APPENDIX A. ATSDR MINIMAL RISK LEVEL WORKSHEETS

MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration for a given route of exposure. An MRL is an estimate of the daily human exposure to a hazardous substance that is likely to be without appreciable risk of adverse noncancer health effects over a specified route and duration of exposure. MRLs are based on noncancer health effects only; cancer effects are not considered. These substance-specific estimates, which are intended to serve as screening levels, are used by ATSDR health assessors to identify contaminants and potential health effects that may be of concern at hazardous waste sites. It is important to note that MRLs are not intended to define clean-up or action levels.

MRLs are derived for hazardous substances using the NOAEL/uncertainty factor approach. They are below levels that might cause adverse health effects in the people most sensitive to such chemical-induced effects. MRLs are derived for acute (1–14 days), intermediate (15–364 days), and chronic (≥365 days) durations and for the oral and inhalation routes of exposure. Currently, MRLs for the dermal route of exposure are not derived because ATSDR has not yet identified a method suitable for this route of exposure. MRLs are generally based on the most sensitive substance-induced endpoint considered to be of relevance to humans. Serious health effects (such as irreparable damage to the liver or kidneys, or birth defects) are not used as a basis for establishing MRLs. Exposure to a level above the MRL does not mean that adverse health effects will occur.

MRLs are intended only to serve as a screening tool to help public health professionals decide where to look more closely. They may also be viewed as a mechanism to identify those hazardous waste sites that are not expected to cause adverse health effects. Most MRLs contain a degree of uncertainty because of the lack of precise toxicological information on the people who might be most sensitive (e.g., infants, elderly, nutritionally or immunologically compromised) to the effects of hazardous substances. ATSDR uses a conservative (i.e., protective) approach to address this uncertainty consistent with the public health principle of prevention. Although human data are preferred, MRLs often must be based on animal studies because relevant human studies are lacking. In the absence of evidence to the contrary, ATSDR assumes that humans are more sensitive to the effects of hazardous substance than animals and that certain persons may be particularly sensitive. Thus, the resulting MRL may be as much as 100-fold below levels that have been shown to be nontoxic in laboratory animals.

APPENDIX A

Proposed MRLs undergo a rigorous review process: Health Effects/MRL Workgroup reviews within the Division of Toxicology and Human Health Sciences, expert panel peer reviews, and agency-wide MRL Workgroup reviews, with participation from other federal agencies and comments from the public. They are subject to change as new information becomes available concomitant with updating the toxicological profiles. Thus, MRLs in the most recent toxicological profiles supersede previously published MRLs. For additional information regarding MRLs, please contact the Division of Toxicology and Human Health Sciences, Agency for Toxic Substances and Disease Registry, 1600 Clifton Road NE, Mailstop S102-1, Atlanta, Georgia 30329-4027.

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Antimony
CAS Numbers: 7440-36-0
Date: October 2019
Profile Status: Final
Route: Inhalation
Duration: Acute
MRL 0.001 mg Sb/m^3
Critical Effect: Squamous metaplasia of the epiglottis
Reference: NTP 2016
Point of Departure: $BMCL_{10}$ of 0.94 mg Sb/m^3
Uncertainty Factor: 30
LSE Graph Key: 3
Species: Mouse

MRL Summary: An acute-duration inhalation MRL of 0.001 mg Sb/m^3 was derived for antimony based on an increased incidence of squamous metaplasia of the epiglottis observed in mice exposed to antimony trioxide for 17 days (NTP 2016). The MRL is based on a $BMCL_{10}$ of 0.94 mg Sb/m^3 (human equivalent $BMCL_{10}$ of 0.035 mg Sb/m^3) and an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

Selection of the Critical Effect: No human studies have evaluated the acute inhalation toxicity of antimony. In laboratory animals, the acute toxicity has been evaluated for stibine, antimony trisulfide, and antimony trioxide. These studies clearly identify the respiratory tract as one of the most sensitive targets of antimony toxicity (Brieger et al. 1954; NIOSH 1979; NTP 2016). A 30-minute exposure to 1,395 mg Sb/m^3 as stibine resulted in pulmonary edema and congestion and death in rats and guinea pigs (NIOSH 1979). Chronic lung inflammation was observed in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide for 5 days (7 hours/day) and in rats exposed to 25 mg Sb/m^3 as antimony trioxide for 12 exposures over a 16-day period (6 hours/day) (NTP 2016). NTP (2016) also found squamous metaplasia in the epiglottis of rats and mice exposed to 25 or 12 mg Sb/m^3, respectively. The primary extrarespiratory effects also observed following acute exposure were degenerative changes in the heart and altered EKGs in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide.

Selection of the Principal Study: The Brieger et al. (1954) and NTP (2016) studies were considered for derivation of an acute-duration inhalation MRL. Although the rats and mice in the NTP (2016) study were exposed to antimony trioxide over a 16- or 17-day period, the animals were only exposed for 12 or 13 times and the study was considered to be more reflective of effects associated with acute-duration exposure than intermediate-duration exposure. Potential points of departure (PODs) were calculated for both studies (see Selection of the POD section). The lowest POD was identified for the NTP (2016) mouse study, which was selected as the principal study.

Summary of the Principal Study:

NTP. 2016. Toxicology and carcinogenicity studies of antimony trioxide (CAS No. 1309-64-4) in Wistar HAN [Crl:WI (Han)] rats and B6C3F1/N mice (inhalation studies). National Toxicology Program, Research Triangle Park, NC. NTP TR 590. Draft for Peer Review.

Groups of five male and five female B6C3F1/N mice were exposed to 0, 3.75, 7.5, 15, 30, or 60 mg/m^3 antimony trioxide (0, 3.1, 6.3, 12, 25, and 50 mg Sb/m^3) 6 hours/day, 5 days/week for 13 exposures in a 17-day period. An additional group of five female mice was similarly exposed and held for a 28-day

recovery period. The actual concentrations were 3.71, 7.43, 14.7, 30.2, and 59.4 mg Sb_2O_3/m^3. The MMADs (geometric standard deviations) for the particles were 1.4 (1.9), 1.3 (1.9), 1.5 (1.9), 1.4 (1.9), and 1.4 (1.9) μm for the 3.1, 6.3, 12, 25, and 50 mg Sb/m^3 concentrations, respectively. The following parameters were used to assess toxicity: twice daily observations; body weights on days 1, 6, and 13, and at termination; organ weights (kidney, liver, lung, testis, thymus); and histopathological examination in the control and 50 mg Sb/m^3 group (histopathological examinations of the larynx, lung, lymph nodes, nose, pharynx, and trachea were conducted to a no-effect level). In the animals allowed to recover, antimony levels were measured in blood samples collected at the end of the exposure and recovery periods and in the lungs.

Although the mice were exposed to antimony trioxide over a 17-day period, the animals were only exposed for 13 times and the study was considered to be more reflective of effects associated with acute-duration exposure than intermediate-duration exposure.

No deaths, clinical findings, or alterations in body weight gain were observed. Significant increases in absolute lung weights were observed in males at ≥6.3 mg Sb/m^3 and in females at ≥12 mg Sb/m^3; increases in relative lung weights were observed in males at 50 mg Sb/m^3 and in females at ≥3.1 mg Sb/m^3. Minimal to mild squamous metaplasia was observed in the epiglottis epithelium at ≥25 mg Sb/m^3; the incidences were 0/10 in controls and 2/10, 4/9, 10/10, and 10/10 in the 6.3, 12, 25, and 50 mg Sb/m^3 groups, respectively. Increases in the presence of foreign body (presumably antimony trioxide) were observed in the lungs of mice exposed to ≥3.1 mg Sb/m^3. No concentration-related alterations in lung clearance were observed. The clearance half-times ranged from 47 to 62 days.

Selection of the Point of Departure for the MRL: The MRL is based on a $BMCL_{10}$ of 0.94 mg Sb/m^3 for squamous metaplasia of the epiglottis in male and female mice.

Several endpoints were considered for derivation of an acute-duration inhalation MRL for antimony: altered EKGs and degenerative changes in the heart in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide (Brieger et al. 1954), lung inflammation in rabbits exposed to 19.9 mg Sb/m^3 as antimony trisulfide (Brieger et al. 1954), squamous metaplasia of the epiglottis in male and female rats exposed to ≥25 mg Sb/m^3 as antimony trioxide (NTP 2016), chronic lung inflammation in rats exposed to ≥25 mg Sb/m^3 as antimony trioxide (NTP 2016), and squamous metaplasia of the epiglottis in male and female mice exposed to ≥12 mg Sb/m^3 as antimony trioxide (NTP 2016).

For the NTP (2016) study, the incidence data (Table A-1) for squamous metaplasia in rats and mice were fit to all available dichotomous models in EPA's Benchmark Dose Software (BMDS; version 2.6.0) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined benchmark response (BMR). Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest Akaike's Information Criterion (AIC) was chosen. For all lesion types, a BMR of 10% was used. Since the response level for chronic inflammation was the same for all non-control concentrations (see Table A-1), BMD modeling was not conducted for this endpoint and the NOAEL was used as the POD. The model predictions for the epiglottal squamous metaplasia for rats and mice are presented in Tables A-2 and A-3 and the fits of the selected models are presented in Figures A-1 and A-2. The Brieger et al. (1954) study only tested one concentration of antimony trisulfide, and was not considered suitable for BMD modeling; the LOAEL of 19.9 mg Sb/m^3 for lung and cardiovascular effects was considered the POD for this study.

Table A-1. Incidence of Respiratory Tract Effects in Male and Female Rats and Mice Exposed to Antimony Trioxide[a]

	Concentrations (mg Sb/m^3)					
Effect	0	3.1	6.3	12	25	50
Rats						
Squamous metaplasia of epiglottis	0/10	–[b]	–[b]	1/10	4/9[c]	5/10[c]
Chronic lung inflammation	0/10	0/10	0/10	0/10	10/10[c]	10/10[b]
Mice						
Squamous metaplasia of epiglottis (male and female)	0/10	–[d]	2/10	4/9[c]	10/10[c]	10/10[c]

[a]Male and female incidences were combined.
[b]Incidence in the female rats was 1/5; males were not examined at these concentrations.
[c]Significantly different from controls.
[d]Incidence in the female mice was 2/5; males were not examined at this concentration.

Source: NTP 2016

Table A-2. Model Predictions for the Incidence of Squamous Metaplasia of the Epiglottis in Male and Female Rats (Combined) Exposed to Antimony Trioxide (NTP 2016)

				Scaled residuals[b]					
Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg Sb/m^3)	$BMCL_{10}$ (mg Sb/m^3)
Gamma[c]	2	1.04	0.60	0.00	-0.49	0.83	37.76	7.77	4.18
Logistic	2	3.09	0.21	-0.28	1.41	1.41	40.25	16.36	10.83
LogLogistic[d,e]	***2***	***0.90***	***0.64***	***0.00***	***-0.46***	***0.75***	***37.62***	***8.47***	***2.95***
LogProbit[d]	3	0.99	0.80	0.00	-0.16	0.78	35.68	10.99	7.27
Multistage (1-degree)[f]	3	1.03	0.79	0.00	-0.59	0.79	35.78	6.79	4.17
Multistage (2-degree)[f]	3	1.03	0.79	0.00	-0.59	0.79	35.78	6.79	4.17
Multistage (3-degree)[f]	3	1.03	0.79	0.00	-0.59	0.79	35.78	6.79	4.17
Probit	2	2.86	0.24	-0.22	1.38	1.38	39.91	15.35	10.31
Weibull[c]	2	1.04	0.59	0.00	-0.53	0.82	37.77	7.40	4.17

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMCL was selected (Log Logistic).
[f]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-1. Fit of LogLogistic Model to Data on Incidence of Epiglottal Squamous Metaplasia in Male and Female Rats Exposed to Antimony Trioxide (mg Sb/m^3)

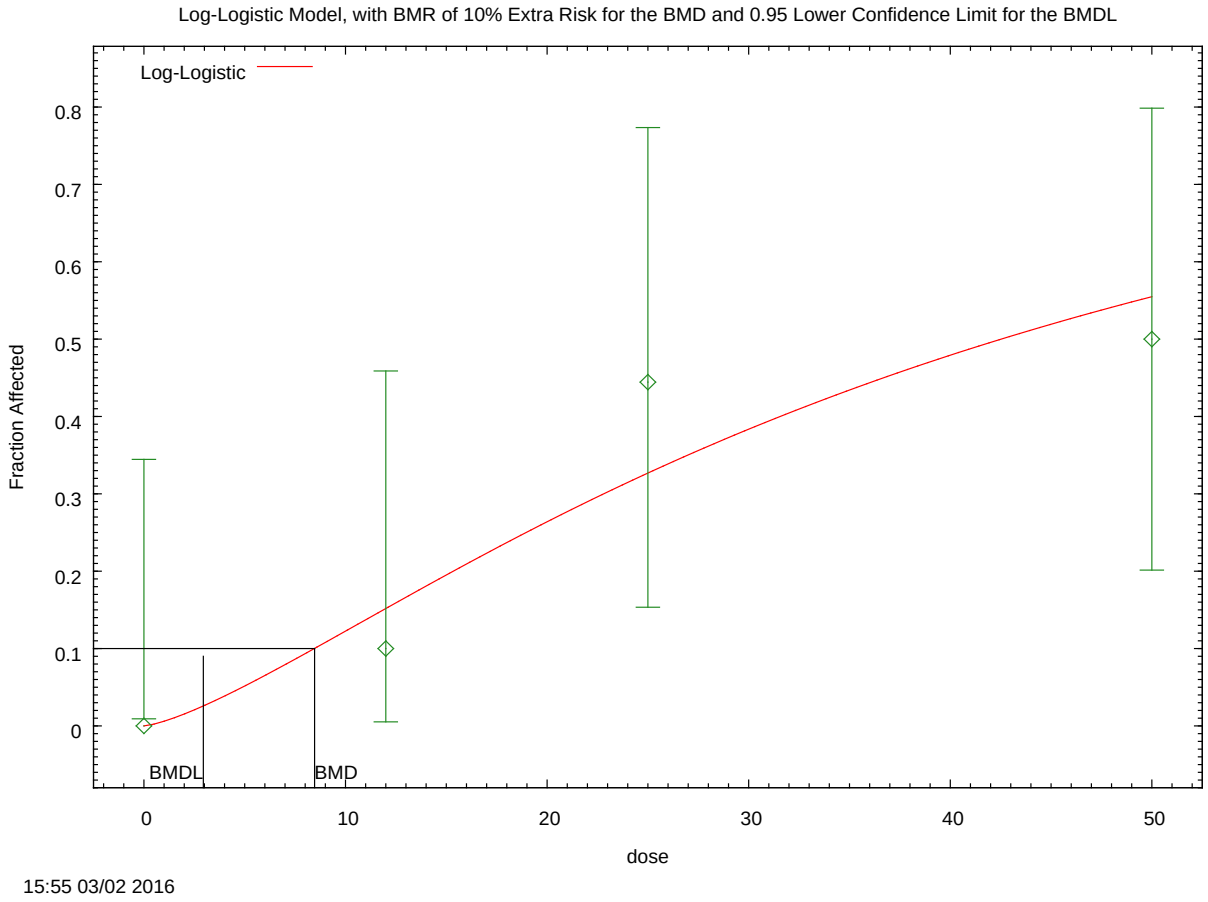


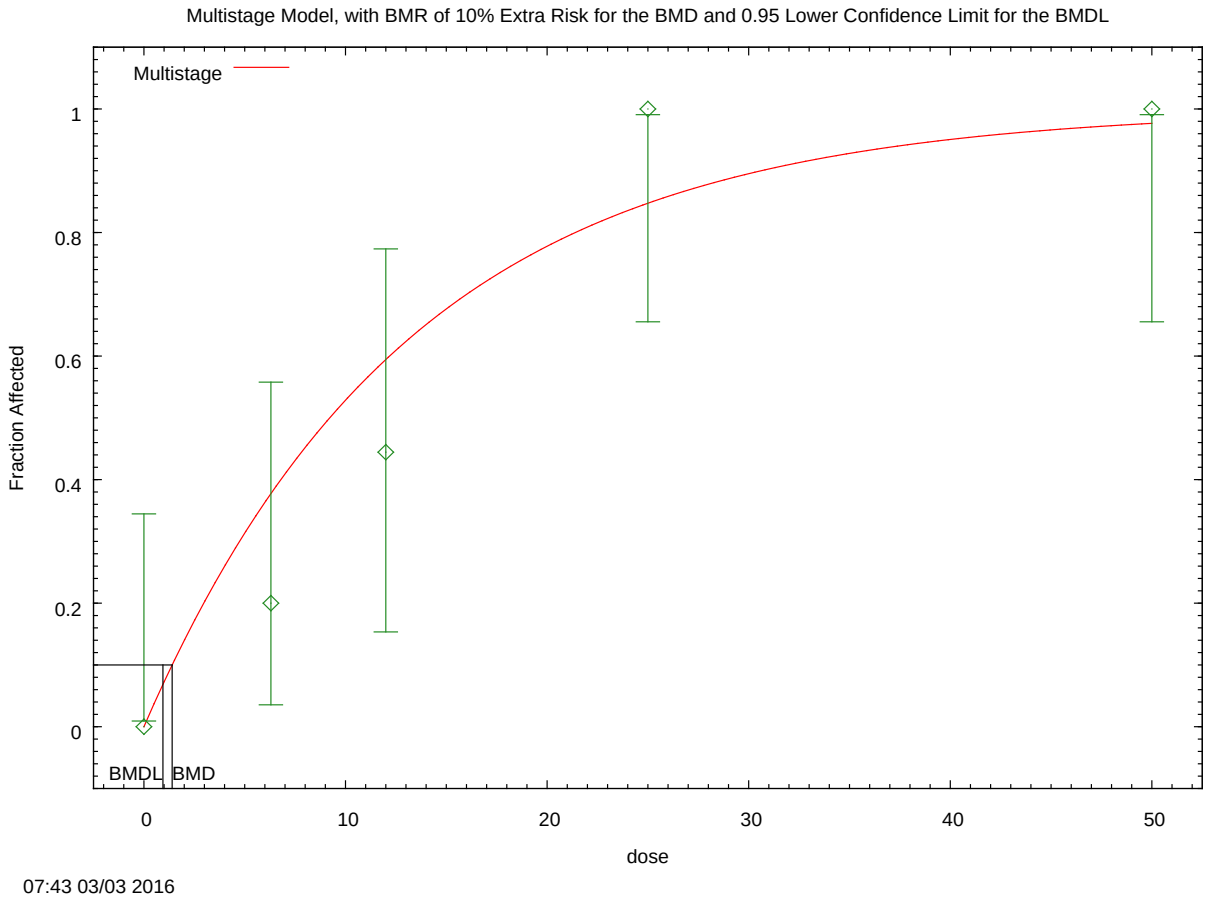
Table A-3. Model Predictions for the Incidence of Squamous Metaplasia of the Epiglottis in Male and Female Mice (Combined) Exposed to Antimony Trioxide (NTP 2016)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg Sb/m^3)	$BMCL_{10}$ (mg Sb/m^3)
Gamma[c]	3	1.04	0.79	0.00	0.48	-0.71	27.68	5.49	2.39
Logistic	3	0.85	0.84	-0.43	0.62	0.62	27.48	5.83	3.53
LogLogistic[d]	3	1.77	0.62	0.00	0.66	-0.86	28.64	5.79	3.17
LogProbit[d]	3	1.55	0.67	0.00	0.56	-0.89	28.31	5.73	3.25
Multistage (1-degree)[e,f]	***4***	***4.22***	***0.38***	***0.00***	***-1.16***	***-1.16***	***30.45***	***1.40***	***0.94***
Multistage (2-degree)[e]	4	0.70	0.95	0.00	0.05	0.59	25.41	4.41	1.74
Multistage (3-degree)[e]	3	0.27	0.97	0.00	0.24	-0.36	26.73	4.34	1.60
Multistage (4-degree)[e]	3	0.06	1.00	0.00	0.12	0.15	26.46	3.56	1.49
Probit	3	0.59	0.90	-0.34	0.51	0.51	27.12	5.48	3.28
Weibull[c]	3	0.61	0.89	0.00	0.48	-0.51	27.08	5.33	2.40

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were not sufficiently close (differed by >3-fold). Therefore, the model with lowest BMCL was selected (Multistage 1 degree).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-2. Fit of 1-Degree Multistage Model to Data on Incidence of Epiglottal Squamous Metaplasia in Male and Female Mice Exposed to Antimony Trioxide (mg Sb/m^3)



A summary of the potential PODs (BMCLs for the selected models, LOAELs, or NOAELs for models without adequate fit) is presented in Table A-4.

Table A-4. Summary of Potential Points of Departures (PODs) and Human Equivalent Concentrations (HECs) for Acute-Duration Inhalation MRL for Antimony

Endpoint (reference)	PODs (mg Sb/m^3)	RDDR values[a]	HECs[b] (mg Sb/m^3)
Squamous metaplasia of the epiglottis in male and female rats (NTP 2016)	2.95 ($BMCL_{10}$)	0.162[c]	0.085
Chronic lung inflammation (NTP 2016)	12 (NOAEL)	0.545[c]	1.1
Squamous metaplasia of the epiglottis in male and female mice (NTP 2016)	0.94 ($BMCL_{10}$)	0.206[c]	0.035
Lung inflammation in rabbits (Brieger et al. 1954)	19.9 (LOAEL)	0.203[d]	1.2
Degenerative changes in heart and altered EKG readings in rabbits (Brieger et al. 1954)	19.9 (LOAEL)	1.060[d]	6.2

[a]RDDR values specific for each region of the respiratory tract (extrathoracic and pulmonary) were calculated using EPA's RDDR calculator with the average of the male and female terminal body weights of 0.189 and 0.0281 kg for rats and mice, respectively, and 4.0 kg for rabbits.
[b]HEC calculated by multiplying the duration-adjusted POD (POD x 6 hours/24 hours x 5 days/7 days for the NTP [2016] study and POD x 7 hours/24 hours x 5 days/7 days for the Brieger et al. [1954] study) by the RDDR value.
[c]Calculated using a particle size of 1.4 µm (sigma g of 1.9).
[d]Calculated using a particle size of 2 µm (sigma g of 1.9); this is an assumed value; the investigators noted that most of the particles were <2 µm, but did not provide any additional information.

BMCL = 95% lower confidence limit on the benchmark concentration; EKG = electrocardiogram; EPA = Environmental Protection Agency; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; NTP = National Toxicology Program; RDDR = regional deposited dose ratio

Calculations

Intermittent Exposure: Concentrations tested in the NTP (2016) and Brieger et al. (1954) studies were adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days for NTP [2016] and 7 hours/day for Brieger et al. [1954]).

Human Equivalent Concentration: HECs were calculated for each potential POD by multiplying the POD_{ADJ} by the regional deposited dose ratio (RDDR) for the appropriate region of the respiratory tract. The RDDRs were calculated using EPA's RDDR calculator with the calculated average male and female terminal body weights of 0.189 and 0.0281 kg for rats and mice, respectively, for the NTP (2016) study and a reference body weight of 4.0 kg for the rabbits. The POD_{HEC} values are presented in Table A-4.

Uncertainty Factor:

- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability

MRL = $BMCL_{HEC}$ ÷ uncertainty factors
0.001 mg Sb/m^3 = 0.0.035 mg Sb/m^3 ÷ 30

Other Additional Studies or Pertinent Information that Lend Support to this MRL: There are limited data for comparing the relative toxicity of antimony compounds following acute inhalation exposure. The respiratory tract was a sensitive target in animals exposed to stibine, antimony trioxide, or antimony

trisulfide, but differences in the study designs do not allow for a direct comparison. Additionally, there are no data to allow for an assessment of the influence of valence state on the respiratory toxicity of antimony.

Agency Contacts (Chemical Managers): Melanie Buser

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Antimony
CAS Numbers: 7440-36-0
Date: October 2019
Profile Status: Final
Route: Inhalation
Duration: Intermediate

MRL Summary: The acute-duration inhalation MRL of 0.001 mg Sb/m^3 was adopted as the intermediate-duration inhalation MRL. The intermediate-duration database was not considered suitable for derivation of an MRL. An MRL based on the lowest POD_{HEC} estimated from an intermediate-duration study is slightly higher than the acute-duration inhalation MRL.

Rationale for Not Deriving an MRL: Information on the toxicity of inhaled antimony following intermediate-duration exposure primarily comes from a 13-week study in rats exposed to antimony trioxide (Newton et al. 1994) that identified the respiratory tract as the most sensitive effect and 6–10-week studies in rats, rabbits, and dogs (Brieger et al. 1954) that examined a limited number of endpoints and identified the respiratory tract and myocardium as the most sensitive endpoints. The systematic review identified the respiratory effects as presumed health effects in humans and myocardial damage and alterations in EKGs as suspected health effect in humans. In the Newton et al. (1994) study, exposure to ≥4.11 mg Sb/m^3 resulted in increases in alveolar/intra-alveolar macrophages, increases in relative lung weights, and increases in lung clearance half-times in rats killed at the end of the exposure period. In rats allowed to recover for 27 weeks, significant increases in the incidences of chronic interstitial inflammation and fibrosis were observed in rats exposed to 19.60 mg Sb/m^3. Mild congestion and focal hemorrhages were also observed in the lungs of rats exposed to 2.20 mg Sb/m^3 as antimony trisulfide for 6 weeks (Brieger et al. 1954); however, the investigators did not report the incidence of this effect, which precludes assessing the significance of the finding. Brieger et al. (1954) also found antimony trisulfide-induced alterations in EKGs and histological alterations in the myocardium of rats exposed to 2.20 mg Sb/m^3 for 6 weeks, dogs exposed to 3.98 mg Sb/m^3 for 10 weeks (no alterations were observed in dogs exposed to 3.81 mg Sb/m^3 for 7 weeks), and rabbits exposed to 4.02 mg Sb/m^3 for 6 weeks. A third intermediate-duration study reported unspecified lesions in the lungs, liver, kidneys, and pancreas (only qualitative data were provided), decreases in fertility, and decreases in litter size in rats exposed to 209 mg Sb/m^3 as antimony trioxide for 1.5–2 months (Belyaeva 1967).

The lung effects (increases in lung clearance time, chronic interstitial inflammation, and interstitial fibrosis) and the myocardial effects (histological alterations and altered EKGs) observed in the rats and rabbits were considered as the basis for an intermediate-duration MRL for antimony; the effects observed in dogs were not considered because reference values are not available for estimating the RDDR. BMD modeling was utilized to estimate the potential PODs for the histological alterations in the lungs observed in the Newton et al. (1994) study, but could not be utilized for the cardiac effects from the Brieger et al. (1954) studies due to the lack of incidence data. These incidence data were fit to all available dichotomous models in EPA's BMDS (version 2.6.0) using the extra risk option; see Appendix A for details on the BMD modeling results. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL (95% lower confidence limit on the benchmark concentration) was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. For all lesion types, a BMR of 10% was used. The results of the BMD modeling for the chronic interstitial inflammation and lung fibrosis are presented in Tables A-5 and A-6 and the fits of the selected models are presented in Figures A-3 and A-4.

Table A-5. Model Predictions for the Incidence of Chronic Lung Interstitial Inflammation in Rats Exposed to Antimony Trioxide for 13 Weeks Followed by a 27-Week Recovery Period (Newton et al. 1994)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg Sb/m^3)	$BMCL_{10}$ (mg Sb/m^3)
Gamma[c]	2	1.01	0.60	0.66	-0.01	-0.75	277.38	2.97	0.69
Logistic	3	1.85	0.60	0.45	0.45	-0.93	276.71	0.87	0.61
LogLogistic[d]	2	1.02	0.60	0.66	0.00	-0.76	277.38	3.68	1.76
LogProbit[d]	2	1.02	0.60	0.66	0.00	-0.76	277.38	3.44	1.68
Multistage (1-degree)[f]	3	3.05	0.38	0.49	0.30	-1.30	278.32	0.64	0.43
Multistage (2-degree)[e]	2	0.79	0.67	0.56	-0.21	-0.59	277.19	1.81	0.59
Multistage (3-degree)[e]	2	0.53	0.77	0.43	-0.14	-0.52	276.90	1.33	0.57
Multistage (4-degree)[e]	2	0.47	0.79	0.39	-0.13	-0.50	276.83	1.19	0.55
Probit[f]	**3**	**1.23**	**0.75**	**0.46**	**-0.73**	**-0.73**	**275.81**	**0.95**	**0.66**
Weibull[c]	2	0.90	0.64	0.62	-0.08	-0.70	277.27	2.30	0.67

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with lowest AIC was selected (Probit).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-3. Fit of Probit Model to Data on Incidence of Chronic Lung Interstitial Inflammation in Rats Exposed to Antimony Trioxide (mg Sb/m^3)

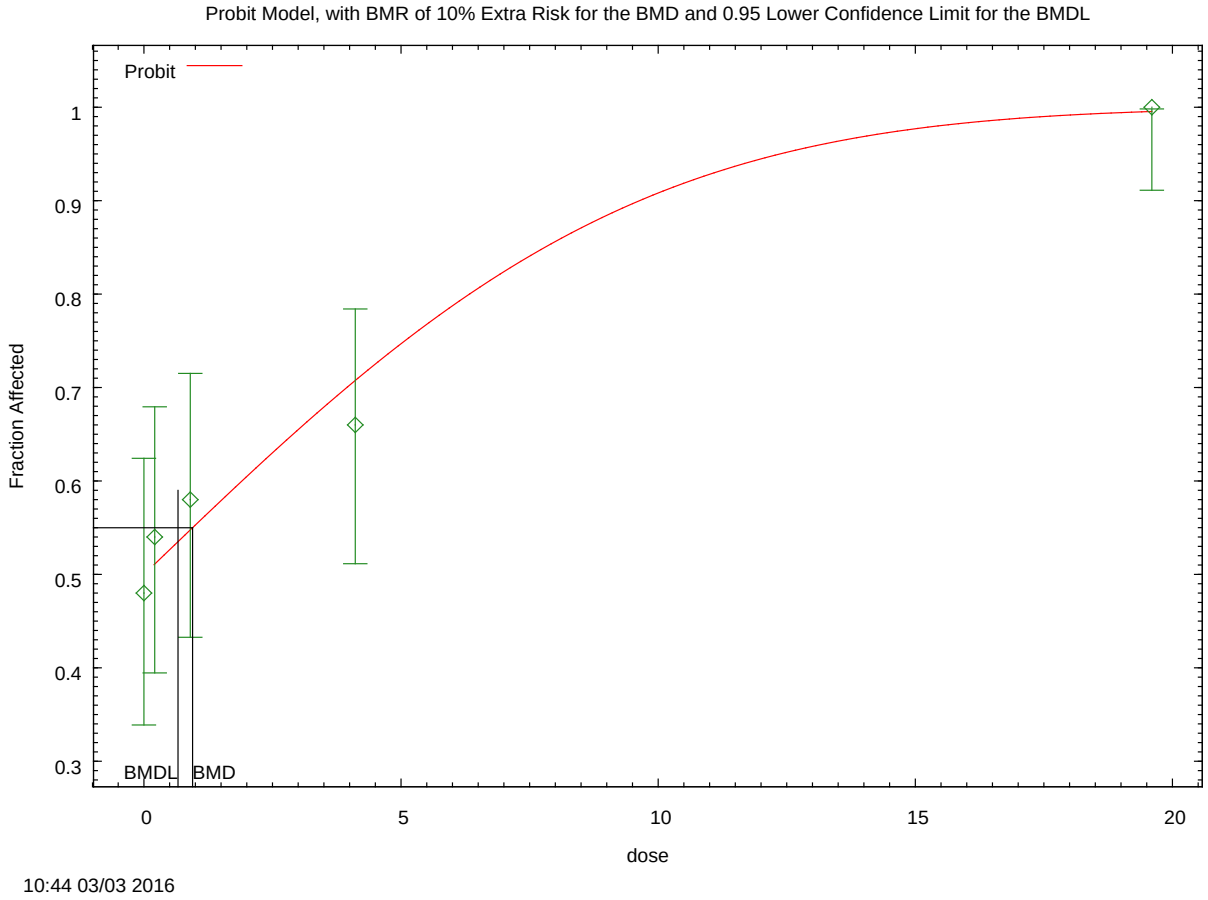


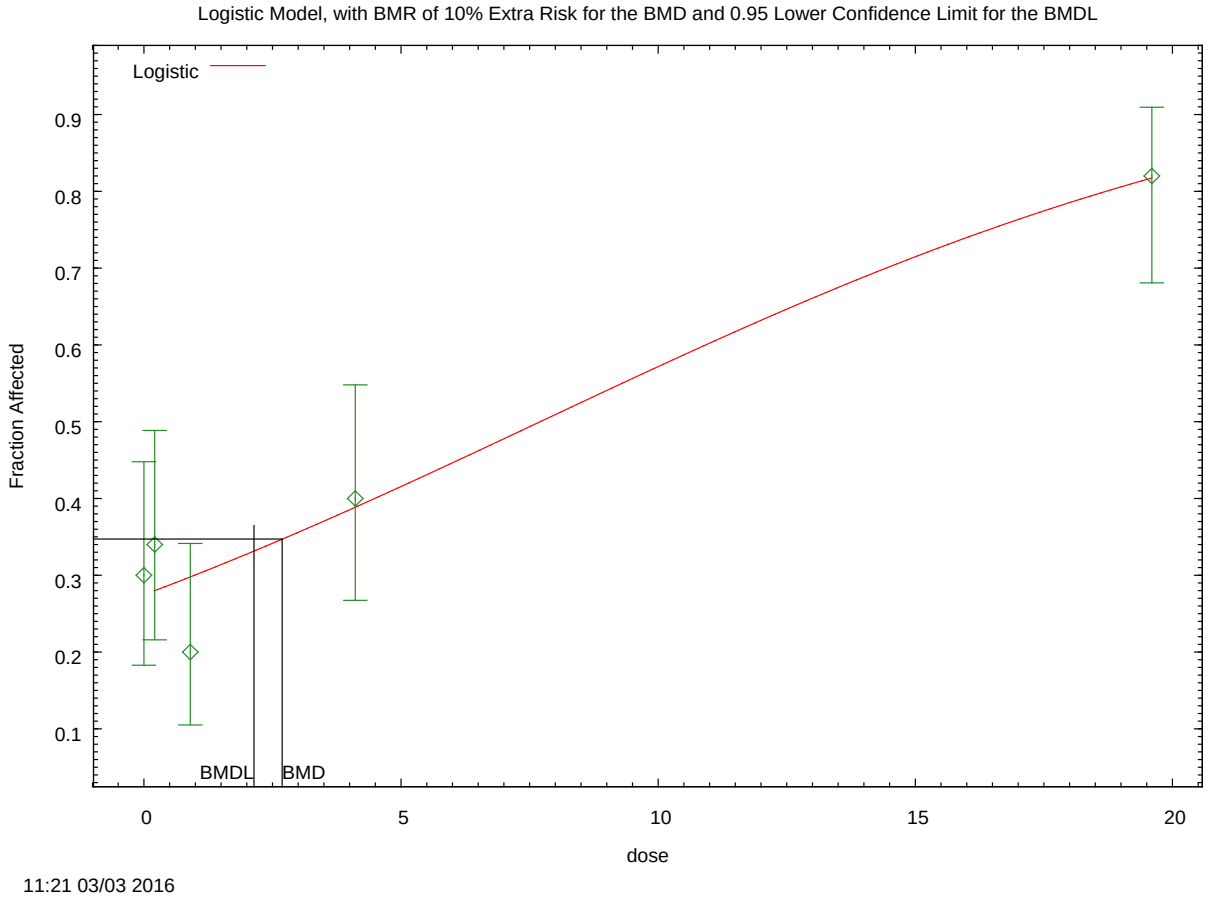
Table A-6. Model Predictions for the Incidence of Lung Fibrosis in Rats Exposed to Antimony Trioxide for 13 Weeks Followed by a 27-Week Recovery Period (Newton et al. 1994)

Model	DF	χ^2	χ^2 Goodness-of-fit p-value[a]	Scaled residuals[b] Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg Sb/m^3)	$BMCL_{10}$ (mg Sb/m^3)
Gamma[c]	2	2.97	0.23	-1.42	0.32	-1.42	298.77	3.40	1.31
Logistic[f]	***3***	***3.37***	***0.34***	***1.51***	***0.16***	***-1.51***	***297.19***	***2.69***	***2.14***
LogLogistic[d]	2	2.88	0.24	-1.38	0.22	-1.38	298.66	3.29	1.41
LogProbit[d]	2	2.69	0.26	-1.32	0.13	-1.32	298.45	3.25	2.08
Multistage (1-degree)[e]	3	4.56	0.21	-1.60	-0.52	-1.60	298.39	1.61	1.17
Multistage (2-degree)[e]	2	3.26	0.20	-1.51	0.41	-1.51	299.09	3.40	1.27
Multistage (3-degree)[e]	2	3.26	0.20	-1.51	0.41	-1.51	299.09	3.40	1.27
Multistage (4-degree)[e]	2	3.26	0.20	-1.51	0.41	-1.51	299.09	3.40	1.27
Probit	3	3.39	0.34	-1.52	0.16	-1.52	297.20	2.67	2.18
Weibull[c]	2	3.07	0.22	-1.45	0.33	-1.45	298.88	3.36	1.30

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Slope restricted to ≥1.
[e]Betas restricted to ≥0.
[f]Selected model. All models provided adequate fit to the data. BMCLs for models providing adequate fit were sufficiently close (differed by <3-fold). Therefore, the model with lowest AIC was selected (Logistic).

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-4. Fit of Logistic Model to Data on Incidence of Lung Fibrosis in Rats Exposed to Antimony Trioxide (mg Sb/m^3)



A summary of the PODs and HECs are presented in Table A-7. The POD_{HEC} values, which were based on $BMCL_{10}$ or NOAEL values, ranged from 0.19 to 0.078 mg Sb/m^3 and the POD_{HEC} values, based on LOAEL values, were 0.89 and 1.5 mg Sb/m^3. To compare the two types of PODs, the POD_{HEC} values based on LOAELs were divided by an uncertainty factor of 10 resulting in values of 0.15 and 0.089 mg Sb/m^3. The POD_{HEC} values for the increased lung clearance half-time, chronic lung interstitial inflammation, and degenerative heart effects and altered EKG readings in rabbits were similar, and the lowest value of 0.057 mg Sb/m^3 for chronic lung inflammation was selected as the basis of the MRL. This human equivalent value of 0.057 mg Sb/m^3 was divided by an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability), resulting in an MRL of 0.002 mg Sb/m^3. However, this MRL is slightly higher than the acute-duration inhalation MRL, and ATSDR adopted the acute-duration MRL of 0.001 mg Sb/m^3 for intermediate-duration exposure.

Table A-7. Summary of Potential Points of Departures (PODs) and Human Equivalent Concentrations (HECs) for Intermediate-Duration Inhalation MRL for Antimony

Endpoint (reference)	PODs (mg Sb/m^3)	RDDR values[a]	HECs[b] (mg Sb/m^3)
Increased lung clearance half-times in rats (Newton et al. 1994)	0.902 (NOAEL)	0.487[c]	0.078
Chronic lung interstitial inflammation in rats (Newton et al. 1994)	0.66 ($BMCL_{10}$)	0.487[c]	0.057
Chronic lung fibrosis in rats (Newton et al. 1994)	2.14 ($BMCL_{10}$)	0.487[c]	0.19
Degenerative changes in heart and altered EKG readings in rats (Brieger et al. 1954)	2.20 (LOAEL)	3.185[d]	1.5
Degenerative changes in heart and altered EKG readings in dogs (Brieger et al. 1954)	3.98 (LOAEL)	NA[e]	NA
Degenerative changes in heart and altered EKG readings in rabbits (Brieger et al. 1954)	4.02 (LOAEL)	1.060[d]	0.89

[a]RDDR values specific for each region of the respiratory tract (extrathoracic and pulmonary) were calculated using EPA's RDDR calculator, with estimated body weight of 0.230 kg for the Newton et al. (1994) study and reference body weights of 0.267 and 4.0 kg for rats and rabbits in the Brieger et al. (1954) study.
[b]HEC calculated by multiplying the duration-adjusted POD (POD x 6 hours/24 hours x 5 days/7 days for the Newton et al. [1994] study and 7 hours/day, 5 days/week for the Brieger et al. [1954] study) by the RDDR value.
[c]Calculated using a particle size of 3.05 µm (sigma g of 1.57).
[d]Calculated using a particle size of 2 µm (sigma g of 1.9), which is an assumed value; the investigators noted that most of the particles were <2 µm, but did not provide any additional information.
[e]RDDR calculator does not have default values for dogs and HECs could not be calculated.

BMCL = 95% lower confidence limit on the benchmark concentration; EKG = electrocardiogram; EPA = Environmental Protection Agency; LOAEL = lowest-observed-adverse-effect level; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; RDDR = regional deposited dose ratio

Agency Contacts (Chemical Managers): Melanie Buser

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Antimony
CAS Numbers: 7440-36-0
Date: October 2019
Profile Status: Final
Route: Inhalation
Duration: Chronic
MRL 0.0003 mg Sb/m^3
Critical Effect: Lung inflammation in rats
Reference: Newton et al. 1994
Point of Departure: $BMCL_{10}$ of 0.10 mg Sb/m^3
Uncertainty Factor: 30
LSE Graph Key: 16
Species: Rat

MRL Summary: A chronic-duration inhalation MRL of 0.0003 mg Sb/m^3 was derived for antimony based on an increased incidence of lung inflammation in female rats exposed to antimony trioxide 6 hours/day, 5 days/week for 12 months (Newton et al. 1994). The MRL is based on a $BMCL_{10}$ of 0.10 mg Sb.m^3 (human equivalent BMCL of 0.008 mg Sb/m^3) and an uncertainty factor of 30 (3 for extrapolation from animals to humans with dosimetric adjustments and 10 for human variability).

Selection of the Critical Effect: The toxicity of airborne antimony has not been extensively studied in humans. Several occupational exposure studies have reported lung effects (pneumoconiosis, chronic bronchitis) in workers at antimony smelters (Cooper et al. 1968; Potkonjak and Pavlovich 1983; Schnorr et al. 1995). Signs of upper respiratory tract irritation including bleeding of the nose, rhinitis, upper airway inflammation, and laryngitis (Potkonjak and Pavlovich 1983; Renes 1953) have also been reported in workers. Other effects that have been observed in workers include altered EKGs (Brieger et al. 1954) and dermatitis, which is likely due to direct contact with skin (Potkonjak and Pavlovich 1983; Renes 1953). One study also reported reproductive disturbances and developmental effects (decreases in infant growth) in female workers exposed to metallic antimony, antimony trioxide, and antimony pentasulfide (Belyaeva 1967). Although some studies provided exposure levels, these studies were not considered suitable for derivation of a chronic MRL because many studies did not include control groups, wide ranges of antimony levels were reported, and many involved co-exposure to other compounds including arsenic.

A number of studies have evaluated the chronic toxicity of antimony compounds in rats and mice. These studies provide strong evidence that the respiratory tract is the primary target of antimony toxicity, which is supported by the systematic review of the toxicity data that concluded that respiratory tract toxicity is a presumed health effect in humans. The lowest LOAEL values were identified in three studies involving antimony trioxide exposure for 1–2 years (Newton et al. 1994; NTP 2016; Watt 1983). Higher LOAELs for lung effects were identified for other antimony compounds: 17.5 mg Sb/m^3 as antimony ore for interstitial fibrosis (Groth et al. 1986) and 84 mg Sb/m^3 as antimony trisulfide for lipoid pneumonia (Gross et al. 1952). Although these LOAELs are higher than those identified for antimony trioxide, the available data do not allow a comparison between compounds since adverse effects were often observed at the lowest concentration tested. A summary of the NOAEL and LOAEL values for the respiratory effects is presented in Table A-8. In addition to the pulmonary effects, effects have also been observed in the nasal cavity (respiratory epithelial hyperplasia), lymph nodes (lymphoid hyperplasia in bronchial and mediastinal lymph nodes), eyes (lenticular degeneration), and bone marrow (hyperplasia); the LOAELs for these effects (see Table A-8) are similar to those identified for respiratory effects.

Table A-8. Summary of NOAEL and LOAEL Values for Effects Observed in Target Tissues

NOAEL (mg Sb/m^3)	LOAEL (mg Sb/m^3)	Effect	Reference
Respiratory effects			
0.05	0.43	Chronic interstitial inflammation in female rats exposed to antimony trioxide for 1 year	Newton et al. 1994
	1.6	Focal fibrosis, pneumocyte hyperplasia in rats exposed to antimony trioxide for 55 weeks	Watt 1983
	2.5	Lung inflammation, proteinosis, alveolar epithelial hyperplasia, bronchiole epithelial hyperplasia, lung fibrosis in rats exposed to antimony trioxide for 2 years	NTP 2016
	2.5	Nasal respiratory epithelial hyperplasia in rats exposed to antimony trioxide for 2 years	NTP 2016
	2.5	Nasal respiratory epithelial inflammation in male mice exposed to antimony trioxide for 2 years	NTP 2016
	2.5	Lung inflammation, alveolar fibrosis, pleural fibrosis and inflammation, alveolar and bronchiolar epithelial hyperplasia in mice exposed to antimony trioxide for 2 years	NTP 2016
0.43	3.8	Chronic interstitial inflammation in male rats exposed to antimony trioxide for 1 year	Newton et al. 1994
	17.5	Interstitial fibrosis and alveolar wall hypertrophy and hyperplasia in rats exposed to antimony ore for 1 year	Groth et al. 1986
	36	Interstitial fibrosis and alveolar wall hypertrophy and hyperplasia in rats exposed to antimony trioxide for 1 year	Groth et al. 1986
	84	Lipoid pneumonia in rats exposed to antimony trisulfide for 14.5 months	Gross et al. 1952
Bone marrow effects			
	2.5	Bone marrow hyperplasia in mice exposed to antimony trioxide for 2 years	NTP 2016
Lymphoreticular effects			
	2.5	Lymphoid hyperplasia in bronchial and mediastinal lymph nodes in rats exposed to antimony trioxide for 2 years	NTP 2016
	2.5	Lymphoid hyperplasia of bronchial lymph nodes in mice exposed to antimony trioxide for 2 years	NTP 2016
Ocular effects			
0.05	0.43	Lenticular degeneration in rats exposed to antimony trioxide for 1 year	Newton et al. 1994

LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level

Selection of the Principal Study: Four studies identified LOAEL values of <5 mg Sb/m^3 for lung effects in rats (Newton et al. 1994; NTP 2016; Watt 1983) and mice (NTP 2016). Watt (1983) found increases in the incidence of focal fibrosis, adenomatous hyperplasia, cholesterol clefts, and pneumocyte hyperplasia in rats exposed to 1.6 mg Sb/m^3 for 55 weeks. In rats and mice exposed to 2.5 mg Sb/m^3 as antimony trioxide for 2 years, inflammation, proteinosis, alveolar/bronchiolar hyperplasia, and fibrosis were observed in the lungs (NTP 2016). An increase in lung clearance times was observed in rats exposed to

3.8 mg Sb/m^3 as antimony trioxide for 12 months and an increase in the severity and incidence of chronic lung inflammation was observed at 0.43 (females only) and 3.8 mg Sb/m^3 was after a 1-year recovery period (Newton et al. 1994). Some non-respiratory effects have also been seen at similar concentrations, including lenticular degeneration in rats exposed to 0.43 mg Sb/m^3 (Newton et al. 1994), bone marrow hyperplasia in mice exposed to 2.5 mg Sb/m^3 (NTP 2016), and lymphoid hyperplasia in bronchial and/or mediastinal lymph nodes in rats and mice exposed to 2.5 mg Sb/m^3 (NTP 2016). Newton et al. (1994) identified the lowest LOAEL value for chronic interstitial lung inflammation and lenticular degeneration in rats exposed to 0.43 mg Sb/m^3 for 1 year with a 1-year recovery period; these effects were not observed at 0.05 mg Sb/m^3. The other chronic-duration studies identified higher LOAEL values.

Summary of the Principal Study:

Newton PE, Bolte HF, Daly IW, et al. 1994. Subchronic and chronic inhalation toxicity of antimony trioxide in the rat. Fundam Appl Toxicol 22(4):561-576.

Groups of 65 male and 65 female Fischer 344 rats were exposed to 0, 0.06, 0.51, or 4.50 mg/m^3 antimony trioxide dust (0, 0.05, 0.43, or 3.8 mg Sb/m^3, respectively) 6 hours/day, 5 days/week for 12 months followed by a 12-month observation period. Groups of five rats/sex were terminated after 6 and 12 months of exposure and at 6 months postexposure; the remaining animals were terminated 12 months postexposure. The MMAD was 3.76±0.84 µm with a geometric standard deviation of 1.79±0.326. The following parameters were used to assess toxicity: weekly detailed observations, body weight measurements (weekly for the first 13 weeks and monthly thereafter), ophthalmoscopic examination, hematological (hemoglobin, hematocrit, erythrocyte count, mean corpuscular hemoglobin, hemoglobin concentration, and volume, and total leukocyte counts) and clinical chemistry (aspartate aminotransferase, alanine aminotransferase, alkaline phosphatase, blood urea nitrogen, fasting glucose, total protein, chloride, sodium, and potassium) indices assessed at 12, 18, and 24 months, and histopathological examination of the heart, nasal turbinates, larynx, trachea, lung, and peribronchial lymph nodes.

No increases in mortality were observed. Corneal effects were observed during the study; however, the investigators noted that the effects were equally distributed among exposed and control groups and were similar to spontaneous degenerative conditions observed in Fischer 344 rats. The investigators noted a concentration-related increase in the occurrence of chromodacryorrhea (incidence data not provided); they noted that microscopic periodontal disease was also observed in some rats and that the chromodacryorrhea may be secondary to this effect. At the end of the recovery period, an increase in the occurrence of cataracts (focal posterior cataract, posterior subcapsular cataract, complete cataract) was observed (incidences of 6/55, 12/49, 18/64, and 19/60 were reported in Bio/Dynamics 1990); the incidence was statistically significant at ≥0.43 mg Sb/m^3 (Fisher Exact Test conducted by SRC). No treatment-related alterations in body weight gain, hematological indices, clinical chemistry indices, or lung weights were observed. At the end of the exposure period and at the end of the recovery period, statistically significant (Fisher Exact Test conducted by ATSDR) increases in the incidence of alveolar/intraalveolar macrophages were observed at ≥0.05 mg Sb/m^3. Histological alterations were observed in the lungs of rats killed at the end of the recovery periods: chronic interstitial inflammation at 0.43 (females only) and 3.8 mg Sb/m^3 and interstitial fibrosis at 3.8 mg Sb/m^3. Although a high incidence of lung inflammation was also observed in controls, the investigators noted that the inflammation observed in the controls was considered a “spontaneous lesion” and that the incidence and severity of the inflammation was concentration-related (see Table A-9). Increases in antimony trioxide lung clearance half-times were observed; the half-times (data reported in Bio/Dynamics 1990) in the male and female rats were 3.0 and 4.2 months, respectively, at 0.43 mg Sb/m^3 and 8.7 and 10.2 months, respectively, at 3.8 mg Sb/m^3, as compared to 2.5 and 2.2 months, respectively, in the 0.05 mg Sb/m^3 group. No significant increases in the incidence of neoplastic lesions were observed.

Table A-9. Incidence and Severity of Chronic Interstitial Lung Inflammation in Rats Exposed to Antimony Trioxide for 1 Year with a 1-Year Recovery

	Concentration (mg Sb/m^3)			
Severity	0	0.05	0.43	3.8
Males				
Minimal	4/52 (12.5)[a]	7/52 (18.9)	12/53 (33.3)	0/52 (0)
Slight	19/52 (59.4)	27/52 (73)	24/53 (66.7)	14/52 (29.2)
Moderate	8/52 (25)	3/52 (8.1)	0/53 (0)	32/52 (66.7)
Moderately severe	1/52 (3.1)	0/52 (0)	0/53 (0)	2/52 (3.8)
Females				
Minimal	3/49 (9.1)	12/52 (30)	14/54 (29.1)	1/50 (2.1)
Slight	24/49 (72.7)	23/52 (57.5)	23/54 (47.9)	29/50 (60.4)
Moderate	6/49 (18.2)	5/52 (12.5)	11/54 (22.9)	18/50 (37.5)
Moderately severe	0/49 (0)	0/52 (0)	0/54 (0)	0/50 (0)

[a]Percentage of total lesions with a specific severity score.

Source: Newton et al. 1994

Selection of the Point of Departure for the MRL: $BMCL_{10}$ of 0.10 mg Sb/m^3 ($BMCL_{HEC}$ of 0.008 mg Sb/m^3) for lung inflammation in female rats.

BMD modeling was utilized to estimate the potential PODs for the histological alterations observed in lungs and eyes. The incidence data from the Newton et al. (1994) (Table A-10) study were fit to all available dichotomous models in EPA's BMDS (version 2.6.0) using the extra risk option. Adequate model fit was judged by three criteria: goodness-of-fit statistics (p-value >0.1), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. The results of the BMD modeling for lung inflammation in female rats is presented in Table A-11 and the model fit is presented in Figure A-5. The incidence data for lung inflammation in males were not considered suitable for modeling since only the highest concentration group showed a response; thus, the data provide limited information on the shape of the concentration-response curve. For lenticular degeneration, none of the available models provided an adequate fit to the data.

Table A-10. Incidence of Nonneoplastic Lesions in Rats Exposed to Antimony Trioxide for 1 Year with a 1-Year Recovery

	Concentration (mg Sb/m^3)			
Effect	0	0.05	0.43	3.8
Chronic lung inflammation in males	32/52	37/52	36/53	48/52[a]
Chronic lung inflammation in females	33/49	40/52	48/54[a]	48/50[a]
Lenticular degeneration	6/55	12/49	18/64[a]	19/60[a]

[a]Significantly different from controls.

Source: Newton et al. 1994

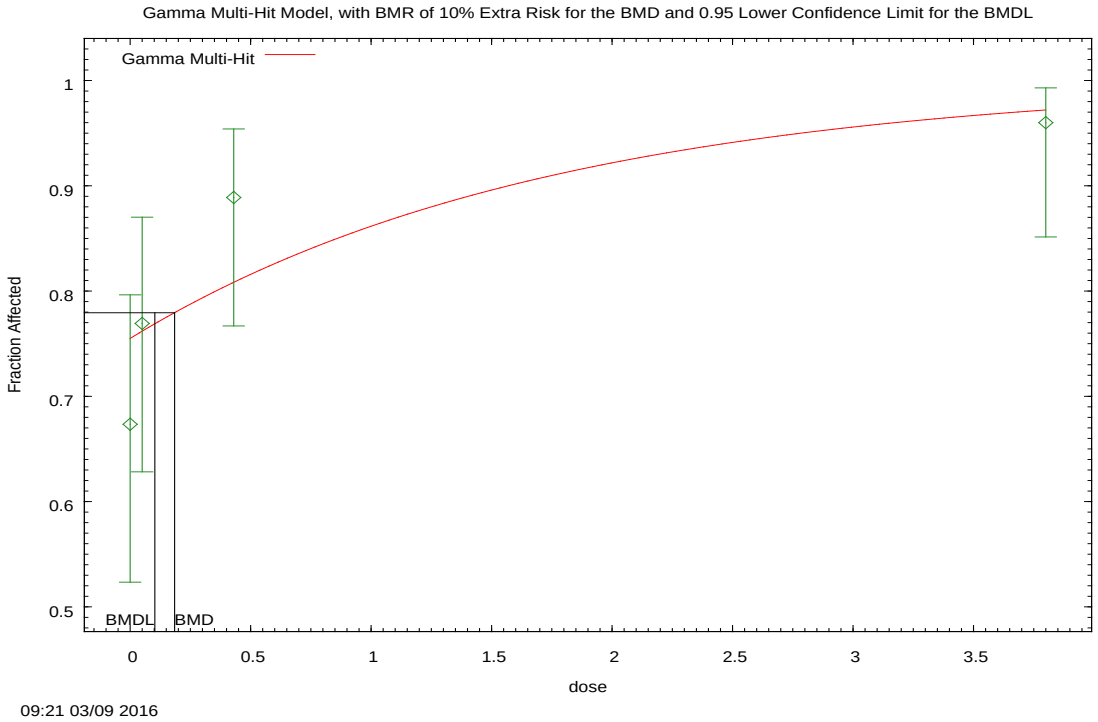
Table A-11. Model Predictions for Antimony Trioxide, Incidence of Chronic Lung Inflammation in Female Rats Exposed to Antimony Trioxide for 1 Year with a 1-Year Recovery Period (Newton et al. 1994)

				Scaled residuals[b]					
Model	DF	χ^2	χ^2 Goodness of fit p-value[a]	Dose below BMC	Dose above BMC	Overall largest	AIC	BMC_{10} (mg Sb/m^3)	$BMCL_{10}$ (mg Sb/m^3)
Gamma[c,d]	***2***	***4.3***	***0.12***	***0.13***	***1.51***	***1.51***	***181.03***	***0.18***	***0.10***
Logistic	2	4.63	0.10	0.07	1.56	1.56	181.38	0.22	0.13
LogLogistic[e,f]	2	1.15	0.56	-0.43	0.44	-0.81	177.59	0.04	0.01
LogProbit[d]	2	5.21	0.07	0.26	1.47	1.47	181.64	ND	ND
Multistage (1-degree)[g]	2	4.3	0.12	0.13	1.51	1.51	181.03	0.18	0.10
Multistage (2-degree)[g]	2	4.3	0.12	0.13	1.51	1.51	181.03	0.18	0.10
Multistage (3-degree)[g]	2	4.3	0.12	0.13	1.51	1.51	181.03	0.18	0.10
Probit	2	4.9	0.09	0.03	1.62	1.62	181.68	ND	ND
Weibull[c]	2	4.3	0.12	0.13	1.51	1.51	181.03	0.18	0.10

[a]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[b]Scaled residuals at doses immediately below and above the BMC; also the largest residual at any dose.
[c]Power restricted to ≥1.
[d]Selected model. BMCLs for models providing adequate fit were sufficiently close; therefore the model with the lowest AIC was selected
[e]Slope restricted to ≥1.
[f]Model considered an outlier because the BMCL was 10 times lower than the other models.
[g]Betas restricted to ≥0.

AIC = Akaike Information Criterion; BMC = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMCL = 95% lower confidence limit on the BMC (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); DF = degrees of freedom; ND = not determined, goodness-of-fit criteria, p<0.10; ND (LS) = not determined; largest scaled residual >2

Figure A-5. Fit of Gamma Model to Data on Incidence of Lung Interstitial Inflammation in Female Rats Exposed to Antimony Trioxide (mg Sb/m^3)



The PODs for each endpoint are presented in Table A-12; for lung inflammation in males and lenticular degeneration, the NOAEL was used as the POD since the incidence data were not considered suitable for BMD modeling. The lowest POD_{HEC} was 0.008 mg Sb/m^3 for lung inflammation in female rats.

Table A-12. Summary of Potential Points of Departure (PODs) for Derivation of Chronic-Duration Inhalation MRL for Antimony

Endpoint (reference)	POD (mg Sb/m^3)	RDDR[a]	HEC[b] (mg Sb/m^3)
Chronic interstitial inflammation in male rats (Newton et al. 1994)	0.43 (NOAEL)	0.330	0.025
Chronic interstitial inflammation in female rats (Newton et al. 1994)	0.10 ($BMCL_{10}$)	0.436	0.008
Lenticular degeneration in rats (Newton et al. 1994)	0.05 (NOAEL)	2.797	0.025

[a]RDDR values specific for each region of the respiratory tract (pulmonary and extrarespiratory) were calculated using EPA's RDDR calculator with reference body weights of 0.380 and 0.229 kg for male and female rats in the Newton et al. (1994) study and particle size of 3.76 µm (sigma g of 1.79).
[b]HEC calculated by multiplying the duration-adjusted POD (POD x 6 hours/24 hours x 5 days/7 days) by the RDDR value.

BMCL = 95% lower confidence limit on the benchmark concentration; HEC = human equivalent concentration; MRL = Minimal Risk Level; NOAEL = no-observed-adverse-effect level; POD = point of departure; RDDR = regional deposited dose ratio

Calculations

Intermittent Exposure: Each potential POD was adjusted for intermittent exposure (6 hours/24 hours, 5 days/7 days).

Human Equivalent Concentration: HECs were calculated by multiplying the POD_{ADJ} by the RDDR for the appropriate region of the respiratory tract. The RDDRs were calculated using EPA's RDDR calculator with reference body weights of 0.380 and 0.229 kg for male and female rats and particle size of 3.76 μm (sigma g of 1.79). The POD_{HEC} values are presented in Table A-12.

Uncertainty Factor:

- 3 for extrapolation from animals to humans with dosimetric adjustments
- 10 for human variability

MRL = POD_{HEC} ÷ uncertainty factors
0.0003 mg Sb/m^3 = 0.008 mg Sb/m^3 ÷ 30

Other Additional Studies or Pertinent Information that Lend Support to this MRL: There are limited data to compare the relative toxicity of antimony compounds. Chronic studies have tested antimony trioxide, antimony trisulfide, and antimony ore; the respiratory tract was the most sensitive target in all of these studies. It is difficult to compare the potency of the different compounds because in most cases, the lowest concentration tested was a LOAEL. No data were available to compare the toxicity of trivalent and pentavalent antimony compounds.

Agency Contacts (Chemical Managers): Melanie Buser

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Antimony
CAS Numbers: 7440-36-0
Date: October 2019
Profile Status: Final
Route: Oral
Duration: Acute
MRL 1 mg Sb/kg/day
Critical Effect: Hepatocellular cytoplasmic vacuolization and forestomach focal ulceration
Reference: NTP 1992
Point of Departure: NOAEL of 99 mg Sb/kg/day
Uncertainty Factor: 100
LSE Graph Key: 2
Species: Mouse

MRL Summary: An acute-duration oral MRL of 1 mg Sb/kg/day was derived for antimony based on an increased incidence of cytoplasmic vacuolization in the liver and focal ulceration in the forestomach of mice exposed to antimony potassium tartrate in drinking water for 14 days (NTP 1992). The MRL is based on a NOAEL of 99 mg Sb/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Studies conducted in the 1920s and 1940s demonstrate that antimony potassium tartrate is a gastrointestinal irritant in humans (Dunn 1928) and animals (as reviewed by Elinder and Friberg 1986) resulting in vomiting and diarrhea shortly after exposure. Houpt et al. (1984) demonstrated that the mean latency to vomit was 30 minutes after dogs drank 4.8 mg Sb/kg as antimony potassium tartrate. These gastrointestinal effects are likely due to the antimony concentration rather than the dose. NTP (1992) evaluated the acute toxicity of antimony potassium tartrate in 14-day drinking water studies in rats and mice. In rats, the highest concentration (61 mg Sb/kg/day) did not result in significant alterations in body weight or histopathological alterations in major tissues and organs. In mice, exposure to 150 mg Sb/kg/day resulted in focal ulceration in the forestomach and minimal to moderate hepatocellular cytoplasmic vacuolization. Exposure to 99 and 150 mg Sb/kg/day resulted in a transient decrease in body weight gain; at termination, body weights were within 93% of controls. The decreases in body weight may have been secondary to the dramatic decrease in water intake, which was also observed in the exposed mice.

Selection of the Principal Study: Although the Houpt et al. (1984) study identified the lowest LOAEL for acute exposure, this study was not selected as the basis of the MRL because the study only evaluated overt signs of gastrointestinal irritation and was a single exposure study. The mouse NTP (1992) study was selected as the principal study for derivation of the MRL.

Summary of the Principal Study:

NTP. 1992. Toxicology studies of antimony potassium tartrate in F344/N rats and B6C3F1/N mice (drinking water and intraperitoneal injection studies). National Toxicology Program, Research Triangle Park, NC. NTP TOX 11.

This study is also reported in: Dieter MP, Jameson CW, Elwell MR. 1991. Comparative toxicity and tissue distribution of antimony potassium tartrate in rats and mice dosed by drinking water or intraperitoneal injection. J Toxicol Environ Health 34:51-82.

Groups of 10 male and 10 female B6C3F1 mice were exposed to 0, 0.30, 0.65, 1.25, 2.5, or 5.0 mg/mL antimony potassium tartrate (99–100% purity) in drinking water for 14 days. The investigators used water consumption data and body weight averages to calculate doses of 0, 59, 98, 174, 273, and 407 mg/kg/day antimony potassium tartrate (0, 21, 36, 63, 99, and 150 mg Sb/kg/day). The following parameters were evaluated to assess toxicity: twice daily observations, body weight measurements (days 1 and 8 and at termination), water consumption (days 7 or 8 and day 15), organ weights, histopathology of major tissues and organs in control and high-dose groups (five mice/sex/group) and all early deaths, and histopathological examination of the liver and forestomach of mice in all groups (five mice/sex/group).

One female mouse in the 150 mg Sb/kg/day group died prior to the end of the study. On day 8, decreases in body weight gain were observed in males exposed to 99 mg Sb/kg/day and in males and females exposed to 150 mg Sb/kg/day. However, by the end of the study, the final weights of all antimony groups were within 93% of the controls. Decreases in water consumption were observed at all antimony levels. The investigators noted that overt signs of toxicity (rough haircoat, emaciation, abnormal posture, hypoactivity, and decreased fecal material, consistent with avoidance of the antimony potassium tartrate containing water) were observed, but did not specify if this was observed in all groups. Histological alterations were observed in the forestomach and liver of mice in the 150 mg/kg/day group. In the forestomach, focal areas of ulceration with necrosis and inflammation of the squamous mucosa were observed; the incidence was not reported, although the investigators noted that gross forestomach lesions were observed in one male and three females. In the liver, minimal to moderate cytoplasmic vacuolization was observed in all mice in the 150 mg Sb/kg/day group; the vacuolization had a centrilobular distribution with some extension into portal areas.

Selection of the Point of Departure for the MRL: The NOAEL of 99 mg Sb/kg/day for liver lesions was selected as the POD for the MRL.

BMD modeling was not conducted since lesions were only observed in the high-dose group. The transient decrease in body weight observed at 99 and 150 mg Sb/kg/day was not selected as the POD because this decrease may have been the result of decreased water consumption likely due to taste aversion.

Uncertainty Factor:

- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = NOAEL ÷ uncertainty factors
1 mg Sb/kg/day = 99 mg Sb/kg/day ÷ 100

Other Additional Studies or Pertinent Information that Lend Support to this MRL: Support for identifying the liver as the critical effect for antimony is supported by intermediate-duration studies in which histological alterations were observed in rats exposed to antimony metal or antimony trioxide (Sunagawa 1981) and increases in alanine aminotransferase and aspartate aminotransferase in humans receiving injections of pentavalent antimony (Andersen et al. 2005). Insufficient evidence is available to allow for a comparison of the hepatotoxicity of different antimony compounds or valence states. The absorption rate of antimony potassium tartrate is greater than that of other antimony compounds (ICRP [1981] recommends rates of 10 and 1%, respectively), which likely results in a higher toxicity. More side effects (all effects) were observed in patients treated with antimony potassium tartrate than with pentavalent antimony compounds, although studies directly comparing the valency states on antimony hepatotoxicity were not identified. Alverez et al. (2005) reported greater cardiotoxicity and lethality in

guinea pigs receiving intramuscular injections of 10 mg Sb/kg/day as antimony potassium tartrate, as compared to guinea pigs administered 16 mg Sb/kg/day as meglumine antimoniate.

Agency Contacts (Chemical Managers): Melanie Buser

APPENDIX A

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Antimony
CAS Numbers: 7440-36-0
Date: October 2019
Profile Status: Final
Route: Oral
Duration: Intermediate
MRL 0.0006 mg Sb/kg/day
Critical Effect: Decreased serum glucose in female rats
Reference: Poon et al. 1998
Point of Departure: NOAEL of 0.06 mg Sb/kg/day
Uncertainty Factor: 100
LSE Graph Key: 12
Species: Rat

MRL Summary: An intermediate-duration oral MRL of 0.0006 mg Sb/kg/day was derived for antimony based on decreases in serum glucose levels in female rats exposed to antimony potassium tartrate in drinking water for 13 weeks (Poon et al. 1987). The MRL is based on a NOAEL of 0.06 mg Sb/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Selection of the Critical Effect: Several studies have evaluated the intermediate-duration toxicity of antimony compounds. Observed effects include reductions in body weight gain, decreases in serum glucose levels, and developmental effects (decreased pup body weight and altered vasomotor response in pups). The NOAEL and LOAEL values for these effects are presented in Table A-13. The results of several 12–24-week studies provide evidence for compound-specific differences in toxicity that are likely reflective of differences in the relative absorption of the compounds. More soluble compounds such as antimony potassium tartrate and antimony trichloride appear to be more toxic than antimony trioxide.

Table A-13. List of NOAEL and LOAEL Values in Rats Exposed to Antimony or Antimony Compounds for Intermediate Durations

Exposure duration, compound	NOAEL (mg Sb/kg/day)	LOAEL (mg Sb/kg/day)	Effect	Reference
Body weight effects				
GDs 1–22 Antimony trichloride (W)	0.07	0.7	Decreased maternal body weight gain (11%)	Marmo et al. 1987; Rossi et al. 1987
12 weeks Antimony metal (F)		85	Decreased body weight gain (10%)	Hiraoka 1986

Table A-13. List of NOAEL and LOAEL Values in Rats Exposed to Antimony or Antimony Compounds for Intermediate Durations

Exposure duration, compound	NOAEL (mg Sb/kg/day)	LOAEL (mg Sb/kg/day)	Effect	Reference
13 weeks Antimony potassium tartrate (W)	42.17		No alterations in body weight gain	Poon et al. 1998
13 weeks Antimony trioxide (F)	1,408		No alterations in body weight gain	Hext et al. 1999
Serum glucose levels				
13 weeks Antimony potassium tartrate (W)	0.06	0.64	Decreases in serum glucose in female rats	Poon et al. 1998
Developmental effects				
LDs 0–22; PNDs 22–60 Antimony trichloride (W)		0.1 (post-weaning dose)	Altered vasomotor response in pups	Angrisani et al. 1988; Marmo et al. 1987
GDs 0–22; pups exposed on PNDs 22–60 Antimony trichloride (W)		0.1 (post-weaning dose)	Altered vasomotor response in pups	Rossi et al. 1987; Marmo et al. 1987
GDs 0–22; pups exposed on PNDs 22–60 Antimony trichloride (W)	0.07	0.7	Decreased pup growth on PNDs 10–60	Rossi et al. 1987

(F) = dietary exposure; GD = gestation day; LD = lactation day; LOAEL = lowest-observed-adverse-effect level; NOAEL = no-observed-adverse-effect level; PND = postnatal day; (W) = drinking water exposure

Based on the limited available data, the toxicity of antimony potassium tartrate appears to be higher than antimony metal and antimony trioxide, which is likely due to the differences in absorption. ICRP (1981) recommends an absorption rate of 10% for antimony potassium tartrate and 1% for all other antimony compounds. A study (Alkhawajah et al. 1996) comparing the developmental toxicity of antimony trichloride (trivalent), sodium stibogluconate (pentavalent), and meglumine antimonate (pentavalent) in rats following intramuscular injections reported similar effects for the three compounds; although no direct comparisons were made, the magnitude of the alterations (decreases in fetal viability and body weight) appears to be similar for the three compounds.

Selection of the Principal Study: Three studies identified LOAEL values of 0.1–0.64 mg Sb/kg/day in rats exposed to antimony trichloride or antimony potassium tartrate. The effects observed at these concentrations included altered vasomotor response in rat pups exposed to antimony trichloride during

gestation and/or lactation and on PNDs 22–60 (Angrisani et al. 1988; Rossi et al. 1987), decreases in pup growth on PNDs 10–60 (Rossi et al. 1987), and decreases in serum glucose levels in rats exposed to antimony potassium tartrate for 13 weeks (Poon et al. 1998). These three endpoints were considered for the basis of the intermediate-duration MRL. Developmental toxicity and decreases in serum glucose levels were both considered suspected health effects in humans based on the systematic review of the available data on antimony; of the two developmental effects, only the decrease in growth was considered due to the uncertainty associated with estimating the dose for the vasopressor studies. In these studies, rats were exposed during gestation and/or lactation and then exposed on PNDs 22–60; the 0.1 mg Sb/kg/day dose is an estimate of the postnatal exposure, but does not include an estimate of prenatal exposure or exposure via breast milk.

Selection of the Point of Departure for the MRL: NOAEL of 0.06 mg Sb/kg/day for decreased serum glucose in female rats.

BMD modeling was considered for the decreases in serum glucose levels and decreases in pup body weight on PNDs 10 and 22. The serum glucose levels (Table A-14) and pup body weights (Table A-15) were fit to all available continuous models in EPA's BMDS (version 2.6.0). The following procedure for fitting continuous data was used. The simplest model (linear) was first applied to the data while assuming constant variance. If the data were consistent with the assumption of constant variance ($p \geq 0.1$), then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data while assuming constant variance. Adequate model fit was judged by three criteria: goodness-of-fit p-value ($p > 0.1$), visual inspection of the dose-response curve, and scaled residual at the data point (except the control) closest to the predefined BMR. Among all of the models providing adequate fit to the data, the lowest BMCL was selected as the POD when the difference between the BMCLs estimated from these models was >3-fold; otherwise, the BMCL from the model with the lowest AIC was chosen. If the test for constant variance was negative, the linear model was run again while applying the power model integrated into the BMDS to account for nonhomogenous variance. If the nonhomogenous variance model provided an adequate fit ($p \geq 0.1$) to the variance data, then the fit of the linear model to the means was evaluated and the polynomial, power, and Hill models were fit to the data and evaluated while the variance model was applied. Model fit and POD selection proceeded as described earlier. If the test for constant variance was negative and the nonhomogenous variance model did not provide an adequate fit to the variance data, then the data set was considered unsuitable for modeling. For all models, a BMR of 1 standard deviation change from the control was used.

Table A-14. Serum Glucose Concentrations in Female Rats Exposed to Antimony Potassium Tartrate for 13 Weeks

Dose (mg Sb/kg/day)	Serum glucose concentration (mean±standard deviation, mg/dL)
0	242±55
0.06	217±22
0.64	200±25[a]
6.13	207±27[a]
45.69	198±25[a]

[a]Significantly different from controls.

Source: Poon et al. 1988

Table A-15. Alterations in Pup Body Weight on Postnatal Days (PNDs) 10 and 22 in Pups Exposed to Antimony Trichloride During Gestation and Lactation

	Pup body weight (mean±standard error)	
Dose (mg Sb/kg/day)	PND 10	PND 22
0	23±1.8 (73)[a]	58±5.1 (66)
0.07	20±2.6 (80)	52±4.0 (72)
0.7	17±0.4[b] (63)	31±2.8[b] (56)

[a]Number in parentheses is the number of pups examined; data were not presented in a way that would allow analysis on a per-litter basis.
[b]Significantly different from controls.

Source: Rossi et al. 1987

None of the models provided adequate fit to the serum glucose data or the PND 10 body weight data. Although adequate statistical fit was found for the PND 22 body weight data (model results are presented in Table A-16), the BMDL for the model with the lowest AIC (Exponential, model 3) was 0.72 mg Sb/kg/day, which is the same value as the empirical LOAEL identified in the study and was not considered a suitable basis for an MRL. Thus, a NOAEL/LOAEL approach was utilized to identify the POD for the intermediate-duration oral MRL. The NOAEL and LOAEL values for the decreased serum glucose level and the decreased pup body weight were similar and the endpoint with the lowest LOAEL (decreased serum glucose level) was selected as the basis of the MRL.

Table A-16. Model Predictions for Alterations in Pup Body Weight on Postnatal Day (PND) 22 in Pups Exposed to Antimony Trichloride During Gestation and Lactation (Rossi et al. 1987)

				Scaled residuals[c]					
Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Dose below BMD	Dose above BMD	Overall largest	AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
Constant variance									
Linear[e]	<0.0001	<0.0001	0.54	0.05	NA	-0.44	1,562.44	NA	NA
Nonconstant variance									
Exponential (model 2)[d]	<0.0001	0.61	0.27	0.03	NA	-0.31	1,540.28	1.32	0.86
Exponential (model 3)[d,e]	***<0.0001***	***0.61***	***0.27***	***0.03***	***NA***	***-0.31***	***1,540.28***	***1.32***	***0.72***
Exponential (model 4)[d]									ND
Exponential (model 5)[d]									ND
Hill[d]									ND
Linear[f]	<0.0001	0.61	0.20	0.00	NA	0.39	1,540.70	1.07	0.81

Table A-16. Model Predictions for Alterations in Pup Body Weight on Postnatal Day (PND) 22 in Pups Exposed to Antimony Trichloride During Gestation and Lactation (Rossi et al. 1987)

Model	Test for significant difference p-value[a]	Variance p-value[b]	Means p-value[b]	Scaled residuals[c]			AIC	BMD_{1SD} (mg/kg/day)	$BMDL_{1SD}$ (mg/kg/day)
				Dose below BMD	Dose above BMD	Overall largest			
Polynomial (2-degree)[f]	<0.0001	0.61	0.20	0.00	NA	0.39	1,540.70	1.07	0.80
Power[d]	<0.0001	0.61	0.20	0.00	NA	0.39	1,540.70	1.07	0.71

[a]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[b]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals at doses immediately below and above the benchmark dose; also the largest residual at any dose.
[d]Power restricted to ≥1.
[e]Selected model. Constant variance model did not provide adequate fit to the variance data. With nonconstant variance model applied, all models (except for the Exponential 4, and 5, and Hill models) provided adequate fit to the means. BMDLs for models providing adequate fit were sufficiently close (differed by <2–3-fold), so the model with the lowest AIC was selected (Exponential 3; the Exponential 2 and 3 had the same AIC, so the model with the more conservative BMDL was selected out of these two).
[f]Coefficients restricted to be negative.

AIC = Akaike Information Criterion; BMD = maximum likelihood estimate of the exposure concentration associated with the selected benchmark response; BMDL = 95% lower confidence limit on the BMD (subscripts denote benchmark response: i.e., $_{10}$ = exposure concentration associated with 10% extra risk); NA = not applicable; ND = not determined (BMDL computation failed); SD = standard deviation

Summary of the Principal Study:

Poon R, Chu I, Lecavalier P, et al. 1998. Effects of antimony on rats following 90-day exposure via drinking water. Food Chem Toxicol 36:21-35.

Groups of 15 male and 15 female Sprague-Dawley rats were exposed to 0, 0.5, 5, 50, or 500 ppm antimony as potassium antimony tartrate (99.95% pure) in drinking water for 13 weeks. Based on average water consumption and body weight data, the investigators calculated antimony doses of 0, 0.06, 0.56, 5.58, and 42.17 mg Sb/kg/day in males and 0, 0.06, 0.64, 6.13, and 45.69 mg Sb/kg/day in females. An additional group of 10 male and 10 female rats was exposed to 0 or 500 ppm for 13 weeks followed by a 4-week recovery period. The following parameters were used to assess toxicity: weekly body weight, food consumption, and water intake measurements; hematological indices (erythrocyte counts hemoglobin, hematocrit, mean corpuscular volume, and total and differential leukocyte counts); clinical chemistry indices (albumin, alkaline phosphatase, aspartate aminotransferase, creatine kinase, sorbitol dehydrogenase, bilirubin, calcium, cholesterol, creatinine, glucose, inorganic phosphate, lactic dehydrogenase, total protein, urea nitrogen, and uric acid); serum thyroxin and thyroid hormone binding ratio; organ weights (brain, thymus, heart, kidney, spleen, liver); and histopathological examination (brain, pituitary, thyroid and trachea, salivary glands, thymus, lung, heart, liver, kidneys, adrenals, spleen, pancreas, esophagus, stomach, small and large intestine, urinary bladder, skin, bone marrow, and gonadal tissues).

No alterations in survival or overt signs of toxicity were observed. Decreases in water consumption (35% lower than controls) and food consumption (12%) were observed in the 42.17/45.69 mg Sb/kg/day group during the exposure period but not during the recovery period.

- Body weight: A decrease in body weight gain, significant in males starting at week 6 and females at week 12, was observed at 42.17/45.69 mg Sb/kg/day; the body weights appeared to be within 10% of the controls. A significant increase in relative kidney weights was observed in the 42.17/45.69 mg Sb/kg/day group.
- Metabolic: A dose-related decrease (15–17%) in serum glucose levels was observed in females exposed to ≥0.64 mg Sb/kg/day; lower values were also observed in the males, but were not statistically different from controls. No differences in serum glucose levels were observed at the end of the recovery period. ATSDR notes that serum glucose levels in all groups (including controls) were higher than the range of normal values reported by the animal supplier (Charles River Laboratories 2006).
- Clinical chemistry: Decreases in serum creatinine levels and alkaline phosphatase levels were observed in males and females exposed to 42.17/45.69 mg Sb/kg/day at the end of the exposure period, but not at the end of the observation period. A decrease (24%) in serum cholesterol level was observed in females exposed to 45.69 mg Sb/kg/day; the toxicological significance of this alteration is not known.
- Hematological: Decreases in red blood cells and platelet counts and increases in mean corpuscular volume were observed in males exposed to 42.17 mg Sb/kg/day; in females, the only hematological alteration was an increase in monocytes at 45.69 mg Sb/kg/day. Significant increases in hepatic ethoxyresorufin-O-deethylase and glutathione-S-transferase activities were observed in males at 42.17 mg Sb/kg/day; glutathione-S-transferase activity was also increased in females at 45.69 mg Sb/kg/day.
- Hepatic: Histological alterations included anisokaryosis in the liver in all antimony exposed groups; dose-related increases in the severity were also observed. Anisokaryosis was also observed at the end of the recovery period. Other hepatic effects included an increase in hepatocellular portal density in all antimony groups and minimal nuclear hyperchromicity at ≥0.56/0.64 mg Sb/kg/day, but there was not consistent dose-response relationship for this endpoint. The severity scores for the anisokaryosis were 0.1, 0.6, 1.0, 1.9, and 2.8 in the 0, 0.06, 0.56, 5.58, and 42.17 mg Sb/kg/day males; a severity score of 1 is considered minimal, 2 is mild, and 3 is moderate. In the females, the respective severity scores were 0.9, 1.5, 2.3, 2.3, and 2.6. Similarly, the increase in portal density in the hepatocellular cytoplasm was graded as minimal at the two lowest doses in the males and females and mild at the two highest doses. The anisokaryosis, hepatocellular density, and hyperchromicity are considered adaptive changes and were not considered adverse.
- Skeletal: In the bone marrow, an increase in myeloid hyperplasia was observed at ≥5.58 mg Sb/kg/day in males and ≥0.64 mg Sb/kg/day in females.
- Spleen: The following alterations were observed in the spleen: sinus congestion at ≥0.56 mg Sb/kg/day in males, sinus hyperplasia at 42.17 mg Sb/kg/day in males and ≥0.64 mg Sb/kg/day in females, and arterial cuff atrophy at 42.17 mg Sb/kg/day in males. In the recovery period, increases in incidence of sinus congestion (males only), arterial cuff atrophy, periarteriolar lymphocyte sheath cell density, and sinus hematopoiesis were observed.
- Endocrine: Statistically significant increases in thyroid hormone binding ratio were observed in females at 6.13 and 45.69 mg Sb/kg/day. Thyroid histological alterations included an increase in epithelial height, reduced follicle size, and nuclear vesiculation in antimony rats; an increased occurrence of collapsed follicles was observed in the antimony recovery group. These thyroid effects did not show a strong dose-response relationship and did not appear to affect thyroid function; the investigators did not consider them adverse.

Uncertainty Factor:

- 10 for extrapolation from animals to humans
- 10 for human variability

MRL = NOAEL ÷ uncertainty factors
0.006 mg Sb/kg/day = 0.06 mg Sb/kg/day ÷ 100

Other Additional Studies or Pertinent Information that Lend Support to this MRL: The MRL is based on health effects observed in animals exposed to soluble antimony compounds; it is likely that oral exposure to insoluble antimony compounds would result in adverse effects occurring at higher dose levels.

Agency Contacts (Chemical Managers): Melanie Buser

MINIMAL RISK LEVEL (MRL) WORKSHEET

***Chemical Name*:** Antimony
CAS Numbers: 7440-36-0
Date: October 2019
Profile Status: Final
Route: Oral
Duration: Chronic

MRL Summary: The chronic-duration oral database was considered inadequate for derivation of an MRL. The two available studies examined a limited number of endpoints and decreases in survival were observed in the only doses tested.

Rationale for Not Deriving an MRL: Two studies have evaluated the chronic toxicity of antimony (Kanisawa and Schroeder 1969; Schroeder et al. 1970) in rats and mice exposed to antimony potassium tartrate in drinking water for a lifetime. Decreases in survival were observed in rats exposed to 0.63 mg Sb/kg/day (Schroeder et al. 1970) and in mice exposed to 0.35 mg Sb/kg/day (Kanisawa and Schroeder 1969). Both studies examined a limited number of endpoints. In rats, no cardiovascular or body weight alterations were observed; however, a decrease in nonfasting glucose levels was found at 0.63 mg Sb/kg/day. No hepatic or body weight alterations were observed in mice. Given the limited number of endpoints examined and decreases in survival at the only dose tested, neither study was considered suitable for derivation of a chronic-duration oral MRL.

Agency Contacts (Chemical Managers): Melanie Buser

APPENDIX B. LITERATURE SEARCH FRAMEWORK FOR ANTIMONY

The objective of the toxicological profile is to evaluate the potential for human exposure and the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to antimony.

B.1 LITERATURE SEARCH AND SCREEN

A literature search and screen was conducted to identify studies examining health effects, toxicokinetics, mechanisms of action, susceptible populations, biomarkers, chemical interactions, physical and chemical properties, production, use, environmental fate, environmental releases, and environmental and biological monitoring data for antimony. ATSDR primarily focused on peer-reviewed articles without publication date or language restrictions. Non-peer-reviewed studies that were considered relevant to the assessment of the health effects of antimony have undergone peer review by at least three ATSDR-selected experts who have been screened for conflict of interest. The inclusion criteria used to identify relevant studies examining the health effects of antimony are presented in Table B-1.

Table B-1. Inclusion Criteria for the Literature Search and Screen

- Health Effects
  - Species
    - Human
    - Laboratory mammals
  - Route of exposure
    - Inhalation
    - Oral
    - Dermal (or ocular)
    - Parenteral (these studies will be considered supporting data)
  - Health outcome
    - Death
    - Systemic effects
    - Body weight effects
    - Respiratory effects
    - Cardiovascular effects
    - Gastrointestinal effects
    - Hematological effects
    - Musculoskeletal effects
    - Hepatic effects
    - Renal effects
    - Dermal effects
    - Ocular effects
    - Endocrine effects
    - Immunological effects
    - Neurological effects
    - Reproductive effects
    - Developmental effects
    - Other noncancer effects

Table B-1. Inclusion Criteria for the Literature Search and Screen

Cancer
Toxicokinetics
Absorption
Distribution
Metabolism
Excretion
PBPK models
Biomarkers
Biomarkers of exposure
Biomarkers of effect
Interactions with other chemicals
Potential for human exposure
Releases to the environment
Air
Water
Soil
Environmental fate
Transport and partitioning
Transformation and degradation
Environmental monitoring
Air
Water
Sediment and soil
Other media
Biomonitoring
General populations
Occupation populations

B.1.1 Literature Search

The current literature search was intended to update the draft toxicological profile for antimony released for public comment in 2017. The following main databases were searched in January 2018:

- PubMed
- National Library of Medicine's TOXLINE
- Scientific and Technical Information Network's TOXCENTER

The search strategy used the chemical names, Chemical Abstracts Service (CAS) numbers, synonyms, Medical Subject Headings (MeSH) headings, and keywords for antimony. The query strings used for the literature search are presented in Table B-2.

The search was augmented by searching the Toxic Substances Control Act Test Submissions (TSCATS), NTP website, and National Institute of Health Research Portfolio Online Reporting Tools Expenditures and Results (NIH RePORTER) databases using the queries presented in Table B-3. Additional databases

were searched in the creation of various tables and figures, such as the TRI Explorer, the Substance Priority List (SPL) resource page, and other items as needed. Regulations applicable to antimony were identified by searching international and U.S. agency websites and documents.

Review articles were identified and used for the purpose of providing background information and identifying additional references. ATSDR also identified reports from the grey literature, which included unpublished research reports, technical reports from government agencies, conference proceedings and abstracts, and theses and dissertations.

Table B-2. Database Query Strings

Database search date	Query string
PubMed	
01/2018	((7440-36-0[rn] OR 1315-04-4[rn] OR 1314-60-9[rn] OR 28300-74-5[rn] OR 10025-91-9[rn] OR 1309-64-4[rn] OR 1345-04-6[rn] OR 7803-52-3[rn]) AND (2014/02/01:3000[dp] OR 2015/02/01:3000[mhda])) OR (("Antimony"[tw] OR "Antimonyl potassium tartrate"[tw] OR "Potassium antimonyl tartrate"[tw] OR "Sb2O3"[tw] OR "Senarmontite"[tw] OR "Potassium antimonyltartrate"[tw] OR "Stibine"[tw] OR "Stibium"[tw] OR "Stibnite"[tw] OR "Tartar emetic"[tw] OR "Trichlorostibine"[tw] OR "Valentinite"[tw]) NOT medline[sb]) AND (2014/02/01:3000[dp] OR 2015/02/01:3000[crdat] OR 2015/02/01:3000[edat]))
	("A 1550"[tw] OR "A 1582"[tw] OR "A 1588LP"[tw] OR "A 2550"[tw] OR "AGO 40"[tw] OR "Amspec-KR"[tw] OR "AN 800"[tw] OR "Anchimonzol A 2550"[tw] OR "Antimonate(2)-, bis(mu-tartrato(4-))di-, dipotassium, trihydrate"[tw] OR "Antimonate(2-), bis(mu-(2,3-di(hydroxy-kappaO)butanedioato(4-)-kappaO1:kappaO4))di-, dipotassium, trihydrate, stereoisomer"[tw] OR "Antimonate(2-), bis(mu-(2,3-dihydroxybutanedioato(4-)-O(sup 1),O(sup 2):O(sup 3),O(sup 4)))-di-, dipotassium, trihydrate, stereoisomer"[tw] OR "Antimonate(2-), bis(u-(2,3-dihydroxybutanedioato(4-)-O1,O2,O3,O4))di-, dipotassium, trihydrate"[tw] OR "Antimonate(2-), bis[.mu.-[2,3-di(hydroxy-,kappa.O)butanedioato(4-)-.kappa.O(1):.kappa.O4]]di-, dipotassium, trihydrate, stereoisomer"[tw] OR "Antimonate(2-), bis[.mu.-[2,3-di(hydroxy-.kappa.O)butanedioato(4-)-.kappa.O1:.kappa.O4]]di-, dipotassium, trihydrate, stereoisomer"[tw] OR "Antimonial saffron"[tw] OR "Antimonic oxide"[tw] OR "Antimonic sulfide"[tw] OR "Antimonious oxide"[tw] OR "Antimonous chloride"[tw] OR "Antimonous sulfide"[tw] OR "Apox S"[tw] OR "AT 3 (fireproofing agent)"[tw] OR "AT 3B"[tw] OR "Atox B"[tw] OR "Atox F"[tw] OR "Atox R"[tw] OR "Atox S"[tw] OR "C.I. 77060"[tw] OR "C.I. Pigment Red 107"[tw] OR "C.I. Pigment White 11"[tw] OR "Chemetron fire shield"[tw] OR "CI 77060"[tw] OR "CI Pigment Red 107"[tw] OR "CI Pigment white 11"[tw] OR "Dechlorane A-O"[tw] OR "Diantimony pentaoxide"[tw] OR "Diantimony pentasulphide"[tw] OR "Diantimony pentoxide"[tw] OR "Diantimony trioxide"[tw] OR "Diantimony trisulfide"[tw] OR "Dipotassium bis(mu-(L-(+)-tartrato(4-)))diantimonate(2-) trihydrate"[tw] OR "ENT 50,434"[tw] OR "Exitelite"[tw] OR "Fireshield FSPO 405"[tw] OR "FireShield H"[tw] OR "FireShield LS-FR"[tw] OR "Flame Cut 610"[tw] OR "Flame Cut 610R"[tw] OR "Flameguard VF 59"[tw] OR "HFR 201"[tw] OR "HM 203P"[tw] OR "Hydrogen antimonide"[tw] OR "LS-FR"[tw] OR "LSB 80"[tw] OR "Microfine A 05"[tw] OR "NCI-C55152"[tw] OR "Nyacol 1550"[tw] OR "Nyacol A 1510LP"[tw] OR "Nyacol A 1530"[tw] OR "Nyacol A 1590"[tw] OR "Nyacol ADP 480"[tw] OR "Nyacol ADP 494"[tw] OR "Nyacol AGO 40"[tw] OR "Octoguard FR 10"[tw] OR "Patox C"[tw] OR "Patox H"[tw] OR "Patox L"[tw] OR "Patox M"[tw] OR "Patox S"[tw] OR "Potassium antimonyl D-tartrate"[tw] OR "Sanka Anchimonzol A 2550M"[tw] OR "Stibic anhydride"[tw] OR "Stibiox MS"[tw] OR "Sun Epoch NA 100"[tw] OR "Sun Epoch NA 3070P"[tw] OR "Sun Epoch NA 3080P"[tw] OR "Suncolloid AME 130"[tw] OR "Suncolloid AMT 130"[tw] OR "Thermoguard B"[tw] OR "Thermoguard L"[tw] OR "Thermoguard S"[tw] OR "Timonox"[tw] OR "Timonox White

Table B-2. Database Query Strings

Database search date	Query string
	Star"[tw] OR "Twinkling star"[tw]) NOT medline[sb]) AND (2014/02/01:3000[dp] OR 2015/02/01:3000[crdat] OR 2015/02/01:3000[edat])
Toxline	
01/2018	((7440-36-0 [rn] OR 1315-04-4 [rn] OR 1314-60-9 [rn] OR 28300-74-5 [rn] OR 10025-91-9 [rn] OR 1309-64-4 [rn] OR 1345-04-6 [rn] OR 7803-52-3 [rn]) OR "antimony" OR "antimonyl potassium tartrate" OR "potassium antimonyl tartrate" OR "sb2o3" OR "senarmontite" OR "potassium antimonyltartrate" OR "stibine" OR "stibium" OR "stibnite" OR "tartar emetic" OR "trichlorostibine" OR "valentinite") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
	("anchimonzol a 2550" OR "antimonial saffron" OR "antimonic oxide" OR "antimonic sulfide" OR "antimonious oxide" OR "antimonous chloride" OR "antimonous sulfide" OR "apox s" OR "atox b" OR "atox f" OR "atox r" OR "atox s" OR "chemetron fire shield" OR "dechlorane a o" OR "diantimony pentaoxide" OR "diantimony pentasulphide" OR "diantimony pentoxide" OR "diantimony trioxide" OR "diantimony trisulfide" OR "ent 50 434" OR "exitelite" OR "fireshield fspo 405" OR "fireshield h" OR "fireshield ls fr" OR "flame cut 610" OR "flame cut 610r" OR "flameguard vf 59" OR "hfr 201" OR "hm 203p" OR "hydrogen antimonide" OR "ls fr" OR "lsb 80" OR "microfine a 05" OR "nci c55152" OR "nyacol 1550" OR "nyacol a 1510lp" OR "nyacol a 1530" OR "nyacol a 1590" OR "nyacol adp 480" OR "nyacol adp 494" OR "nyacol ago 40" OR "octoguard fr 10" OR "patox c" OR "patox h" OR "patox l" OR "patox m" OR "patox s" OR "potassium antimonyl d tartrate" OR "sanka anchimonzol a 2550m" OR "stibic anhydride" OR "stibiox ms" OR "sun epoch na 100" OR "sun epoch na 3070p" OR "sun epoch na 3080p" OR "suncolloid ame 130" OR "suncolloid amt 130" OR "thermoguard b" OR "thermoguard l" OR "thermoguard s" OR "timonox" OR "timonox white star" OR "twinkling star") AND 2014:2017 [yr] AND (ANEUPL [org] OR BIOSIS [org] OR CIS [org] OR DART [org] OR EMIC [org] OR EPIDEM [org] OR HEEP [org] OR HMTC [org] OR IPA [org] OR RISKLINE [org] OR MTGABS [org] OR NIOSH [org] OR NTIS [org] OR PESTAB [org] OR PPBIB [org]) AND NOT PubMed [org] AND NOT pubdart [org]
Toxcenter	
01/2018	FILE 'TOXCENTER' ENTERED AT 08:52:47 ON 10 JAN 2018 => s 7440-36-0 OR 1315-04-4 OR 1314-60-9 OR 28300-74-5 OR 10025-91-9 OR 1309-64-4 OR 1345-04-6 OR 7803-52-3 L1 22076 7440-36-0 OR 1315-04-4 OR 1314-60-9 OR 28300-74-5 OR 10025-91-9 OR 1309-64-4 OR 1345-04-6 OR 7803-52-3 => s l1 not tscats/fs L2 21927 L1 NOT TSCATS/FS => s l2 not patent/dt L3 17767 L2 NOT PATENT/DT => s l3 and py>2014 L4 1973 L3 AND PY>2014 => s l3 and 20141201 L5 0 L3 AND 20141201 => s l3 and ed>=20141201 L6 2222 L3 AND ED>=20141201 => activate toxquery/q

Table B-2. Database Query Strings

Database search date	Query string
	L7 QUE (CHRONIC OR IMMUNOTOX? OR NEUROTOX? OR TOXICOKIN? OR BIOMARKER? OR NEUROLOG?)
	L8 QUE (PHARMACOKIN? OR SUBCHRONIC OR PBPK OR EPIDEMIOLOGY/ST,CT,IT)
	L9 QUE (ACUTE OR SUBACUTE OR LD50# OR LD(W)50 OR LC50# OR LC(W)50)
	L10 QUE (TOXICITY OR ADVERSE OR POISONING)/ST,CT,IT
	L11 QUE (INHAL? OR PULMON? OR NASAL? OR LUNG? OR RESPIR?)
	L12 QUE ((OCCUPATION? OR WORKPLACE? OR WORKER?) AND EXPOS?)
	L13 QUE (ORAL OR ORALLY OR INGEST? OR GAVAGE? OR DIET OR DIETS OR DIETARY OR DRINKING(W)WATER?)
	L14 QUE (MAXIMUM AND CONCENTRATION? AND (ALLOWABLE OR PERMISSIBLE))
	L15 QUE (ABORT? OR ABNORMALIT? OR EMBRYO? OR CLEFT? OR FETUS?)
	L16 QUE (FOETUS? OR FETAL? OR FOETAL? OR FERTIL? OR MALFORM? OR OVUM?)
	L17 QUE (OVA OR OVARY OR PLACENTA? OR PREGNAN? OR PRENATAL?)
	L18 QUE (PERINATAL? OR POSTNATAL? OR REPRODUC? OR STERIL? OR TERATOGEN?)
	L19 QUE (SPERM OR SPERMAC? OR SPERMAG? OR SPERMATI? OR SPERMAS? ORSPERMATOB? OR SPERMATOC? OR SPERMATOG?)
	L20 QUE (SPERMATOI? OR SPERMATOL? OR SPERMATOR? OR SPERMATOX? OR SPERMATOZ? OR SPERMATU? OR SPERMI? OR SPERMO?)
	L21 QUE (NEONAT? OR NEWBORN? OR DEVELOPMENT OR DEVELOPMENTAL?)
	L22 QUE (ENDOCRIN? AND DISRUPT?)
	L23 QUE (ZYGOTE? OR CHILD OR CHILDREN OR ADOLESCEN? OR INFANT?)
	L24 QUE (WEAN? OR OFFSPRING OR AGE(W)FACTOR?)
	L25 QUE (DERMAL? OR DERMIS OR SKIN OR EPIDERM? OR CUTANEOUS?)
	L26 QUE (CARCINOG? OR COCARCINOG? OR CANCER? OR PRECANCER? OR NEOPLAS?)
	L27 QUE (TUMOR? OR TUMOUR? OR ONCOGEN? OR LYMPHOMA? OR CARCINOM?)
	L28 QUE (GENETOX? OR GENOTOX? OR MUTAGEN? OR GENETIC(W)TOXIC?)
	L29 QUE (NEPHROTOX? OR HEPATOTOX?)
	L30 QUE (ENDOCRIN? OR ESTROGEN? OR ANDROGEN? OR HORMON?)
	L31 QUE (OCCUPATION? OR WORKER? OR WORKPLACE? OR EPIDEM?)
	L32 QUE L7 OR L8 OR L9 OR L10 OR L11 OR L12 OR L13 OR L14 OR L15 OR L16 OR L17 OR L18 OR L19 OR L20 OR L21 OR L22 OR L23 OR L24 OR L25 OR L26 OR L27 OR L28 OR L29 OR L30 OR L31
	L33 QUE (RAT OR RATS OR MOUSE OR MICE OR GUINEA(W)PIG? OR MURIDAE OR DOG OR DOGS OR RABBIT? OR HAMSTER? OR PIG OR PIGS OR SWINE OR PORCINE OR MONKEY? OR MACAQUE?)
	L34 QUE (MARMOSET? OR FERRET? OR GERBIL? OR RODENT? OR LAGOMORPHA OR BABOON? OR CANINE OR CAT OR CATS OR FELINE OR MURINE)
	L35 QUE L32 OR L33 OR L34

Table B-2. Database Query Strings

Database search date	Query string
	L36 QUE (NONHUMAN MAMMALS)/ORGN L37 QUE L35 OR L36 L38 QUE (HUMAN OR HUMANS OR HOMINIDAE OR MAMMALS OR MAMMAL? OR PRIMATES OR PRIMATE?) L39 QUE L37 OR L38 => s l6 and l39 L40 1007 L6 AND L39 => s l40 and medline/fs L41 141 L40 AND MEDLINE/FS => s l40 and biosis/fs L42 185 L40 AND BIOSIS/FS => s l40 and caplus/fs L43 681 L40 AND CAPLUS/FS => s l40 not (medline/fs or biosis/fs or caplus/fs) L44 0 L40 NOT (MEDLINE/FS OR BIOSIS/FS OR CAPLUS/FS) => dup rem l41 l42 l43 => s l45 not medline/fs L46 141 S L45 L47 169 S L45 L48 597 S L45 3757645 MEDLINE/FS L49 766 (L46 OR L47 OR L48) NOT MEDLINE/FS => d scan l49

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
TSCATS[a]	
01/2018	Compounds searched: 7440-36-0; 1315-04-4; 1314-60-9; 28300-74-5; 10025-91-9; 1309-64-4; 1345-04-6; 7803-52-3
NTP	
05/2019	"antimony" "stibine" "7440-36-0" "1309-64-4" "1315-04-4" "1314-60-9" "28300-74-5" "10025-91-9" "1345-04-6" "7803-52-3" "antimonyl potassium tartrate" "potassium antimonyl tartrate" "sb2o3" "senarmontite" "potassium antimonyltartrate" "stibium" "stibnite" "tartar emetic" "trichlorostibine" "valentinite"
NIH RePORTER	
05/2019	Text Search: "Antimony" OR "Antimonyl potassium tartrate" OR "Potassium antimonyl tartrate" OR "Sb2O3" OR "Senarmontite" OR "Potassium antimonyltartrate" OR "Stibine" OR "Stibium" OR "Stibnite" OR "Tartar emetic" OR "Trichlorostibine" OR "Valentinite" OR "Antimonial saffron" OR "Antimonic oxide" OR "Antimonic sulfide" OR "Antimonious oxide" OR "Antimonous chloride" OR "Antimonous sulfide" OR "Diantimony pentaoxide" OR "Diantimony pentasulphide" OR "Diantimony pentoxide" OR "Diantimony trioxide" OR "Diantimony trisulfide" OR "Hydrogen antimonide" OR "Potassium antimonyl D-tartrate" OR "Stibic anhydride" (Advanced), Search in: Projects AdminIC: All, Fiscal Year: Active Projects

Table B-3. Strategies to Augment the Literature Search

Source	Query and number screened when available
Other	Identified throughout the assessment process

[a]Several versions of the TSCATS database were searched, as needed, by CASRN including TSCATS1 via Toxline (no date limit), TSCATS2 via https://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearch?OpenForm (date restricted by EPA receipt date), and TSCATS via CDAT (date restricted by 'Mail Received Date Range'), as well as google for recent TSCA submissions.

The 2018 results were:

- Number of records identified from PubMed, TOXLINE, and TOXCENTER (after duplicate removal): 1,465
- Number of records identified from other strategies: 40
- Total number of records to undergo literature screening: 1,505

B.1.2 Literature Screening

A two-step process was used to screen the literature search to identify relevant studies on antimony:

- Title and abstract screen
- Full text screen

Title and Abstract Screen. Within the reference library, titles and abstracts were screened manually for relevance. Studies that were considered relevant (see Table B-1 for inclusion criteria) were moved to the second step of the literature screening process. Studies were excluded when the title and abstract clearly indicated that the study was not relevant to the toxicological profile.

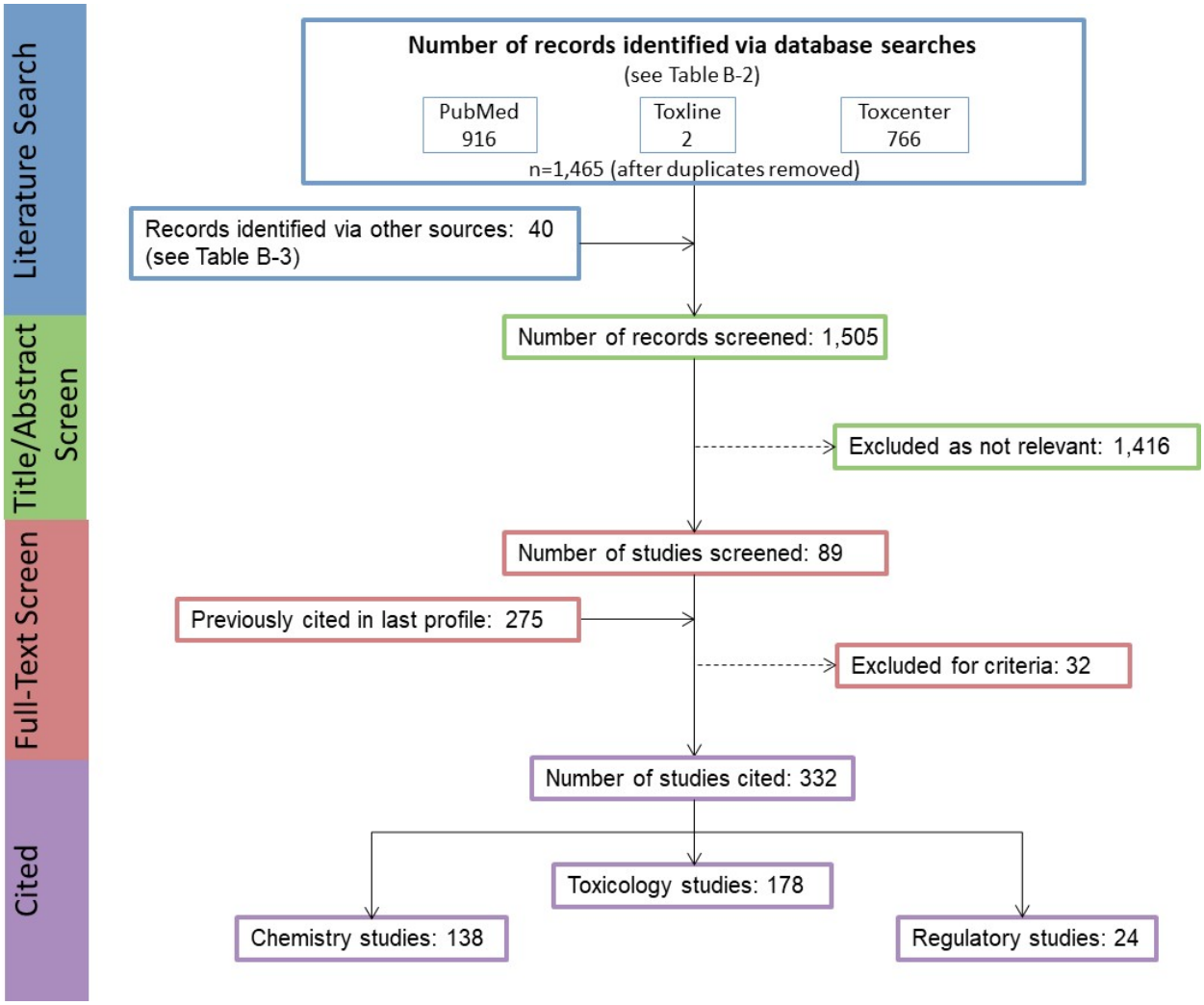
- Number of titles and abstracts screened: 1,505
- Number of studies considered relevant and moved to the next step: 89

Full Text Screen. The second step in the literature screening process was a full text review of individual studies considered relevant in the title and abstract screen step. Each study was reviewed to determine whether it was relevant for inclusion in the toxicological profile.

- Number of studies undergoing full text review: 89
- Number of studies cited in the pre-public draft of the toxicological profile: 275
- Total number of studies cited in the profile: 332

A summary of the results of the literature search and screening is presented in Figure B-1.

Figure B-1. January 2018 Literature Search Results and Screen for Antimony



APPENDIX C. FRAMEWORK FOR ATSDR'S SYSTEMATIC REVIEW OF HEALTH EFFECTS DATA FOR ANTIMONY

To increase the transparency of ATSDR's process of identifying, evaluating, synthesizing, and interpreting the scientific evidence on the health effects associated with exposure to antimony, ATSDR utilized a slight modification of NTP's Office of Health Assessment and Translation (OHAT) systematic review methodology (NTP 2013, 2015; Rooney et al. 2014). ATSDR's framework is an eight-step process for systematic review with the goal of identifying the potential health hazards of exposure to antimony:

- Step 1. Problem Formulation
- Step 2. Literature Search and Screen for Health Effects Studies
- Step 3. Extract Data from Health Effects Studies
- Step 4. Identify Potential Health Effect Outcomes of Concern
- Step 5. Assess the Risk of Bias for Individual Studies
- Step 6. Rate the Confidence in the Body of Evidence for Each Relevant Outcome
- Step 7. Translate Confidence Rating into Level of Evidence of Health Effects
- Step 8. Integrate Evidence to Develop Hazard Identification Conclusions

C.1 PROBLEM FORMULATION

The objective of the toxicological profile and this systematic review was to identify the potential health hazards associated with inhalation, oral, or dermal/ocular exposure to antimony. The inclusion criteria used to identify relevant studies examining the health effects of antimony are presented in Table C-1.

Data from human and laboratory animal studies were considered relevant for addressing this objective. Human studies were divided into two broad categories: observational epidemiology studies and controlled exposure studies. The observational epidemiology studies were further divided: cohort studies (retrospective and prospective studies), population studies (with individual data or aggregate data), and case-control studies.

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Species
Human
Laboratory mammals
Route of exposure
Inhalation
Oral
Dermal (or ocular)
Parenteral (these studies will be considered supporting data)
Health outcome
Death
Systemic effects
Body weight effects
Respiratory effects
Cardiovascular effects

Table C-1. Inclusion Criteria for Identifying Health Effects Studies

Gastrointestinal effects
Hematological effects
Musculoskeletal effects
Hepatic effects
Renal effects
Dermal effects
Ocular effects
Endocrine effects
Immunological effects
Neurological effects
Reproductive effects
Developmental effects
Other noncancer effects
Cancer

C.2 LITERATURE SEARCH AND SCREEN FOR HEALTH EFFECTS STUDIES

A literature search and screen was conducted to identify studies examining the health effects of antimony. The literature search framework for the toxicological profile is discussed in detail in Appendix B.

C.2.1 Literature Search

As noted in Appendix B, the current literature search was intended to update the draft toxicological profile for antimony released for public comment in 2017. See Appendix B for the databases searched and the search strategy.

A total of 1,505 records relevant to all sections of the toxicological profile were identified (after duplicate removal).

C.2.2 Literature Screening

As described in Appendix B, a two-step process was used to screen the literature search to identify relevant studies examining the health effects of antimony.

Title and Abstract Screen. In the Title and Abstract Screen step, 1,505 records were reviewed; 14 studies were considered to meet the health effects inclusion criteria in Table C-1 and were moved to the next step in the process.

Full Text Screen. In the second step in the literature screening process for the systematic review, a full text review of the 14 health effects studies identified in the update literature was performed. Additionally, 71 studies cited in the LSE tables for the existing profile were included in the full study screen bringing the total number of studies for the qualitative review to 85.

C.3 EXTRACT DATA FROM HEALTH EFFECTS STUDIES

Relevant data extracted from the individual studies selected for inclusion in the systematic review were collected in customized data forms. A summary of the type of data extracted from each study is presented in Table C-2. For references that included more than one experiment or species, data extraction records were created for each experiment or species.

Table C-2. Data Extracted From Individual Studies

Citation
Chemical form
Route of exposure (e.g., inhalation, oral, dermal)
Specific route (e.g., gavage in oil, drinking water)
Species
Strain
Exposure duration category (e.g., acute, intermediate, chronic)
Exposure duration
Frequency of exposure (e.g., 6 hours/day, 5 days/week)
Exposure length
Number of animals or subjects per sex per group
Dose/exposure levels
Parameters monitored
Description of the study design and method
Summary of calculations used to estimate doses (if applicable)
Summary of the study results
Reviewer's comments on the study
Outcome summary (one entry for each examined outcome)
No-observed-adverse-effect level (NOAEL) value
Lowest-observed-adverse-effect level (LOAEL) value
Effect observed at the LOAEL value

A summary of the extracted data for each study is presented in the Supplemental Document for Antimony and overviews of the results of the inhalation, oral, and dermal exposure studies are presented in Sections 2.2–2.18 of the profile and in the Levels Significant Exposures tables in Section 2.1 of the profile (Tables 2-3, 2-4, and 2-5, respectively).

C.4 IDENTIFY POTENTIAL HEALTH EFFECT OUTCOMES OF CONCERN

Overviews of the potential health effect outcomes for antimony identified in human and animal studies are presented in Tables C-3 and C-4, respectively. The available human studies examined a limited number of endpoints and reported respiratory, cardiovascular, gastrointestinal, musculoskeletal, immunological, reproductive, and developmental effects. Animal studies examined a number of endpoints following inhalation, oral, or dermal exposure. These studies examined most systemic endpoints and reported respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, dermal, ocular, body weight, and metabolic effects. Additionally, animal studies have reported immunological, reproductive, and developmental effects.

APPENDIX C

Table C-3. Overview of the Health Outcomes for Antimony Evaluated In Human Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological	Neurological	Reproductive	Developmental	Other Noncancer	Caner
Inhalation studies																	
Observational		7	2 (1)	3					3	1		1	2	1	1		2
		5	2	3					3	1		1	1	1	1		1
Experimental																	
Oral studies																	
Observational	1	1	5(0)	1		1	1				1	1	5	1	2[a]	2	3
	0	0	3	1		1	0				0	1	1	0	0	1	1
Experimental																	
Dermal studies																	
Observational																	
Experimental																	

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10	
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10	

Numbers in parentheses represent those studies looking at the specific cardiovascular endpoints of interest to this systematic review (damage to the myocardium and/or EKG alterations).

[a]One study (Zheng et al. 2014) was excluded because it measured risk of "adverse pregnancy outcome," but did not provide information on the endpoints examined and was not considered suitable for the systematic review.

1

APPENDIX C

Table C-4. Overview of the Health Outcomes for Antimony Evaluated in Experimental Animal Studies

	Body weight	Respiratory	Cardiovascular	Gastrointestinal	Hematological	Musculoskeletal	Hepatic	Renal	Dermal	Ocular	Endocrine	Immunological[a]	Neurological[a]	Reproductive[a]	Developmental	Other Noncancer	Caner
Inhalation studies																	
Acute-duration	3	5	2(1)				2	3			2						
	0	5	1				1	2			0						
Intermediate-duration	5	4	5		5		3	2			1			1	1		
	0	4	3		1		2	1			1			1	1		
Chronic-duration	7	8	7	6	1	4	6	6		2	6	6	5	6		4	7
	2	7	2	1	0	2	0	1		2	0	3	0	0		0	5
Oral Studies																	
Acute-duration	3	2	2	3		2	2	2			2						
	1	1	0	2		0	1	0			0						
Intermediate-duration	11	2	4(2)	3	7	1	4	3	1	1	2	1		4	3	1	
	5	0	1	0	4	0	2	0	0	0	0	1		0	3	1	
Chronic-duration	2		1(0)				1									1	2
	0		0				0									1	0
Dermal studies																	
Acute-duration									1	4		1					
									0	2		0					
Intermediate-duration	1		1				1	1	1	1				1			
	0		0				0	0	0	1				0			
Chronic-duration									4	3							
									1	0							

Number of studies examining endpoint	0	1	2	3	4	5–9	≥10
Number of studies reporting outcome	0	1	2	3	4	5–9	≥10

Numbers in parentheses represent those studies looking at the specific cardiovascular endpoints of interest to this systematic review (damage to the myocardium and/or EKG alterations).

Respiratory, cardiovascular (damage to the myocardium and/or EKG alterations), gastrointestinal, metabolic (alterations in blood glucose levels), and developmental effects were considered sensitive outcomes, i.e., effects were observed at low concentrations or doses. Eighty-five studies (published in 54 documents) examining these potential outcomes were carried through to Steps 4–8 of the systematic review.

C.5 ASSESS THE RISK OF BIAS FOR INDIVIDUAL STUDIES

C.5.1 Risk of Bias Assessment

The risk of bias of individual studies was assessed using OHAT's Risk of Bias Tool (NTP 2015). The risk of bias questions for observational epidemiology studies, human-controlled exposure studies, and animal experimental studies are presented in Tables C-5, C-6, and C-7, respectively. Each risk of bias question was answered on a four-point scale:

- **Definitely low risk of bias (++)**
- **Probably low risk of bias (+)**
- **Probably high risk of bias (-)**
- **Definitely high risk of bias (– –)**

In general, "definitely low risk of bias" or "definitely high risk of bias" were used if the question could be answered with information explicitly stated in the study report. If the response to the question could be inferred, then "probably low risk of bias" or "probably high risk of bias" responses were typically used.

Table C-5. Risk of Bias Questionnaire for Observational Epidemiology Studies

Selection bias
Were the comparison groups appropriate?
Confounding bias
Did the study design or analysis account for important confounding and modifying variables?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-6. Risk of Bias Questionnaire for Human-Controlled Exposure Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were the research personnel and human subjects blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

Table C-7. Risk of Bias Questionnaire for Experimental Animal Studies

Selection bias
Was administered dose or exposure level adequately randomized?
Was the allocation to study groups adequately concealed?
Performance bias
Were experimental conditions identical across study groups?
Were the research personnel blinded to the study group during the study?
Attrition/exclusion bias
Were outcome data complete without attrition or exclusion from analysis?
Detection bias
Is there confidence in the exposure characterization?
Is there confidence in outcome assessment?
Selective reporting bias
Were all measured outcomes reported?

After the risk of bias questionnaires were completed for the health effects studies, the studies were assigned to one of three risk of bias tiers based on the responses to the key questions listed below and the responses to the remaining questions.

- Is there confidence in the exposure characterization? (only relevant for observational studies)
- Is there confidence in the outcome assessment?
- Does the study design or analysis account for important confounding and modifying variables? (only relevant for observational studies)

First Tier. Studies placed in the first tier received ratings of "definitely low" or "probably low" risk of bias on the key questions **AND** received a rating of "definitely low" or "probably low" risk of bias on the responses to at least 50% of the other applicable questions.

Second Tier. A study was placed in the second tier if it did not meet the criteria for the first or third tiers.

Third Tier. Studies placed in the third tier received ratings of "definitely high" or "probably high" risk of bias for the key questions **AND** received a rating of "definitely high" or "probably high" risk of bias on the response to at least 50% of the other applicable questions.

The results of the risk of bias assessment for the different types of antimony health effects studies (observational epidemiology and animal experimental studies) are presented in Tables C-8 and C-9, respectively.

C.6 RATE THE CONFIDENCE IN THE BODY OF EVIDENCE FOR EACH RELEVANT OUTCOME

Confidences in the bodies of human and animal evidence were evaluated independently for each potential outcome. ATSDR did not evaluate the confidence in the body of evidence for carcinogenicity; rather, the Agency defaulted to the cancer weight-of-evidence assessment of other agencies including HHS, EPA, and IARC. The confidence in the body of evidence for an association or no association between exposure to antimony and a particular outcome was based on the strengths and weaknesses of individual studies. Four descriptors were used to describe the confidence in the body of evidence for effects or when no effect was found:

- **High confidence:** the true effect is highly likely to be reflected in the apparent relationship
- **Moderate confidence:** the true effect may be reflected in the apparent relationship
- **Low confidence:** the true effect may be different from the apparent relationship
- **Very low confidence:** the true effect is highly likely to be different from the apparent relationship

Confidence in the body of evidence for a particular outcome was rated for each type of study: case-control, case series, cohort, population, human-controlled exposure, and experimental animal. In the absence of data to the contrary, data for a particular outcome were collapsed across animal species, routes of exposure, and exposure durations. If species (or strain), route, or exposure duration differences were noted, then the data were treated as separate outcomes.

Table C-8. Summary of Risk of Bias Assessment for Antimony—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — **Did the study design or analysis account for important confounding and modifying variables?***	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — **Is there confidence in the exposure characterization?***	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Outcome: Respiratory effects							
Cohort studies							
Jones 1994 (antimony metal and antimony trioxide)	–	–	+	NA	–	+	Second
Renes 1953 (antimony oxides)	NA	–	+	+	+	+	Second
Schnorr et al. 1995 (antimony oxides)	+	–	+	–	+	+	Second
Cross-sectional studies							
Brieger et al. 1954 (antimony trisulfide)	NA	–	+	+	+	+	Second
Cooper et al. 1968 (antimony trioxide)	NA	–	+	NA	+	+	Second
Case series							
Potkonjak and Pavlovich 1983 (antimony oxides)	NA	–	+	NA	+	+	Second
Taylor 1966 (antimony trichloride)	NA	–	+	–	–	+	Third
Outcome: Cardiovascular effects (myocardium damage and/or EKG alterations)							
Cross Sectional studies							
Brieger et al. 1954 (antimony trisulfide)	NA	-	+	+	+	+	Second
Outcome: Gastrointestinal Effects							
Cohort studies							
Renes 1953 (antimony oxides)	NA	–	+	+	+	+	Second
Cross-sectional studies							
Brieger et al. 1954 (antimony trisulfide)	NA	–	+	+	+	+	Second

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Table C-8. Summary of Risk of Bias Assessment for Antimony—Observational Epidemiology Studies

Reference	Risk of bias criteria and ratings: Selection bias — Were the comparison groups appropriate?	Confounding bias — **Did the study design or analysis account for important confounding and modifying variables?***	Attrition / exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — **Is there confidence in the exposure characterization?***	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Risk of bias tier
Case series							
Taylor 1966 (antimony trichloride)	NA	–	+	–	–	+	Third
Outcome: Developmental Effects							
Cohort studies							
Belyaeva 1967 (antimony metal, antimony trioxide, antimony pentasulfide)	–	–	+	+	–	+	Second
Case-control studies							
Longerich et al. 1991 (not reported)	+	–	+	–	+	+	Second
Cross-sectional studies							
Bloom et al. 2015	NA	-	+	-	+	+	Second

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable

*Key question used to assign risk of bias tier

Table C-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Outcome: Respiratory effects (inhalation only)										
Inhalation acute exposure										
Brieger et al. 1954 (rabbit) (antimony trisulfide)	NA	NA	NA	NA	+	-	**+**	+	NA	Second
NTP 2016 (rat, antimony trioxide)	++	+	++	+	++	++	**++**	++	NA	First
NTP 2016 (mouse, antimony trioxide)	++	+	++	+	++	++	**++**	++	NA	First
NIOSH 1979 (rat, stibine)	–	+	+	+	+	+	**–**	–	NA	Second
NIOSH 1979 (guinea pig, stibine)	–	+	+	+	+	+	**–**	–	NA	Second
Inhalation intermediate exposure										
Belyaeva 1967 (rat, antimony trisulfide)	+	+	+	–	+	–	**–**	+	NA	Second
Brieger et al. 1954 (rat, antimony trisulfide)	NA	NA	NA	NA	+	–	**+**	+	NA	Second
Dernehl et al. 1945 (guinea pig, antimony trioxide)	–	–	–	–	+	–	**–**	+	NA	Third
Newton et al. 1994 (rat, antimony trioxide)	–	+	+	–	++	++	**+**	+	NA	First

Table C-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Inhalation chronic exposure										
Gross et al. 1952 (rat, antimony trisulfide)	–	+	+	–	+	–	+	+	NA	First
Groth et al. 1986 (rat, antimony trioxide)	+	+	+	+	+	++	+	–	NA	First
Groth et al. 1986 (rat, antimony ore)	+	+	+	+	+	++	+	–	NA	First
Newton et al. 1994 (rat, antimony trioxide)	–	+	+	–	++	++	+	+	NA	First
NTP 2016 (rat, antimony trioxide)	++	+	++	+	++	++	++	++	NA	First
NTP 2016 (mouse, antimony trioxide)	++	+	++	+	++	++	++	++	NA	First
Watt 1983 (rat, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First
Watt 1983 (pig, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First
Outcome: Cardiovascular effects(myocardium damage and/or EKG alterations)										
Inhalation acute exposure										
Brieger et al. 1954 (rabbit, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second
Inhalation intermediate exposure										
Brieger et al. 1954 (rat, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second
Brieger et al. 1954 (rabbit, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second

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Table C-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Brieger et al. 1954 (dog, 7 weeks, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second
Brieger et al. 1954 (dog, 10 weeks, antimony trisulfide)	NA	NA	NA	NA	+	–	+	+	NA	Second
Dernehl et al. 1945 (guinea pig, antimony trioxide)	–	–	–	–	+	–	–	+	NA	Third
Newton et al. 1994 (rat, antimony trioxide)	–	+	+	–	++	++	+	+	NA	First
Inhalation chronic exposure										
Groth et al. 1986 (rat, antimony trioxide)	+	+	+	+	+	++	+	–	NA	First
Groth et al. 1986 (rat, antimony ore)	+	+	+	+	+	++	+	–	NA	First
Newton et al. 1994 (rat, antimony trioxide)	–	+	+	–	++	++	+	+	NA	First
NTP 2016 (rat, antimony trioxide)	++	+	++	+	++	++	++	++	NA	First
NTP 2016 (mouse, antimony trioxide)	++	+	++	+	++	++	++	++	NA	First
Watt 1983 (rat, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First
Watt 1983 (pigs, antimony trioxide)	–	+	++	+	++	+	+	++	NA	First
Oral acute exposure										
NTP 1992 (rat, antimony potassium tartrate)	+	+	++	+	++	++	++	++	NA	First

Table C-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
NTP 1992 (mouse, antimony potassium tartrate)	+	+	++	+	++	++	**++**	++	NA	First
Oral intermediate exposure										
Hext et al. 1999 (rat, antimony trioxide)	+	+	+	+	+	++	**+**	+	NA	First
Poon et al. 1998 (rat, antimony potassium tartrate)	+	+	++	+	+	++	**+**	+	NA	First
Outcome: Gastrointestinal effects										
Inhalation chronic exposure										
Groth et al. 1986 (rat, antimony trioxide)	+	+	+	+	+	++	**+**	–	NA	First
Groth et al. 1986 (rat, antimony ore)	+	+	+	+	+	++	**+**	–	NA	First
NTP 2016 (rat, antimony trioxide)	++	+	++	+	++	++	**++**	++	NA	First
NTP 2016 (mouse, antimony trioxide)	++	+	++	+	++	++	**++**	++	NA	First
Watt 1983 (rat, antimony trioxide)	–	+	++	+	++	+	**+**	++	NA	First
Watt 1983 (pig, antimony trioxide)	–	+	++	+	++	+	**+**	++	NA	First
Oral acute exposure										
Houpt et al. 1984 (dog, antimony potassium tartrate)	–	+	+	+	+	–	**+**	+	NA	First
NTP 1992 (rat, antimony potassium tartrate)	+	+	++	+	++	++	**++**	++	NA	First

Table C-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
NTP 1992 (mouse, antimony potassium tartrate)	+	+	++	+	++	++	**++**	++	NA	First
Oral intermediate exposure										
Hext et al. 1999 (rat, antimony trioxide)	+	+	+	+	+	++	**+**	+	+	First
Poon et al. 1998 (rat, antimony potassium tartrate)	+	+	+	+	+	+	**+**	–	NA	First
Outcome: Metabolic effects (altered blood glucose levels)										
Oral intermediate exposure										
Poon et al. 1998 (rat, antimony potassium tartrate)	+	+	+	+	+	+	**+**	–	NA	First
Oral chronic exposure										
Schroeder et al. 1970 (rat, antimony potassium tartrate)	+	+	+	+	+	–	**+**	–	NA	First
Outcome: Developmental effects										
Inhalation intermediate exposure										
Belyaeva 1967 (rat, antimony trisulfide)	+	+	+	–	+	–	**–**	+	NA	Second
Oral intermediate exposure										
Angrisani et al. 1988 (rat pup CV, antimony trichloride)	+	+	+	+	+	–	**+**	+	NA	First

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Table C-9. Summary of Risk of Bias Assessment for Antimony—Experimental Animal Studies

Reference	Risk of bias criteria and ratings: Selection bias — Was administered dose or exposure level adequately randomized?	Selection bias — Was the allocation to study groups adequately concealed?	Performance bias — Were experimental conditions identical across study groups?	Performance bias — Were the research personnel blinded to the study group during the study?	Attrition/ exclusion bias — Were outcome data complete without attrition or exclusion from analysis?	Detection bias — Is there confidence in the exposure characterization?	Detection bias — **Is there confidence in the outcome assessment?***	Selective reporting bias — Were all measured outcomes reported?	Other bias — Did the study design or analysis account for important confounding and modifying variables?	Risk of bias tier
Rossi et al. 1987 (rat, antimony trichloride)	+	+	+	+	+	–	**+**	+	NA	First
Rossi et al. 1987 (rat pup CV, antimony trichloride)	+	+	+	+	+	–	**+**	+	NA	First

++ = definitely low risk of bias; + = probably low risk of bias; – = probably high risk of bias; – – = definitely high risk of bias; NA = not applicable
*Key question used to assign risk of bias tier

C.6.1 Initial Confidence Rating

In ATSDR's modification to the OHAT approach, the body of evidence for an association (or no association) between exposure to antimony and a particular outcome was given an initial confidence rating based on the key features of the individual studies examining that outcome. The presence of these key features of study design was determined for individual studies using four "yes or no" questions in Distiller, which were customized for epidemiology, human controlled exposure, or experimental animal study designs. Separate questionnaires were completed for each outcome assessed in a study. The key features for observational epidemiology (cohort, population, and case-control) studies, human controlled exposure, and experimental animal studies are presented in Tables C-10, C-11, and C-12, respectively. The initial confidence in the study was determined based on the number of key features present in the study design:

- **High Initial Confidence:** Studies in which the responses to the four questions were "yes".
- **Moderate Initial Confidence:** Studies in which the responses to only three of the questions were "yes".
- **Low Initial Confidence:** Studies in which the responses to only two of the questions were "yes".
- **Very Low Initial Confidence:** Studies in which the response to one or none of the questions was "yes".

Table C-10. Key Features of Study Design for Observational Epidemiology Studies

Exposure was experimentally controlled
Exposure occurred prior to the outcome
Outcome was assessed on individual level rather than at the population level
A comparison group was used

Table C-11. Key Features of Study Design for Human-Controlled Exposure Studies

A comparison group was used or the subjects served as their own control
A sufficient number of subjects were tested
Appropriate methods were used to measure outcomes (i.e., clinically-confirmed outcome versus self-reported)
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

Table C-12. Key Features of Study Design for Experimental Animal Studies

A concurrent control group was used
A sufficient number of animals per group were tested
Appropriate parameters were used to assess a potential adverse effect
Appropriate statistical analyses were performed and reported or the data were reported in such a way to allow independent statistical analysis

The presence or absence of the key features and the initial confidence levels for studies examining respiratory, cardiovascular, gastrointestinal, metabolic, and developmental effects observed in the observational epidemiology and animal experimental studies are presented in Tables C-13 and C-14, respectively.

Table C-13. Presence of Key Features of Study Design for Antimony—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Outcome: Respiratory effects (inhalation only)					
Cohort studies					
Jones 1994 (antimony metal and antimony trioxide)	No	Yes	Yes	Yes	Moderate
Renes 1953 (antimony oxides)	No	Yes	Yes	No	Low
Schnorr et al. 1995 (antimony oxides)	No	Yes	Yes	Yes	Moderate
Cross-sectional studies					
Brieger et al. 1954 (antimony trisulfide)	No	Yes	Yes	No	Low
Cooper et al. 1968 (antimony trioxide)	No	Yes	Yes	No	Low
Case series					
Potkonjak and Pavlovich 1983 (antimony oxides)	No	Yes	Yes	No	Low
Taylor 1966 (antimony trichloride)	No	Yes	Yes	No	Low
Outcome: Cardiovascular effects					
Cross-sectional studies					
Brieger et al. 1954 (antimony trisulfide)	No	Yes	Yes	No	Low
Outcome: Gastrointestinal effects					
Cohort studies					
Renes 1953 (antimony oxides)	No	Yes	Yes	No	Low
Cross-sectional studies					
Brieger et al. 1954 (antimony trisulfide)	No	Yes	Yes	No	Low

Table C-13. Presence of Key Features of Study Design for Antimony—Observational Epidemiology Studies

Reference	Key features: Controlled exposure	Exposure prior to outcome	Outcomes assessed on an individual level	Comparison group	Initial study confidence
Case series					
Taylor 1966 (antimony trichloride)	No	Yes	Yes	No	Low
Outcome: Developmental effects					
Cohort studies					
Belyaeva 1967 (antimony metal, antimony trioxide, antimony pentasulfide)	No	No	Yes	Yes	Low
Case-control studies					
Longerich et al. 1991 (not reported)	No	No	Yes	Yes	Low

Table C-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Outcome: Respiratory effects (inhalation only)					
Inhalation acute exposure					
Brieger et al. 1954 (rabbit, antimony trisulfide)	Yes	No	Yes	No	Moderate
NTP 2016 (rat, antimony trioxide)	Yes	No	Yes	Yes	Moderate
NTP 2016 (mouse, antimony trioxide)	Yes	No	Yes	Yes	Moderate
NIOSH 1979 (rat, stibine)	Yes	No	Yes	No	Low
NIOSH 1979 (guinea pig, stibine)	Yes	No	Yes	No	Low
Inhalation intermediate exposure					
Belyaeva 1967 (rat, antimony trisulfide)	Yes	Yes	Yes	No	Moderate
Brieger et al. 1954 (rat, antimony trisulfide)	Yes	Yes	Yes	No	Moderate
Dernehl et al. 1945 (guinea pig, antimony trioxide)	Yes	No	Yes	No	Low

Table C-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature				Initial study confidence
	Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	
Newton et al. 1994 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Inhalation chronic exposure					
Gross et al. 1952 (rat, antimony trisulfide)	Yes	Yes	Yes	Yes	High
Groth et al. 1986 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Groth et al. 1986 (rat, antimony ore)	Yes	Yes	Yes	Yes	High
Newton et al. 1994 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
NTP 2016 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
NTP 2016 (mouse, antimony trioxide)	Yes	Yes	Yes	Yes	High
Watt 1983 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Watt 1983 (pig, antimony trioxide)	Yes	No	Yes	Yes	Moderate
Outcome: Cardiovascular effects (myocardium damage or altered EKG)					
Inhalation acute exposure					
Brieger et al. 1954 (rabbit, antimony trisulfide)	Yes	No	Yes	No	Low
Inhalation intermediate exposure					
Brieger et al. 1954 (rat, antimony trisulfide)	Yes	Yes	Yes	No	Moderate
Brieger et al. 1954 (rabbit, antimony trisulfide)	Yes	No	Yes	No	Low
Brieger et al. 1954 (dog, 7 weeks, antimony trisulfide)	Yes	No	Yes	No	Low
Brieger et al. 1954 (dog, 10 weeks, antimony trisulfide)	Yes	No	Yes	No	Low
Dernehl et al. 1945 (guinea pig, antimony trioxide)	Yes	No	Yes	No	Low
Newton et al. 1994 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Inhalation chronic exposure					
Groth et al. 1986 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Groth et al. 1986 (rat, antimony ore)	Yes	Yes	No	Yes	Moderate
Newton et al. 1994 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
NTP 2016 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
NTP 2016 (mouse, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Watt 1983 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Watt 1983 (pigs, antimony trioxide)	Yes	No	Yes	No	Low

Table C-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Sufficient number of animals per group	Appropriate parameters to assess potential effect	Adequate data for statistical analysis	Initial study confidence
Oral acute exposure					
NTP 1992 (rat, antimony potassium tartrate)	Yes	No	No	Yes	Low
NTP 1992 (mouse, antimony potassium tartrate)	Yes	No	No	Yes	Low
Oral intermediate exposure					
Hext et al. 1999 (rat, antimony trioxide)	Yes	Yes	No	Yes	Moderate
Poon et al. 1998 (rat, antimony potassium tartrate)	Yes	Yes	No	Yes	Moderate
Outcome: Gastrointestinal effects					
Inhalation chronic exposure					
Groth et al. 1986 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Groth et al. 1986 (rat, antimony ore)	Yes	Yes	Yes	Yes	High
NTP 2016 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
NTP 2016 (mouse, antimony trioxide)	Yes	Yes	Yes	Yes	High
Watt 1983 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Watt 1983 (pig, antimony trioxide)	Yes	No	Yes	Yes	Moderate
Oral acute exposure					
Houpt et al. 1984 (dog, antimony potassium tartrate)	Yes	Yes	Yes	Yes	High
NTP 1992 (rat, antimony potassium tartrate)	Yes	No	Yes	Yes	Moderate
NTP 1992 (mouse, antimony potassium tartrate)	Yes	No	Yes	Yes	Moderate
Oral intermediate exposure					
Hext et al. 1999 (rat, antimony trioxide)	Yes	Yes	Yes	Yes	High
Poon et al. 1998 (rat, antimony potassium tartrate)	Yes	Yes	Yes	Yes	High
Outcome: Metabolic effects (altered blood glucose levels)					
Oral intermediate exposure					
Poon et al. 1998 (rat, antimony potassium tartrate)	Yes	Yes	Yes	Yes	High
Oral Chronic exposure					
Schroeder et al. 1970 (rat, antimony potassium tartrate)	Yes	Yes	Yes	Yes	High
Outcome: Developmental effects					
Inhalation intermediate exposure					
Belyaeva 1967 (rat, antimony trisulfide)	Yes	Yes	Yes	No	Moderate

Table C-14. Presence of Key Features of Study Design for Antimony—Experimental Animal Studies

Reference	Key feature: Concurrent control group	Key feature: Sufficient number of animals per group	Key feature: Appropriate parameters to assess potential effect	Key feature: Adequate data for statistical analysis	Initial study confidence
Oral intermediate exposure					
Angrisani et al. 1988 (rat pup CV, antimony trichloride)	Yes	Yes	Yes	Yes	High
Rossi et al. 1987 (rat, antimony trichloride)	Yes	Yes	Yes	Yes	High
Rossi et al. 1987 (rat pup CV, antimony trichloride)	Yes	Yes	Yes	Yes	High

A summary of the initial confidence ratings for each outcome is presented in Table C-15. If individual studies for a particular outcome and study type had different study quality ratings, then the highest confidence rating for the group of studies was used to determine the initial confidence rating for the body of evidence; any exceptions were noted in Table C-15.

Table C-15. Initial Confidence Rating for Antimony Health Effects Studies

	Initial study confidence	Initial confidence rating
Outcome: Respiratory effects		
Studies finding effects		
Inhalation acute exposure		
Animal studies		
Brieger et al. 1954 (rabbit, antimony trisulfide)	Moderate	
NTP 2016 (rat, antimony trioxide)	Moderate	
NTP 2016 (mouse, antimony trioxide)	Moderate	Moderate
NIOSH 1979 (rat, stibine)	Low	
NIOSH 1979 (guinea pig, stibine)	Low	
Inhalation intermediate exposure		
Animal studies		
Belyaeva 1967 (rat, antimony trisulfide)	Moderate	
Brieger et al. 1954 (rat, antimony trisulfide)	Moderate	High
Dernehl et al. 1945 (guinea pig, antimony trioxide)	Low	
Newton et al. 1994 (rat, antimony trioxide)	High	

Table C-15. Initial Confidence Rating for Antimony Health Effects Studies

	Initial study confidence	Initial confidence rating
Inhalation chronic exposure		
Human studies		
Renes 1953 (antimony oxides)	Low	
Schnorr et al. 1995 (antimony oxides)	Moderate	
Cooper et al. 1968 (antimony trioxide)	Low	Moderate
Potkonjak and Pavlovich 1983 (antimony oxides)	Low	
Taylor 1966 (antimony trichloride)	Low	
Animal studies		
Gross et al. 1952 (rat, antimony trisulfide)	High	
Groth et al. 1986 (rat, antimony trioxide)	High	
Groth et al. 1986 (rat, antimony ore)	High	
Newton et al. 1994 (rat, antimony trioxide)	High	High
NTP 2016 (rat, antimony trioxide)	High	
NTP 2016 (mouse, antimony trioxide)	High	
Watt 1983 (rat, antimony trioxide)	High	
Watt 1983 (pig, antimony trioxide)	Moderate	
Studies finding no effects		
Inhalation chronic exposure		
Human studies		
Brieger et al. 1954 (antimony trisulfide)	Low	
Jones 1994 (antimony metal and antimony trioxide)	Moderate	Moderate
Outcome: Cardiovascular effects		
Studies finding effects on myocardium and/or EKGs		
Inhalation acute exposure		
Animal studies		
Brieger et al. 1954 (rabbit, antimony trisulfide)	Low	Low
Inhalation intermediate exposure		
Animal studies		
Brieger et al. 1954 (rat, antimony trisulfide)	Moderate	
Brieger et al. 1954 (rabbit, antimony trisulfide)	Low	Moderate
Brieger et al. 1954 (dog, 10 weeks, antimony trisulfide)	Low	
Inhalation chronic exposure		
Human studies		
Brieger et al. 1954 (antimony trisulfide)	Low	Low

Table C-15. Initial Confidence Rating for Antimony Health Effects Studies

	Initial study confidence	Initial confidence rating
Studies finding no effects on myocardium and/or EKGs		
Inhalation intermediate exposure		
Animal studies		
Brieger et al. 1954 (dog, 7 weeks, antimony trisulfide)	Low	Moderate
Dernehl et al. 1945 (guinea pig, antimony trioxide)	Low	
Newton et al. 1994 (rat, antimony trioxide)	Moderate	
Inhalation chronic exposure		
Animal studies		
Groth et al. 1986 (rat, antimony trioxide)	Moderate	Moderate
Groth et al. 1986 (rat, antimony ore)	Moderate	
Newton et al. 1994 (rat, antimony trioxide)	Moderate	
NTP 2016 (rat, antimony trioxide)	Moderate	
NTP 2016 (mouse, antimony trioxide)	Moderate	
Watt 1983 (rat, antimony trioxide)	Moderate	
Watt 1983 (pigs, antimony trioxide)	Low	
Oral acute exposure		
Animal studies		
NTP 1992 (rat, antimony potassium tartrate)	Low	Low
NTP 1992 (mouse, antimony potassium tartrate)	Low	
Oral intermediate exposure		
Animal studies		
Hext et al. 1999 (rat, antimony trioxide)	Moderate	Moderate
Poon et al. 1998 (rat, antimony potassium tartrate)	Moderate	
Outcome: Gastrointestinal effects		
Studies finding effects		
Inhalation chronic exposure		
Human studies		
Brieger et al. 1954	Low	Low
Renes 1953	Low	
Taylor 1966	Low	
Animal studies		
NTP 2016 (mouse, antimony trioxide)	High	High
Oral acute exposure		
Animal studies		
Houpt et al. 1984 (dog, antimony potassium tartrate)	High	High
NTP 1992 (mouse, antimony potassium tartrate)	Moderate	

Table C-15. Initial Confidence Rating for Antimony Health Effects Studies

	Initial study confidence	Initial confidence rating
Studies finding no effects		
Inhalation chronic exposure		
Animal studies		
Groth et al. 1986 (rat, antimony trioxide)	High	
Groth et al. 1986 (rat, antimony ore)	High	
NTP 2016 (rat, antimony trioxide)	High	High
Watt 1983 (rat, antimony trioxide)	High	
Watt 1983 (pig, antimony trioxide)	Moderate	
Oral acute exposure		
Animal studies		
NTP 1992 (rat, antimony potassium tartrate)	Moderate	Moderate
Oral intermediate exposure		
Animal studies		
Hext et al. 1999 (rat, antimony trioxide)	High	High
Poon et al. 1998 (rat, antimony potassium tartrate)	High	
Outcome: Metabolic effects		
Studies finding effects on serum glucose levels		
Oral intermediate exposure		
Animal studies		
Poon et al. 1998 (rat, antimony potassium tartrate)	High	High
Oral chronic exposure		
Animal studies		
Schroeder et al. 1970 (rat, antimony potassium tartrate)	High	High
Outcome: Developmental effects		
Studies finding effects		
Inhalation intermediate exposure		
Animal studies		
Belyaeva 1967 (rat, antimony trisulfide)	Moderate	Moderate
Inhalation chronic exposure		
Human studies		
Belyaeva 1967 (metallic antimony, antimony trioxide, antimony pentasulfide)	Low	Low
Oral intermediate exposure		
Animal studies		
Angrisani et al. 1988 (rat, pup CV, antimony trichloride)	High	
Rossi et al. 1987 (rat, pup CV, antimony trichloride)	High	High
Rossi et al. 1987 (rat, antimony trichloride)	High	

Table C-15. Initial Confidence Rating for Antimony Health Effects Studies

	Initial study confidence	Initial confidence rating
Studies finding no effects		
Inhalation chronic exposure		
Human studies		
Longerich et al. 1991 (not reported)	Low	Low

C.6.2 Adjustment of the Confidence Rating

The initial confidence rating was then downgraded or upgraded depending on whether there were substantial issues that would decrease or increase confidence in the body of evidence. The nine properties of the body of evidence that were considered are listed below. The summaries of the assessment of the confidence in the body of evidence for respiratory, cardiovascular, gastrointestinal, metabolic, and developmental effects are presented in Table C-16. If the confidence ratings for a particular outcome were based on more than one type of human study, then the highest confidence rating was used for subsequent analyses. An overview of the confidence in the body of evidence for all health effects associated with antimony exposure is presented in Table C-17.

Five properties of the body of evidence were considered to determine whether the confidence rating should be downgraded:

- **Risk of bias.** Evaluation of whether there is substantial risk of bias across most of the studies examining the outcome. This evaluation used the risk of bias tier groupings for individual studies examining a particular outcome (Tables C-8 and C-9). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for risk of bias:
    - No downgrade if most studies are in the risk of bias first tier
    - Downgrade one confidence level if most studies are in the risk of bias second tier
    - Downgrade two confidence levels if most studies are in the risk of bias third tier

- **Unexplained inconsistency.** Evaluation of whether there is inconsistency or large variability in the magnitude or direction of estimates of effect across studies that cannot be explained. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for unexplained inconsistency:
    - No downgrade if there is little inconsistency across studies or if only one study evaluated the outcome
    - Downgrade one confidence level if there is variability across studies in the magnitude or direction of the effect
    - Downgrade two confidence levels if there is substantial variability across studies in the magnitude or direct of the effect

Table C-16. Adjustments to the Initial Confidence in the Body of Evidence

	Initial confidence	Adjustments to the initial confidence rating	Final confidence
Outcome: Respiratory effects			
Studies finding effects			
Human studies	Moderate	-1 risk of bias	Low
Animal studies	High	+1 magnitude, +1 consistency	High
Studies finding no effects			
Human studies	Moderate	-1 risk of bias,	Low
Outcome: Cardiovascular effects			
Studies finding effects on myocardium and/or EKGs			
Human studies	Low	-1 risk of bias,	Very low
Animal studies	Moderate	-1 risk of bias	Low
Studies finding no effects on myocardium and/or EKGs			
Animal studies	Moderate	None	Moderate
Outcome: Gastrointestinal effects			
Studies finding effects			
Human studies	Low	-1 risk of bias	Very low
Animal studies	High	None	High
Studies finding no effects			
Animal studies	High	None	High
Outcome: Metabolic effects			
Studies finding effects on serum glucose levels			
Animal studies	High	None	High
Outcome: Developmental effects			
Studies finding effects			
Human studies	Low	-1 risk of bias	Very low
Animal studies	High	None	High
Studies finding no effects			
Human studies	Low	-1 risk of bias	Very low

Table C-17. Confidence in the Body of Evidence for Antimony

	Confidence in body of evidence	
Outcome	Human studies	Animal studies
Respiratory effects		
Effect	Low	High
No effect	Low	No data
Cardiovascular effects		
Effects on myocardium/EKG	Very low	Low
No effect on myocardium/EKG	No data	Moderate
Gastrointestinal effects		
Effect	Very low	High
No effect	No data	High
Metabolic effects		
Effect	No data	High
No effect	No data	No data
Developmental effects		
Effect	Very low	High
No effect	Very low	No data

- **Indirectness.** Evaluation of four factors that can affect the applicability, generalizability, and relevance of the studies:
    - Relevance of the animal model to human health—unless otherwise indicated, studies in rats, mice, and other mammalian species are considered relevant to humans
    - Directness of the endpoints to the primary health outcome—examples of secondary outcomes or nonspecific outcomes include organ weight in the absence of histopathology or clinical chemistry findings in the absence of target tissue effects
    - Nature of the exposure in human studies and route of administration in animal studies—inhalation, oral, and dermal exposure routes are considered relevant unless there are compelling data to the contrary
    - Duration of treatment in animal studies and length of time between exposure and outcome assessment in animal and prospective human studies—this should be considered on an outcome-specific basis

Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for indirectness:

- No downgrade if none of the factors are considered indirect
- Downgrade one confidence level if one of the factors is considered indirect
- Downgrade two confidence levels if two or more of the factors are considered indirect

- **Imprecision.** Evaluation of the narrowness of the effect size estimates and whether the studies have adequate statistical power. Data are considered imprecise when the ratio of the upper to lower 95% CIs for most studies is ≥10 for tests of ratio measures (e.g., odds ratios) and ≥100 for absolute measures (e.g., percent control response). Adequate statistical power is determined if the study can detect a potentially biologically meaningful difference between groups (20% change from control response for categorical data or risk ratio of 1.5 for

continuous data). Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be downgraded for imprecision:

- No downgrade if there are no serious imprecisions
- Downgrade one confidence level for serious imprecisions
- Downgrade two confidence levels for very serious imprecisions

- **Publication bias.** Evaluation of the concern that studies with statistically significant results are more likely to be published than studies without statistically significant results.
  - Downgrade one level of confidence for cases where there is serious concern with publication bias

Four properties of the body of evidence were considered to determine whether the confidence rating should be upgraded:

- **Large magnitude of effect.** Evaluation of whether the magnitude of effect is sufficiently large so that it is unlikely to have occurred as a result of bias from potential confounding factors.
  - Upgrade one confidence level if there is evidence of a large magnitude of effect in a few studies, provided that the studies have an overall low risk of bias and there is no serious unexplained inconsistency among the studies of similar dose or exposure levels; confidence can also be upgraded if there is one study examining the outcome, provided that the study has an overall low risk of bias

- **Dose response.** Evaluation of the dose-response relationships measured within a study and across studies. Below are the criteria used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence of a monotonic dose-response gradient
  - Upgrade one confidence level for evidence of a non-monotonic dose-response gradient where there is prior knowledge that supports a non-monotonic dose-response and a non-monotonic dose-response gradient is observed across studies

- **Plausible confounding or other residual biases.** This factor primarily applies to human studies and is an evaluation of unmeasured determinants of an outcome such as residual bias towards the null (e.g., “healthy worker” effect) or residual bias suggesting a spurious effect (e.g., recall bias). Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level for evidence that residual confounding or bias would underestimate an apparent association or treatment effect (i.e., bias toward the null) or suggest a spurious effect when results suggest no effect

- **Consistency in the body of evidence.** Evaluation of consistency across animal models and species, consistency across independent studies of different human populations and exposure scenarios, and consistency across human study types. Below is the criterion used to determine whether the initial confidence in the body of evidence for each outcome should be upgraded:
  - Upgrade one confidence level if there is a high degree of consistency in the database

C.7 TRANSLATE CONFIDENCE RATING INTO LEVEL OF EVIDENCE OF HEALTH EFFECTS

In the seventh step of the systematic review of the health effects data for antimony, the confidence in the body of evidence for specific outcomes was translated to a level of evidence rating. The level of evidence rating reflected the confidence in the body of evidence and the direction of the effect (i.e., toxicity or no toxicity); route-specific differences were noted. The level of evidence for health effects was rated on a five-point scale:

- **High level of evidence:** High confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Moderate level of evidence:** Moderate confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Low level of evidence:** Low confidence in the body of evidence for an association between exposure to the substance and the health outcome
- **Evidence of no health effect:** High confidence in the body of evidence that exposure to the substance is not associated with the health outcome
- **Inadequate evidence:** Low or moderate confidence in the body of evidence that exposure to the substance is not associated with the health outcome OR very low confidence in the body of evidence for an association between exposure to the substance and the health outcome

A summary of the level of evidence of health effects for antimony is presented in Table C-18.

Table C-18. Level of Evidence of Health Effects for Antimony

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Human studies			
Respiratory effects (inhalation only)			
	Low	Health effect	Low
	Low	No effect	Inadequate
Cardiovascular—myocardial and EKG alterations			
	Very Low	Health effect	Inadequate
Gastrointestinal effect			
	Very Low	Health effect	Inadequate
Metabolic—serum glucose alterations			
	No data	–	No data
Developmental effects			
	Very Low	Health effect	Inadequate
Animal studies			
Respiratory effects (inhalation only)			
	High	Health effect	High
Cardiovascular—myocardial and EKG alterations			
	Low	Health effect	Low
	Moderate	No effect	Inadequate

Table C-18. Level of Evidence of Health Effects for Antimony

Outcome	Confidence in body of evidence	Direction of health effect	Level of evidence for health effect
Gastrointestinal effects			
	High	Health effect	High
	High	No effect	Evidence of no health effect
Metabolic—serum glucose alterations			
	High	Health effect	High
Developmental effects			
	High	Health effect	High
	No data	–	No data

C.8 INTEGRATE EVIDENCE TO DEVELOP HAZARD IDENTIFICATION CONCLUSIONS

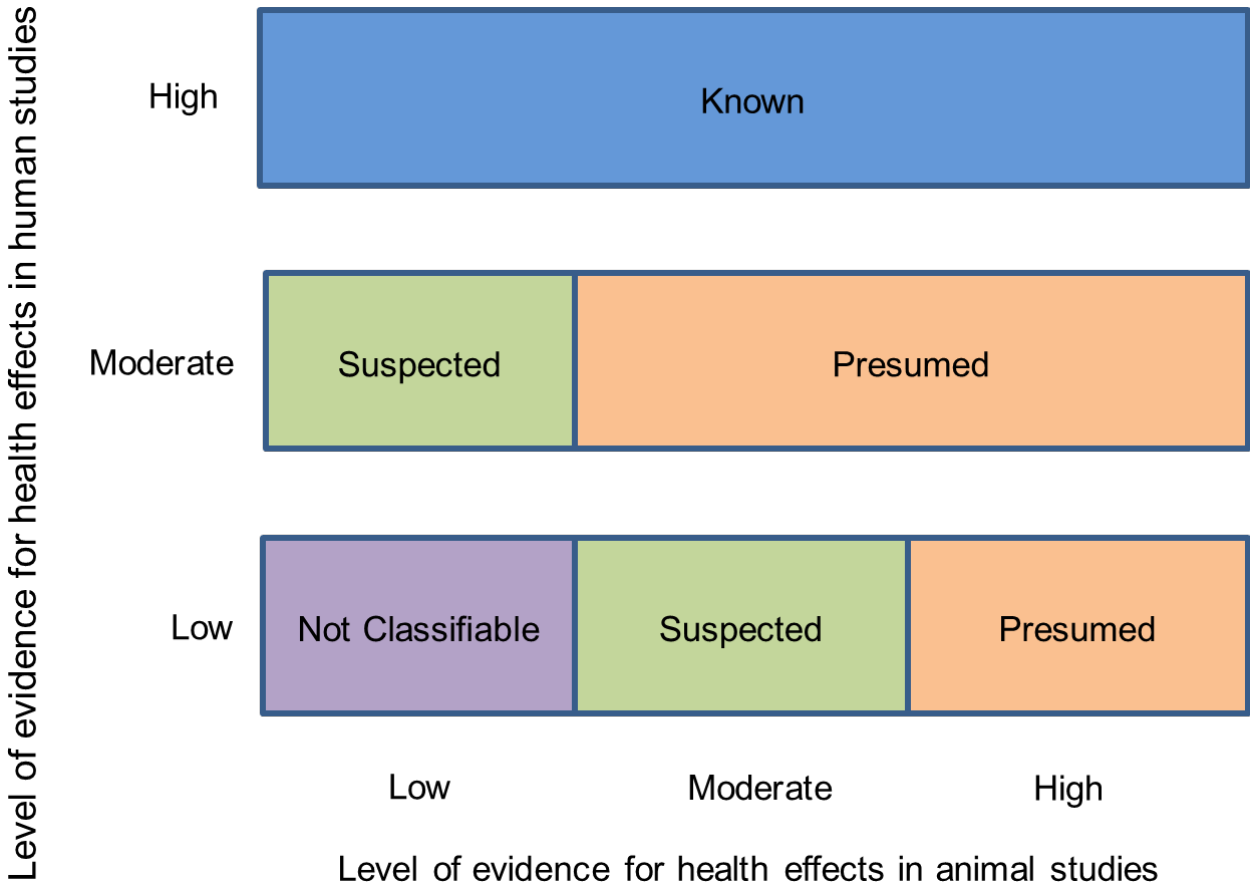
The final step involved the integration of the evidence streams for the human studies and animal studies to allow for a determination of hazard identification conclusions. For health effects, there were four hazard identification conclusion categories:

- **Known** to be a hazard to humans
- **Presumed** to be a hazard to humans
- **Suspected** to be a hazard to humans
- **Not classifiable** as to the hazard to humans

The initial hazard identification was based on the highest level of evidence in the human studies and the level of evidence in the animal studies; if there were no data for one evidence stream (human or animal), then the hazard identification was based on the one data stream (equivalent to treating the missing evidence stream as having low level of evidence). The hazard identification scheme is presented in Figure C-1 and described below:

- **Known:** A health effect in this category would have:
  - High level of evidence for health effects in human studies **AND** a high, moderate, or low level of evidence in animal studies.
- **Presumed:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** high or moderate level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** high level of evidence in animal studies
- **Suspected:** A health effect in this category would have:
  - Moderate level of evidence in human studies **AND** low level of evidence in animal studies **OR**
  - Low level of evidence in human studies **AND** moderate level of evidence in animal studies
- **Not classifiable:** A health effect in this category would have:
  - Low level of evidence in human studies **AND** low level of evidence in animal studies

Figure C-1. Hazard Identification Scheme



Other relevant data such as mechanistic or mode-of-action data were considered to raise or lower the level of the hazard identification conclusion by providing information that supported or opposed biological plausibility.

Two hazard identification conclusion categories were used when the data indicated that there may be no health effect in humans:

- **Not identified** to be a hazard in humans
- **Inadequate** to determine hazard to humans

If the human level of evidence conclusion of no health effect was supported by the animal evidence of no health effect, then the hazard identification conclusion category of "not identified" was used. If the human or animal level of evidence was considered inadequate, then a hazard identification conclusion category of "inadequate" was used. As with the hazard identification for health effects, the impact of other relevant data was also considered for no health effect data.

The hazard identification conclusions for antimony are listed below and summarized in Table C-19.

Presumed Health Effects

- Respiratory effects following inhalation exposure
  - Low evidence from studies of antimony workers (Cooper et al. 1968; Potkonjak and Pavlovich 1983; Renes 1953; Schnorr et al. 1995; Taylor 1966).
  - High level of evidence in rats, mice, rabbits, guinea pigs, and pigs from acute exposure to antimony trisulfide, antimony trioxide, and stibine (Brieger et al. 1954; NIOSH 1979; NTP 2016), intermediate exposure to antimony trisulfide and antimony trioxide (Belyaeva 1967; Brieger et al. 1954; Dernehl et al. 1945; Newton et al. 1994), and chronic exposure to antimony trisulfide, antimony trioxide, and antimony ore (Gross et al. 1952; Groth et al. 1986; Newton et al. 1994; NTP 2016; Watt 1983).
- Gastrointestinal effects
  - Inadequate evidence from studies of antimony workers (Brieger et al. 1954; Renes 1953; Taylor 1966).
  - High level of evidence for gastrointestinal irritation in dogs (Houpt et al. 1984) and mice (NTP 1992, 2016). Inhalation and oral studies in rats with initial confidences of high or moderate did not find histological alterations in the gastrointestinal tract following inhalation exposure to antimony trioxide (Groth et al. 1986; NTP 2016; Watt 1983) or antimony ore (Groth et al. 1986) or oral exposure to antimony trioxide (Hext et al. 1999) or antimony potassium tartrate (NTP 1992; Poon et al. 1998).

Suspected Health Effects

- Cardiovascular-myocardial and EKG alterations
  - Inadequate evidence in humans exposed to antimony trisulfide (Brieger et al. 1954)
  - Low evidence in rats, rabbits, and dogs exposed via inhalation to antimony trisulfide (Brieger et al. 1954) and in rats exposed to antimony potassium tartrate (Schroeder et al. 1970). No myocardial alterations were observed in rat, mouse, pig, or guinea pig antimony ore or antimony trioxide inhalation studies with initial moderate confidence levels (Dernehl et al. 1945; Groth et al. 1986; Newton et al. 1994; Watt 1983) or in antimony trioxide and antimony potassium tartrate oral studies with initial moderate confidence level (Hext et al. 1999; NTP 1992; Poon et al. 1998).
  - Although the hazard identification for myocardial and EKG alterations should be not classifiable based on inadequate evidence in humans and low evidence in animals, the level of the hazard identification was raised to suspected health effect based on consistent evidence of EKG alterations in patients treated with injected trivalent or pentavalent antimony compounds (Dancaster et al. 1966; Honey 1960; Lawn et al. 2006; Neves et al. 2009; Sundar et al. 1998; Thakur 1998) and in animal studies involving parenteral administration (Alvarez et al. 2005; Bromberger-Barnea and Stephens 1965; Cotten and Logan 1966).
- Metabolic effect (decreases in blood glucose levels)
  - No data are available on whether inhalation, oral, or dermal exposure to antimony alters blood glucose levels in humans.
  - High evidence in animal studies based on two studies that found decreases in blood glucose levels following intermediate (Poon et al. 1998) or chronic (Schroeder et al. 1970) oral exposure. Decreases in blood glucose levels were also found in rats following repeated intramuscular injection of two organic pentavalent compounds (Alkhawajah et al. 1992b).
  - Based on the high evidence found in the two animal studies, decreases in blood glucose levels should be classified as a presumed health effect. However, because blood glucose levels have only been assessed in two studies administering antimony via

environmentally relevant routes of exposure, the hazard identification was downgraded to suspected health effect.

- Developmental effects
  - Inadequate evidence of developmental effects (decreases in infant growth) from an occupational exposure study (Belyaeva 1967).
  - High evidence of developmental toxicity from animal studies. An inhalation study found decreases in the number of offspring in rats exposed to antimony trioxide during gestation (Belyaeva 1967). An antimony trichloride oral exposure study found decreases in postnatal growth resulting from gestation and lactation exposure, but no effect on the number of offspring or abnormalities (Rossi et al. 1987).
  - Decreases in birth weight and decreases in the number of viable offspring were observed in rat studies involving gestation and/or lactation exposure to subcutaneously administered meglumine antimoniate (Coelho et al. 2014a; Miranda et al. 2006) or intramuscularly administered sodium stibogluconate, meglumine antimoniate, or antimony trichloride (Alkhawajah et al. 1992a).
  - Although the hazard identification for developmental effects, particularly for decreased growth, should be presumed health effect based on inadequate evidence in humans and high evidence in humans, the hazard identification was lowered to suspected health effect based on the small number of studies evaluating the developmental toxicity of antimony by environmentally relevant routes of exposure.

Table C-19. Hazard Identification Conclusions for Antimony

Outcome	Hazard identification
Respiratory effects	Presumed health effect following inhalation exposure
Cardiovascular-myocardial and EKG alterations	Suspected health effect following exposure to soluble antimony compounds
Gastrointestinal effects	Presumed health effect
Metabolic effects (decreased serum glucose levels)	Suspected health effect
Developmental effects	Suspected health effect

APPENDIX D. USER'S GUIDE

Chapter 1. Relevance to Public Health

This chapter provides an overview of U.S. exposures, a summary of health effects based on evaluations of existing toxicologic, epidemiologic, and toxicokinetic information, and an overview of the minimal risk levels. This is designed to present interpretive, weight-of-evidence discussions for human health endpoints by addressing the following questions:

1. What effects are known to occur in humans?

2. What effects observed in animals are likely to be of concern to humans?

3. What exposure conditions are likely to be of concern to humans, especially around hazardous waste sites?

Minimal Risk Levels (MRLs)

Where sufficient toxicologic information is available, ATSDR derives MRLs for inhalation and oral routes of entry at each duration of exposure (acute, intermediate, and chronic). These MRLs are not meant to support regulatory action, but to acquaint health professionals with exposure levels at which adverse health effects are not expected to occur in humans.

MRLs should help physicians and public health officials determine the safety of a community living near a hazardous substance emission, given the concentration of a contaminant in air or the estimated daily dose in water. MRLs are based largely on toxicological studies in animals and on reports of human occupational exposure.

MRL users should be familiar with the toxicologic information on which the number is based. Section 1.2, Summary of Health Effects, contains basic information known about the substance. Other sections, such as Section 3.2 Children and Other Populations that are Unusually Susceptible and Section 3.4 Interactions with Other Substances, provide important supplemental information.

MRL users should also understand the MRL derivation methodology. MRLs are derived using a modified version of the risk assessment methodology that the Environmental Protection Agency (EPA) provides (Barnes and Dourson 1988) to determine reference doses (RfDs) for lifetime exposure.

To derive an MRL, ATSDR generally selects the most sensitive endpoint which, in its best judgement, represents the most sensitive human health effect for a given exposure route and duration. ATSDR cannot make this judgement or derive an MRL unless information (quantitative or qualitative) is available for all potential systemic, neurological, and developmental effects. If this information and reliable quantitative data on the chosen endpoint are available, ATSDR derives an MRL using the most sensitive species (when information from multiple species is available) with the highest no-observed-adverse-effect level (NOAEL) that does not exceed any adverse effect levels. When a NOAEL is not available, a lowest-observed-adverse-effect level (LOAEL) can be used to derive an MRL, and an uncertainty factor of 10 must be employed. Additional uncertainty factors of 10 must be used both for human variability to protect sensitive subpopulations (people who are most susceptible to the health effects caused by the substance) and for interspecies variability (extrapolation from animals to humans). In deriving an MRL, these individual uncertainty factors are multiplied together. The product is then divided into the inhalation concentration or oral dosage selected from the study. Uncertainty factors used in developing a

substance-specific MRL are provided in the footnotes of the levels of significant exposure (LSE) tables that are provided in Chapter 2. Detailed discussions of the MRLs are presented in Appendix A.

Chapter 2. Health Effects

Tables and Figures for Levels of Significant Exposure (LSE)

Tables and figures are used to summarize health effects and illustrate graphically levels of exposure associated with those effects. These levels cover health effects observed at increasing dose concentrations and durations, differences in response by species and MRLs to humans for noncancer endpoints. The LSE tables and figures can be used for a quick review of the health effects and to locate data for a specific exposure scenario. The LSE tables and figures should always be used in conjunction with the text. All entries in these tables and figures represent studies that provide reliable, quantitative estimates of NOAELs, LOAELs, or Cancer Effect Levels (CELs).

The legends presented below demonstrate the application of these tables and figures. Representative examples of LSE tables and figures follow. The numbers in the left column of the legends correspond to the numbers in the example table and figure.

TABLE LEGEND

See Sample LSE Table (page D-5)

(1) Route of exposure. One of the first considerations when reviewing the toxicity of a substance using these tables and figures should be the relevant and appropriate route of exposure. Typically, when sufficient data exist, three LSE tables and two LSE figures are presented in the document. The three LSE tables present data on the three principal routes of exposure (i.e., inhalation, oral, and dermal). LSE figures are limited to the inhalation and oral routes. Not all substances will have data on each route of exposure and will not, therefore, have all five of the tables and figures. Profiles with more than one chemical may have more LSE tables and figures.

(2) Exposure period. Three exposure periods—acute (<15 days), intermediate (15–364 days), and chronic (≥365 days)—are presented within each relevant route of exposure. In this example, two oral studies of chronic-duration exposure are reported. For quick reference to health effects occurring from a known length of exposure, locate the applicable exposure period within the LSE table and figure.

(3) Figure key. Each key number in the LSE table links study information to one or more data points using the same key number in the corresponding LSE figure. In this example, the study represented by key number 51 identified NOAELs and less serious LOAELs (also see the three "51R" data points in sample LSE Figure 2-X).

(4) Species (strain) No./group. The test species (and strain), whether animal or human, are identified in this column. The column also contains information on the number of subjects and sex per group. Chapter 1, Relevance to Public Health, covers the relevance of animal data to human toxicity and Section 3.1, Toxicokinetics, contains any available information on comparative toxicokinetics. Although NOAELs and LOAELs are species specific, the levels are extrapolated to equivalent human doses to derive an MRL.

(5) Exposure parameters/doses. The duration of the study and exposure regimens are provided in these columns. This permits comparison of NOAELs and LOAELs from different studies. In this case (key number 51), rats were orally exposed to “Chemical X” via feed for 2 years. For a

more complete review of the dosing regimen, refer to the appropriate sections of the text or the original reference paper (i.e., Aida et al. 1992).

(6) Parameters monitored. This column lists the parameters used to assess health effects. Parameters monitored could include serum (blood) chemistry (BC), behavioral (BH), biochemical changes (BI), body weight (BW), clinical signs (CS), developmental toxicity (DX), enzyme activity (EA), food intake (FI), fetal toxicity (FX), gross necropsy (GN), hematology (HE), histopathology (HP), lethality (LE), maternal toxicity (MX), organ function (OF), ophthalmology (OP), organ weight (OW), teratogenicity (TG), urinalysis (UR), and water intake (WI).

(7) Endpoint. This column lists the endpoint examined. The major categories of health endpoints included in LSE tables and figures are death, body weight, respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, dermal, ocular, endocrine, immunological, neurological, reproductive, developmental, other noncancer, and cancer. "Other noncancer" refers to any effect (e.g., alterations in blood glucose levels) not covered in these systems. In the example of key number 51, three endpoints (body weight, hematological, and hepatic) were investigated.

(8) NOAEL. A NOAEL is the highest exposure level at which no adverse effects were seen in the organ system studied. The body weight effect reported in key number 51 is a NOAEL at 25.5 mg/kg/day. NOAELs are not reported for cancer and death; with the exception of these two endpoints, this field is left blank if no NOAEL was identified in the study.

(9) LOAEL. A LOAEL is the lowest dose used in the study that caused an adverse health effect. LOAELs have been classified into "Less Serious" and "Serious" effects. These distinctions help readers identify the levels of exposure at which adverse health effects first appear and the gradation of effects with increasing dose. A brief description of the specific endpoint used to quantify the adverse effect accompanies the LOAEL. Key number 51 reports a less serious LOAEL of 6.1 mg/kg/day for the hepatic system, which was used to derive a chronic exposure, oral MRL of 0.008 mg/kg/day (see footnote "c"). MRLs are not derived from serious LOAELs. A cancer effect level (CEL) is the lowest exposure level associated with the onset of carcinogenesis in experimental or epidemiologic studies. CELs are always considered serious effects. The LSE tables and figures do not contain NOAELs for cancer, but the text may report doses not causing measurable cancer increases. If no LOAEL/CEL values were identified in the study, this field is left blank.

(10) Reference. The complete reference citation is provided in Chapter 8 of the profile.

(11) Footnotes. Explanations of abbreviations or reference notes for data in the LSE tables are found in the footnotes. For example, footnote "c" indicates that the LOAEL of 6.1 mg/kg/day in key number 51 was used to derive an oral MRL of 0.008 mg/kg/day.

FIGURE LEGEND

See Sample LSE Figure (page D-6)

LSE figures graphically illustrate the data presented in the corresponding LSE tables. Figures help the reader quickly compare health effects according to exposure concentrations for particular exposure periods.

(13) Exposure period. The same exposure periods appear as in the LSE table. In this example, health effects observed within the chronic exposure period are illustrated.

(14) Endpoint. These are the categories of health effects for which reliable quantitative data exist. The same health effect endpoints appear in the LSE table.

(15) Levels of exposure. Concentrations or doses for each health effect in the LSE tables are graphically displayed in the LSE figures. Exposure concentration or dose is measured on the log scale "y" axis. Inhalation exposure is reported in mg/m^3 or ppm and oral exposure is reported in mg/kg/day.

(16) LOAEL. In this example, the half-shaded circle that is designated 51R identifies a LOAEL critical endpoint in the rat upon which a chronic oral exposure MRL is based. The key number 51 corresponds to the entry in the LSE table. The dashed descending arrow indicates the extrapolation from the exposure level of 6.1 mg/kg/day (see entry 51 in the sample LSE table) to the MRL of 0.008 mg/kg/day (see footnote "c" in the sample LSE table).

(17) CEL. Key number 59R is one of studies for which CELs were derived. The diamond symbol refers to a CEL for the test species (rat). The number 59 corresponds to the entry in the LSE table.

(18) Key to LSE figure. The key provides the abbreviations and symbols used in the figure.

Table 2-X. Levels of Significant Exposure to [Chemical X] – Oral (1)

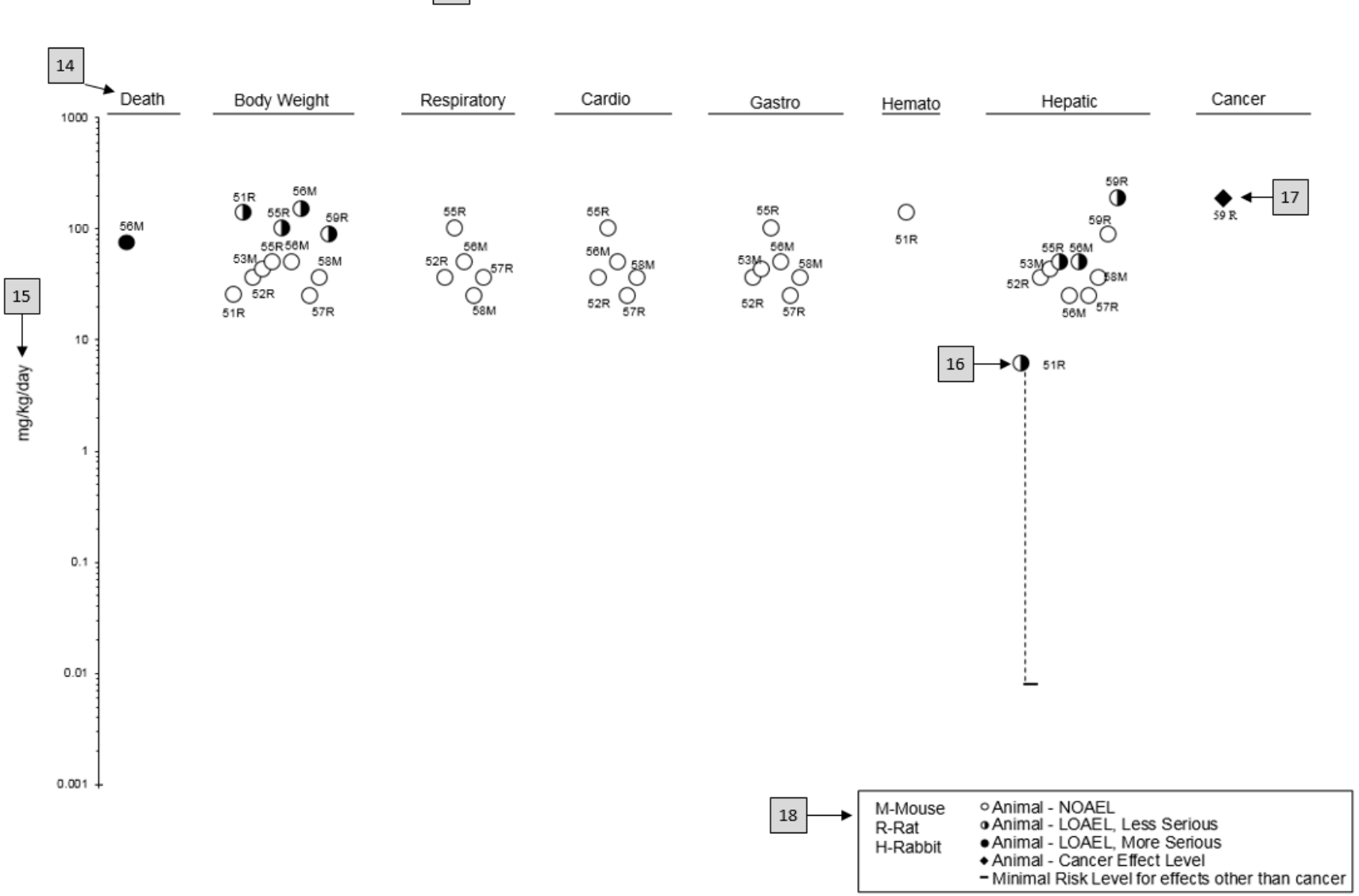
Figure key[a] (4)	Species (strain) No./group (4)	Exposure parameters (5)	Doses (mg/kg/day) (5)	Parameters monitored (6)	Endpoint (7)	NOAEL (mg/kg/day) (8)	Less serious LOAEL (mg/kg/day) (9)	Serious LOAEL (mg/kg/day) (9)	Effect
CHRONIC EXPOSURE (2)									
51 (3)	Rat (Wistar) 40 M, 40 F	2 years (F)	M: 0, 6.1, 25.5, 138.0 F: 0, 8.0, 31.7, 168.4	CS, WI, BW, OW, HE, BC, HP	Bd wt	25.5	138.0		Decreased body weight gain in males (23–25%) and females (31–39%)
					Hemato	138.0			
					Hepatic		6.1[c]		Increases in absolute and relative weights at ≥6.1/8.0 mg/kg/day after 12 months of exposure; fatty generation at ≥6.1 mg/kg/day in males and at ≥31.7 mg/kg/day in females, and granulomas in females at 31.7 and 168.4 mg/kg/day after 12, 18, or 24 months of exposure and in males at ≥6.1 mg/kg/day only after 24 months of exposure
Aida et al. 1992 (10)									
52	Rat (F344) 78 M	104 weeks (W)	0, 3.9, 20.6, 36.3	CS, BW, FI, BC, OW, HP	Hepatic	36.3			
					Renal	20.6	36.3		Increased incidence of renal tubular cell hyperplasia
					Endocr	36.3			
George et al. 2002									
59	Rat (Wistar) 58M, 58F	Lifetime (W)	M: 0, 90 F: 0, 190	BW, HP	Cancer		190 F		Increased incidence of hepatic neoplastic nodules in females only; no additional description of the tumors was provided
Tumasonis et al. 1985									

[a]The number corresponds to entries in Figure 2-x.

(11) [b]Used to derive an acute-duration oral minimal risk level (MRL) of 0.1 mg/kg/day based on the $BMDL_{05}$ of 10 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

[c]Used to derive a chronic-duration oral MRL of 0.008 mg/kg/day based on the $BMDL_{10}$ of 0.78 mg/kg/day and an uncertainty factor of 100 (10 for extrapolation from animals to humans and 10 for human variability).

Figure 2-X. Levels of Significant Exposure to [Chemical X] - Oral



APPENDIX E. QUICK REFERENCE FOR HEALTH CARE PROVIDERS

Toxicological Profiles are a unique compilation of toxicological information on a given hazardous substance. Each profile reflects a comprehensive and extensive evaluation, summary, and interpretation of available toxicologic and epidemiologic information on a substance. Health care providers treating patients potentially exposed to hazardous substances may find the following information helpful for fast answers to often-asked questions.

Primary Chapters/Sections of Interest

Chapter 1: Relevance to Public Health: The Relevance to Public Health Section provides an overview of exposure and health effects and evaluates, interprets, and assesses the significance of toxicity data to human health. A table listing minimal risk levels (MRLs) is also included in this chapter.

Chapter 2: Health Effects: Specific health effects identified in both human and animal studies are reported by type of health effect (e.g., death, hepatic, renal, immune, reproductive), route of exposure (e.g., inhalation, oral, dermal), and length of exposure (e.g., acute, intermediate, and chronic).
NOTE: Not all health effects reported in this section are necessarily observed in the clinical setting.

Pediatrics:
Section 3.2 Children and Other Populations that are Unusually Susceptible
Section 3.3 Biomarkers of Exposure and Effect

ATSDR Information Center

Phone: 1-800-CDC-INFO (800-232-4636) or 1-888-232-6348 (TTY)
Internet: http://www.atsdr.cdc.gov

The following additional materials are available online:

Case Studies in Environmental Medicine are self-instructional publications designed to increase primary health care providers' knowledge of a hazardous substance in the environment and to aid in the evaluation of potentially exposed patients (see https://www.atsdr.cdc.gov/csem/csem.html).

Managing Hazardous Materials Incidents is a three-volume set of recommendations for on-scene (prehospital) and hospital medical management of patients exposed during a hazardous materials incident (see https://www.atsdr.cdc.gov/MHMI/index.asp). Volumes I and II are planning guides to assist first responders and hospital emergency department personnel in planning for incidents that involve hazardous materials. Volume III—*Medical Management Guidelines for Acute Chemical Exposures*—is a guide for health care professionals treating patients exposed to hazardous materials.

Fact Sheets (ToxFAQs™) provide answers to frequently asked questions about toxic substances (see https://www.atsdr.cdc.gov/toxfaqs/Index.asp).

Other Agencies and Organizations

The National Center for Environmental Health (NCEH) focuses on preventing or controlling disease, injury, and disability related to the interactions between people and their environment outside the workplace. Contact: NCEH, Mailstop F-29, 4770 Buford Highway, NE, Atlanta, GA 30341-3724 • Phone: 770-488-7000 • FAX: 770-488-7015 • Web Page: https://www.cdc.gov/nceh/.

The National Institute for Occupational Safety and Health (NIOSH) conducts research on occupational diseases and injuries, responds to requests for assistance by investigating problems of health and safety in the workplace, recommends standards to the Occupational Safety and Health Administration (OSHA) and the Mine Safety and Health Administration (MSHA), and trains professionals in occupational safety and health. Contact: NIOSH, 395 E Street, S.W., Suite 9200, Patriots Plaza Building, Washington, DC 20201 • Phone: 202-245-0625 or 1-800-CDC-INFO (800-232-4636) • Web Page: https://www.cdc.gov/niosh/.

The National Institute of Environmental Health Sciences (NIEHS) is the principal federal agency for biomedical research on the effects of chemical, physical, and biologic environmental agents on human health and well-being. Contact: NIEHS, PO Box 12233, 104 T.W. Alexander Drive, Research Triangle Park, NC 27709 • Phone: 919-541-3212 • Web Page: https://www.niehs.nih.gov/.

Clinical Resources (Publicly Available Information)

The Association of Occupational and Environmental Clinics (AOEC) has developed a network of clinics in the United States to provide expertise in occupational and environmental issues. Contact: AOEC, 1010 Vermont Avenue, NW, #513, Washington, DC 20005 • Phone: 202-347-4976 • FAX: 202-347-4950 • e-mail: AOEC@AOEC.ORG • Web Page: http://www.aoec.org/.

The American College of Occupational and Environmental Medicine (ACOEM) is an association of physicians and other health care providers specializing in the field of occupational and environmental medicine. Contact: ACOEM, 25 Northwest Point Boulevard, Suite 700, Elk Grove Village, IL 60007-1030 • Phone: 847-818-1800 • FAX: 847-818-9266 • Web Page: http://www.acoem.org/.

The American College of Medical Toxicology (ACMT) is a nonprofit association of physicians with recognized expertise in medical toxicology. Contact: ACMT, 10645 North Tatum Boulevard, Suite 200-111, Phoenix AZ 85028 • Phone: 844-226-8333 • FAX: 844-226-8333 • Web Page: http://www.acmt.net.

The Pediatric Environmental Health Specialty Units (PEHSUs) is an interconnected system of specialists who respond to questions from public health professionals, clinicians, policy makers, and the public about the impact of environmental factors on the health of children and reproductive-aged adults. Contact information for regional centers can be found at http://pehsu.net/findhelp.html.

The American Association of Poison Control Centers (AAPCC) provide support on the prevention and treatment of poison exposures. Contact: AAPCC, 515 King Street, Suite 510, Alexandria VA 22314 • Phone: 701-894-1858 • Poison Help Line: 1-800-222-1222 • Web Page: http://www.aapcc.org/.

APPENDIX F. GLOSSARY

Absorption—The process by which a substance crosses biological membranes and enters systemic circulation. Absorption can also refer to the taking up of liquids by solids, or of gases by solids or liquids.

Acute Exposure—Exposure to a chemical for a duration of ≤14 days, as specified in the Toxicological Profiles.

Adsorption—The adhesion in an extremely thin layer of molecules (as of gases, solutes, or liquids) to the surfaces of solid bodies or liquids with which they are in contact.

Adsorption Coefficient (K_{oc})—The ratio of the amount of a chemical adsorbed per unit weight of organic carbon in the soil or sediment to the concentration of the chemical in solution at equilibrium.

Adsorption Ratio (Kd)—The amount of a chemical adsorbed by sediment or soil (i.e., the solid phase) divided by the amount of chemical in the solution phase, which is in equilibrium with the solid phase, at a fixed solid/solution ratio. It is generally expressed in micrograms of chemical sorbed per gram of soil or sediment.

Benchmark Dose (BMD) or Benchmark Concentration (BMC)—is the dose/concentration corresponding to a specific response level estimate using a statistical dose-response model applied to either experimental toxicology or epidemiology data. For example, a BMD_{10} would be the dose corresponding to a 10% benchmark response (BMR). The BMD is determined by modeling the dose-response curve in the region of the dose-response relationship where biologically observable data are feasible. The BMDL or BMCL is the 95% lower confidence limit on the BMD or BMC.

Bioconcentration Factor (BCF)—The quotient of the concentration of a chemical in aquatic organisms at a specific time or during a discrete time period of exposure divided by the concentration in the surrounding water at the same time or during the same period.

Biomarkers—Indicators signaling events in biologic systems or samples, typically classified as markers of exposure, effect, and susceptibility.

Cancer Effect Level (CEL)—The lowest dose of a chemical in a study, or group of studies, that produces significant increases in the incidence of cancer (or tumors) between the exposed population and its appropriate control.

Carcinogen—A chemical capable of inducing cancer.

Case-Control Study—A type of epidemiological study that examines the relationship between a particular outcome (disease or condition) and a variety of potential causative agents (such as toxic chemicals). In a case-control study, a group of people with a specified and well-defined outcome is identified and compared to a similar group of people without the outcome.

Case Report—A report that describes a single individual with a particular disease or exposure. These reports may suggest some potential topics for scientific research, but are not actual research studies.

Case Series—Reports that describe the experience of a small number of individuals with the same disease or exposure. These reports may suggest potential topics for scientific research, but are not actual research studies.

Ceiling Value—A concentration that must not be exceeded.

Chronic Exposure—Exposure to a chemical for ≥365 days, as specified in the Toxicological Profiles.

Clastogen—A substance that causes breaks in chromosomes resulting in addition, deletion, or rearrangement of parts of the chromosome.

Cohort Study—A type of epidemiological study of a specific group or groups of people who have had a common insult (e.g., exposure to an agent suspected of causing disease or a common disease) and are followed forward from exposure to outcome, and who are disease-free at start of follow-up. Often, at least one exposed group is compared to one unexposed group, while in other cohorts, exposure is a continuous variable and analyses are directed towards analyzing an exposure-response coefficient.

Cross-sectional Study—A type of epidemiological study of a group or groups of people that examines the relationship between exposure and outcome to a chemical or to chemicals at a specific point in time.

Data Needs—Substance-specific informational needs that, if met, would reduce the uncertainties of human health risk assessment.

Developmental Toxicity—The occurrence of adverse effects on the developing organism that may result from exposure to a chemical prior to conception (either parent), during prenatal development, or postnatally to the time of sexual maturation. Adverse developmental effects may be detected at any point in the life span of the organism.

Dose-Response Relationship—The quantitative relationship between the amount of exposure to a toxicant and the incidence of the response or amount of the response.

Embryotoxicity and Fetotoxicity—Any toxic effect on the conceptus as a result of prenatal exposure to a chemical; the distinguishing feature between the two terms is the stage of development during which the effect occurs. Effects include malformations and variations, altered growth, and *in utero* death.

Epidemiology—The investigation of factors that determine the frequency and distribution of disease or other health-related conditions within a defined human population during a specified period.

Excretion—The process by which metabolic waste products are removed from the body.

Genotoxicity—A specific adverse effect on the genome of living cells that, upon the duplication of affected cells, can be expressed as a mutagenic, clastogenic, or carcinogenic event because of specific alteration of the molecular structure of the genome.

Half-life—A measure of rate for the time required to eliminate one-half of a quantity of a chemical from the body or environmental media.

Health Advisory—An estimate of acceptable drinking water levels for a chemical substance derived by EPA and based on health effects information. A health advisory is not a legally enforceable federal standard, but serves as technical guidance to assist federal, state, and local officials.

Immediately Dangerous to Life or Health (IDLH)—A condition that poses a threat of life or health, or conditions that pose an immediate threat of severe exposure to contaminants that are likely to have adverse cumulative or delayed effects on health.

Immunotoxicity—Adverse effect on the functioning of the immune system that may result from exposure to chemical substances.

Incidence—The ratio of new cases of individuals in a population who develop a specified condition to the total number of individuals in that population who could have developed that condition in a specified time period.

Intermediate Exposure—Exposure to a chemical for a duration of 15–364 days, as specified in the Toxicological Profiles.

***In Vitro*—**Isolated from the living organism and artificially maintained, as in a test tube.

***In Vivo*—**Occurring within the living organism.

Lethal Concentration$_{(LO)}$ (LC_{LO})—The lowest concentration of a chemical in air that has been reported to have caused death in humans or animals.

Lethal Concentration$_{(50)}$ (LC_{50})—A calculated concentration of a chemical in air to which exposure for a specific length of time is expected to cause death in 50% of a defined experimental animal population.

Lethal Dose$_{(LO)}$ (LD_{Lo})—The lowest dose of a chemical introduced by a route other than inhalation that has been reported to have caused death in humans or animals.

Lethal Dose$_{(50)}$ (LD_{50})—The dose of a chemical that has been calculated to cause death in 50% of a defined experimental animal population.

Lethal Time$_{(50)}$ (LT_{50})—A calculated period of time within which a specific concentration of a chemical is expected to cause death in 50% of a defined experimental animal population.

Lowest-Observed-Adverse-Effect Level (LOAEL)—The lowest exposure level of chemical in a study, or group of studies, that produces statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control.

Lymphoreticular Effects—Represent morphological effects involving lymphatic tissues such as the lymph nodes, spleen, and thymus.

Malformations—Permanent structural changes that may adversely affect survival, development, or function.

Metabolism—Process in which chemical substances are biotransformed in the body that could result in less toxic and/or readily excreted compounds or produce a biologically active intermediate.

Minimal Risk Level (MRL)—An estimate of daily human exposure to a hazardous substance that is likely to be without an appreciable risk of adverse noncancer health effects over a specified route and duration of exposure.

Modifying Factor (MF)—A value (greater than zero) that is applied to the derivation of a Minimal Risk Level (MRL) to reflect additional concerns about the database that are not covered by the uncertainty factors. The default value for a MF is 1.

Morbidity—The state of being diseased; the morbidity rate is the incidence or prevalence of a disease in a specific population.

Mortality—Death; the mortality rate is a measure of the number of deaths in a population during a specified interval of time.

Mutagen—A substance that causes mutations, which are changes in the DNA sequence of a cell's DNA. Mutations can lead to birth defects, miscarriages, or cancer.

Necropsy—The gross examination of the organs and tissues of a dead body to determine the cause of death or pathological conditions.

Neurotoxicity—The occurrence of adverse effects on the nervous system following exposure to a hazardous substance.

No-Observed-Adverse-Effect Level (NOAEL)—The dose of a chemical at which there were no statistically or biologically significant increases in frequency or severity of adverse effects seen between the exposed population and its appropriate control. Although effects may be produced at this dose, they are not considered to be adverse.

Octanol-Water Partition Coefficient (K_{ow})—The equilibrium ratio of the concentrations of a chemical in *n*-octanol and water, in dilute solution.

Odds Ratio (OR)—A means of measuring the association between an exposure (such as toxic substances and a disease or condition) that represents the best estimate of relative risk (risk as a ratio of the incidence among subjects exposed to a particular risk factor divided by the incidence among subjects who were not exposed to the risk factor). An odds ratio that is greater than 1 is considered to indicate greater risk of disease in the exposed group compared to the unexposed group.

Permissible Exposure Limit (PEL)—An Occupational Safety and Health Administration (OSHA) regulatory limit on the amount or concentration of a substance not to be exceeded in workplace air averaged over any 8-hour work shift of a 40-hour workweek.

Pesticide—General classification of chemicals specifically developed and produced for use in the control of agricultural and public health pests (insects or other organisms harmful to cultivated plants or animals).

Pharmacokinetics—The dynamic behavior of a material in the body, used to predict the fate (disposition) of an exogenous substance in an organism. Utilizing computational techniques, it provides the means of studying the absorption, distribution, metabolism, and excretion of chemicals by the body.

Pharmacokinetic Model—A set of equations that can be used to describe the time course of a parent chemical or metabolite in an animal system. There are two types of pharmacokinetic models: data-based and physiologically-based. A data-based model divides the animal system into a series of compartments, which, in general, do not represent real, identifiable anatomic regions of the body, whereas the physiologically-based model compartments represent real anatomic regions of the body.

Physiologically Based Pharmacodynamic (PBPD) Model—A type of physiologically based dose-response model that quantitatively describes the relationship between target tissue dose and toxic endpoints. These models advance the importance of physiologically based models in that they clearly describe the biological effect (response) produced by the system following exposure to an exogenous substance.

Physiologically Based Pharmacokinetic (PBPK) Model—A type of physiologically based dose-response model that is comprised of a series of compartments representing organs or tissue groups with realistic weights and blood flows. These models require a variety of physiological information, including tissue volumes, blood flow rates to tissues, cardiac output, alveolar ventilation rates, and possibly membrane permeabilities. The models also utilize biochemical information, such as blood:air partition coefficients, and metabolic parameters. PBPK models are also called biologically based tissue dosimetry models.

Prevalence—The number of cases of a disease or condition in a population at one point in time.

Prospective Study—A type of cohort study in which a group is followed over time and the pertinent observations are made on events occurring after the start of the study.

Recommended Exposure Limit (REL)—A National Institute for Occupational Safety and Health (NIOSH) time-weighted average (TWA) concentration for up to a 10-hour workday during a 40-hour workweek.

Reference Concentration (RfC)—An estimate (with uncertainty spanning perhaps an order of magnitude) of a continuous inhalation exposure to the human population (including sensitive subgroups) that is likely to be without an appreciable risk of deleterious noncancer health effects during a lifetime. The inhalation RfC is expressed in units of mg/m^3 or ppm.

Reference Dose (RfD)—An estimate (with uncertainty spanning perhaps an order of magnitude) of the daily oral exposure of the human population to a potential hazard that is likely to be without risk of deleterious noncancer health effects during a lifetime. The oral RfD is expressed in units of mg/kg/day.

Reportable Quantity (RQ)—The quantity of a hazardous substance that is considered reportable under the Comprehensive Environmental Response, Compensation, and Liability Act (CERCLA). RQs are (1) ≥1 pound or (2) for selected substances, an amount established by regulation either under CERCLA or under Section 311 of the Clean Water Act. Quantities are measured over a 24-hour period.

Reproductive Toxicity—The occurrence of adverse effects on the reproductive system that may result from exposure to a hazardous substance. The toxicity may be directed to the reproductive organs and/or the related endocrine system. The manifestation of such toxicity may be noted as alterations in sexual behavior, fertility, pregnancy outcomes, or modifications in other functions that are dependent on the integrity of this system.

Retrospective Study—A type of cohort study based on a group of persons known to have been exposed at some time in the past. Data are collected from routinely recorded events, up to the time the study is undertaken. Retrospective studies are limited to causal factors that can be ascertained from existing records and/or examining survivors of the cohort.

Risk—The possibility or chance that some adverse effect will result from a given exposure to a hazardous substance.

Risk Factor—An aspect of personal behavior or lifestyle, an environmental exposure, existing health condition, or an inborn or inherited characteristic that is associated with an increased occurrence of disease or other health-related event or condition.

Risk Ratio/Relative Risk—The ratio of the risk among persons with specific risk factors compared to the risk among persons without risk factors. A risk ratio that is greater than 1 indicates greater risk of disease in the exposed group compared to the unexposed group.

Short-Term Exposure Limit (STEL)—A STEL is a 15-minute TWA exposure that should not be exceeded at any time during a workday.

Standardized Mortality Ratio (SMR)—A ratio of the observed number of deaths and the expected number of deaths in a specific standard population.

Target Organ Toxicity—This term covers a broad range of adverse effects on target organs or physiological systems (e.g., renal, cardiovascular) extending from those arising through a single limited exposure to those assumed over a lifetime of exposure to a chemical.

Teratogen—A chemical that causes structural defects that affect the development of an organism.

Threshold Limit Value (TLV)—An American Conference of Governmental Industrial Hygienists (ACGIH) concentration of a substance to which it is believed that nearly all workers may be repeatedly exposed, day after day, for a working lifetime without adverse effect. The TLV may be expressed as a Time-Weighted Average (TLV-TWA), as a Short-Term Exposure Limit (TLV-STEL), or as a ceiling limit (TLV-C).

Time-Weighted Average (TWA)—An average exposure within a given time period.

Toxicokinetic—The absorption, distribution, metabolism, and elimination of toxic compounds in the living organism.

Toxics Release Inventory (TRI)—The TRI is an EPA program that tracks toxic chemical releases and pollution prevention activities reported by industrial and federal facilities.

Uncertainty Factor (UF)—A factor used in operationally deriving the Minimal Risk Level (MRL), Reference Dose (RfD), or Reference Concentration (RfC) from experimental data. UFs are intended to account for (1) the variation in sensitivity among the members of the human population, (2) the uncertainty in extrapolating animal data to the case of human, (3) the uncertainty in extrapolating from data obtained in a study that is of less than lifetime exposure, and (4) the uncertainty in using lowest-observed-adverse-effect level (LOAEL) data rather than no-observed-adverse-effect level (NOAEL) data. A default for each individual UF is 10; if complete certainty in data exists, a value of 1 can be used; however, a reduced UF of 3 may be used on a case-by-case basis (3 being the approximate logarithmic average of 10 and 1).

Xenobiotic—Any substance that is foreign to the biological system.

APPENDIX G. ACRONYMS, ABBREVIATIONS, AND SYMBOLS

AAPCC	American Association of Poison Control Centers
ACGIH	American Conference of Governmental Industrial Hygienists
ACOEM	American College of Occupational and Environmental Medicine
ACMT	American College of Medical Toxicology
ADI	acceptable daily intake
ADME	absorption, distribution, metabolism, and excretion
AEGL	Acute Exposure Guideline Level
AIC	Akaike's information criterion
AIHA	American Industrial Hygiene Association
ALT	alanine aminotransferase
AOEC	Association of Occupational and Environmental Clinics
AP	alkaline phosphatase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
AWQC	Ambient Water Quality Criteria
BCF	bioconcentration factor
BMD/C	benchmark dose or benchmark concentration
BMD_X	dose that produces a X% change in response rate of an adverse effect
$BMDL_X$	95% lower confidence limit on the BMD_X
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
C	centigrade
CAA	Clean Air Act
CAS	Chemical Abstract Services
CDC	Centers for Disease Control and Prevention
CEL	cancer effect level
CERCLA	Comprehensive Environmental Response, Compensation, and Liability Act
CFR	Code of Federal Regulations
Ci	curie
CI	confidence interval
cm	centimeter
CPSC	Consumer Products Safety Commission
CWA	Clean Water Act
DNA	deoxyribonucleic acid
DOD	Department of Defense
DOE	Department of Energy
DWEL	drinking water exposure level
EAFUS	Everything Added to Food in the United States
ECG/EKG	electrocardiogram
EEG	electroencephalogram
EPA	Environmental Protection Agency
ERPG	emergency response planning guidelines
F	Fahrenheit
F1	first-filial generation
FDA	Food and Drug Administration
FIFRA	Federal Insecticide, Fungicide, and Rodenticide Act
FR	Federal Register

FSH	follicle stimulating hormone
g	gram
GC	gas chromatography
gd	gestational day
GGT	γ-glutamyl transferase
GRAS	generally recognized as safe
HEC	human equivalent concentration
HED	human equivalent dose
HHS	Department of Health and Human Services
HPLC	high-performance liquid chromatography
HSDB	Hazardous Substance Data Bank
IARC	International Agency for Research on Cancer
IDLH	immediately dangerous to life and health
IRIS	Integrated Risk Information System
Kd	adsorption ratio
kg	kilogram
kkg	kilokilogram; 1 kilokilogram is equivalent to 1,000 kilograms and 1 metric ton
K_{oc}	organic carbon partition coefficient
K_{ow}	octanol-water partition coefficient
L	liter
LC	liquid chromatography
LC_{50}	lethal concentration, 50% kill
LC_{Lo}	lethal concentration, low
LD_{50}	lethal dose, 50% kill
LD_{Lo}	lethal dose, low
LDH	lactic dehydrogenase
LH	luteinizing hormone
LOAEL	lowest-observed-adverse-effect level
LSE	Level of Significant Exposure
LT_{50}	lethal time, 50% kill
m	meter
mCi	millicurie
MCL	maximum contaminant level
MCLG	maximum contaminant level goal
MF	modifying factor
mg	milligram
mL	milliliter
mm	millimeter
mmHg	millimeters of mercury
mmol	millimole
MRL	Minimal Risk Level
MS	mass spectrometry
MSHA	Mine Safety and Health Administration
Mt	metric ton
NAAQS	National Ambient Air Quality Standard
NAS	National Academy of Science
NCEH	National Center for Environmental Health
ND	not detected
ng	nanogram
NHANES	National Health and Nutrition Examination Survey
NIEHS	National Institute of Environmental Health Sciences

NIOSH	National Institute for Occupational Safety and Health
NLM	National Library of Medicine
nm	nanometer
nmol	nanomole
NOAEL	no-observed-adverse-effect level
NPL	National Priorities List
NR	not reported
NRC	National Research Council
NS	not specified
NTP	National Toxicology Program
OR	odds ratio
OSHA	Occupational Safety and Health Administration
PAC	Protective Action Criteria
PAH	polycyclic aromatic hydrocarbon
PBPD	physiologically based pharmacodynamic
PBPK	physiologically based pharmacokinetic
PEHSU	Pediatric Environmental Health Specialty Unit
PEL	permissible exposure limit
PEL-C	permissible exposure limit-ceiling value
pg	picogram
PND	postnatal day
POD	point of departure
ppb	parts per billion
ppbv	parts per billion by volume
ppm	parts per million
ppt	parts per trillion
REL	recommended exposure level/limit
REL-C	recommended exposure level-ceiling value
RfC	reference concentration
RfD	reference dose
RNA	ribonucleic acid
SARA	Superfund Amendments and Reauthorization Act
SCE	sister chromatid exchange
SD	standard deviation
SE	standard error
SGOT	serum glutamic oxaloacetic transaminase (same as aspartate aminotransferase or AST)
SGPT	serum glutamic pyruvic transaminase (same as alanine aminotransferase or ALT)
SIC	standard industrial classification
SMR	standardized mortality ratio
sRBC	sheep red blood cell
STEL	short term exposure limit
TLV	threshold limit value
TLV-C	threshold limit value-ceiling value
TRI	Toxics Release Inventory
TSCA	Toxic Substances Control Act
TWA	time-weighted average
UF	uncertainty factor
U.S.	United States
USDA	United States Department of Agriculture
USGS	United States Geological Survey
USNRC	U.S. Nuclear Regulatory Commission

VOC	volatile organic compound
WBC	white blood cell
WHO	World Health Organization
>	greater than
≥	greater than or equal to
=	equal to
<	less than
≤	less than or equal to
%	percent
α	alpha
β	beta
γ	gamma
δ	delta
μm	micrometer
μg	microgram
q_1^*	cancer slope factor
–	negative
+	positive
(+)	weakly positive result
(–)	weakly negative result