevenson [78] also pointed out the importance of heat in the occurrence of the dermatitis. Two furnacemen who worked with one side of their bodies next to heat had lesions only on that side. The major site of irritation in other workers was the antecubital area of the forearms where rubbing and perspiration occurred. Patch tests using dry antimony trioxide or antimony trioxide suspended in water produced no positive reactions. These findings are compatible with those of Thivolet et al [81], who observed that dermatitis was produced in patch tests with scarification, but not without scarification. Skin tests on rats and rabbits by Gross et al [108] showed no effects.

Microscopic examination of the lesions studied by Stevenson [78] showed them to be adjacent to sweat ducts. Stevenson noted that antimony trioxide is slightly soluble in water, but soluble in lactic acid, which is present in sweat in increased amounts following heavy exercise. He believed the dermatitis resulted from antimony penetrating the sweat ducts and causing local irritation of the underlying dermal tissues.

Although Paschoud [77] regarded the dermatitides as allergic, the local irritant response appears to be a more reasonable conclusion. The observed irritant effects appear to be attributable to antimony, even though arsenic may have been a factor.

(d) Effects on Blood

Exposure to antimony has been associated with blood profile alterations. Gallina and Luvoni [16] found evidence of slightly abnormal leukopoiesis in all six workers they studied who were exposed to antimony pentasulfide.

Metamyelocytes were present as 2-6% of the differential white cell counts, and monocytes were also elevated.

Thrombocytopenia and lymphocytosis in type foundry workers were noted by Seitz [24], and one case of slight anisocytosis in a worker exposed to antimony trioxide was reported by Oliver [10]. These two reports are more than 40 years old and probably represent high exposures.

Lowered white cell counts, a decrease in polymorphonuclear leukocytes, and lymphocytosis were found in guinea pigs following very heavy exposure to antimony trioxide (such that at least 293 mg was retained in the lungs), according to Dernehl et al [102]. Bradley and Fredrick [17] reported eosinophilia in rats that had received the LD50 dose of antimony.

Severe hemolysis occurred in three metal refinery workers exposed to a gaseous mixture containing unspecified high concentrations of stibine, arsine, and hydrogen sulfide, according to Nau et al [97].

Antimony therapy for schistosomiasis, which has involved very high therapeutic doses of antimony, has been linked to hemolytic anemia, thrombocytopenic purpura, and eosinophilia [56-58]. These cases are rare. It is significant that all human and animal blood changes that have followed exposure to antimony have involved extreme levels of exposure that would be unusual in the workplace.

(e) Hepatic Effects

Gallina and Luvoni [16] reported hepatic involvement in six workers exposed to a coloring mixture containing 1.04-1.74% antimony pentasulfide. The livers were enlarged in all cases and painful upon palpation in some. Urobilinuria was present in all six workers. Karajovic [6], however, noted a lack of liver symptoms among smelter workers. Antimony has not been implicated in liver involvement by other authors.

In animals, fatty degeneration of the liver was demonstrated by Dernehl et al [102] in rats retaining 77 mg or more of antimony trioxide. Bradley and Fredrick [17] found that the livers of nearly all LD50 experimental rats showed moderate periportal congestion. There was functional hypertrophy, with many hepatic cells appearing cloudy with finely reticulated cytoplasm. Plasma cells were found in the liver.

Elevated liver enzymes, SGOT and SGPT, in patients receiving antimony drugs [44,57,61,62] indicate that antimony may adversely affect the liver at therapeutic doses. Elevated SGOT and SGPT, however, may also indicate damage to the heart. ECG alteration was not correlated with SGOT elevations by Waye et al, indicating to them [44] that SGOT was a measure only of hepatic damage during antimony treatment. It was noted, however, that more frequent SGOT determinations might have revealed a higher incidence of SGOT elevation in patients showing ECG alterations [44]. Consequently, the effect of antimony on the liver remains unclear.

(f) Gastrointestinal Effects

Gastrointestinal effects related to occupational antimony exposure have not received extensive investigation, but have been mentioned in several

studies. Brieger et al [15] recorded a higher incidence of gastrointestinal ulcers in workers exposed at 0.58-5.5 mg antimony trisulfide/cu m than in unexposed workers. Renes [5] considered abdominal cramps, diarrhea, vomiting, dizziness, nerve tingling, and severe headaches to be systemic effects resulting from heavy exposure to antimony smelter fumes.

Gallina and Luvoni [16] noted malaise, nausea, frequent vomiting, abundant salivation, a pasty metallic taste, and diarrhea in six workers exposed to a mixture containing 1.04-1.74% antimony pentasulfide. The disturbances began 15-20 days after the introduction of the mixture and were thought to be systemic [16].

Gastrointestinal symptoms noted by Taylor [96] were also considered to be of systemic origin. Five of seven men exposed to high concentrations of antimony metal (up to 73 mg/cu m) and hydrochloric acid (up to 146 mg/cu m) experienced nausea, vomiting, abdominal pain, and anorexia. Because antimony in urine of five workers exceeded 1.0 mg/liter, and because the symptoms persisted for up to 10 days, systemic action is more probable than local irritant effects arising from ingestion of the chemical. The same symptoms have been observed following parenteral administration of antimony drugs [35,37,43,47,56,58].

Carcinogenicity, Mutagenicity, Teratogenicity, and Effects on Reproduction

Firm conclusions cannot be drawn from the Davies [14] report suggesting an increased tendency to contract lung cancer in antimony workers. A retrospective survey was undertaken in 1962 following the lung cancer death of an antimony worker and the subsequent discovery of seven other lung cancer deaths among antimony workers in the preceding 8 years. Of 1,081 people formerly employed at the factory in question, 56 were known to be dead. Ten of these deaths were ascribed to lung cancer; 8 were to be expected from local mortality rates. Nine of the ten lung cancer deaths occurred among the factory subgroup engaged in smelting or related activies; 5.7 lung cancer deaths were to be expected in this group.

Recent followup information (KP Duncan, written communication, July 1978) again showed a disparity between observed and expected deaths due to lung cancer in the antimony factory population (21 vs 14.03), most of which occurred in the factory subgroup engaged in smelting and related activities (18 vs 10.25). The difference was especially prominent in workers 45-64 years old (13 vs 7.22). The absence of pertinent information, including community and factory population descriptions, data analysis, and environmental, blood, and urine antimony concentrations make it impossible to accept the findings without further scientific evaluation and confirmation.

Erusalimski and Suspa [116] reported that when the carcinogen 3,4 benzo(a)pyrene was injected simultaneously with antimony into rats, it was taken up by the lungs in greater amounts than in animals treated with benzo(a)pyrene alone.

Kanisawa and Schroeder [117] reported no increase in the incidence of tumors in mice given 5 μg antimony potassium tartrate/ml of drinking water throughout their lifetimes. Further animal studies to evaluate the cancer potential of antimony are in progress under a NIOSH contract.

Evidence of effects of antimony on reproduction is confined to a single report by Belyaeva [13]. A group of 318 antimony-exposed female workers was stated to have had higher incidences than controls of late-occurring spontaneous abortions (12.5% vs 4.1%), premature births (3.4% vs 1.2%), and gynecologic problems (77.5% vs 56%), which included menstrual cycle disorders, inflammatory disease, and other diseases of the reproductive apparatus. Inflammatory disease was the only category in which there were more cases among controls than exposed women, an unexplained finding. Exactly what constituted a menstrual cycle disorder was not stated.

The antimony workers studied by Belyaeva were exposed to mixed dusts of antimony metal, trioxide, and pentasulfide. Exposure duration and concentrations were not given, but concentrations of antimony in the blood of the exposed workers ranged from 0.5 to 20.0 mg/100 ml, and, in the urine, from 0.5 to 18.2 mg/100 ml [13]. These levels are probably common among antimony workers.

Antimony was also found in the breast milk, placental tissue, amniotic fluid, and umbilical cord blood of the exposed group, indicating the presence of antimony in the developing fetus, as well as in the mother [13]. Belyaeva noted that antimony affected the taste of breast milk, a possible explanation for differences in mean weight of babies in control and exposed groups at 1 year of age, assuming that breastfeeding was practiced. There was no followup of the children to ascertain trends in weight gain after the period of breastfeeding.

Belyaeva's [13] animal studies supported the findings of human reproductive effects due to antimony. Rats given metallic antimony in a single ip dose of 50 mg/kg showed decreased ability to conceive, produced fewer offspring, and showed microscopic uterine and ovarian changes that were believed to complicate normal development of ova. Rats repeatedly exposed by inhalation to antimony trioxide at 250 mg/cu m produced fewer offspring than controls, but no clearly expressed changes were seen in the reproductive organs. The offspring of treated rats were unaffected.

The high control figures reported by Belyaeva [13] for the category of gynecologic problems were unexplained. Reproductive effects ascribed to antimony have apparently not been studied by other investigators and need to be confirmed. Casals [113] reported that no antimony was detected in rat fetuses whose mothers had received im antimony dextran glycoside during gestation; these results tend to conflict with those of Belyaeva. However, Bradley and Fredrick [17] noted frequent abortions in rabbits given repeated high oral doses of metallic antimony.

Summary Tables of Exposure and Effect

The effects of short- and long-term exposures to antimony on humans and animals, presented in Chapter III, are summarized in Tables III-13, III-14, and III-15. Human data appear in Tables III-13 and III-14 and animal toxicity data are listed in Table III-15.

TABLE III-13

EFFECTS OF OCCUPATIONAL EXPOSURE TO ANTIMONY

Compound and Ref. No.	Concentration mg/cu m (particle size)	Duration	Sb in Urine, mg/l	Effects
		Inhalation		
Antimony trisulfide [15]	0.58-5.5	8-24 mo	0.8-9.6	ECG changes, cardiac deaths, ulcers
Antimony pentasulfide [16]	NR*	15-20 d	.03-.24	GI upset, hepatic involvement, blood profile alterations
Antimony trisulfide and antimony trioxide [11]	1.3-237 g/cu m (sic)	NR	NR	ECG changes, hard breathing, weakness, sweating, cough, chest pain
Antimony trisulfide, metal, and trioxide [13]	NR	NR	5-182	Female reproductive problems, infant weight gain lower than normal
Antimony trioxide [5]	0.40-70.7 (most <1 μm)	<6 mo	Trace-600	Skin and mucous membrane irritation, respiratory illness, GI disturbance
Antimony trioxide and pentoxide, arsenic trioxide (also silicon) [6]	16-248 for antimony (most <0.5 μm)	NR	.025	Skin and mucous membrane irritation, tuberculosis
Antimony trioxide and antimony metal [12]	<0.5 (<1 μm)	NR	.425-.68	Pneumoconiosis, skin irritation

TABLE III-13 (CONTINUED)

EFFECTS OF OCCUPATIONAL EXPOSURE TO ANTIMONY

Compound and Ref. No.	Concentration mg/cu m (particle size)	Duration	Sb in Urine, mg/l	Effects
		Inhalation		
Antimony trioxide, antimony ore [9]	0.081-138	1-15 yr	.007-1.02; most .07-.8	Pneumoconiosis
Antimony trioxide [8]	NR (<1 μm)	.5-35 yr	NR	"
Antimony oxide (also silica, SO2) [7]	0.3-14.7 (most <3 μm)	NR	Undetected	"
Antimony trioxide [14]	NR	NR	NR	Possible increased risk of lung cancer
" [10]	NR	2-13 yr	Undetected	Mild dermatitis, slight anisocytosis
" [82]	0.3-56 (0.57-1.46 μm)	NR	.052-1.02	No effects
Antimony trichloride and HCl [96]	73 146	Several min-8 hr	>1	Respiratory tract irritation, gastro-intestinal symptoms
		Skin Contact With Liquid		
Antimony pentachloride [95]	-	One-time	NR	2nd and 3rd degree burns, respiratory distress

*NR-Not reported

TABLE III-14

EXPERIMENTAL AND THERAPEUTIC EFFECTS OF ANTIMONY ON HUMANS

Compound and Ref. No.	Dose, mg	Duration	Effects
	Experimental Patch Tests		
Antimony trioxide (arsenic contaminant) [77]	-	-	Dermatitis
" [81]	-	-	Dermatitis with scarification, none without
Antimony trioxide (0.29% arsenic) [82]	-	-	No effects
	Therapeutic		
Antimony potassium tartrate [50]	Therapeutic dose	-	Death, liver damage
Antimony tartrate (K or Na) [37]	522-913	10-41 d	ECG changes
Antimony tartrate (K or Na) stibophen, or anthiolimine [64-66]	Therapeutic dose	-	Rise of Herpes zoster infections
Antimony sodium tartrate [56]	"	-	Hemolytic anemia
" [58]	"	-	Thrombocytopenic purpura
Antimony dimercaptosuccinate [57]	"	-	Eosinophilia, elevated SGOT, ECG alteration
n-Methyl glucamine antimonate [63]	"	-	Nephritis
Trivalent organic antimony [52]	214-510 iv	2-9 d	ECG changes
Pentavalent organic antimony [52]	4,950-19,350 iv	5-10 d	No ECG changes

TABLE III-15

EFFECTS OF ANTIMONY ON ANIMALS

Compound	Species	Dose or Exposure	Effects	Ref. No.
Antimony potassium tartrate Antimony metal Antimony trisulfide Antimony pentasulfide Antimony trioxide Antimony pentoxide	Rat	11 mg/kg 100 mg/kg 1000 mg/kg 1500 mg/kg 3250 mg/kg 4000 mg/kg	All LD50's, myocardial failure, liver damage, eosinophilia, splenic changes with metal and tartrate	[17]
Antimony potassium tartrate Antimony metal Antimony trisulfide Antimony pentasulfide Antimony trioxide Antimony pentoxide	"	Single sublethal ip dose	Chronic heart changes, liver damage with tartrate	[17]
Antimony sodium or potassium tartrate	Dog	10-15 mg/kg single iv dose	Progressive decrease in myocardial contractile force, then death	[106]
Antimony potassium tartrate	Mouse	5 μg/ml drinking water for lifetime	No increase in incidence of tumors	[117]
Antimony trisulfide	Rat, dog, rabbit	3.07-5.6 mg/cu m 7 hr/d, 5 d/wk, for 6 wk	Heart disorders in rats and rabbits	[15]
Metallic antimony	Rat	50 mg/kg single ip dose	Failure to conceive, fewer offspring, changes in reproductive organs in females	[13]
"	"	5 cc single intratracheal dose	Increased uptake of carcinogen 3,4 benzo-a-pyrene in lungs	[116]
"	"	5 ip injections totaling 300 mg/kg	Higher antimony levels in blood, lungs, muscles, and skin of tumorous rats than in controls	[115]

TABLE III-15 (CONTINUED)

EFFECTS OF ANTIMONY ON ANIMALS

Compound	Species	Dose or Exposure	Effects	Ref. No.
Metallic antimony	Rabbit	5-55 mg orally every other day for 30, 60, 90 d Larger doses	No effects Frequent abortions	[17]
Antimony trifluoride	Rat	2.5-20 mg single intratracheal dose	Labored breathing, convulsions, death	[103]
"	"	1.0-1.5 mg single intratracheal dose	Lung edema	[103]
"	"	15 mg/kg 25 sc doses over 1 mo	Liver, kidney damage	[103]
Antimony trioxide or trisulfide	Rat	20-mg single intratracheal dose	Weight reduction, macrophage reaction	[103]
Antimony trioxide	Guinea pig	av 45.4 mg/cu m 33-609 hr	Pneumonitis, subpleural hemorrhage	[102]
"	"	av 45.4 mg/cu m 138-609 hr	Liver degeneration, splenic damage, blood profile alterations	[102]
"	Rat	100-125 mg/cu m 25 hr/wk 14.5 mo	Lipoid pneumonia	[105]
Antimony ore	"	1,700 mg/cu m 1 hr/2 mo over 66-366 d	Acute pulmonary congestion, phagocytic response	[9]
Antimony trioxide	"	1,700 mg/cu m 1 hr/2 mo over 66-311 d	"	[9]
"	"	165 mg sc 5 times/wk over 3 mo	Habituating effect on adrenals and biologic amines, biochemical imbalance in liver and brain	[107]
"	"	250 mg/cu m 4 hr/d 7 d/wk, 1.5-2 mo	Fewer offspring, lung, liver, kidney and pancreatic changes	[13]

TABLE III-15 (CONTINUED)

EFFECTS OF ANTIMONY ON ANIMALS

Compound	Species	Dose or Exposure	Effects	Ref. No.
Antimony trioxide <2% arsenic	Rabbit	1.5 mg/d to eyes for 1, 2, or 7 d	No effects	[108]
"	"	25 g to skin for 1 wk	"	[108]
"	Rat	1 g into wound	Healed slowly	[108]
"	Rat, Rabbit	100 mg on wound for 1, 2, or 4 wk	No effects	[108]
Antimony dextran glycoside	Rat	125 or 250 mg/kg of mother's weight im 5 times between days 8 and 14 of gestation	No fetal abnormalities, no antimony detected in fetuses	[113]