Public Health Goal for Antimony in Drinking Water

Prepared by
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

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**LIST OF CONTRIBUTORS**

<table>
<thead>
<tr>
<th>PHG PROJECT MANAGEMENT</th>
<th>REPORT PREPARATION</th>
<th>SUPPORT</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Project Director</strong></td>
<td><strong>Author</strong></td>
<td><strong>Administrative Support</strong></td>
</tr>
<tr>
<td>Anna Fan, Ph.D.</td>
<td>Lubow Jowa, Ph.D.</td>
<td>Hermelinda Jimenez</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Michael Baes</td>
</tr>
<tr>
<td><strong>PHG Program Leader</strong></td>
<td><strong>Primary Reviewers</strong></td>
<td><strong>Library Support</strong></td>
</tr>
<tr>
<td>Robert Howd, Ph.D.</td>
<td>.</td>
<td>Janet Rennert</td>
</tr>
<tr>
<td></td>
<td>.</td>
<td></td>
</tr>
<tr>
<td><strong>Comment Coordinator</strong></td>
<td><strong>Final Reviewers</strong></td>
<td><strong>Website Posting</strong></td>
</tr>
<tr>
<td>Michael Baes</td>
<td>Anna Fan, Ph.D.</td>
<td>Charleen Kubota, M.L.S.</td>
</tr>
<tr>
<td></td>
<td>George Alexeff, Ph.D.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Robert Howd, Ph.D.</td>
<td>Laurie Monserrat</td>
</tr>
</tbody>
</table>
PREFACE

Drinking Water Public Health Goals
Pesticide and Environmental Toxicology Branch
Office of Environmental Health Hazard Assessment
California Environmental Protection Agency

This Public Health Goal (PHG) technical support document provides information on health effects from contaminants in drinking water. PHGs are developed for chemical contaminants based on the best available toxicological data in the scientific literature. These documents and the analyses contained in them provide estimates of the levels of contaminants in drinking water that would pose no significant health risk to individuals consuming the water on a daily basis over a lifetime.

The California Safe Drinking Water Act of 1996 (Health and Safety Code, Section 116365) requires the Office of Environmental Health Hazard Assessment (OEHHA) to perform risk assessments and adopt PHGs for contaminants in drinking water based exclusively on public health considerations. The Act requires that PHGs be set in accordance with the following criteria:

1. PHGs for acutely toxic substances shall be set at levels at which no known or anticipated adverse effects on health will occur, with an adequate margin of safety.

2. PHGs for carcinogens or other substances that may cause chronic disease shall be based solely on health effects and shall be set at levels that OEHHA has determined do not pose any significant risk to health.

3. To the extent the information is available, OEHHA shall consider possible synergistic effects resulting from exposure to two or more contaminants.

4. OEHHA shall consider potential adverse effects on members of subgroups that comprise a meaningful proportion of the population, including but not limited to infants, children, pregnant women, the elderly, and individuals with a history of serious illness.

5. OEHHA shall consider the contaminant exposure and body burden levels that alter physiological function or structure in a manner that may significantly increase the risk of illness.

6. OEHHA shall consider additive effects of exposure to contaminants in media other than drinking water, including food and air, and the resulting body burden.

7. In risk assessments that involve infants and children, OEHHA shall specifically assess exposure patterns, special susceptibility, multiple contaminants with toxic mechanisms in common, and the interactions of such contaminants.
8. In cases of insufficient data for OEHHA to determine a level that creates no significant risk, OEHHA shall set the PHG at a level that is protective of public health with an adequate margin of safety.

9. In cases where scientific evidence demonstrates that a safe dose response threshold for a contaminant exists, then the PHG should be set at that threshold.

10. The PHG may be set at zero if necessary to satisfy the requirements listed above in items seven and eight.

11. PHGs adopted by OEHHA shall be reviewed at least once every five years and revised as necessary based on the availability of new scientific data.

PHGs are not regulatory requirements, but instead represent non-mandatory goals. Using the criteria described above, PHGs are developed for use by the California Department of Public Health (DPH) in establishing primary drinking water standards (State Maximum Contaminant Levels, or MCLs). Thus, PHGs are not developed as target levels for cleanup of ground or ambient surface water contamination, and may not be applicable for such purposes, given the regulatory mandates of other environmental programs.

Whereas PHGs are to be based solely on scientific and public health considerations, drinking water standards adopted by DPH are to consider economic factors and technical feasibility. Each primary drinking water standard adopted by DPH shall be set at a level that is as close as feasible to the corresponding PHG, with emphasis on the protection of public health. Each primary drinking standard adopted by DPH is required to be set at a level that is as close as feasible to the corresponding PHG, with emphasis on the protection of public health. MCLs established by DPH must be at least as stringent as the federal MCL, if one exists.

Additional information on PHGs can be obtained at the OEHHA Web site at www.oehha.ca.gov.
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PUBLIC HEALTH GOAL FOR ANTIMONY IN DRINKING WATER

SUMMARY

A Public Health Goal (PHG) of 0.0007 mg/L or 0.7 parts per billion (ppb) is proposed for antimony in drinking water, based on data from use of antimonials in medical practice. In 1997, the Office of Environmental Health Hazard Assessment (OEHHA) developed a PHG for antimony of 20 ppb in drinking water, based on extrapolation from effect levels in rats. The original PHG has been reviewed and revised to reflect the large body of human data available from the medical literature, based primarily on the knowledge of 19th century physicians regarding effectual and ineffectual doses of antimonyl potassium tartrate (tartar emetic), a common drug used at the time. We describe a critical experiment conducted during this medicinal use period to illustrate these effects as well as for risk assessment purposes. In this study an experienced clinician in the mid-nineteenth century reported detailed observations on the results of administering doses to himself (a healthy adult) in a graded fashion, starting with a tartar emetic dose that caused no clinical effects for five days, and continuing through several days of increasing doses and increasing severity of effects from mild diaphoresis, leading to emesis. His observations are supported by an extensive database on clinical observations in both adults and children from the earliest reported effects from the 15th century to the present. These data indicate that humans are substantially more sensitive to antimony exposure than are rodents.

Humans who ingest large amounts of antimony have severe stomach upset, resulting in vomiting. Antimony fumes and dusts inhaled by workers are associated with the development of benign tumors of the lungs, dermatitis and less commonly, effects on the heart and kidneys. There is limited evidence to suggest that antimony compounds cause malignant tumors by inhalation in humans or animals. By ingestion, there is no evidence that antimony compounds are associated with increased development of tumors.

The original PHG for antimony was based on minor clinical signs and a slight decrease in longevity noted in a chronic oral study conducted in rats. However, the rodent study has many deficiencies that give us low confidence in its applicability for the risk assessment, as we acknowledged earlier. Most experimental studies have been conducted in animals, particularly in rodents. Unfortunately, rodents are not a good model for emetic effects and many other symptoms reported in humans, including diaphoretic, cardiac and respiratory effects. We searched more widely for information that could be used for risk assessment, and found that the historical data on antimony usage in humans provide several advantages over the data derived from rodents.

Antimony-containing compounds, particularly antimonyl potassium tartrate (tartar emetic), were used in clinical medicine for hundreds of years. During the 19th century treatment, lethal and emetic doses were well-known, and approximate doses for milder health conditions were recommended. Tartar emetic use was phased out, including its use as an emetic, toward the end of the 19th century, in favor of safer and more efficacious medicines. From textbooks of the period, the range of doses for adults and
children which produced minimum clinical effects such as mild congestion in the head, sweating, headaches, to slight GI upset were identified: 1.4 mg of antimony/day for adults and 0.9 mg/day for small children.

The doses that the clinician discussed above administered to himself began at 0.22 mg/day for five days, with no effects. The next day the dose was tripled to 0.65 mg, and mild effects (congestion) occurred on the first day this higher dose was administered. The dose the first five days is estimated as 0.0031 mg/kg-day (using a default value for body weight of an adult male of 70 kg). This no observed adverse effect level (NOAEL) is consistent with a wide variety of other human reports from the literature of the period. The proposed PHG of 0.0007 mg/L or 0.7 ppb has been derived by applying an uncertainty factor of ten to estimate human population variation, a factor of ten for extrapolation from subacute to lifetime exposure, and an adult water consumption rate of 0.044 L/kg-day.

The Maximum Contaminant Level Goal (MCLG) and the Maximum Contaminant Level utilized by the U.S. Environmental Protection Agency (U.S. EPA) for antimony in drinking water are both 6 ppb. The MCL and the Detection Limit for the Purpose of Reporting (DLR) of the California Department of Public Health (DPH) for California regulatory purposes are also both 6 ppb.

INTRODUCTION

Antimony is an element present in relatively small concentrations in the earth’s crust. It is rarely found in pure form in nature, a fact recognized since antiquity. This may be the source of the name, which comes from the Greek words “anti” (not) and “monos” (alone). Antimony compounds are found in several types of ore and in petroleum. Although not used in large quantities, antimony is used extensively for many purposes, including being alloyed with a number of metals to improve their properties. By far the most significant use of antimony is for the production of antimony trioxide for flame retardation (ATSDR, 1992; Butterman and Carlin, 2004).

Antimony has been used since antiquity as a medicinal, to induce emesis and to treat other conditions, as well as in cosmetics. However, little was understood concerning antimony toxicity until major processing of ore began at around the turn of the 20th century and specific toxic effects were noticed in workers processing antimony. These effects included “antimony spots” a form of dermatitis; later, respiratory, pulmonary and heart effects were noted, and cancer was suspected. The U.S. EPA has a reference dose (RfD) for antimony of 0.4 µg/kg-day (IRIS, 2007; last updated 02/01/1991) derived from a study of potassium antimony tartrate administered to rats in drinking water at 5 ppm. The federal and state MCL for antimony of 6 ppb is based on this study. In 1997, OEHHA published the first PHG for antimony of 20 ppb. Since that time the World Health Organization (WHO, 2003) has published a Guideline for antimony in drinking water of 20 ppb as well. We have reviewed the earlier PHG on the basis of newly found studies and revised interpretations of studies reviewed earlier.
CHEMICAL PROFILE

**Chemical Identity**

Antimony is a metalloid residing in the fourth row of group 15A in the periodic table between arsenic and bismuth. It has four oxidation states: Sb(-3), (0), (+3), (+5) and two stable isotopes of atomic weights 121 (57 percent) and 123 (43 percent). Antimony in its elemental form is a silvery white, brittle, fusible, crystalline solid that exhibits poor electrical and heat conductivity properties and can sublimate upon heating. A metalloid, antimony resembles a metal in its appearance and in many of its physical properties, but does not chemically react as a metal. It is also attacked by oxidizing acids and halogens (CRC, 1989). Metallic antimony is insoluble and inert at room temperature, but can burn when heated, forming white fumes of Sb₂O₃. Antimony compounds are soluble in very strong acid and basic solutions; under neutral conditions the predominant species is Sb(OH)₆ for pentavalent forms and Sb(OH)₃ for trivalent forms. Antimony is not readily convertible between its two cationic forms under neutral conditions (ATSDR, 1992).

Antimony is geochemically found in the common ore stibnite, which is primarily Sb₂S₃. The substance has been used since antiquity as a cosmetic to darken eyebrows. In ancient Egypt it was called “mâdmt” (variant mesdemet) which is derived from the Coptic CTDM [stem]. The Greeks borrowed that and called it στιμι [stimi] or στιβι [stibi] basically meaning a “mark.” The Latin name of stibium is derived from the Greek, and is also the source of the chemical symbol, Sb. The Arabic designation “uthmod” or “al-ithmid” is postulated to be the basis for the latinized medieval/ alchemical designation of “athimodium,” “atimodium,” “atimonium,” and “antimonium” (Van der Krogt, 2007), although the explanations for the term antimony are very speculative. The term “antimonium” was first mentioned by Constantinius Africanus (circa 1050) (McLean, 2007). The Arabic designation for stibnite is “kohl.”

**Physical and Chemical Properties**

A summary of the chemical and physical properties of antimony is presented in Table 1.

<table>
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<th>Table 1. Chemical and Physical Properties of Antimony (ACGIH, 1991; ATSDR, 1992; Wikipedia, 2007)</th>
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<td><strong>Antimony (Sb)</strong></td>
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<tr>
<td>Atomic number: 51</td>
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<tr>
<td>Atomic weight: 121.75</td>
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<tr>
<td>Specific gravity: 6.68</td>
</tr>
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**Diagram:**

- Semi-metal
- Arsenic-Bismuth series
Melting point: 630.5°C
Boiling point: 1,750°C
Solubility: Insoluble in water and cold, dilute acids
Appearance: silvery, grey metal
Crystal structure: rhombohedral
Oxidation states -3, 0, +3, +5
Natural Occurrence 0.2-0.5 ppm in earth’s crust
CAS Registry #: 7440-36-0
Isotopes:
\[ ^{121}\text{Sb} \text{ 57.36 percent Sb is stable with 70 neutrons} \]
\[ ^{123}\text{Sb} \text{ 42.64 percent Sb is stable with 72 neutrons} \]
\[ ^{125}\text{Sb} \text{ is unstable (t}_{1/2} \text{ 2.76 years) with 74 neutrons; numerous other isotopes are known with shorter half-lives.} \]

Some notable antimony compounds:
Antimony trioxide: \( \text{Sb}_2\text{O}_3 \)

Solubility: Very slightly soluble in water, soluble in acetic and hydrochloric acids

Antimony potassium tartrate: \( \text{Sb}_2\text{K}_2(\text{C}_4\text{H}_2\text{O}_6)_2\ 3\text{H}_2\text{O} \)

Solubility: Very soluble in water (83 g/L), insoluble in alcohol (Merck, 1996)

Stibine: \( \text{SbH}_3 \)
Form: Gas

Production and Uses
Antimony sulfides have been used as pigments, especially for cosmetic purposes, for over 5,000 years. Red Antimony, \( \text{Sb}_2\text{S}_2 \), comes from kermasite ore used in the Egyptian Old Kingdom (6th dynasty from 2352-2181 BCE). Egyptian Queen Hatshepsut negotiated land to obtain antimony deposits (Bencze, 1994). Another significant antimony pigment is stibnite “Black Antimony,” \( \text{Sb}_2\text{S}_3 \), a metallic grey-black form of antimony used as eyeliner or mascara. This pigment appeared to be extensively used, as evidenced by facial displays of personages of the Pharonic era. Antimony occurs in the Bible (II Kings 9:30) with reference to Queen Jezebel “painting her eyes” in Jerome’s Vulgate version, which uses the word “stibi” to refer to Jezebel’s painting her eyes. However the word “kohl,” representing antimony, is not present in the original Hebrew. Rather, “kohl” is used in another reference from the Old Testament in the Book of Ezekiel addressing another eye painting situation. The ancient Greek physician Dioscorides (Wang, 1919) called this metal or\( \text{rif\text{iu}}, \) and mentioned that it was known also by \text{irkarvo}^\text{\textmaci\textmaci} \text{OaXf}xov (meaning "eye-expander"), \text{yvwatKetov} (meaning "womankind"). Dioscorides, the author of \text{De Materia Medica}, the precursor to all modern pharmacopeias, also mentioned that the roasting of crude antimony could be done in a current of air under moderate heat until it burnt, and that if it were heated more strongly it would melt like lead. This statement might suggest the idea that he was acquainted with the metal itself. Antimony in preparations known as “kohl” continues to be used in various cosmetic preparations to
this day (Alkofahi et al., 1989). However, kohl is also commonly made with lead in some parts of the world, and this form is prohibited in the U.S. because of the dangers of lead exposure (Al-Ashban et al., 2004; U.S. FDA, 2006).

Abir ibn-Hayyan (c. 760-c.815), who was known to Europeans centuries later as “Geber,” wrote about antimony, as did Persian alchemist Al-Razi (c.850-c.925), later known to Europeans as “Rhazes,” who studied and described metallic antimony (Wang, 1919; Wikipedia, 2007).

For art work, several antimony-based pigments have been used; one is Naples yellow SbPb or lead (II) antimonite, used in painting by the old masters from the 16th to the early 20th century until replaced by less hazardous pigments. Other pigments still used include Permanent Orange, a pyrazolone antimony pigment, and nickel-antimony titanate (yellow) (Eastaugh et al., 2004; Wikipedia, 2007).

Early uses of antimony included tableware. An antimony vessel was recovered dating from 3000 BCE. Antimony was also present in significant quantities in tableware referred to as “Britannia metal,” an antimony-tin alloy. In the colonial period this metal was used in eating utensils, candlesticks and figurines; more recently, its most prominent use has been in Hollywood’s Oscar statues (Roscoe and Schorlemmer, 1880; Fendelman and Rosson, 2007; Wikipedia, 2007).

The earliest known account of antimony compounds used as medicinals is from Pliny the Elder (Pliny, 1st century BCE), who described using antimony to make eyelashes grow. Furthermore, although not exactly a “medicinal use,” the Romans used wine stored in antimony containing vessels (calices vomitorum) to purge themselves as they partook of Lucullian feasts (Bencze, 1994). Later, medicinal uses were described in a treatise attributed to medieval scientist Roger Bacon (Bacon, unknown), by the monk Basil Valentine (Latin Basillus Valentinus) in the 16th century, and by Paracelsus in Opera omnia published in 1556 (McCallum, 1989). These medicinals were principally antimonial compounds, including possibly tartar emetic (antimony potassium tartrate) and lead sibocaptate used in the treatment of schistosomiasis (Roscoe and Schorlemmer, 1880; McCallum, 1989). Antimony tartrates have been used even more recently in the treatment of bilharziasis (schistosomiasis) (ATSDR, 1992; U.S. EPA, 1995). Pentavalent antimonials were used to treat leischmaniasis. These uses have been largely superseded by better compounds as the parasites appear to develop resistance to the antimonials.

Very popular with alchemists, antimony was referred to as Lupus metalorum or grey wolf, for its reputed magical properties (Iavicoli et al., 2006). Considered as an important intermediary in the conversion/transmutation to gold, it was regarded as a super type of mercury. Alchemists recognized that antimony could be either harmful or beneficial (Bacon, Valentine and others, elucidated in the human toxicology section). The misuse or perhaps impure preparations of tartar emetic resulted in judicial action in France in the 16th century, in which a prohibition was enacted against the use of antimonial drugs, dated 1566 (Iavicoli et al., 2006). This was rescinded about a hundred years later only to be reinstated with the cautionary proviso that the emetic be used under a physician’s care. Antimonials remained popular medicines for the next couple of centuries, until the 20th century, whereupon their use greatly diminished. Homeopathic formulations of tartar emetic are still being promoted for many purported uses (in
extreme dilutions). More information concerning the medicinal use of antimony is presented in the human toxicology section of this document.

Pure metallic antimony is a silvery white, strong but brittle metal that rarely occurs naturally. Because antimony metal is too brittle to be used alone, it is used in alloys with other metals to significantly increase their hardness, mechanical strength, corrosion resistance and electrochemical stability or decrease their coefficient of friction. Most metallic antimony produced (55 percent) goes into grid metal in lead storage batteries. Other uses include solder, sheet and pipe metal, type metal, castings, ammunition and pewter (ATSDR, 1992).

Antimony trioxide (+3 antimony), a white powder, is the single most important economic form, used primarily as a fire retardant. It is a stable substance that is not volatile and dissolves in water slightly. According to Butterman and Carlin (2004), “More than one-half of the primary antimony consumed in the United States goes into flame retardants. The remainder is used principally in glass for television picture tubes and computer monitors, in pigments, in stabilizers and catalysts for plastics, and in ammunition, cable covering, friction bearings, lead-acid (LA) batteries, and solders. It is used in the same applications worldwide, but its distribution among applications differs from country to country.”

Stibine, SbH3, the only form of antimony in the (-3) state, is a gaseous antimony compound formed by the action of acids on metal antimony alloys or during the electrolysis of acid/base solutions where antimony is present in the cathode. Release of stibine is reported with the overcharge of lead acid batteries. Other stibine-related, reduced and methylated antimony compounds may be produced by microorganisms in the aquatic environment (ATSDR, 1992).

Sources

The principal sources of antimony are antimony-laden ores (Wang, 1919). The most common is antimony glance: Sb2S3 (stibnite, grey antimony ore, antimonite); then, valentinite, Sb2O3, also known as “white antimony” or “antimony bloom,” a rhombic-shaped crystal of the oxide of antimony; senarmonite, Sb2O3, a cubic form of the oxide of antimony; kermesite, 2Sb2S3O3, also known as antimony oxysulphide, “red antimony ore” or “antimony blend,” and pyrostibite; cervantite, Sb2O4, also known as “antimony ochre.”

Over 80 percent of the world’s antimony is mined in China (Bencze, 1997; ATSDR, 1992; Wikipedia, 2007), followed by Russia, South Africa, Tajikistan, and Bolivia.

ENVIRONMENTAL OCCURRENCE AND HUMAN EXPOSURE

Releases to the environment of antimony and its compounds occur from natural discharges as windblown dust, volcanic eruption, sea spray, forest fires and other natural processes. Anthropogenic sources include mining and processing of ores and the production of antimony metal, alloys, antimony oxide, and compounds containing
antimony and recycling and incineration of antimony containing products. Toxic Release Inventory (TRI) data (1987 to 1993) indicate that approximately 12 million pounds of antimony were released during that period to the land and 330,000 pounds to the water from anthropogenic sources (U.S. EPA, 1995).

**Air**

Virtually no antimony ore is mined in the United States. Imports of antimony ore for processing and smelter operations have been steadily increasing and appear to be primarily from China. Recycling operations to recover antimony from lead acid batteries, type metal and bearings have become as significant a source of antimony in the U.S. as smelting. Antimony volatilizes during combustion processes, but subsequently condenses on suspended particulate matter of less than 1 μm in size. These fine particles remain suspended in the atmosphere for long periods of time (in days) and can be widely distributed. The range of airborne antimony concentrations measured in the U.S. in remote, rural and urban areas is 0.0045 to 1, 0.6 to 7 and 0.5 to 171 ng/m³, respectively (ATSDR, 1992). Studies of antimony in ice cores in Canada and in lake sediments in Sweden showed that antimony levels have increased significantly since the industrial revolution, presumably from dust deposition (Krachler *et al.*, 2005; Grahn *et al.*, 2006).

U.S. EPA estimated that 4,000 workers are exposed to high concentrations of antimony in processing and production facilities. The highest exposure level reported in workplace surveys was 6.2 mg/m³ (ATSDR, 1992).

Soil methylation of antimony by microbes has been reported, with the resultant antimony products being made airborne (Bentley and Chasteen, 2002). This appears to be a very minor process compared to the amount of methylation that occurs with arsenic. Stibine, a very toxic gaseous compound of antimony (SbH₃), can also be released by the action of microorganisms.

**Soil**

Antimony is not especially abundant in the earth’s crust and soil concentrations range from less than 1 to 8.8 ppm, with a mean of 0.48 ppm (ATSDR, 1992). Even at old mining and smelting sites, most of the antimony is immobile due to the low solubility of the common antimony compounds (Flynn *et al.*, 2003).

**Water**

Very low concentrations of antimony are found in pristine ambient waters. Dissolved antimony concentrations in 3 mountain watersheds in Switzerland, representing different lithogenic origins, were 0.13, 0.08, and 0.16 ppb (Nirel *et al.*, 2008). Groundwater samples from Ontario, Canada, averaged 0.002 ppb (Shotyk *et al.*, 2005). Antimony is transported into streams mostly from soil runoff. In a USGS survey of dissolved antimony in surface waters, only 70 of 1077 measurements were above the detection limit of 5 ppb. The geometric mean of the values above 5 ppb was 12 ppb (HSDB, 2008).
Mean antimony concentrations of surface and ground water at various hazardous waste sites were 27 and 35 ppb, respectively.

Antimony occurs predominantly in the pentavalent state in aerobic fresh water and sea water. The trivalent state is more common under anaerobic conditions. Some soluble forms of antimony are quite mobile in water (antimony potassium oxalate and antimony potassium tartrate) and do not precipitate out into the sediment (Callahan et al., 1979). Furthermore, it has been demonstrated that anaerobic microorganisms in the sediment of aqueous environments may release methylated antimony compounds that are volatile (ATSDR, 1992).

Ninety percent of the worldwide manufacture of polyethylene terephthalate (PET), a polyester of terephthalic acid and ethylene glycol, employs Sb\textsubscript{2}O\textsubscript{3} as a catalyst (Shotyk et al., 2006). Antimony levels in pristine Canadian ground water, averaging 0.002 ppb Sb were compared against 12 brands of Canadian water bottled in PET. The bottled waters averaged 1.6 ppb Sb, and three brands of deionized water, also bottled in PET, averaged 0.2 ppb. Levels were higher in imported German bottled water. A single lot of German bottled water, originally analyzed at 0.36 ppb antimony, rose to 0.63 ppb after three months of storage at room temperature (Shotyk et al., 2006). Westerhoff et al. (2008) showed that Sb leaching from PET containers was time and temperature dependent. Nine commercial samples of bottled waters collected in Arizona ranged from 0.1 to 0.5 ppb (mean 0.20 ppb) at the start of their study, and after 3 months of storage at 22 °C, had increased to only 0.23 ppb. However, storage of the water in PET bottles at 60 to 85 °C resulted in an increasing rate of Sb release into the water (Westerhoff et al., 2008). At 60 °C, the 6 ppb antimony MCL was achieved in the water stored in plastic bottles in 187 days, while at 85 °C, only 1.3 days was required to reach this level. These authors noted that Arizona summer temperatures inside cars, garages, and enclosed storage areas can exceed 65 °C.

**Food**

The average intake of antimony from food and water has been roughly estimated at 4.6 µg/day (Iyengar et al., 1987). More precise monitoring using isotopes indicated that the contribution from the diet is approximately 4.5 µg/day (Cunningham and Stroube, 1987). In contrast, an earlier study of metal content of food given to institutionalized children showed about 0.209 to 0.693 mg/kg of antimony in food (Murthy et al., 1971). Even at highly contaminated smelter sites, studies indicate that uptake of antimony from soil in grass and subsequent translocation in shoots is slight (ATSDR, 1992). Studies on fish and aquatic organisms indicate that bioconcentration is low (Callahan et al., 1979). There is also little indication that antimony bioaccumulates through the food chain (ATSDR, 1992).

**Other Sources**

Antimony in small amounts would be available for exposure to the public from its use in fireworks (ATSDR, 1992), pigments (Bencze, 1994), medicines (not officially sanctioned
except for certain diseases caused by parasites), and cosmetics (Al-Asban et al., 2004; FDA, 2006).

**METABOLISM AND PHARMACOKINETICS**

Pharmacokinetics of antimony was studied during the 19th century by pioneering scientists in the field of toxicology and physiology, including Orfila and Magendie. Orfila (as quoted by Chittenden and Blake, 1886 from *Traite de Toxicologie*), proved that “antimony like other metallic salts was absorbed and detected in animal tissues and secretions, especially in the liver and kidneys and further that absorbed antimony is slowly discharged from these quarters through the medium of urine.” Orfila gave a dog 46.5 grains of tartar emetic; the dog died three and a half months later. He found antimony in the fat, liver and bones of the dog. Richardson and Nevins (as cited by Chittenden and Blake, 1886) gave doses of tartar emetic to rabbits and upon their death found large amount of antimony in the liver, and lesser amounts in the spleen and stomach. Their experiments with dogs showed that these animals could also absorb tartar emetic from the skin.

In a series of experiments, Chittenden and Blake (1886) studied the distribution of antimony in cat and rabbits upon hypodermic injection at varying doses, evaluating its deposition in the kidneys, liver, brain, stomach and intestines, heart, lungs and back muscle. They found again that the liver had the highest concentration of antimony per gram of tissue followed by the brain and heart and lungs (one-fifth that of the liver), and smaller amounts in kidneys, stomach and muscle. In smaller doses given over a period of several hours, the proportion changed to the kidney having the highest, followed by the liver (half as much as the kidney), brain, stomach and intestines, heart and lungs, and muscle. They also fed small doses of antimonious oxide (146 mg/kg total) to one dog or tartar emetic (100 mg/kg total) to another dog for 17 days (animals were dosed with one to three doses daily such that individually the doses would not induce vomiting). In both cases, the liver had the highest concentration of antimony, but with tartar emetic there was a greater distribution throughout the body than with antimonious oxide, suggesting to them that either the antimonious oxide was more likely to be excreted by the kidney or was not absorbed as much as the tartrate form.

**Absorption**

Antimony absorption from the gastrointestinal system is relatively low. About 15 to 20 percent of $^{124}$SbCl$_3$ was absorbed by cows (Van Bruwaene et al., 1982). Administered as potassium antimony tartrate, about 15 percent was orally absorbed in rats (Moskalev, 1959). Syrian hamsters absorbed from 7 to 15 percent of both valence states of $^{124}$Sb tartrate complex by aerosol (antimony tartrate in tartaric acid was treated to oxidize antimony from the trivalent to pentavalent form) (Felicetti et al., 1974). In a repeated oral dosing protocol with SbCl$_3$, BALB/c mice were estimated to absorb about 7 percent (Gerber et al., 1982). A number of factors are likely to affect the absorption of antimony, including chemical form, particle size and solubility, species, age and diet.
No modern studies were located regarding dermal penetration of antimony compounds. Antimony or its compounds are generally not sufficiently water or lipid soluble to make this a significant avenue of exposure. However, with antimony potassium tartrate some penetration appears to occur in human, to produce a condition called “antimony spots,” which are dermal papules and pustules around the sweat and sebaceous glands (IPCS, 2007). From the older literature, the tartrate form was mixed with fat and applied to the skin or neck for the treatment of rheumatism and other conditions; absorption can be assumed since this dermal application also induced vomiting (Haller, 1975). Administration of tartar emetic dermally was actually recommended to prevent the irritation of the stomach that would occur by ingestion of the drug.

Some inhalation uptake is possible; Felicetti et al. (1974) exposed hamsters to aerosols of trivalent and pentavalent radioactive antimony tartrate, and found uptake in various organs, with rapid clearance. Increased antimony excretion has also been measured in the urine of antimony process workers (Cooper et al., 1968; Ludersdorf et al., 1987; Bailly et al., 1991). Absorption of antimony from the respiratory tract is probably a function of particle size, where smaller particles are retained and are likely to be absorbed over a period of time (ATSDR, 1992).

**Distribution**

Several studies that have monitored the disposition of antimony in experimental animals indicate that antimony mostly concentrates in the skeleton, liver, spleen, lung, fur/pelt, adrenal and thyroid (Westrick 1953; Van Bruwaene et al., 1982).

Hamsters were exposed to aerosols of trivalent and pentavalent radioactive antimony tartrate by Felicetti et al. (1974). These workers found that 90 percent of initial whole body activity cleared rapidly and that most of the remaining antimony concentrated in the liver, skeleton and pelt. More trivalent antimony concentrated in the liver, while the pentavalent form predominated in the skeleton. More trivalent than pentavalent antimony was found in red blood cells.

Otto et al. (1947) administered two trivalent antimony compounds (lithium antimony thiomalate and monosodium antimony thioglycolate) intramuscularly and two pentavalent antimony compounds (stibinose and neostibosan) intravenously to 14 male filariasis patients. Trivalent and pentavalent antimony plasma concentrations were sustained for less than 24 hours. For both trivalent compounds, antimony was found inside the red blood cells with very little in plasma, and the converse was observed for both pentavalent compounds.

Gerber et al. (1982) measured tissue distribution in pregnant BALB/c mice exposed to radioactively-labeled SbCl₃ in the diet, while another group of mice received an intraperitoneal (ip) injection of radioactively-labeled SbCl₃ on day 12 of pregnancy. These adult mice were compared with mice receiving arsenic in a similar fashion. Mice receiving antimony in the diet had little of the label (7 percent) absorbed by the gastrointestinal tract, and the organ concentrations were low. This was not the case for arsenic, which had a 20 percent absorption rate. The highest levels of antimony were found in the liver, 60 percent, followed by about 35 percent in uterus and skin and 20
percent or lower in the thyroid, brain and blood. With ip dosing, approximately half of
the label was concentrated in the intestinal tract tissues and bone surfaces. Other tissues
received up to 1 percent of the label, particularly the brain; even lower amounts were
found in the placenta and fetus. In fetuses, little arsenic and even less antimony was
found, particularly when fed. Pups continued to be fed both agents through their mothers
for 15 days after birth, with the result that antimony concentrations increased and later
decreased (some pups were sampled at 50 days after birth). In summary, the authors
conclude that antimony and arsenic can pass the placental barrier when injected, but less
readily so when fed.

**Metabolism**

Antimony is an element and cannot be catabolized. However, covalent interactions are
possible with sulfhydryl or phosphate groups (ATSDR, 1992). There is also the
possibility of valence state inter-conversions *in vivo*, but the reports have not been
definitive. It is likely that if such inter-conversions occur, they are relatively
insignificant.

It has been suggested that trivalent but not pentavalent antimony enters erythrocytes
when patients are injected with antimony pharmaceuticals (Felicetti *et al.*, 1974;
Molokhia and Smith, 1969). Otto and Maren (1950), however, found large amounts of
antimony in erythrocytes following intramuscular injection of stibanose (6 mg/kg) in 11
dogs. Otto and Maren (1950) suggest that pentavalent antimony may have been reduced
to the trivalent form *in vivo*. However, a lower dose of pentavalent antimony did not
enter red blood cells in the same study. In a study by Goodwin and Page (1943) using
polargraphy to analyze the valence state of antimony in blood and urine of seven humans
administered pentavalent antimony intravenously (iv), about 83.5 percent (average of
three subjects) of the administered dose was excreted in the urine as pentavalent and 2.5
percent as trivalent antimony, suggesting a slight reduction potential (Goodwin and Page,
1943). Otto and Maren (1950) pointed out, however, that the trivalent antimony found
could have been formed during sample preparation in hydrochloric acid for polargraphic
examination.

Antimony chloride was found to be conjugated with glutathione and excreted through the
bile (Bailly *et al.*, 1991). Unlike arsenic, it did not appear to be methylated. When rats
were administered antimony and depleted of their liver glutathione levels, more antimony
was secreted in the urine and higher levels of antimony were found in the liver (Bailly *et

Soil methylation by microbials of the similar elements arsenic, antimony and bismuth has
been observed. In their review, Bentley and Chasteen (2002) indicate that there is limited
evidence for the bacterial methylation of antimony compounds in the environment, but
not in higher organisms. Potential for methylation is important since the toxic
trimethylstibene compound of antimony would be formed.
Excretion

Van Bruwaene et al. (1982) administered single oral doses of 21.1 mg of antimony (as \(^{124}\text{SbCl}_3\)) to three lactating cows. Excretion of antimony in feces totaled 82 percent of the dose and excretion in urine totaled only about one percent of the dose.

Antimony was administered to asymptomatic patients of a hospital (Barter et al., 1947), all of whom were being observed for signs of schistosomiasis. All but one had undergone treatment with antimony for confirmed or suspected schistosomiasis. They were injected iv with synthetically made \(^{124}\text{Sb}\) at doses varying from 0.253 to 1.6 mg/kg. Those patients who received the higher doses (1.5, 1.6 mg/kg) suffered stomach pain, severe cough, vomiting, diarrhea or disorientation. Sb appeared in the urine in half an hour, and in the feces within 24 hours. About half was eliminated via the urine in 2-4 days.

Human subjects were administered antimony compounds ip or iv for the treatment of filariasis or schistosomiasis (Otto et al., 1947; Lippincott et al., 1947). Subjects administered potassium antimony tartrate excreted over half the dose within 48 hours (Lippincott et al., 1947). Subjects given pentavalent antimony compounds excreted over half into the urine within 24 hours, while those receiving trivalent excreted about 15 percent during the same period (Otto et al., 1947). A woman ingested an unknown amount of antimony sulfate intended for veterinary use. Due perhaps to clinical intervention, no signs of intoxication were evident. Antimony appeared in the bile, blood and gastric fluid within 20 hours; in the urine it peaked at 20 hours and then dropped rapidly to near baseline levels within 100 hours (Bailly et al., 1991).

Physiological/Nutritional Role

No nutritional or physiological role for antimony has been found.

TOXICOLOGY

Toxicological Effects in Animals

Testing of antimonials in animals goes back into history as animals were treated with antimonials just like humans. Furthermore, testing in animals, particularly in the nineteenth century, was also done to elucidate basic physiological and anatomical science. A number of physicians, in addition to using antimonials in their practice, also conducted experiments in animals to study mechanisms of antimony effects in detail (Mayerhofer, 1846; Ringer and Sainbury, 1897). Besides treating animal diseases, antimonials were used to “fatten up” animals, to increase their weight. An example of this was reported by Blyth and Blyth (1906) where the prized liver from The Duchy of Brunswick resulted from farmers customarily giving their geese small amounts of antimony oxide in their food. The Veterinary State Board Questions and Answers [Pennsylvania] (Kimball, 1920) lists animal doses using tartar emetic as a systemic and local emetic, diaphoretic, cardiac, and arterial sedative, gastrointestinal irritant,
expectorant, and vermicide. It was used as an emetic in dogs at 1 to 4 grains and as an expectorant at 1/10 to ¼ grain. In the dry stage of bronchitis and for intestinal worms in horses, use of ½ to 2 drachms of tartar emetic was recommended.

Animal experiments from before the 20th century will not be covered in detail in this section because of the difficulty of using that information for risk extrapolation. These studies, although pioneering efforts in science, provide little quantitative information regarding dose.

**Acute Toxicity**

Acute oral LD$_{50}$ values for potassium antimony tartrate (tartar emetic) in mice and rats range from 115 to 600 mg/kg (Bradley and Fredrick, 1941), and an LD$_{50}$ of 120 mg/kg has been reported for rabbits (HSDB, 2008)). The iv and ip LD$_{50}$ values for antimony and its various compounds in mice, rats, guinea pigs and rabbits are generally somewhat lower, ranging from 11 to 329 mg/kg (Bradley and Fredrick, 1941; HSDB, 2008). The toxicity varies among the different antimony compounds. Bradley and Fredrick (1941), using antimony compounds “of high purity” with negligible arsenic content, rated antimony trioxide as among the least toxic of five inorganic antimony compounds tested by the ip route. Organic antimony compounds like the tartrate appear to be more toxic than inorganic forms, but this may be due to the higher solubility of the organic forms, increasing their apparent uptake.

Antimony is well known for its emetic effects to humans and some animals. Rodents are known not to show emesis, and therefore they do not vomit when exposed to antimony. Good (1829) describes the pioneering experiments of M. Magendie to study emetic action. In one, two grains of tartar emetic were introduced into a dog’s crural vein, inducing nausea immediately. The abdominal cavity was opened and spasms of contractility were seen through the action of the diaphragm and abdominal muscles, but the stomach was not contracting when it was allowed to protrude from the abdomen. In another experiment, the same situation was repeated but the stomach was excised and replaced by a bladder; then tartar emetic was injected as before, resulting in the bladder contracting. Majendie thus showed that irritation of the stomach alone was not enough to induce emesis.

Much later, Weiss and Hatcher (1923) studied the mechanism of vomiting in cats, finding that injected tartar emetic will induce vomiting reflexes after the removal of the entire gastrointestinal tract. Cutting the vagi alone will also inhibit emesis in a tartar emetic-injected cat. In a cat orally administered tartar emetic, cutting the vagi would inhibit emesis, but not in massive doses. Cutting certain ganglia led the authors to suggest that orally introduced tartar emetic induces afferent emetic impulses that pass partly by way of the sympathetic nerve and partly by the vagus.

Flury (1927) determined the most effective emetic doses of six antimony compounds (antimony trioxide, antimony pentoxide, sodium antimonate, potassium antimonate, sodium meta-antimonate and potassium antimony tartrate) in dogs. Potassium antimony tartrate was the most potent at 33 mg/kg (about 12 mg/kg antimony). Cats were sensitive
to the emetic effects of potassium antimony tartrate at doses of 4.3 or 5.2 mg/kg (Flury, 1927).

Subchronic Toxicity

Flury (1927) extended his studies by dosing rats (two per test group) to potassium antimony tartrate, antimony trioxide and sodium meta-antimonate (Na₃SbO₄) or in food for 131 days. Dosing was begun in a graduated fashion for the first two compounds, starting with 1 mg/day and increasing over 86 days to 200 mg/day. The last compound was given from 3 to 1,000 mg/day in a similar pattern. No effects were seen even at the highest doses for antimony trioxide and sodium meta-antimonate, but potassium antimony tartrate caused a systemic deterioration and death at 200 mg/day. This corresponds to an average daily dose of 485 mg/kg-day based on mean body weight of 155 grams as stated by the author.

Rats were administered potassium antimony tartrate (8 mg/kg-day) or finely granulated antimony metal (8 or 40 mg/kg-day) in the diet for 4 to 12 months, or potassium antimony tartrate or antimony metal for six months with doses increasing up to 100 and 1,000 mg/kg-day, with the final dose continued for an additional month (Bradley and Fredrick, 1941). All animals maintained normal growth rates. Pathologic changes were evident upon sacrifice, including congestion and polymorphonuclear leukocyte infiltration in the liver, congestion with glomerulonephritis and tubular necrosis of the kidney, congested viscera with hemorrhages in the small intestine, and congestion of the spleen.

The National Toxicology Program (NTP, 1992) conducted limited studies on potassium antimony tartrate in mice and rats of each sex. NTP studied the effects on groups of five rats and mice drinking potassium antimony tartrate for fourteen days at concentrations of 150, 300, 650, 1,250 or 2,500 ppm. Doses were approximately 0, 16, 28, 59, 94 or 168 mg Sb/kg-day for rats; doses for mice were 0, 59, 98, 174, 273, or 407 mg Sb/kg-day. No particular effects where noted in rats or mice at any dose except for the high dose in mice, which resulted in lesions of the forestomach and liver. Next NTP injected potassium antimony tartrate ip twelve times over the course of 16 days to groups of five rats or mice at doses of 0, 1.5, 3.0, 6.0, 12, or 24 mg Sb/kg. Rats exhibited increased mortality and decreased body weight at 12 and 24 mg/kg-day, with males showing decreases in body weight at 6 mg/kg-day, while females showed hepatocellular degeneration and necrosis at the two highest doses.

In a 90-day study commissioned by the Associated Plastic Manufacturers of Europe (Hext et al., 1999), twelve male and female Alpk:AP;SD (Wistar-derived) rats were fed diets containing 0, 1,000, 5,000 or 20,000 ppm antimony trioxide for 90 days. Mean dose rates for males were 84.2, 421.2 and 1,686 mg antimony trioxide/kg-day. Female mean doses were 97.1, 484.1 and 1,879 mg antimony trioxide/kg-day. At the highest dose, elevated levels of alanine aminotransferase, aspartate aminotransferase and creatine kinase, plasma triglyceride (males) and plasma cholesterol were noted. Absolute and relative liver weights and the number of pituitary cysts were increased in both sexes at the high dose. Based upon the above information, a NOAEL of 421.2 mg/kg-day of antimony trioxide can be assigned.
Poon et al. (1998) treated male and females SD rats (15 per group) with potassium antimony tartrate in drinking water at concentrations of 0, 0.5, 5, 50 or 500 ppm (calculated by the authors to be 0, 0.06, 0.56, 5.58 and 42.17 mg of antimony/kg-day for 13 weeks (Poon et al., 1998). Additional groups of 10 rats were added to the control and 500 ppm groups and held for an additional four-week recovery period after the dosing. During treatment the highest dose group had decreased food intake and showed decreased body weight gain, but during the recovery period, the food intake and body weight gain resumed. Water consumption increased dramatically during the recovery period. In the highest-dose males, one rat had a cirrhotic liver and three males had gross hematuria. The authors reported a dose-dependent drop in the blood glucose levels for both males and females, which changes in females occurring as low as 5 ppm. However, this appears to be debatable, as the control group glucose levels dropped during the recovery period to the same level as that of the highest dose group during both treatment and recovery periods. Cholesterol levels for the highest-dose females were significantly lower (p<0.05) than controls; alkaline phosphate and total protein were also decreased compared with controls. Hematological parameters (red blood cell counts, mean corpuscular volume, platelets) were significantly different from controls (p<0.05) for high-dose males, while for high-dose females the only significant hematological difference was a depression of monocyte counts.

Mild histological changes were noted in the thyroid, spleen, liver, thymus and pituitary gland, some persisting during the recovery period. Changes with an apparent dose trend include: in the thyroid, reduced follicular size, collapsed follicles and nuclear fasciculation; in the liver, anisokaryosis (increased nuclear size), hyperchromaticity, increased portal density, increased perivenous homogeneity and fibrosis (only at the high dose). However, the authors acknowledged a general lack of dose response and severity in the results (there was no statistical testing either for significance or trend). These data are shown in Table 2.

The authors also followed the retention of antimony in tissues after sacrifice. Antimony was detected in tissues in the spleen and red blood cells of male and female rats at the lowest exposure concentration of 0.5 ppm. At the next higher concentration, 5 ppm, antimony residues were also detected in liver and kidney; at 50 ppm antimony was detected also in abdominal fat, brain and serum. Based on the blood glucose levels, histological changes and the tissue retention of antimony, the authors selected 0.5 ppm or 0.06 mg/kg-day as the NOAEL for this study, although they reported effects to the thyroid at this dose. They argued that the changes to the thyroid were marginal and reversible at 0.5 ppm antimony, based on observations in the recovery period. Another reason given for the 0.5 ppm level selection as the NOAEL was a marked accumulation of antimony at the 5 ppm level, and persistence of antimony in the spleen, along with a decrease in the glucose levels in females at the same level. The authors note that:

“…antimony compound tested in the present study is in the form of a trivalent, highly soluble salt. Other speciations of antimony and less soluble forms may present different and probably milder effects.”
Table 2. Histopathologic Changes Caused by Potassium Antimony Tartrate in Rats (adapted from Poon et al., 1998).

| Endpoint                  | Dose          | Recovery     |   |   |   |   |   |
|--------------------------|---------------|--------------|---------------|---------------|---------------|---------------|---------------|---------------|
|                          | Sex 0 ppm 0.5 ppm 5 ppm 50 ppm 500 ppm 0 ppm 500 ppm |              |               |               |               |               |               |               |
| Thyroid Architecture     |               |              |               |               |               |               |               |               |
| Reduced follicle size    | M 0.5 (39)b 1.6 (87) 1.1 (71) 2.5 (93) 2.2 (100) 0.5 (30) 1.1 (70) | F 0.6 (38) 1.9 (93) 1.9 (93) 2.1 (100) 2.2 (100) 0.6 (44) 1.3 (67) |
|                          |              |              |               |               |               |               |               |               |
| Collapsed follicles      | M 0.3 (33) 0.5 (50) 0.4 (29) 0.3 (27) 0.6 (57) 0.5 (30) 0.6 (44) 1.7 (90) |
|                          | F 0.3 (26) 0.5 (53) 0.2 (13) 0.4 (33) 0.6 (44) 0.6 (44) 0.6 (44) 0.3 (44) |
| Spleen                   |               |              |               |               |               |               |               |               |
| Sinus hyperplasia        | M N 0.3 (13) 0.3 (29) 0.7 (47) 1.4 (67) 0.5 (33) N N | F N 0.3 (13) 0.3 (29) 0.7 (47) 1.4 (67) 0.5 (33) N N |
| Liver nuclei             |               |              |               |               |               |               |               |               |
| Anisokaryosis            | M 0.1 (24) 0.6 (87) 1.0 (87) 1.9 (100) 2.8 (100) 0.1 (14) 1.2 (100) 1.9 (100) |
|                          | F 0.9 (75) 1.5 (100) 2.3 (100) 2.3 (100) 2.6 (100) 0.7 (78) 1.9 (100) 1.9 (100) |
| Hyperchromicity          | M N 0.8 (67) 0.6 (33) 1.4 (73) 0.1 (7) 0.9 (60) N N | F 0.1 (7) 0.8 (53) 0.6 (33) 0.1 (7) 0.9 (60) N N |
| Liver Cytoplasm          |               |              |               |               |               |               |               |               |
| Incr. portal density     | M 0.2 (35) 0.6 (73) 1.1 (87) 1.9 (80) 2.0 (67) 0.6 (71) 0.6 (60) 1.3 (80) |
|                          | F 1.3 (88) 1.4 (100) 1.5 (100) 1.8 (100) 1.2 (93) 0.9 (100) 0.6 (60) 1.3 (80) |
| Incr. perivenous homogeneity | M 0.3 (65) 0.6 (93) 1.3 (100) 1.6 (100) 1.9 (100) 0.4 (71) 0.7 (100) 0.7 (100) |
|                          | F 0.5 (75) 0.7 (93) 1.4 (100) 1.4 (100) 1.1 (100) 0.2 (44) 0.7 (100) 0.7 (100) |
| Fibrosis                 | M N N N N 0.1 (7) N | F N N N N 0.1 (7) N |

a Average severity index, 1-4 in increasing severity
b Percent of examined animals showing abnormality (14-15 animals per treatment group and 7-10 animals per recovery group).
c N = normal.

Although the Poon et al. (1998) study is one of the more complete reports, albeit for a shorter term, there are notable limitations mentioned even by the authors. For the most part the changes/effects observed were relatively minor at exposure concentrations from 0.5 to 50 ppm, and without a discernable dose response. The authors attempted to control for noncompound-specific effects (such as caused by suppression of eating or drinking behavior by the animals) by having a “recovery” period after dosing. This procedure did appear to reverse some of the effects; nevertheless, it was not clear whether the four weeks were enough to reverse all the dose-related effects.

Lynch et al. (1999) reviewed the Poon et al. (1998) study. They reflected on the adaptive nature of the histopathological effects and that they were not detected in other studies.
conducted on the same compound. This led them to conclude that the NOAEL would have been more appropriately designated as 50 ppm. The thyroid findings were determined on a graded scale based on subjective interpretation of the histopathology, and were not supported with other data such as basic thyroid function tests including measurement of levels of the circulating thyroid hormones TSH and triiodothyronine. For liver histopathology, Lynch and colleagues discuss the significance of anisokaryosis and hyperchromaticity as to be expected in maturing rats as the mononuclear diploid state converts to the tetraploid state. Furthermore, in spite of the large 1,000-fold dose range, minor increases in these parameters were observed, and no effects were noted on absolute or relative liver weights or on the liver enzymes indicative of liver damage, aminotransferase and sorbitol dehydrogenase. Caloric restriction and dehydration also could explain the lowering of glucose, cholesterol and alkaline phosphatase, which are not necessarily the result of antimony toxicity (Lynch et al., 1999).

Poon and colleagues (Valli et al., 2000) rebutted the review of Lynch et al. (1999), stating that mild physiological changes, which may be adaptive in nature, are still important because within a lifetime of drinking water with elevated concentrations of antimony, the possible reversal of effects may not occur. Also the graded changes in the thyroid, although subjective, were consistent. In explaining the hepatic changes, Poon and colleagues insisted that the biochemical parameters (decreased alkaline phosphatase, serum glucose, serum creatinine and cholesterol and total protein in high dose-females) confirmed the liver changes. As we noted earlier, the biochemical changes were neither remarkable nor consistent. Poon and colleagues did not address the effects of caloric restriction as a possible explanation for the effects seen, particularly at the high dose, as indicated in the comments of Lynch et al. (2000).

We conclude that the evidence of dose-related effects is not convincing except at the highest dose. The effects claimed to be dose-related were rather weak, as acknowledged by the authors. In our view, the data only establish solidly the lowest effect level of 42.17 mg of antimony/kg-day, and thus a NOAEL of 5.58 mg/kg-day, which is close to the Schroeder (1970) lowest observed adverse effect level (LOAEL) of 4.3 mg/kg-day. This view was also asserted by WHO (2003), who used this endpoint as the basis of their drinking water risk assessment. WHO applied an uncertainty factor of 1,000 to derive their guideline value of 20 ppb, with a source contribution factor of 0.10.

Hepatic Toxicity

As noted earlier, antimony was used for some time to increase the weight of livers of animals as well as the overall body weight. Specific increases in the weight of livers is noted in NTP (1992) and the Hext (1999) studies. From the 19th century, Ringer and Sainsbury (1897) believed that antimony destroys the glycogenic function of the liver, and thereby induces fatty degeneration of it and other organs. Without citing a source (it could be their work), they note an increased production of leucin[e], tyrosin[e] and urea, resulting in increased urea excretion.
Genetic Toxicity

Genotoxicity and mutagenicity testing of antimony-containing compounds has yielded highly variable results. This can be expected because of the wide range of solubility and reactivity of antimony-containing compounds; the results seem characteristic of many other metals and metalloid-salts in such tests. There appears to be some potential for chromosomal aberrations and clastogenicity, particularly for the more soluble salts, as described below.

In vitro assays

Antimony trichloride, antimony pentachloride, and antimony trioxide were tested by the Rec assay with the Bacillus subtilis (H17 and M45) recombinant assay (Kanematsu et al., 1980; Kanematsu and Kada, 1978) and found to be positive (more strongly for the chlorinated forms than the oxide). The same compounds were found to cause no reversions in E. coli B/r WP 2 try and Wp2 her try and five strains of S. typhimurium, TA98, TA100, TA1534, TA1537 and TA1538 for histidine reversions with metabolic activation (Kanematsu and Kada, 1978). Antimony trioxide was reported not to be mutagenic at concentrations up to 5 mg/plate when tested in S. typhimurium strains TA98, TA100, TA1535, TA1537 and E. coli WP2P and WP2P uvrA with or without S9 fraction (Elliott et al., 1998).

Clastogenic effects with antimony trioxide were reported in the sister chromatid exchange assay using V79 cells in vitro (Kuroda et al., 1991), but induction levels were weak, about two to three-fold above background. Potassium antimony tartrate (Hashem and Shawki, 1976), sodium antimony tartrate (Paton and Allison, 1972) and antimony trioxide (Elliott et al., 1998) induced chromosomal aberrations in cultured human leukocytes and lymphocytes. Mouse lymphoma cells (L5178Y TK+/- were exposed to 6.0 to 50 µg/mL of antimony trioxide in the presence or absence of S9 (Elliott et al., 1998; Paton and Allison, 1972); no mutagenic potential was indicated.

The potential for five antimony compounds: stibine, trimethylstibine, potassium antimony tartrate, potassium hydroxyantimonate and trimethyl antimony dichloride to nick plasmid DNA from pBR 322 was evaluated by Andrewes et al. (2004). They found trimethylstibine and stibine to be equipotent to trimethylarsine to nick DNA. The others were inert. The authors speculate that damage done to DNA by stibine or trimethylstibine probably proceeds from the generation of reactive oxygen intermediates, as it is presumed to do with trimethylarsine.

Antimony trichloride and antimony potassium tartrate have been evaluated for their potential to prevent DNA repair of γ-irradiation damage of Chinese hamster ovary cells (CHO) (Takahashi et al., 2002). Cells were incubated with several concentrations of these antimonials from about 0.1 to 8 mM for two hours, then irradiated with γ-rays at a dose of 40 Gy, and DNA strand breaks were quantified. Both the trichloride and tartrate entities inhibited DNA repair in a dose-related fashion, with 0.2 mM being the least significant concentration for the trichloride, and 0.4 mM for the tartrate. The mean lethal concentrations to the cells were 0.21 mM for the trichloride and 0.12 mM for the tartrate.
A micronucleus assay alone and in combination with fluorescence in situ hybridization (FISH) technique was performed on human lymphocytes exposed to several metals including potassium antimonate (+5) (Migliore et al., 1999). Two donor cell lines were used. In both cases there was some variability in the dose-related increases in induction of micronuclei. With the FISH technique it should be possible to discriminate clastogenic activity from whole chromosome loss. With potassium antimonite both clastogenic and aneuploidogenic events occurred.

**In vivo assays**

Piperazine antimony tartrate and potassium antimony tartrate induced chromosomal aberrations in bone marrow cells of rats injected ip with 2, 8.4 or 14.8 mg/kg of tartar emetic, and 1, 10 or 19.1 mg/kg of bilharcid (piperazine antimony tartrate) (El Nahas et al., 1982). Antimony trioxide suspended in water was given by gavage to mice, which were monitored for chromosomal aberrations in the bone marrow and clastogenic assays (Gurnani et al., 1992). Daily exposure to 400, 668 and 1,000 mg/kg-day for periods up to 21 days induced chromosomal aberrations, but not clastogenic effects. In other mouse bone marrow micronucleus tests with antimony trioxide, no clastogenic effects were observed either with one dose of 5,000 mg/kg or with repeated dosing at 400, 668, and 1,000 mg/kg-day for 7, 14, or 21 days (Elliott et al., 1998).

In another study of clastogenic effects (Kirkland et al., 2007), rats were exposed in vivo to antimony trioxide for 21 days at doses of 250, 500 and 1,000 mg/kg-day. The only clinical sign was a loss of body weight at the high dose. Chromosomal aberrations and micronuclei were scored from blood cells and compared with controls (positive and negative). No significant (p< 0.05) differences were observed between treated groups and controls, and there was no dose-related trend.

**Interactions**

Other elements such as arsenic appear to share some chemical and toxicological effects with antimony, which has led to investigation of plausible interactions. Gebel (1998) pointed out that both arsenic and antimony at least in their trivalent states appear not to be point mutagens, but are clastogenic. While environmental exposure to arsenic has been associated with cancer induction, antimony exposure has not been proven to be associated with cancer. However, arsenic and antimony can be found together in deposits (Gebel et al., 1996). Thus it would be of some interest to see if the presence of one can modulate the effects of the other.

Sister-chromatid exchange levels were monitored in white blood cells extracted from the blood of sheep pastured in areas of elevated arsenic, antimony and mercury content in soils as a result of mining residuals (Gebel et al., 1996). These were compared with those cells from sheep pastured in areas without this particular environment. No differences were observed between the various populations in this parameter.

The clastogenic activity of arsenic(III) was compared with Sb(III) (as antimony trichloride) (Schaumlof&l and Gebel, 1998) on cultured human lymphocytes.
Micronuclei were induced in both cases but arsenic was ten-fold more potent than antimony. Little of either element appeared to be converted to the pentavalent form (less than 10 percent). Based on intracellular contents, both trivalent forms were able to enter the cells. Adding catalase and superoxide dismutase did not inhibit induction of micronuclei; thus oxidative stress (free radical generation) did not appear to be a factor in this process. A comet assay was performed to evaluate DNA-protein crosslink formation, and it was found that arsenic was much more capable of generating DNA-protein crosslinks than antimony.

In a study analogous to the above, instead of using human lymphocytes, Gebel et al. (1998) used V79 Chinese hamster ovary cells to compare arsenic (III) and antimony (III) (as antimony trichloride). The authors found that trivalent antimony was five times less clastogenic than arsenic, and 10-fold less genotoxic. The comet assay showed that antimony induced DNA strand lesions, but not DNA-protein crosslinks.

In another work, Gebel (1998) reported that antimony suppressed the clastogenic action of arsenic. Cellular uptake of arsenic (As2O3) and antimony (SbCl3) was studied in V79 cells, cell death as a result of exposure to both was studied, and an in vivo micronucleus test was conducted. SbCl3 was less toxic than arsenic; 100 percent viability was reported at concentrations up to 10 µM, and 50 percent survival rate with 75 µM. With arsenic, 12.5 µM As2O3 (25 µM As) produced 50 percent lethality. Combining the two and examining the response at the fifty percent survival level, 10 µM SbCl3 + 15 µM As2O3 or 50 µM SbCl3 + 10 µM As2O3, suggested an additive relationship, assuming that arsenic was three times as toxic as antimony. Arsenic and antimony, presented alone, appeared to be taken up by the cells at comparable rates, while together, the corresponding uptake was lower at equivalent concentrations. In the micronucleus test, arsenic proved to be forty-fold more mutagenic than antimony, while the combination (varied antimony with a minimal constant concentration of arsenic) resulted in less than additive effects, suggesting that antimony suppressed the clastogenicity of arsenic.

In a more recent study by Gebel and colleagues (Hasgekar et al., 2006), the authors attempted to elucidate the nature of the interactions of arsenic and several other elements upon viability, genotoxicity and metabolic methylation of these elements in primary rat hepatocytes. Arsenite (As III) was incubated alone and with antimonite (+3, as antimony trichloride), selenite, and mercury (II). Co-incubation with a constant concentration of arsenite and graduated levels of the above elements generally resulted in additive decrease in viability. With the micronucleus test, only arsenite and antimonite alone produced a dose-dependent increase in micronuclei; selenite and mercury (II) did not. In contrast, the presence of antimonite with arsenite resulted in no additional increase in micronuclei than would be expected with arsenite alone (or decreased with 10 mM antimonite below the level induced by arsenite alone). This effect upon the number of micronuclei was similar to what was indicated in Gebel (1998). Finally, the authors also did not find methylated arsenic products and judged that the process of methylation did not appear to influence the results. It is thought that methylation is a significant detoxification pathway for arsenic, but that did not appear to be the case here.
Developmental and Reproductive Toxicity

Hodgson et al. (1927) studied the effects of 7 to 17 injected doses of sodium antimony tartrate (2.2 mg/kg), or 9 to 16 doses of 50 mg of an unknown organic antimony compound over 16 to 38 days in rabbits. They also injected male and female English white mice with 30 to 39 doses of 10 mg of another unknown organic antimony salt over 60 to 77 days. Both female rabbits and mice were reported to exhibit contraception, abortion and fetal damage, but no fertility effects were noted on male mice with these antimony salts (Hodgson et al., 1927).

A group in the Soviet Union (Belyaeva, 1967) investigated the reproductive effects of antimony trioxide in female rats following repeated inhalation exposures to 250 mg/m³ dust over a two-month period. Sterility or fewer offspring were noted in exposed rats when compared to the control group.

Potassium antimony tartrate was orally administered to four-year-old ewes at 2 mg/kg-day for 45 days or throughout gestation. All ewes administered antimony gave birth to normal, full-term lambs. No adverse effects were noted in ewes at necropsy (James et al., 1966). In another study, the antimonial drug RL-712 (antimony dextran glycoside) was administered as five intramuscular injections of 125 or 250 mg/kg between days 8 and 14 of gestation. No abnormalities were reported (Casals, 1972).

In the Gerber et al. (1982) study, described previously, that measured tissue distribution of Sb in pregnant BALB/c mice exposed to radioactively-labeled SbCl₃ in the diet or after an intraperitoneal (ip) injection of radioactively-labeled SbCl₃ on day 12 of pregnancy, no effect was noted on fetuses.

Rossi et al. (1987) exposed 30 pregnant female rats with antimony trichloride at 0.1 and 1 mg/dL in drinking water from the first day of pregnancy until weaning. Pups were given antimony trichloride at the same concentrations in their drinking water ad libitum from the 22nd until the 60th day of life. No effects were noted for the standard parameters including length of gestation, number of pups per litter or in the presence of any terata. Significant decreases from controls in pup weight (p<0.05) were noted at the highest dose of antimony starting at ten days after birth. No effects were noted on the maternal or pup systolic arterial blood pressure. No effects were noted on the pressor response to carotid occlusion. The pressor response was evaluated at the two concentrations of antimony and 0.1 µg/kg and higher for noradrenaline, or 0.1 µg/kg and higher of 1-isoprenaline or acetylcholine on the 30th or 60th day. Dose-dependent increases in pressor response trended higher for all three compounds, but was significantly enhanced (p<0.05) for the 60 day time point for both doses of antimony except with acetylcholine, which was significant only at the higher dose of antimony.

An in vitro study to evaluate embryotoxicity of antimony metal was done by Imai and Nakamura (2006) using an embryonic stem cell line. Cells were cultured with solutions of mercury, silver, cobalt, chromium, copper, nickel, palladium, antimony, tin, vanadium and zinc, which were selected as being components of dental amalgam. Using a biopredictive statistical model, the metals were evaluated for effects on the cellular differentiation potential and viability. The results for antimony indicated a weak...
embryotoxic potential, similar to tin or vanadium. Chromium and mercury had the highest potential for embryotoxicity.

**Neurotoxicity**

Neurotoxicity has long been noted in humans, as part of the profile of toxic effects with antimonial administration. Neurotoxicity in experimental animals appears to have been studied in the nineteenth century (Ringer and Sainsbury, 1897), indicating that antimony is toxic to both sensory and motor nerves. Apparently no modern studies exist.

**Chronic Toxicity/Carcinogenicity**

**Ingestion**

Two chronic studies were conducted by Schroeder et al. (1968 and 1970) with potassium antimony tartrate (along with several other trace elements) administered by drinking water to animals. Male and female Charles River CD mice received 0 or 5 ppm antimony in drinking water from weaning until death (Schroeder et al., 1968). Mean body weights and water consumption for mice have been estimated as 0.04 kg and 4 mL/day, respectively (U.S. EPA, 1992b). Based on the reported data and these U.S. EPA estimates, an average dose of 0.5 mg/kg-day antimony was calculated by U.S. EPA (1992b). Antimony treatment resulted in weight loss in male mice after 18 months (p<0.025) and decreased weight gain in females measured at 12 and 18 months (p<0.005). In female mice, antimony appeared to shorten the median survival by 49 days, and at the 75 percent survival level the difference was 85 days when compared with controls. However, no significant differences were noted in longevity (defined as the mean age at death of the oldest ten percent of the animals) between antimony-treated animals and controls. Male mice survival patterns essentially mirrored that of controls. No increases in tumor incidence were noted in exposed animals.

A similar study was performed in groups of about 50 male and female Long-Evans rats receiving 0 or 5 ppm of potassium antimony tartrate in drinking water from weaning until death (Schroeder et al., 1970). Based on the authors’ calculations, the estimated daily dose was 0.35 Sb/kg-day. Unlike the results in mice, there was no significant effect on body weight gain, but there was a significant decrease in longevity. Mean longevity was 1,160 ± 27.8 (SE) days for control males, 1,304 ± 36 days for control females, 999 ± 7.8 days for treated males and 1,092 ± 30 days for treated females. Serum cholesterol levels were increased in male rats but decreased in female rats. Fasting glucose levels were not significantly different in either males or females but non-fasting glucose levels were lower in exposed males and females. Deposition of antimony in kidney, liver, heart, lung and spleen was also observed, which increased with age. No increase in tumor incidence was noted. An epidemic of viral pneumonia during the experiment was reported for this colony of rats, but the investigators claimed that they saved enough of the animals to make the results valid. U.S. EPA used this study as the basis for their MCL derivation, using a LOAEL of 0.0.43 mg/kg-day based on their own dose calculations. No discussion was included of the experimental issues including colony infections, which
would ordinarily render a study of limited use for risk assessment (U.S. EPA, 1992b, 1995).

Inhalation

Carcinogenic effects have been reported in studies of antimony trioxide by the inhalation route. Watt (1983) reported that antimony trioxide induced fibrosis and neoplasms in female rats when inhaled at levels close to the threshold limit value (TLV). Female SDF rats and S-1 miniature swine were exposed to antimony trioxide dust at 1.6 ± 1.5 or 4.2 ±3.2 mg/m³ for six hours/day, five days/week, for one year followed by another year of observation. Lungs of exposed animals of both species were reported to be mottled and heavier than non-exposed animals and these effects were related to increases in exposure level and exposure time. The female rats showed neoplasms, mostly at the higher dose (62 percent incidence). Neoplasms were identified as scirrhous carcinomas, squamous cell carcinomas or bronchial alveolar adenomas.

In another experiment (Groth et al., 1986), three groups of eight month-old male and female Wistar rats were exposed via inhalation to either antimony trioxide [mean time-weighted average (TWA) = 45.0 and 46.0 mg/m³ antimony], or to antimony ore concentrate (mean TWA = 36.0 and 40.1 mg/m³) (the two concentrations reflect two chambers used with equal representation of male and females, with 90 animals per chamber) or to filtered air for one year, followed by about one-half year of observation. Efforts were made to assure as uniform a particle size as possible, although the antimony ore was larger in aerodynamic mass median diameter than the antimony trioxide. The authors noted lung neoplasms (squamous cell carcinomas, bronchioalveolar adenomas, bronchioalveolar carcinomas or scirrhous carcinomas) in both treated female groups (27 percent in the antimony oxide and 25 percent in the antimony ore group), but none in the treated male groups. Analysis of antimony content of the lungs of treated animals demonstrated that antimony oxide-exposed males had nearly two times higher levels of antimony than the corresponding females, and the lungs of oxide-exposed animals had five times more antimony than ore-treated animals.

Subchronic and chronic inhalation toxicity tests were performed with several doses of antimony trioxide dust on groups of 25 Fischer 344 rats (Newton et al., 1994). For the subchronic study the concentrations were 0.025, 1.08, 4.92 or 23.46 mg/m³ for six hours/day, five days/week for 13 weeks followed by a 27-week observation period. The chronic study was conducted at levels of 0.06, 0.51 or 4.5 mg/m³, six hours/day, five days/week, for 12 months; some animals were held for a one-year observation period following treatment. Data on lung weight and antimony content were collected at interim sacrifices for both experiments (at four-month intervals for the chronic study). Corneal opacities were noted in animals starting at two weeks of exposure in the subchronic study, and cataracts were observed in all dose groups of the chronic study in a dose-related fashion. No other clinical effects were noted for either study. Body weights were significantly lower (6 percent) in males exposed to the highest concentration in the subchronic study. No other differences in body weights were observed. No dose-related effects were noted in the clinical chemistry or hematology parameters in either study. Mean absolute and relative lung weights were increased in the mid and high dose groups.
for the subchronic study, while the lung weights for rats at the highest concentration did not recover during the following observation period. The lung weights were not affected in the chronic experimental groups. Microscopic changes were noted in the lungs of subchronic and chronically exposed animals. These were limited to subacute to chronic interstitial inflammation (more prominent in the shorter study than the chronic one), granulomatous inflammation, increased numbers of alveolar to intra-alveolar macrophages, and foreign material in the alveolar-intra-alveolar macrophages in the peribronchial and perivascular lymphoid aggregates. In the peribronchial lymph nodes, granulomatous inflammation/granulomas were found along with signs of fibrosis (rare in the chronic study, while more frequent in the subchronic study, but without a particular trend). No increase in lung tumors was found. In the chronic study, the rate of clearance of antimony trioxide from the lungs was reduced by 80 percent in the highest concentration group compared with the lowest concentration, which can be interpreted as a particle overload effect.

There are some notable differences in effects among these inhalation studies in rats. The Groth (1986) study reported nearly half as many lung tumors as did the Watt (1983) study, although the antimony concentration was at least ten-fold higher in Groth (1986). The Groth (1986) study did have a shorter observation period. The exposure concentration of the Newton et al. (1994) study most closely approximates the Watt (1983) study, but the tumor incidence does not. A possible explanation for this could be inaccuracy in determining the concentration, as pointed out by Newton et al. (1994), which compared the increased amounts of test material found in the lungs of the animals from the Watt (1983) study with their own. A pathologist evaluating slides from both studies noted that the rat lungs from the Watt (1983) study had more test material and considerably more injury than the rat lungs from the Newton et al. (1994) study. Furthermore, they noted that Watt (1983) exposed rats in the same chamber with the swine, and there were pine shavings on the floor, which are conditions that promote infections. In addition, the effect of overloading the lungs with foreign particles, which can lead to neoplastic effects due to prolonged stress on the lung cells by foreign materials (ILSI, 2000), must be considered.

Antimony trioxide is listed as a Group 2B carcinogen (possibly carcinogenic to humans) by IARC (1989) on the basis of the increased tumors found in female rats in the studies of Watt (1983) and Groth et al. (1986). It was also listed as a carcinogen by OEHHA in 1990 under Proposition 65 (OEHHA, 2008). The National Toxicology Program has an inhalation carcinogenicity study of antimony trioxide currently in progress in Wistar rats and B6C3F1 mice (NTP, 2008).

**Toxicological Effects in Humans**

**History of Antimonial Medicinal Use and Misuse**

From the writings of medieval alchemists, we can get a crude understanding of what was known about the medicinal properties of antimony in those days. A treatise attributed to Roger Bacon (1214-1294) but probably produced/or elaborated upon by Joachim Tanckius (Bacon, unknown) describes the synthesis of antimonials, possibly a tartrate
compound (assumed based on the synthesis protocol). This is followed by a description of the conditions for which the resultant tincture, Oleum Antimonii, was administered, often with wine, with the author attributing the medicinal benefit as a function of their co-administration. The first condition this preparation was used for was gout, for which the prescription was to take three drops on an empty stomach for three days. The sequence of symptoms or events that followed include: the removal of pain, intense and particularly odoriferous sweating, and diarrhea. For leprosy, the dose was doubled, and the effects were also increased, with the skin peeling on day two. On day four the dose was decreased to three drops. By the eighth or ninth day a resolution should be had: complete healing by “Divine mercy,” or else. For perhaps less severe ailments, a lower dose was prescribed, such as for apoplexia (stroke), just one drop to begin with to “unstuck” the part. For consumption and dehydration, two drops were given on the first day and then again on the second. It must be assumed that the dose of one to two drops per day for a limited period (two days) was supposed to be minimally effective, while three drops could cause more severe effects including sweating. Curiously, no dosing seemed to last beyond nine days.

In the fifteenth century a very significant work in science appeared, thought to be the first treatise on a specific element, which was The Triumphal Chariot of Antimony, a work of Brother Basil Valentine (1394?) annotated and published by Kirkringus (Valentine, 1678), although his authorship is somewhat controversial (Wikipedia, 2007). The work provides a detailed description for the purification of antimony from ore, and the synthesis of several compounds containing antimony from it. Foremost, a discussion and exaltation of the virtues of medicinals derived from antimony is presented. There is clear appreciation for the value of dosage:

“For above all things, the Physician ought well to know, whether his Medicament will be weak or strong, also whether it will do good, or hurt, unless he resolve to fatten the church yard, and with the loss of his fame, and hazard of his own soul.”

[Kirkringus comments] “By Use, the Author understands what others call Dose; for what will a good Medicine profit you, if you know not in what quantity to administer it; that the same may rather heal, then hurt or kill... Where a living Voice is wanting, it is safer to be too timorous, then in any wise bold or adventurous, although of Antimony I can affirm, that being duly prepared it is as harmless a medicine as Cassia or Manna. The whole caution is chiefly about its use, after the first preparations; because it may still retain much of its own crude Venom.”

Valentine, like Bacon above, presents a very thorough purification of antimony, and described the synthesis of various compounds and their uses:

“Also let the well meaning and sincere observer of Art know, that there are two kinds of Antimony very different from each other: one is fair, pure, and of a golden property, and that contains very much Mercury, but the other which hath much Sulphur is not so friendly to gold as the first, and is distinguished by fair long and white shining streaks. Therefore one is more fit for Medicine and
Alchemy, then the other: as when the Flesh of Fishes is compared with the Flesh of other Animals, although both these are, and are called Flesh, yet each of these very much differs from the Flesh of the other; even so of Antimony the difference is the same…”

Antimony preparations could be used for:

“Antimony extracted with Spirit of Wine, all its venomous purging virtue passeth away, and no sign thereof remains, nor assumes it to itself any power of provoking Stools; but it performs its Operations by Sweat, and other ways, chiefly by Salivation and Ejection by the Mouth; it searcheth out all hurtful Evils in the Body, purgeth the Blood, heals the Diseases of the Lungs, and profits those who are strait-breasted, and troubled with a frequent Cough. In a word it Cures very many Disease, also asswageth a Malignant Cough, and whatsoever is of that Disposition, and is a Medicine very admirable.”

Little regarding actual medicinal doses can be derived from this treatise, assuming someone from the present day could attempt the purification with this method. Three to four grains of powder was recommended as a purgative. Other conditions, including leprosy, syphilis, etc., required daily drops for several days, and rarely progressed beyond a week.

The authors of these ancient texts recognized that antimony was a unique element different from mercury and lead. Compounds of mercury with antimony were used commonly, but antimony was judged to be safer than mercury. Furthermore, the concept that antimony could be purified to something beneficial rather than something with purely harmful effects was recognized early in the first millennium. Again from Valentine (Valentine, 1678):

“I say; since Antimony, is to produce such admirable Fruits, it is to be taken out of the Mountains; but first, by the Care of the Miners spiracles, or breathing places, are to made for it, and afterward it must be prepared with Water, Air and Fire, as with auxiliary Mediums, lest its fruitlessness be suffocated in the Earth. But with many and laborious Preparations of Artifice, it must be manifested and brought to Light, for the expected Sanation of Diseases, by reason of which it hath been so long sought into.”

Although the alchemists viewed antimony as a wonder drug, they also recognized its perils. No doubt intoxications leading to death occurred, and perhaps too frequently, which resulted in public outcry. Thus in 1566, in the kingdom of France, a prohibition against the use of medicinal antimony was instituted and was not rescinded until about a hundred years later (Iavicoli et al., 2006). A slightly different perspective is proffered by Garrison (1914) in his History of Medicine. He cites other authorities who believe that Basil Valentine may have been actually Paracelsus, who indeed in his time did promote the use of antimonials as well as other pharmaceuticals in medical practice. The prohibition against the antimonials in France may have been the result of rivalries between followers of the prevailing medical views of the time: Galen (Roman physician) and Paracelsus. Followers ascribing to the humoral theories of Galen were likely to use blood-letting methods, while the use of chemical therapeutics was promoted by
Paracelsus and his followers, and these two schools of thought had serious conflicts at the time. The medical establishment of the University of Paris being primarily “Galenists,” probably won out when misuse of antimonials became widespread, and thereby justified promotion of the nationwide prohibition against using medicinal antimonials (Haller, 1975). The rivalry between the Galenists and users of chemical therapeutics, who would be later known as allopathic medical practitioners, would continue for at least another century, with the allopaths ultimately winning out.

As mentioned before, the Romans drank wine from emetic cups made of antimony. This practice probably was resumed in the 17th century and continued for some time afterward. The Gentleman’s magazine (Urban, 1832) cites a reference from 1642 recommending the drinking of wine stored in cups made of metallic antimony for the treatment of various conditions and restoring health. It was recommended to fill the cup with wine in the evening and drink it in the morning. Health benefits could also be achieved by swallowing metallic antimony pills as noted by the magazine with “Frugal people” reusing these pills over and over.

Another important event in the history was isolation and purification of antimonyl potassium tartrate, commonly known as “tartar emetic” by Adrian de Mynsicht in 1631. Tartar emetic provided a purer and convenient form of absorbable antimony which became one of the most popular drugs until the middle of the nineteenth century (Haller, 1975). As Haller (1975) points out (p. 237), “…according to the dose given and the intervals between the doses, tartar emetic acted as an emetic, diaphoretic, expectorant, sedative, cathartic and irritant. He states, “Believing that the mechanical or “shock” effect brought on by perspiration, nauseas, and vomiting would check fevers and other inflammatory diseases if treated at the outset, physicians learned to rely on tartar emetic with a faith bestowed on few other drugs.”

The benefits of using antimonials were also no doubt accompanied with poisonings, both deliberate and inadvertent. Notable historical figures thought to have been poisoned by antimony, at least in part, include Napoleon (Mari et al., 2004). Napoleon was diagnosed to have had invasive gastric carcinoma. He was treated chronically for gastrointestinal symptoms with tartar emetic, but the day he died he was given a huge dose of calomel as a purgative. For years it was thought that he had died of arsenic poisoning because of traces of arsenic found in his hair. Mari et al. (2004) attributed his death to a heart attack caused by loss of potassium as a result of these purgative agents, but in view of antimony’s depression of heart function, an antimony effect cannot be ruled out as well.

**Antimony Medicinal Use, 19th Century to the Present**

As stated before, as the popularity of antimonial drugs increased, along with it came deliberate and unintentional poisoning by physicians. They engaged in extensive experimentation both in animals and in probably unwitting human subjects to understand the mechanisms of antimonial toxicity and to identify traces of it in bodily tissues. These efforts were extensively documented in medically-related books and journals of the 19th to early 20th century. Ironically, some of the most useful information about antimony is the self-dosing with tartar emetic that various physicians practiced upon themselves to understand the action of this agent (Mayerhofer, 1846; Taylor, 1857). Because of
widespread intentional and unintentional poisoning it was necessary for practicing physicians and forensic physicians (Taylor, 1857) to have an understanding of key issues such as: Is tartar emetic toxic to healthy people? Can it kill people at medicinal doses? Does it have to be absorbed to be toxic? Are there lingering effects (chronic toxicity)? These and other questions were such a concern for physicians of the early 19th century that the University of Munich posed the issue as a challenge to the scientists of the day with the reward of a prize (Mayerhofer, 1846).

Dr. Mayerhofer of Munich, Kingdom of Bavaria won the prize on the basis of work he conducted with animals and upon himself (Mayerhofer, 1846). Having described himself as in sound health, he self-administered small doses of tartar emetic to define its effects. He dissolved tartar emetic in distilled water to a concentration of one grain (65 mg) in 100 drops, and gave himself one drop (0.65 mg) before bedtime for five consecutive days. He felt fine afterwards. Dr. Mayerhofer (1846) was also doing [crude] urinalysis during the experiment, and at the end of this five-day period, he demonstrated little change in urinary components from the initial evaluation. The next day (6th day) he gave himself three drops, whereupon he reported that his sleep was disturbed, he had a sense of fullness in his head, and his tongue was dry and clammy; his appetite was unaffected. Apparently feeling these effects were rather mild, he then increased his dose to nine drops (5.85 mg) the next day (day 7). At this dose his sleep was much disturbed, and he felt oppression in the area of the heart, felt constipated, and had a greater sense of fullness in the head, and a clammy taste. His urinary analysis showed that the components and their proportions were dramatically changed. He continued with the previous dose for the next day (day 8), in which the above symptoms worsened with new ones appearing, including constriction of the throat, oppressed breathing, coldness and loss of power in the limbs, constipation, and a sense of oppression in the stomach. On the ninth day, 12 drops were taken with further enhancement of the above symptoms and in addition, great oppression of the heart, small and irregular pulse, nausea, increased flow of saliva and two liquid stools. On the tenth day, with 12 drops, there was further worsening of the symptoms, coldness in the torso area, pain in the abdomen, with increased perspiration and stools colored with bile. On the eleventh day, the same dose, worsening of symptoms and increased perspiration. On the twelfth day, he broke the pattern of nightly administration and gave himself six drops in the morning, and more severe symptoms followed including retching and vomiting. His vomit included traces of antimony, but no antimony in the urine. Two days were allowed to pass without treatment. The next day (day 14 according to Taylor, but not clear from original) 16 drops were taken. Effects similar to day eleven were reported with dizziness in bed. The following day (day 15?) 18 drops were taken, and greatly enhanced symptoms were reported, including vomiting. Apparently, Dr. Mayerhofer (1846) gave up on the experiment at this point. Weeks later (unspecified) after he had recovered from all the symptoms, he gave himself a grain of tartar emetic, whereupon he reported that in ten minutes he had great oppression of the heart, with greatly oppressed breathing and nausea; in fifteen minutes heaviness and fullness of the head, hurried respiration, sinking feeling, and loss of sight and hearing. In thirty minutes, he reported violent retching leading to vomiting. At this time Dr. Mayerhofer (1846) felt completely depressed and exhausted; he fell asleep, and awoke later with copious perspiration.
According to Taylor (1857) the experiment of Mayerhofer (1846) showed that small doses given sequentially can produce substantial poisoning, proving that there is a cumulative effect from antimony dosing. This concept was contrary to a prevailing theory of the time that tolerance to tartar emetic could be developed. He states that:

“The facts here recorded prove affirmatively that the action of tartarized antimony on the healthy human organism, when administered in small and gradually increased doses is far more powerful than it is commonly supposed to be. …[citing besides Mayerhofer, two other physicians who administered tartar emetic to themselves], a slight addition, …or even a persistence in the doses for a still longer period, would have destroyed the lives of these experimentalists. Had some of those writers who, on the occasion of the Rugeley poisonings, manifested so great a desire to prove that tartarized antimony was not a poison, and could not destroy life, showed only a reasonable confidence in their own theories, and had made themselves the subject of experiment with the drug, instead of relying upon rabbits and dogs, much erroneous speculation would have been spared….”

Furthermore, according to Taylor (1857), Mayerhofer (1846) as well others put to rest the theory of Rasori and others who dosed patients with large amounts of tartar emetic, claiming that it induced tolerance to the effects of the emetic (tolerance will be addressed later). The attempt to demonstrate tolerance may explain Mayerhofer’s experimental protocol. When he broke off from his treatment for approximately two days, he still was not able to withstand the effects of tartar emetic upon resumption of dosing. Furthermore, after he had recovered for several weeks, upon dosing himself with what was considered a minimal dose of emetic purposes, he had immediate and severe emetic effects. Taylor (1857) reports that a follower of the Rasori theory, Laennec, claimed to give twenty to forty grains to patients with pneumonia who he claimed to be cured after tolerating these high doses. Taylor disputes this by citing high mortality rates for patients treated by these physicians. He concedes that some patients may be inherently more tolerant of tartar emetic due to some idiosyncrasy. Taylor (1857) cites Magendie, who reported that persons affected with apoplexy, paralysis or mania, seem to bear large doses without injury.

Taylor (1857) was involved in resolving criminal cases of tartar emetic poisoning. A British physician of the time, Palmer, had poisoned his wife, mother-in-law, a friend and his three children, with no one suspecting anything. Being a “gambler” in life insurance, Dr. Palmer figured out how to administer tartar emetic without drawing suspicion by giving low doses of tartar emetic (unknown) that produced few symptoms, but still ultimately caused death. Dr. Taylor was able to prove the culpability of Dr. Palmer by demonstrating high amounts of antimony in the victims’ tissues.

The use of tartar emetic declined gradually, to the point where, although still cited in medical texts of the late 19th and early 20th century, the authors of these texts were very dissuasive or cautious regarding the drug’s use. Although effective as an emetic, tartar emetic was said to not be fast-enough acting, and having too strong a response, which limited its usefulness in fighting intoxications from other substances (Hare, 1905). Many authors considered it to be too toxic to be used in children. This was also true for other metal-based medicinals of the time, i.e., arsenic and mercury (Hare, 1905; Shoemaker,
Better and safer drugs were available and coming to generalized use. Only for fighting parasitical infections have antimonials (particularly the safer, pentavalent forms) continued to be used with success up to the present day.

**Acute Toxicity**

A guide to poisons and their effect (Blyth and Blyth, 1906) describes rather notorious cases of the time dealing with both accidental and intentional poisoning. Medicinal doses for tartar emetic should not exceed 97.2 mg, it is reported, although dosages for emesis were known to exceed that amount. The lowest dose recorded to produce death in an adult was 129.6 mg, while the lowest fatal dose in a child was 48.5 mg. With moderate to large doses (not specified, but may be at the upper therapeutic range) nausea and vomiting were very prominent symptoms, occurring usually within half an hour of intake. First, a metallic taste is noted, then repeated vomiting, sometimes bloody, with great faintness and depression, and pains in the abdomen and stomach. With fatal doses, the face becomes cyanotic, delirium and convulsions supervene, and death occurs from two to six days.

A case (Blyth and Blyth, 1906) was recounted where a servant and two children got ill from ingesting lozenges which (apparently unintentionally) contained 16 mg of antimony present in a non-organic form.

From the Dispensatory of the United States of America (Wood and Bache, 1892) 10 grains (650 mg) is listed as the smallest fatal dose.

In more modern times, several antimony poisoning incidents have been reported, with suicide attempts and inadvertent poisonings, and with the treatment of leishmaniasis. Dunn (1928) reported an incident in which workers began to vomit upon ingestion of approximately 37.5 mg of metallic antimony equivalent (0.53 mg/kg, based on a 70 kg man) after lemonade was contaminated by extraction of antimony from enamel-coated buckets. The author notes that this dose coincides with the minimum required dose range for emesis of 32 to 65 mg, from the British Pharmacopeia. Kaplan and Korff (1937) reported several instances of “food poisoning” that were traced to antimony extracted by acid contents from enamel-coated vessels. Humans surviving acute exposures appeared to have no lasting sequelae. Reported poisoning from use of antimony-glazed enamelware occurred both in the U.S. and in Europe (Dunn, 1928; Flury, 1927; Kaplan and Korff, 1937). Antimony’s use in enamelware was banned by Germany and Austria in the late 19th centuries due to the ability of food acids to leach antimony (Flury, 1927; Kaplan and Korff, 1937). Less leaching with acids occurred when silica was added to the glaze, perhaps stabilizing antimony by binding to it (Kaplan and Korff, 1937).

Four adults were admitted to a hospital suffering from severe abdominal cramps, nausea, and continuous vomiting and water diarrhea after ingestion of cake in which “tarter emetic” (antimony potassium tartrate) was substituted for cream of tartar. Moderate leukocytosis, hemoconcentration and decreased extracellular volume were noted. All patients exhibited anorexia and asthenia, but no other pathologic signs were found in three patients. Electroencephalogram rhythms were abnormal for two patients. The remaining patient, a 93-year-old man, exhibited severe gastrointestinal bleeding and died.
from cardiac and respiratory failure. Estimated dose of tartar emetic was 850 mg per person (Lauwers et al., 1990), which is at least ten times the minimum emetic dose.

Subacute to Subchronic Effects

A pharmaceutical text in its 11th edition (Hare, 1905), reports that antimony compounds in various preparations were used in pharmaceuticals, including antimony potassium tartrate or tartar emetic, antimony sulfide (several forms, including Kermes mineral) and antimony oxide. Tartar emetic was considered the most desirable form by the author; Kermes mineral was also commonly used, but considered inferior by the author. Kermes mineral was used to induce circulatory depression, sedation and as an expectorant at 0.01 mg every hour or two, and for emesis at a dose of 0.06-0.25 mg.

Tartar emetic was considered to be more difficult than the other forms to put into solution, but once suspended, the author warned against taking it with alkalis and acids, since that enhanced the action of the emetic. Tannic acid was considered inhibitory, as it reacted with the emetic to essentially precipitate out the antimony. Tartar emetic was considered to be depressant to the sensory nervous system, paralyzing spinal centers and motor and sensory neurons at a poisonous dose and producing convulsions at higher doses. The author attributes its action to lowering the pulse rate and simultaneously decreasing arterial function by direct action on the blood vessel walls. Death as a result of poisonous doses is said to ensue from circulatory and respiratory depression. Respiratory depression stems from an action of antimony upon the medullary centers, and results in a large amount of mucous production, which fills the lungs and results in suffocation. As for the gastric system, the compound is a powerful irritant and emetic attributed by the author to action upon both the medullary emetic center and directly upon the stomach (Hare, 1905).

Emetic and Nauseating Action

The hallmark effect of antimony and particularly of tartar emetic has been emesis. Hare (1905) noted that the early signs of poisoning by tartar emetic include at first a slightly weakened pulse and a sense of relaxation, followed by violent emetic episodes, cold sweats and cramps. These were similar to the signs of Asiatic Cholera, a common disease of the times, thus some intoxications with antimony were probably missed. Intoxications with arsenic would also have similar signs, but usually this was a characteristic of antimonials (Sollmann, 1917). It should be noted that antimonials are corrosive to the stomach, which was often evident upon autopsy (Taylor, 1857), and no doubt localized gastric disturbance also provokes an emetic response.

As an emetic, recommended doses of tartar emetic were from 30 to 60 mg every three hours (Ringer, 1880). From the Dispensary of the United States of America (Wood and Bache, 1892) one grain (65 mg) produces severe nausea and vomiting.

To suppress the emetic action of tartar emetic, opium was co-administered (Hare, 1905). Perhaps this was how the emetic was used as an anesthetic, because certainly emetic action is not desirable for patients undergoing surgery. But the intake of opium itself is
nauseating, so could the opiate suppression of emetic action be related to antimony acting upon opiate receptors in the brain?

Ringer (1880) also noted that diets have an effect upon the action of the emetic. Wine and fruits enhanced the action of tartar emetic. We have already discussed that wine can extract antimony from its metallic form. The preferred wine in this case was white or sherry, perhaps because tannic acid also inhibits the action of tartar emetic.

Tolerance to the emetic action of the drug sometimes developed. This was the objective of many early physicians who tried to achieve some of the more beneficial effects of tartar emetic instead of the nausea. As noted before, large doses (10 grains or more at a time) were advocated by physicians Rasori, Lannec, and others to induce emesis, so that tolerance to emesis could be developed (Taylor, 1857). In a variant on this approach, because there was so much individual variation in response to tartar emetic, physicians tried to use medium doses (less than 1 grain) and step them up to achieve the emetic dose and then pull back. Unfortunately, some physicians did not understand that when tolerance developed to emesis, other life-threatening effects still needed to be monitored for during dosing so that the patient wouldn’t succumb to them. An unfortunate example is cited by Beck (1864), in which a child was given continued doses of tartar emetic (unspecified) to control asthma, to the point of emesis. Emesis eventually ceased and ever-increasing doses would not produce it. General prostration set in and the child died. Thus it was generally recommended that physicians employing this approach carefully monitor the respiratory and cardiac depression of the patient.

Cardiac Toxicity

As noted earlier, an early sign of antimony intoxication is a lessening of the pulse. Hare (1905) states that tartar emetic was used most commonly as a sedative and circulatory “quieter,” although the author feels that there are better drugs for this use. A dose of 3 to 6 mg tartar emetic could be used for this purpose every three hours. From the Dispensary of the United States of America (Wood and Bache, 1892) a minute dose of tartar emetic given to man is 1/12 of a grain (5.14 mg), which produces a slight lessening of the force of pulse and tendency to increase perspiration. Trousseau and Pidoux, as cited by Beck (1864) stated that in their practice they noticed the pulse of patients treated with antimony slowing starting at three days from 72 to 44 beats and remain a long time at the latter rate. However in a certain number of cases, the pulse did not slow, but became irregular.

Ringer (1880) indicated that in animal experiments there was direct depressive action of antimony upon the heart, even when it was removed from the body. If tartar emetic was injected into the heart, beating would decrease.

Cardiac effects have been noted in more modern studies. Brieger et al. (1954) examined workmen in a plant where antimony trisulfide was used in the manufacture of grinding wheels. Antimony levels throughout the plant ranged from 0.58 to 5.5 mg/m³ antimony trisulfide, with the majority of readings being over 3.0 mg/m³. About 10 percent of exposed workers had elevated blood pressure, half of those monitored showed significant changes in their electrocardiograms (EKGs), mostly in the T-wave, and an increase in ulcers was also noted in plant workers.
Wars in the tropics resulted in many infections with parasitical diseases such as leishmaniasis, with an increase in use of antimonials to treat these diseases. Schroeder and colleagues (1946) were concerned about cardiac effects of antimonials reported by other authors. They cited Mainzer and Krause (1939) who were investigating the cause of sudden deaths during antimony therapy by looking at EKG changes in 12 schistosomiasis patients treated with tartar emetic. They found ST-interval and T-wave changes which were definitely pathologic in 3 cases, suspicious in 4 cases, and insignificant in 2 cases. They also cite Tar (1946) who reported T wave changes in 80 percent of 66 patients treated with antimony. These changes were reported to be lowering or inversion of the T wave particularly, in all patients administered tartar emetic.

Schroeder and colleagues (1946) studied the effects of sodium antimony bis(pyrocatechol-2,4-sulfonate) (Stibophen NF or fuadin) administered intramuscularly and potassium antimony tartrate iv daily or on alternate days for about one month to patients for treatment of schistosomiasis. Estimated doses ranged from 0.24 to 0.89 mg/kg-day. Total dose of tartar emetic administered during the entire course of 29 days was 1.45 g, with the amount of antimony alone being 0.87 g. Examination of 315 EKGs from 100 patients did not show, in the authors’ opinion, major changes to the heart indicative of damage. The authors did note that the maximum effect of antimony may have been missed while obtaining the EKGs, as some were taken too early in the course of treatment and some several days after treatment was completed. They found no changes in heart rate. They did find an increase in amplitude of the P waves in 11 percent, a fusion of the ST segment and T waves in 45 percent, varying degrees of decrease in amplitude of the T wave with deep inversion of the T wave in 99 percent, and a prolonged Q-T interval in 27 percent of the patients. The changes could persist for two months after cessation of treatment. A few patients were treated with the pentavalent antimonials neostibosan and stibanose, and those patient’s scans were reported to be similar to the rest of the patients taking the trivalent antimonials except to a less marked degree, with some exhibiting no changes at all.

A study followed 59 Kenyans treated with 10, 20 or 40 to 60 mg/kg-day of sodium stibogluconate for leishmaniasis (Chulay et al., 1985). Dose-related increases in EKG abnormalities were noted following 65 courses of antimony treatment over four months. The incidences of EKG abnormalities were 22 percent (2/9) at 10 mg/kg-day; 52 percent (25/48) at 20 to 30 mg/kg-day; and 100 percent (8/8) at 40 to 60 mg/kg-day. The frequency of EKG abnormalities in individuals increased with duration of treatment.

A more recent report (Hepburn et al., 1994) describes the cardiac effects of treatment of twelve soldiers with cutaneous leishmaniasis with pentavalent antimonials in doses of 20 mg/kg-day. They also described the reversible changes to the T wave amplitude, systolic and diastolic blood pressure, and heart rate with some arrhythmic frequencies.

Diaphoretic Action for Fever, Pneumonia, Colds and Asthma

Antimony was used in the treatment of various respiratory conditions since the time of Valentine (Valentine, 1678). It is not clear which of the effects caused by tartar emetic provided the desired relief; perhaps it was respiratory depression or the cathartic effects.
of diaphoretic action (sweating) and increase in bronchial secretions. As noted previously, early into the 19th century certain physicians popularized the concept of giving very large doses (10 grains and over) for the treatment of fever, and patients did survive this course. However, as Taylor (1856) points out, the survival rate was not particularly impressive, meaning that perhaps the patients survived in spite of the large dose of emetic. Nevertheless, in the treatment of fevers, use of tartar emetic was very popular. Later in the century, tartar emetic became the treatment of choice for certain “intermittant” fevers, but not for all types of pneumonia (Waring, 1874). He continues, “As a general rule, it may be said that antimony is best adapted to inflammatory and febrile affection occurring in the young and plethoric, when there is much vascular excitement, with a full, bounding, unyielding pulse, hot, dry skin, and scanty urine....”

In a communication from India in 1849, Moore (1849) reported the successful treatment of sufferers of intermittent fevers, also called “fever and augue,” with small doses of tartar emetic. Doses for males started at 1/50th of a grain and were administered on a half-hour to hourly basis until relief was achieved. For women and children the starting dose was invariably dropped to 1/100th of a grain. The goal was to achieve prostration without severe vomiting. It cannot be excluded that these patients could have been suffering from malaria and related conditions.

Hare (1905) associated tartar emetic with treatment for the state of “sthenic inflammation” (bounding pulse, high fever - with qualification). This category includes treatment of colds, bronchitis (acting as an expectorant), and as a disease “preventative.” Doses were 1 mg every hour or a teaspoon of a solution of 30 mg in 4 oz every hour (considered sub-emetic doses). This treatment and dose was considered valuable for children to stop catarrh attacks (asthma) as it did not produce emesis.

Gerhard (1860) addressed the pneumonia treatment of his day by stating that tartar emetic is not as useful as he once thought it to be for treatment of this condition. Nevertheless, he recommended it in sthenic pneumonia in doses of 1/16th to 1/6 of a grain every two hours. He recommended discontinuation of dosing when signs of prostration or lessening of strength are obvious.

Ringer (1880) highly recommended tartar emetic for colds in children. Recommended dosage for children is one teaspoon of a solution of 1/2 grain (32.5 mg) in a half pint (32.5 mg/235 mL = 0.14 mg/mL x 5 mL/teaspoon = 0.7 mg). This would be administered every quarter hour until one hour, then one dose/hour thereafter, or 2.8 mg for the first hour and 0.7 mg/hour later. Ringer says, “So small a dose, it may seem inefficacious, but when first given, it produces vomiting once or twice a day, and, as it is not necessary to produce sickness, the dose in this case must still be lower.”

Ringer (1880) recommended co-administration of tartar emetic with quinine for treatment of malarial fever [perhaps an early indication of its antiparasitical actions?]. He also recommended tartar emetic to control kerato-conjunctivitis, 1/36th to 1/48 of a grain (1.8 to 1.35 mg) three to four times daily.

From the Dispensary of the United States of America (Wood and Bache, 1892): A dose starting at 1/32 of a grain (2.03 mg) is used as an alterative (a medicine which gradually induces change and restores function without sensible evacuations) [diarrhea; may be a minimum effective dose?]. The doses listed were from 1/12 grain (5 mg) for use as a
diaphoretic and expectorant, up to 1/3 grain (21 mg) as a nauseating sudorific (diaphoretic).

From the eminent pediatrician Kerley (1914), the following prescription was made with tartar emetic compounded with ipecac and ammonium chloride, for children having severe bouts of bronchitis:

Under 6 months: 1/150 grain (0.43 mg) every two hours, eight times a day.
Age 6 months to 1 year: 1/100 grain (0.65 mg) every two hours, eight times a day.
Age 1-3 years: 1/100 grain every two hours, eight times a day.
Over 3 years: 1/80 grain every two hours, eight times a day.

Kerley (1914) did not recommend the administration of tartar emetic for colds or mild bronchitis.

A text by Potter (1903) notes that tartar emetic is practically obsolete for its intended uses as an emetic and depressant, because it acts too slowly as an emetic and is too toxic, particularly for children, as a depressant. As with Kerley (1914), he affirms that its remaining benefit lies in the treatment of bronchopneumonia and bronchitis. His recommended doses are 1/50 grain for adults and 1/100 grain for children every two hours until relief is achieved. For the conditions of acute cold and bronchitis, asthma and emphysema, higher doses can be used, of 1/16 grain (presuming the same dosing schedule).

Consistent with the information in the other books, Buck (1904) describes tartar emetic at 5 mg [likely daily dose] as causing respiratory depression and increased secretions; at 10 mg, nausea begins, and at 30 to 120 mg, vomiting.

**Dermal Toxicity**

Antimonials such as tartar emetic and antimony chloride have been applied as ointments and plasters to the skin for the treatment of various conditions although they were irritating and provoked a rash, “antimony spots.” Waring (1874) and Hare (1905) note that antimony is acting as a counter-irritant in the treatment of enlargement of joints [arthritis?]. Caution was made not to apply to excoriations or wounds (apparently because absorption was increased). Tartar emetic applied to the skin was also used to control the third stage of pneumonia (Gerhard, 1860). Another use in this category was for epilepsy, where antimonials in ointments were applied to the back of the neck (Waring, 1874).

Effects on antimony workers have been primarily signs of lung irritation, gastric irritation, pneumoconiosis, fibrosis, metal “fume” fever, cardiac effects and dermal reactions. Antimony dermatitis, commonly known as “antimony spots,” has been known for as long as antimony processing has occurred (Oliver, 1933). Lesions appear on the forearms, wrists, thighs, lower legs and in the flexures, the trunk, back of neck and scrotum, but they do not occur on the face, hands or feet. These occur mainly in summer months in workers working in the vicinity of furnaces. White et al. (1993) described this dermatitis in three workers melting antimony in the manufacture of brazing rods who were exposed to antimony fumes and antimony trioxide. Beside skin lesions, nosebleeds
were also reported. The TWA was below Occupational Safety and Health Administration (OSHA) limits but was reported to exceed the OSHA Permissible Exposure Limit (PEL).

Antimony pneumoconiosis was described by Karajovic (1958) in a population of antimony miners and smelters in Yugoslavia, based on diffuse x-ray opacities. Other respiratory effects noted in workers include impaired airways obstruction, bronchospasm, hyperinflation, coughing and wheezing, although these effects could have been due to other compounds (Cooper et al., 1968; Potkonjak and Pavlovich, 1983).

Antimonials for Control of Parasitical Infections

A remaining use of antimonials, particularly in 20th century medicine, was to treat certain parasitical infections such as schistosomiasis and leishmaniasis. This treatment was discovered early in the twentieth century and persists to the present day. However, effective doses were often toxic to the patient and increasingly pentavalent antimonials have been used in place of trivalent ones due to their lower toxicity.

Sollmann (1917) stated that Paracelsus recommended antimony’s use against the plague. Sollmann noted that antimony, bismuth and arsenic are highly toxic to trypanosomes but not to all protozoa. Furthermore, he cites other investigators who tested experimentally as well as successfully treated patients with trypanosomal infections with injected tartar emetic. The recommended intravenous dose was 10 mg of tartar emetic.

Effects of treatment with antimonials on these parasitic conditions were described above.

Genetic Toxicity

An association of exposure to antimony and oxidative DNA damage was noted in workers (Cavallo et al., 2002). Twenty-three workers assigned to activities involving antimony trioxide as a textile fire-retardant were assessed for antimony exposure with personal monitoring devices. The exposed group was split into two groups based on job function; one group had substantially more direct exposure to antimony than the other. These groups were tested and compared with controls (selected and matched according to smoking and age). Blood was tested for sister chromatid exchange and micronuclei, and in an FPG (formamido-pyrimidine-glycosylase) enzyme-modified comet assay. While no differences from controls were noted in the sister chromatid exchange and micronucleus assay, the FPG enzyme-modified comet assay showed a significant difference between the high exposure group and controls (p = 0.002); no significant difference was noted between the lower exposure group and controls. Since the FPG comet assay offers a specific measure of DNA damage, the authors concluded that antimony appeared to have the potential for DNA damage.

Developmental and Reproductive Toxicity

One study (Belyaeva, 1967) reported disturbances in menstruation and an increase in the number of spontaneous abortions in women exposed to airborne antimony in the
workplace. No obvious developmental effects were observed in the children of these women.

**Neurotoxicity**

By the middle of the 19th century physicians recognized that besides local action on the stomach, antimonials were affecting the emetic center of the brain. Animal experiments with antimony at the time confirmed that the emetic action was stimulated in part centrally (rather than by direct action upon the gastrointestinal tract), since injection of tartar emetic could stimulate emesis as well (Ringer, 1880). However, not all people treated with tartar emetic vomited. Taylor (1857) noted that there is an individual variation in that effect, although other effects continued to be seen, such as sedation or muscular weakness. Taylor (1857) quotes Magendie, who reported that persons affected with apoplexy, paralysis or mania seemed to bear large doses without injury [serious side effects].

The cardio/respiratory effects of antimony could also be CNS-mediated. Furthermore, Hare (1922) stated that antimony is a depressant to the sensory side of the spinal cord, and a paralyzant to all spinal centers, motor and sensory. Earlier, Hare (1905) commented that tartar emetic had been used as an anesthetic, but apparently this use was obsolete, as the author stated that better agents were available. Sedation is a key effect with acute to subchronic dosing of tartar emetic.

According to Waring (1874), tartar emetic was used to control acute idiopathic mania. He referred to a Dr. Van der Kolk using ¼ to ½ grain of tartar emetic several times a day with a meal to control this condition. Van der Kolk noted that this dosage can depress the brain and vascular system without concomitant vomiting. As the dose is gradually increased (apparently indicating tolerance to the emetic effect), the patient becomes calmer and clearer and proceeds often to recovery. It was also said that when recovered, the patient becomes intolerant to the dose and would vomit.

Waring (1874) also indicated uses of tartar emetic to treat delirium tremens, “purpural convulsions” and epilepsy. For epilepsy a dose of 1/8 to 1/4 grain every four hours was effective, according to Bell (1857), who used it successfully in several cases. Only a few other sources mentioned treatment of neurological disorders with antimonials, so this seems to have been a rare, although interesting, use of the drug, based on a broad survey of the available texts.

There are indications that antimony can cause a sense of depression (despair), as described by Mayerhofer (1846). This could be one reason why it was rarely chronically administered when other drugs were available, or was coadministered with opium and alcohol.

Cerebellar ataxia has been associated with long-term treatment with sodium stibogluconate, a pentavalent antimonial used for visceral leishmaniasis. Two Sudanese patients who were treated with Pentostam® (Khalil et al., 2006) exhibited signs of this condition which went away when the drug was withdrawn.

Antimonials have also been used to treat or control alcohol abuse. Hare (1905) referred to the treatment of alcoholism as a popular, but not medically-indicated use of
antimonials. In one instance (Tarabar et al., 2004), a 19-year old man with symptoms of diarrhea, vomiting and stomatitis presented himself for emergency treatment. With a history of alcohol abuse, he had ingested a 10 mL bottle of “Soluto Vital” (50 mg/mL tartar emetic), a drug from Guatemala. This patient suffered from renal insufficiency and severe dehydration hypokalemia, but fortunately for him, it did not lead to myocardial collapse and death. The authors noted that Dr. Benjamin Rush (a Philadelphia physician, 1745-1813) advocated use of tartar emetic for alcohol dependency. Reportedly this practice persists in some parts of the world, and was explored in the U.S. at one time as well for abstinence therapies.

Chronic Toxicity/Carcinogenicity

Waring (1874) reported that chronic dosing with antimonials (dose unspecified) produces irritation of the throat and ulceration of the mouth. By cautiously increasing the dose, tolerance (to the nausea and emetic effects) may develop to a high dose. With continued dosing the patient was likely to develop great weakness and emaciation, which may ultimately result in death.

According to Hare (1905), chronic poisonings were rare occurrences, and then mostly likely from dermal exposures. Typefounders and typesetters were given as examples, presumably associated with handling antimony allows. Their symptoms were said to include peripheral neuritis, disorders of the bladder and irritability of the prostate, headache, abdominal tenderness, and profound mental and circulatory depression.

Major contributions to the understanding the effects of low, continuous dosing with antimonials can be attributed to 19th century homeopaths. At a time when physicians like Rasori were advocating high doses of tartar emetic, other physicians felt that allopathic medicine had gotten too barbaric and that smaller doses (i.e., a gentler approach) could be used to treat certain conditions. Apparently, homeopathic physicians at the time were interested in discovering the minimum doses of drugs that patients were responding to. They selected what could be considered “threshold” doses to effects they were trying to treat, by paying very close attention to what the patients were relating as to the symptoms they were experiencing at lower and lower doses. Then according to homeopathic principles, they would do make large dilutions of this minimal doses. Thus we must credit these physicians in making the effort to determine minimal to no-effect doses of tartar emetic. One such physician was William Bayes (1871), who discussed treating a female patient who was constantly throwing up, but gradually stopped when given a “minute dose” of tartar emetic, which he defined as 1/100 of a grain. He reported that her symptoms got better after the second dose, and within a week she was cured. He clearly distinguished the medium dose of tartar emetic for an allopathic regimen to treat inflammation of the lungs to be 1/6th to one 1/8th of a grain, while the homeopathic dose for this condition would be 1/100th to 1/1000 grain or less. He noted that giving tartar emetic to children with bronchopneumonia at 1/500 to 1/100 (1st centesimal) of a grain induced mucus rale and softened the cough or breathing, while 1/1,000,000 of a grain (3rd centesimal) did not produce that effect.
Occupational Studies of Antimonial Exposure

Potkonjak and Vishnjich (1983) reported on the health of 51 workers from a smelting plant exposed to dust of predominantly antimony oxide for 9 to 31 years (mean 17.9). Measured dust concentration was 86 mg/m\(^3\) (maximum), and 80 percent of the particles were below 5 \(\mu\)m in size. The study found definite pulmonary changes (pin-point opacities) characteristic of pneumoconiosis, which Potkonjak and Vishnjich designated as antimonosis. These changes were evident in all workers in the study. Other respiratory signs noted were chronic coughing, conjunctivitis and upper airway inflammation. No other evidence of systemic toxicity was noted, including electrocardiograph disturbances. No malignancies were noted in the study population.

A survey of mortality at an antimony smelter in England indicated that workers employed prior to 1960 had double the incidence of lung cancer over a control worker population (Jones, 1994). The cohort recruited after 1960 showed either the same or a diminished cancer rate compared to the control population. The investigator attributed the result to changes in the processing of antimony, which changed from primarily production of antimony alloy to production of antimony trioxide. During this period the ore used was changed to a type that contained more antimony and (implied) less arsenic. The influence of smoking on incidence rates was not accounted for and cannot be ruled out, nor can changes in exposure levels. Jones (1994) proposed that the excess of cancers could be attributed to arsenic exposure and possibly other carcinogens that diminished after 1960 when the type of processing changed.

A mortality study with a large cohort (1,014 men) from a Texas antimony smelter was conducted by Schnorr et al. (1995). Men employed from 1937 to 1971 were evaluated for lung cancer mortality, EKG abnormalities, and heart and lung disease. The population was mostly Hispanic, which led to some difficulty in finding appropriate reference groups for comparisons. There was a slightly elevated rate for lung cancer deaths (standard mortality ratio, or SMR, of 1.39) against a Hispanic surname group, but a SMR of 0.52 against a white population. There was also a positive trend toward increasing lung cancer rates with duration of employment. For ischemic heart disease, SMRs were 0.91, 1.22 and 1.49 against three different comparison groups. For pneumoconiosis or other lung disease the SMR was 1.22 versus white males (a Hispanic comparison population was unavailable was this measure). The ore and smelting process changed little from when the smelter opened in 1930 to 1979. No exposure data were available until National Institute of Occupational Safety and Health (NIOSH) surveys in 1975 and 1976 reported geometric means of 551 and 747 \(\mu\)g/m\(^3\), respectively. Both mean values are above the OSHA standard of 500 \(\mu\)g/m\(^3\).

In a study of 26 art glass workers in Italy (Goi et al., 2003), where workers had been exposed to substantial amounts of antimony and arsenic, several lysosomal enzymes in blood were evaluated. Workers did not exhibit any clinical signs of poisoning. The enzymes studied were N-acetyl-\(\beta\)-D-glucosoaminidase (NAG), \(\beta\)-D-glucuronidase (GCR), \(\alpha\) and \(\beta\)-D-galactosidase, \(\alpha\)-D-glucosidase, and \(\alpha\)-mannosidase in plasma. Results were compared with in vitro actions of Sb and As on human lymphocytes in culture. No significant differences in the plasma levels of the certain enzymes was detected, compared to control subjects. In the cultured cells Sb enhanced release of
lysosomal glucohydrolases by as much as 225 percent, while with As the enzymes were decreased by 57 percent. The plasma levels of the enzymes appeared to be increased in several workers with the highest urinary levels of either As or Sb.

**Interactions with Other Substances and Processes**

As discussed before, Gebel and colleagues investigated the mechanism of arsenic genotoxicity by comparing its interaction with other substances including antimony (Gebel, 1997, 1998, 2001; Gebel et al., 1996, 1997; Hasgekar et al., 2006). Both arsenic and antimony appeared to induce micronuclei and chromosomal aberrations, with arsenic much more potent than antimony (Gebel, 1998). Arsenic’s genotoxicity could be modulated by either selenium or antimony. For example, As (III) chromosome mutations and sister chromatid exchanges can be suppressed by Sb(III) in culture (Gebel, 2001). Gebel (2001) noted that although antimony is not a point mutagen, its role could be like that reported for arsenic, being involved in modulating DNA repair. Takahashi et al. (2002) showed that two compounds of antimony were able to inhibit the repair of double-stranded DNA breaks, perhaps like arsenic through the inhibition of the incision step in the nucleoside excision repair process. Fragmentation of parasitic DNA was suggested as the mechanism of antimonials against leishmaniasis (Sereno et al., 2001).

Huang et al. (1998) noted DNA fragmentation as a marker of apoptosis in human fibroblasts, CHO cells, and human bronchial epithelial cells in a four-hour exposure to SbCl₃. In a followup, potassium antimonyl tartrate induced reactive oxygen intermediates, which appeared to mediate apoptosis in human myeloid leukemic HL60 cells (Lecureur et al., 2002a). Lecureur et al. (2002b) noted that potassium antimonyl tartrate increased caspase and reactive oxygen intermediates in apoptotic human lymphoma cells (Daudi and Jurkat cells). Apoptotic activity was diminished by addition of N-acetylcysteine, with which antimony probably reacts directly (Muller et al., 1998).

Mann et al. (2006) showed that antimonials, like arsenicals (Davison et al., 2003), induce apoptosis in acute promyelocytic leukemia cell lines. Such apoptosis is associated with the production of reactive oxygen intermediates and induction of caspasas, and within the acute promyelocytic leukemia cells, the cascade of reactions mediating apoptosis appears to be dependent upon the factors SEK1/MKK4 and JNK/SAPKβ. Antimony trioxide also inhibits growth of the PLB myelocytic leukemia and HeLa cervical adenocarcinoma cell lines, although those cell lines were not as inhibited as the acute promyelocytic leukemia cell lines. Mann et al. (2006) also reported that MCF-7 breast carcinoma cells and doxorubicin-resistant NIH eT3 cells could be inhibited, but it took 10-20 times the concentration of antimony trioxide to do so. The authors found that antimony trioxide could cleave PARP, a chromatin-associated enzyme involved in DNA repair as well as a mediator of cell death. They also found that antimony, like arsenic, could cause at least a partial differentiation of leukemic cells, based on the expression of a cell surface marker. Antimony-induced apoptosis, like that for arsenic, was increased by buthione sulfoxime treatment, which decreases intracellular glutathione. A leukemic cell line that is resistant to arsenic because of a presumed increase in the glutathione content was shown to be resistant to the effects of antimony. Oxidative stress produced by antimony is thought to be the reason for an increased production of reactive oxygen intermediates. The authors
showed that antimony trioxide increased the activity of JNK in a dose-dependent manner, which enhances the SEK1-JNK cascade thought to be mediated by reactive oxygen intermediates and is apparently involved in antimony-induced apoptosis.

Similarly, Sereno et al. (2001) studied the effects of pentavalent and trivalent antimonials on immature forms of Leishmania infantum amastigotes. They concluded that trivalent antimonials were exceedingly effective (at the low concentration of 10 μg/mL) in inducing DNA fragmentation, leading to cell death. They observed that although certain aspects of antimonial action appeared like late-stage apoptosis to involve endonuclease activity, there was a lack of activation of nucleases caspase-1, caspase-3, calpain, cysteine protease or proteasome activation. More study appears to be needed to determine if a different set of caspases/enzymes are involved in generating DNA fragmentation in this organism.

Anticancer activity for sodium stibogluconate was suggested (Yi et al., 2002) when it was observed that this agent appeared to synergize with IFN-α to eradicate various human tumor cell lines in culture and in vivo in IFN-α refractory human melanoma cell lines in nude mice. Critical to the effect of the antimonial was the induction of tyrosine phosphatase inhibition, which is thought to inhibit IFN-α signaling. IFN-α and other cytokines are thought to function via the Janus kinase (Jak)/Stat pathway. The antimonial inhibited protein phosphatases SHP-1 and SHP-2, which negatively regulate Jak/Stat signaling. The antimonial enhanced IFN-α activity, was shown to alone inhibit the induction of Stat 1 tyrosine phosphorylation, and inhibited growth of tumor lines that lacked the IFN-α signaling pathway altogether.

Tirmenstein et al. (1995) attempted to elucidate the nature of antimony cardiotoxic effects through experiments on cardiomyocytes. Potassium antimonyl tartrate induced formation of reactive oxygen intermediates that could harm normal cells in neonatal cardiomyocytes. However, it was thought that neonatal cardiomyocytes might be more susceptible to reactive intermediates, perhaps due to low glutathione (Tirmenstein et al., 1995, 1997). Using sublethal concentrations of antimony, they noted that intracellular calcium mobilization could be inhibited during the excitation/contraction response.

Carrying this further, Wey et al. (1997) showed that antimony treatment increased intracellular Ca\(^{2+}\) in the myocytes. Addition of a calcium chelator to the culture inhibited the cell toxicity. This work appears to support the thesis that antimony, unlike other metals such as iron, does not directly produce oxygen radicals, but rather produces them through stimulation of existing oxidative processes in the cell (probably at the mitochondrial level). Further work by the same group (Snawder et al., 1999) showed that sublethal levels of antimony increased glutathione and heme oxygenase activity. Furthermore, induction of the heat stress proteins HO-1, HSP70, and HSP25/27 was noted, but with no increase in HSP60. After an 18-hour period of exposure to sublethal levels of potassium antimonyl tartrate, the cardiomyocytes were able to withstand an otherwise lethal concentration of the same agent. The authors reason that this protection was afforded by induction of the stress proteins and increased glutathione concentration. This protection was removed upon addition of protein synthesis inhibitors.

The role of iron, reactive oxygen species, glutathione and Ca\(^{2+}\) were investigated in the antimony- and arsenic-induced death of Leishmania (Mehta and Shaha, 2006). Both
Metalloids can induce cell death through apoptosis and DNA fragmentation, with an increase in reactive oxygen species. Both cause mitochondrial dysfunction with loss of membrane potential. In this study, arsenic increased intracellular levels of Ca\textsuperscript{2+}, while antimony did not. Cellular glutathione levels were reduced by antimony, but not byarsenic, and addition of glutathione rescued cells treated with antimony, but not arsenic. Finally, iron depletion increased cell survival despite exposure to antimony or arsenic.

One of the critical issues for understanding antimony toxicity remains the importance of speciation, which has not been well studied. Arsenite has been proven to be more toxic than arsenate, particularly after being methylated, and this relationship was thought to be true for antimony (Patterson et al., 2003). Using cultured human keratinocytes, Patterson et al. (2003) showed that pentavalent As or Sb added to the cell cultures resulted in little reduction to the trivalent forms. The trivalent Sb was similar to the pentavalent As form in its toxicity to keratinocytes, while pentavalent Sb was virtually without effect.

Metalloid transport is another aspect of interaction of antimony ions with cells that is apparently significant to toxic mechanisms. Uptake of antimony and arsenic depends upon transporter proteins (Bentley and Chasteen, 2002; Tamas and Wysocki, 2001). In bacteria, resistance to the toxic effects of arsenic and antimony has been found to involve induction of specific operons that confer resistance by inhibiting production of these transporter proteins. The toxicological relevance of this is that higher organisms may also have the ability to develop tolerance to antimony based on alteration of cellular uptake resulting from similar mechanisms.

DOSE-RESPONSE ASSESSMENT

Noncarcinogenic Effects

In the previous PHG, the most relevant studies for risk extrapolation for drinking water exposures were judged to be the chronic drinking water studies in mice and rats conducted by Schroeder and colleagues (1968, 1970). These remain the only chronic studies conducted on antimony compounds. Only one dose was studied in each of these studies. Because the estimated dose to rats was lower than to the mice (0.43 mg/kg-day for rats versus 0.83 mg/kg-day for mice) and the observed effect (shorter lifespan) was significant for both male and female rats, the rat study was selected as the most sensitive indicator of antimony toxicity. In this study (Schroeder et al., 1970), 50 male and female Long-Evans rats were exposed to 0 or 5 mg/L of potassium antimony tartrate in drinking water from weaning until death (over 1,000 days). Based on the observed decrease in longevity and altered blood glucose and serum cholesterol levels, a LOAEL of 0.43 mg/kg-day was identified. Deficiencies of these studies for risk assessment are many, but the most important ones are: (1) one dose, (2) loss of animals due to illness, and (3) inadequate/limited toxicity evaluation. The many failings of the Schroeder (1970) study have been discussed by OEHHA in the previous PHG document as well as by other authors (Hext et al., 1999). In the previous PHG document, OEHHA used this study for risk assessment because there no other suitable options were found at that time (before the early medical textbooks became electronically retrievable).
Hext et al. (1999) [cited in the original PHG document as Zeneca, 1997a, because the study was received at the time only as the laboratory report] was a relatively new three-month study in rats using antimony trioxide. Effects on various plasma enzymes and liver weights were noted in this study, but at much higher doses than in the reports of Schroeder et al. (1968, 1970).

The Poon et al. (1997) subchronic exposure study monitored more parameters and more sensitive effects than in the previous studies, and effects are reported at lower levels. A major limitation is the poor dose-response, in which evidence of dose-related effects is not convincing except at the highest dose. In our view, the data only establish solidly the lowest effect level of 42.17 mg of antimony per kg-day, and thus a NOAEL of 5.58 mg/kg-day.

Antimony potassium tartrate provides the greatest oral toxicity of the antimony species because of its greater absorption, largely resulting from a higher water solubility. Because of this, the Poon et al. (1997) study and WHO (2003), which uses this study, both acknowledge that a risk assessment based on it would probably overestimate the risk from more typical antimony species, inorganic trivalent salts of antimony, with a higher potential to be water-borne. However, they reason that the use of a risk value based on this study would provide an additional degree of safety. We feel that the additional degree of safety can be accommodated with a more suitable study and approach than applying numerous uncertainty factors.

Evaluation of the older literature on use of antimonials has provided an option to the animal studies, and has led us to conclude that the above-mentioned studies reflect a lack of sensitivity of rodents to antimonials, compared to human reports and studies in other species. The emetic dose in adult humans of approximately 0.3 mg/kg (assuming 22.6 mg Sb/day and the weight of a 70 kg man; see Table 3 below) is ten-fold lower than the LOAEL (3.5 mg/kg-day) identified from Schroeder (1970), and this represents, according to multiple sources cited, a level with very significant effects. Since emesis is a very toxic event, this leads us to believe that a NOAEL for humans must be well below 0.3 mg/kg-day. Thus we are inclined to dismiss the rodent toxicity data, in support of human information regarding antimony medical uses and poisoning from the older medical literature. This information is summarized in the following tables.

### Table 3. Antimony Potassium Tartrate Effects in Adults (dose presented as total mg, converted from grains; body weights were not reported)

<table>
<thead>
<tr>
<th>Treatment/Effect</th>
<th>Dosea (mg)</th>
<th>Daily Doseb (mg/day)</th>
<th>Daily Dose (mg Sbc/day)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lethal (lowest reported)</td>
<td>129.6</td>
<td>129.6</td>
<td>45.5</td>
<td>Blyth and Blyth, 1906</td>
</tr>
<tr>
<td>Lethal (generally considered)</td>
<td>650</td>
<td></td>
<td>226</td>
<td>Wood and Bache, 1892</td>
</tr>
<tr>
<td>Emesis</td>
<td>30 to 60</td>
<td>30 to 60</td>
<td>10.56 to 22.6</td>
<td>Hare, 1905</td>
</tr>
<tr>
<td>Emesis</td>
<td>65-130</td>
<td>65-130</td>
<td>22.8-45.6</td>
<td>Wood and Bache, 1892; Parke, Davis, 1901</td>
</tr>
<tr>
<td>Treatment/Effect</td>
<td>Dose(^a) (mg)</td>
<td>Daily Dose(^b) (mg/day)</td>
<td>Daily Dose(^c) (mg Sb/day)</td>
<td>Reference</td>
</tr>
<tr>
<td>------------------------------------------</td>
<td>----------------</td>
<td>---------------------------</td>
<td>-------------------------------</td>
<td>------------------------------------------</td>
</tr>
<tr>
<td>Emesis</td>
<td>37.5</td>
<td>37.5</td>
<td>13.2</td>
<td>Dunn, 1928</td>
</tr>
<tr>
<td>Emesis</td>
<td>32-65</td>
<td>32-65</td>
<td>11.26-22.48</td>
<td>Dunn, 1928</td>
</tr>
<tr>
<td>Nausea</td>
<td>10</td>
<td>10?</td>
<td>3.52</td>
<td>Buck, 1904</td>
</tr>
<tr>
<td>Depression (cardiac)</td>
<td>3-6</td>
<td>9-18</td>
<td>3.15-6.30</td>
<td>Hare, 1905</td>
</tr>
<tr>
<td>Alterative</td>
<td>2-4</td>
<td>2-4?</td>
<td>0.70 to 1.4</td>
<td>Wood and Bache, 1892; Parke, Davis, 1901</td>
</tr>
<tr>
<td>Expectorant</td>
<td>5</td>
<td>5?</td>
<td>1.76</td>
<td>Wood and Bache, 1892</td>
</tr>
<tr>
<td>Expectorant</td>
<td>1</td>
<td>5</td>
<td>1.76</td>
<td>Sollmann, 1917</td>
</tr>
<tr>
<td>Bronchial-pneumonia/bronchitis</td>
<td>1.3</td>
<td>5.2</td>
<td>1.83</td>
<td>Potter, 1903</td>
</tr>
<tr>
<td>Expectorant/Diaphoretic</td>
<td>2.7</td>
<td>8.13</td>
<td>2.84</td>
<td>Parke, Davis, 1901</td>
</tr>
<tr>
<td>Decrease in respiratory rate, increased secretions</td>
<td>5</td>
<td>5</td>
<td>1.76</td>
<td>Buck, 1904</td>
</tr>
<tr>
<td>Asthma/emphysema</td>
<td>4.0</td>
<td>4.0</td>
<td>1.40</td>
<td>Potter, 1903</td>
</tr>
<tr>
<td>Keratoconjunctivitis</td>
<td>1.34</td>
<td>4.02</td>
<td>1.42</td>
<td>Ringer, 1880</td>
</tr>
<tr>
<td>Fever</td>
<td>1.0</td>
<td>5.0</td>
<td>1.66</td>
<td>Hare, 1905</td>
</tr>
<tr>
<td>Disturbed sleep, congestion of the head</td>
<td>1.95</td>
<td>1.95</td>
<td>0.68</td>
<td>Mayerhofer, 1846</td>
</tr>
<tr>
<td>None for at least five days</td>
<td>0.65</td>
<td>0.65</td>
<td>0.22</td>
<td>Mayerhofer, 1846</td>
</tr>
<tr>
<td>Homeopathic dose-minute-</td>
<td>0.065-0.65</td>
<td>0.065-0.065</td>
<td>0.022-0.22</td>
<td>Bayes, 1871</td>
</tr>
</tbody>
</table>

\(^a\) The initial or minimal dose of tartar emetic.
\(^b\) The total estimated dose/day. Dosing according to a prescribed schedule, apparently sometimes with, sometimes without, close monitoring for adverse effects (Kerley, 1914). We assumed a maximum of 5 doses/day if specified as every hour, 4 if every two hours and 3 if every 3 to 4 hours, unless the author specified the number.
\(^c\) Conversion from the compound to Sb dose from the molecular weight ratio.

From the above data it is possible to quite accurately define a human NOAEL for antimony. We think that a value based on the pioneering effort of Mayerhofer (1846) is probably most suitable. Mayerhofer apparently selected the lowest dose used in his self-experiment based on common knowledge that this would not likely be an effective dose, and confirmed it in his study. The attention to detail and rigor of his self-experiments furthered the knowledge of his day about the toxicity of antimony to normal, healthy individuals. No doubt this work saved many lives that would otherwise have been lost to either intentional or inadvertent toxic dosing with tartar emetic.
Mayerhofer’s data appear to be reasonably consistent with the observations or recommendations of others shown in Table 3, considering that we do not know his weight or that of any of the treated people, which may have included children or small adults in certain cases. We also know that 1/100 grain (0.65 mg) was the upper limit on the homeopathic dose for adults, which appears to have been carefully evaluated during the same period. In addition, the 1/100 grain dose was the usual initial dose for treatment of respiratory diseases in women and children. This initial dose was probably administered several times a day to achieve cumulative effects, although it is possible effects were achieved after one dose in some cases.

With respect to the other effects, the actual daily dose given during treatment is not precisely known, because physicians generally adjusted the dose and dosing schedule for the individual. Therefore some generalization on the daily dose was made in the table above. The emetic dose, which must be considered as a serious adverse effect for our purposes, was about ten-fold lower than the lethal dose (650 to 65 mg tartar emetic). The medicinal or milder physiological effects were noted over a range to about ten fold lower than the emetic dose (65 to 2 mg tartar emetic). Because Mayerhofer (1846) reported slight effects at 1.95 mg tartar emetic (0.68 mg of antimony) and it is lower than the other doses reported to be effective for milder conditions, we may consider this a LOAEL. Since Mayerhofer (1846) reported no ill effects at the dose of 0.65 mg of tartar emetic (0.22 mg of Sb) per day, we may call it the NOAEL. This dose is three-fold lower than the LOAEL and less than ten-fold lower than other doses of antimony used for treatment of milder illnesses. We recognize that because of the nature of the increase to the next dose level, some might argue that 0.65 mg dose could still be a LOAEL. We feel that that this concern can be accommodated in the risk assessment, as explained below.

An approximate daily dose by weight for adults is estimated by dividing the dose of 0.22 mg Sb by 70 kg, resulting in an estimated NOAEL of 0.0031 Sb mg/kg-day for all effects of orally administered antimony.

Since there is also information on the medicinal and toxic effects of antimony on children, we can use this to develop a LOAEL, as summarized in the following table, derived from data on use of antimony potassium tartrate in treating respiratory symptoms in children (asthma, colds, bronchitis).
Table 4: Antimony Potassium Tartrate Effects in Children

<table>
<thead>
<tr>
<th>Treatment/Effects</th>
<th>Dosea (mg)</th>
<th>Daily Doseb (mg/day)</th>
<th>Daily Dose (mg Sb(^c)/day)</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lethal</td>
<td>48.5</td>
<td>48.5</td>
<td>17</td>
<td>Blyth and Blyth, 1906</td>
</tr>
<tr>
<td>Emesis</td>
<td>16-30</td>
<td>16-30</td>
<td>5.6-10.56</td>
<td>Blyth and Blyth, 1906</td>
</tr>
<tr>
<td>Emesis (actually intended for colds)</td>
<td>2.7</td>
<td>5.5</td>
<td>1.96</td>
<td>Ringer, 1880</td>
</tr>
<tr>
<td>Asthma</td>
<td>0.65</td>
<td>3.25</td>
<td>1.13</td>
<td>Potter, 1899, 1903</td>
</tr>
<tr>
<td>Severe bronchitis: 0-6 months</td>
<td>0.43</td>
<td>3.46</td>
<td>1.21</td>
<td>Kerley, 1914</td>
</tr>
<tr>
<td>Severe bronchitis: 6-month-3 years</td>
<td>0.65</td>
<td>5.2</td>
<td>1.8</td>
<td>Kerley, 1914</td>
</tr>
<tr>
<td>Severe bronchitis: 3 years+</td>
<td>0.81</td>
<td>6.5</td>
<td>2.2</td>
<td>Kerley, 1914</td>
</tr>
<tr>
<td>Increase bronchiolar secretions</td>
<td>0.65</td>
<td>0.65-0.4(?)</td>
<td>2.2-11</td>
<td>Bayes, 1871</td>
</tr>
</tbody>
</table>

\(a\) The initial or minimal dose used.

\(b\) The total estimated dose/day. Often dosing was on a flexible schedule, implying monitoring for toxic effects, while in other instances there appeared to be a prescribed dosing schedule (Kerley, 1914). We assumed a maximum of 5 doses/day if specified as every hour, 4 if every two hours and 3 if every 3 to 4 hours, unless the author specified the number.

\(c\) Conversion from the compound to Sb element dose from the molecular weight ratio.

A NOAEL cannot be estimated from the data for children presented in Table 4. Here again, the lethal dose is apparently about ten-fold higher than the emetic dose (17 vs 2 mg Sb). However, the daily medicinal dose appears to be close to the emetic dose. That could be because less information on children was available related to these mild effects, as well as the fact that there is a great range of children’s ages and body weights. The doses given for children by Kerley (1914) might be considered “high,” that is, not intended to treat minor effects. He may have intended to give tartar emetic at high doses to combat a potentially life-threatening condition or he may be using co-administered agents to mitigate antimony toxicity. We know that he did not recommend tartar emetic for milder bronchitis in children. So that leaves the doses of Potter (1899, 1903) for consideration of the LOAEL, although it is not clear if the stated dose is for a single treatment or part of a series of treatments per day. Ringer (1880) found that a dose of 2 mg Sb/child could induce emesis, so it would be appropriate to consider that a LOAEL must be lower than that. Selecting the Potter daily dose of 1.1 mg Sb/child and using a 10 kg child’s body weight would result in 0.11 mg Sb/kg. The latter child-based estimate...
is higher than would be derived from the estimated adult LOAEL (0.068 mg/kg-day based on a 10 kg child weight), but not exceedingly so.

In our view the human data presented here is more suitable for risk assessment than animal data because it is presents human sensitivity at levels lower than shown with rodent data and reflects less uncertainty regarding human dose-response than the available animal data.

**Carcinogenic Effects**

Insoluble antimony particles in the form of antimony trioxide have been rated as carcinogenic, mainly on the basis of the inhalation studies in animals. Two studies (Watt, 1983; Groth et al., 1986) found increased lung tumors, while another (Newton et al., 1994) failed to do so. These studies did not provide a clear dose-response for increases in lung tumors, and increased tumors were reported in only one species and sex. The International Agency for Research on Cancer (IARC, 1989) evaluated Groth et al. (1986) and Watt (1983), and decided that there was sufficient evidence for the carcinogenicity of antimony trioxide in animals, and that it was possibly carcinogenic to humans (Group 2B). Antimony trisulfide was judged to be not classifiable as to its carcinogenicity to humans (Group 3). Antimony trioxide is also considered to be a carcinogen in California under Proposition 65 (OEHHA, 2008); the listing was October 1, 1990, before the completion of the study of Newton et al. (1994).

For worker exposures (Jones, 1994), an elevated incidence of lung cancer was reported for exposures prior to 1960 in one plant and not thereafter. This cannot be solely explained due to decreases in airborne concentrations of antimony, because the changes in processing did not necessarily change amounts of antimony dust in the environment. Rather it seems that the changes in processing technology (including ore composition) probably altered the form of airborne dust. Schnorr et al. (1995) reported a slight increase in lung cancer rate in an antimony oxide processing plant where little change in processing technology had occurred over many years. These epidemiological evaluations have not confirmed that antimony or its forms are directly carcinogenic. The mechanism for production of lung tumors would presumably be through formation of granulomas, which is related to localized effects of the antimony trioxide particles.

The available data provides limited evidence of genotoxicity of antimony in bacterial and mammalian studies (De Boeck et al., 2003). *In vitro*, antimonials have been demonstrated to produce chromosomal breakage. Specialized studies also indicate that antimonials induce apoptosis, which in certain conditions can protect the organism by removing defective cells, thereby limiting carcinogenic processes. Some authors have considered the mutagenic and carcinogenic risk of antimony exposure to be minimal (Leonard and Gerber, 1996).

There is no evidence that antimony or its compounds are carcinogenic by the oral route, as evidenced by the Schroeder et al. (1968 and 1970) lifetime exposure studies. U.S. EPA has stated that there is inadequate evidence to determine potential carcinogenicity of antimony in drinking water (U.S. EPA, 1995). We concur.
CALCULATION OF PHG

Noncarcinogenic Effects

For estimation of a health-protective concentration of a chemical in drinking water, an acceptable daily dose of the chemical from all sources will first be calculated. This involves incorporation of appropriate estimates of uncertainty in the extrapolation of the critical toxic dose from human or animal studies to the estimation of a lifetime daily dose that is unlikely to result in any toxic effects. For this purpose, the following equation will be used:

\[
ADD = \frac{NOAEL/LOAEL \text{ in mg/kg-day}}{UF}
\]

where,

\[
ADD = \text{acceptable daily dose, an estimate of the maximum daily dose which can be consumed by humans for an entire lifetime without toxic effects};
\]

\[
NOAEL/LOAEL = \text{no-observed-adverse-effect level or lowest-observed-adverse-effect level in the critical study};
\]

\[
UF = \text{uncertainty factor}.
\]

Calculation of a public health-protective concentration (C, in mg/L) for a chemical in drinking water uses the following equation for noncarcinogenic endpoints:

\[
C = \frac{ADD \text{ mg/kg-day} \times RSC \text{ L/kg-day}}{L/kg-day}
\]

where,

\[
RSC = \text{relative source contribution (usually 20 to 80 percent, expressed as 0.20 to 0.80)};
\]

\[
L/kg-day = 0.044 \text{ L/kg-day, the 95th percentile of water consumption for the general adult population, or 0.185 L/kg-day, the 95th percentile consumption of infants aged less than one year (U.S. EPA, 2004)}.
\]

If a health-protective dose were calculated from animal data, the NOAEL in rats of 0.43 mg/kg-day would be used, as in the 1997 PHG document. A UF of 300 would be appropriate, which includes a factor of 3-fold for LOAEL to NOAEL conversion and a non-severe endpoint, 10-fold for inter-species variation and 10-fold for variation in the human population. Thus,
ADD $= \frac{0.43 \text{ mg/kg-day}}{300} = 0.0014 \text{ mg/kg-day} = 1.4 \mu g/\text{kg-day}$

From the human data, the lack of effects upon a healthy adult male of a dose of 0.0031 mg Sb/kg-day, as explained in the Dose Response section above, and the reported effects (disturbed sleep, feeling of fullness in the head, dry, clammy tongue) at three times that dose in the same person (Mayerhofer, 1846) define the lower effect levels more clearly than other reports. We suggest that the NOAEL from this study should be used to determine a reference level for exposure to antimony. However, the dosing period on which this NOAEL is based was only for five days and there is sufficient indication from the medical literature that the toxicity to antimony can be cumulative even at smaller doses (Taylor, 1857). Therefore an uncertainty factor of ten to estimate safe doses for chronic exposure appears necessary. An additional factor of ten to account for variation in human response to antimony, and be protective of infants, children, and other potentially sensitive populations, also is appropriate. Thus,

ADD $= \frac{0.0031 \text{ mg/kg-day}}{100} = 0.000031 \text{ mg/kg-day}, \text{ or } 0.031 \mu g/\text{kg-day}$

Calculation of the human health-protective concentration, C, from the ADD in animals must account for exposure of humans to other sources of antimony. We suggest that the RSC value of 0.4 used in the 1997 risk assessment remains a reasonable value. Incorporating the upper 95th percentile drinking water consumption value for adults, the health-protective concentration based on the rat LOAEL would be:

$C = \frac{1.4 \mu g/\text{kg-day} \times 0.4}{0.044 \text{ L/kg-day}} = 13 \mu g/\text{L} = 13 \text{ ppb}$

If we were to base the above calculation on children’s drinking water consumption, it would require reevaluation of the RSC, because children’s food consumption patterns differ from that of adults, relative atmospheric exposure to antimony could increase because of higher inhalation rate per body mass, and children exhibit much more hand-to-mouth behavior than adults. This effort does not appear justifiable because the health-protective value based on human data (see below) is lower. The value for children using a drinking water consumption rate of 0.185 L/kg-day and an RSC of 0.4 would be 3 ppb.

To calculate the health-protective concentration from the human data, the relative source contribution is set at 1.0, since the critical effect was based on direct dosing with antimony in humans, irrespective of any other exposures. We have no reason to assume that the exposures from other sources are higher at present than in the clinical observations on which the ADD is based. The health-protective concentration for adults can then be estimated as:
A risk to infants and children can be estimated from the children’s exposure data discussed above, and listed in Table 4. We feel that the LOAEL of 1.1 mg/kg-day from Potter (1903), which is derived specifically from clinical data in children, provides an important perspective independent of the calculation for adults from the observations of Mayerhofer (1846). For this purpose we utilize an uncertainty factor of 10 for extrapolation from a LOAEL to a NOAEL, and another 10 for interindividual variation. No uncertainty factor for chronic exposure is being proposed here because children’s exposures are not “chronic” by definition and because the clinical doses are derived from repeated-dosing treatment of childhood diseases. Therefore the ADD could be calculated as:

\[
\text{ADD} = 1.1 \text{ mg/kg-day} = 0.0011 \text{ mg/kg-day} = 1.1 \mu\text{g/kg-day}
\]

A drinking water consumption rate for infants which matches the age-group for which the ADD was calculated, i.e., infants <1 year old, is used in calculating a health-protective drinking water concentration for infants. The upper 95th percentile drinking water consumption rate for this group is 0.185 L/kg-day (U.S. EPA, 2004). A relative source contribution of 1.0 is used for this calculation for the same reason as discussed above, that the critical effect was based on direct dosing with antimony in humans, irrespective of any other exposures. The health-protective concentration for antimony would then be calculated as:

\[
C = 0.0011 \text{ mg/kg-day} \times 1.0 = 0.0059 \text{ mg/L} = 5.9 \mu\text{g/L} = \sim 6 \text{ ppb}
\]

Because the health based protective concentration based on the data derived from adult humans is more protective than that derived from the rat LOAEL or the children data as shown above, we propose to set the public health goal for antimony in water based on the calculation for adults, 0.7 \mu\text{g/L or 0.7 ppb}. This value should sufficiently protect children and other potentially susceptible subgroups because it takes into consideration the specific clinical data, with an adequate margin of safety.

**RISK CHARACTERIZATION**

The proposed PHG of 0.7 ppb is considerably lower than the MCL and Maximum Contaminant Level Goal (MCLG) of 6 ppb established by U.S. EPA’s National Primary Drinking Water Regulations (U.S. EPA, 1992a,b, 1995), and much lower than the previous PHG of 20 ppb. However, the most important difference between these values lies in the information they are based upon. To us it seems more appropriate to base the
risk assessment for antimony on human information than on data from animal experiments. The basis for the proposed new PHG is the reported lack of effects upon a single healthy adult at an antimony dose of 0.22 mg/day (see Table 2), followed by slight effects at the next higher dose of 0.65 mg/day (Mayerhofer, 1846). These effect levels are reasonably consistent with the other available data of the time, including that of homeopathic practitioners. The minimal dose of antimony potassium tartrate used to treat conditions in children or adults of the late nineteen century to early 20th century by skilled clinicians was less than ten-fold higher than this NOAEL. The recommended starting dose for children was the same as the NOAEL from the observations of Mayerhofer. Use of this value based on human data involves less uncertainty, in our opinion (and lower uncertainty factors), than the rodent data that served as the basis for the earlier development of the U.S. EPA MCL or the previous PHG. It would be less appropriate, in our opinion, to extrapolate directly from human emetic doses of antimony tartrate, because this level represents a clear acute toxic effect, which is inconsistent with our expectations from our drinking water supply.

The clinical information about the toxicity of potassium antimonyl tartrate provided by Mayerhofer (1846) should not be discounted. His careful self-administration of doses and reports of clinical effects, with analyses on urinary and fecal output, as crude as they are by modern standards, should be acknowledged for their level of thoroughness and care. Mayerhofer (1846) also conducted experiments on animals and summarized data of others in his long treatise on antimony (Mayerhofer, 1846), for which he won a prize.

We also assume that the average human exposure to antimonials is about the same today as it was at the time of Mayerhofer (1846), the nineteenth century. We cannot be certain about antimonial exposures at the time. It is possible that individuals were more likely to be exposed to antimony in the nineteen century than now due to the large and broad use of the metal in daily commerce, particularly in flatware. However, now we also have potential exposures to antimony from plastics, particularly drinking water bottles and fire retardants. Thus it is difficult to determine the extent of human exposure to antimonials between the older and modern periods.

The application of an uncertainty factor of 10 to account for variability in response in the human population seems necessary to protect potentially susceptible subpopulations such as children, the elderly, and the infirm. Use of the susceptibility factor is backed up in this particular case by clinical discussions in the cited medical textbooks calling for special consideration to be given to the sensitivity of the young and the elderly.

The application of an additional uncertainty factor to account for potential cumulative effects with chronic exposure is also justified by several lines of evidence. There are some reports of tolerance with continued exposure, but Taylor (1857) points out that Mayerhofer (1846) could not achieve sufficient tolerance to the emetic effects of antimony from the sub-emetic doses he was administering to himself. Although it appears that tolerance to emetic effects is possible, this did not appear to be true for the other effects, and some individuals apparently never developed tolerance to any of the effects of antimony. Studies by Taylor and other scientists of the period showed that antimony’s effects were not necessarily immediate, could occur later or could be protracted due to antimony’s retention in the body (Taylor, 1857).
OTHER REGULATORY STANDARDS

The reference dose (RfD) for oral exposure to antimony, from the U.S. EPA Integrated Risk Information System (IRIS), is 4 µg/kg-day, based on animal data (U.S. EPA, 2007a). For antimony trioxide exposure in air the protective value, or reference concentration, is 0.0002 mg/m³ (U.S. EPA, 2007b). U.S. EPA’s MCL for antimony is 0.006 mg/L (6 ppb) (U.S. EPA, 1995). The existing PHG is 20 ppb (OEHHA, 1997). The existing PHG is 20 ppb (OEHHA, 1997). The Canadian guidance value for antimony in drinking water is 6 ppb (CBWA, 2006), while the World Health Organization guideline value is 20 ppb (WHO, 2003) as is also the European Food Safety Authority value (CBWA, 2006). The WHO value is based on a TDI (Tolerable Daily Intake) of 6 mg/kg of body weight, based on a NOAEL of 6.0 mg/kg-day. Most individual states have adopted the U.S. EPA MCL for their drinking water regulations.

The 8-hr time-weighted average (TWA) for antimony dusts in air, as established by NIOSH and OSHA, is 0.5 mg/m³ (ACGIH, 2005; HSDB, 2008). From 1948 to 1963, the TLV-TWA was 0.5 mg/m³ for antimony trioxide and this was later extended to all antimony compounds (ACGIH, 1991). This 0.5 mg/m³ level is also the permissible exposure limit (PEL) adopted by OSHA and NIOSH for all other antimony compounds (expressed as antimony content), and is standard for all reporting countries (RTECS, 1997). Most regulations concerning antimony were formulated to protect workers in either refining or alloy production (ACGIH, 1991).
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