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Provisional Peer-Reviewed Toxicity Values for

Carbonyl Sulfide (Carbon Oxide Sulfide)
(CASRN 463-58-1)

Superfund Health Risk Technical Support Center
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COMMONLY USED ABBREVIATIONS AND ACRONYMS

α2u-g	alpha 2u-globulin
ACGIH	American Conference of Governmental Industrial Hygienists
AIC	Akaike's information criterion
ALD	approximate lethal dosage
ALT	alanine aminotransferase
AST	aspartate aminotransferase
atm	atmosphere
ATSDR	Agency for Toxic Substances and Disease Registry
BMD	benchmark dose
BMDL	benchmark dose lower confidence limit
BMDS	Benchmark Dose Software
BMR	benchmark response
BUN	blood urea nitrogen
BW	body weight
CA	chromosomal aberration
CAS	Chemical Abstracts Service
CASRN	Chemical Abstracts Service Registry Number
CBI	covalent binding index
CHO	Chinese hamster ovary (cell line cells)
CL	confidence limit
CNS	central nervous system
CPN	chronic progressive nephropathy
CYP450	cytochrome P450
DAF	dosimetric adjustment factor
DEN	diethylnitrosamine
DMSO	dimethylsulfoxide
DNA	deoxyribonucleic acid
EPA	Environmental Protection Agency
FDA	Food and Drug Administration
FEV_1	forced expiratory volume of 1 second
GD	gestation day
GDH	glutamate dehydrogenase
GGT	γ-glutamyl transferase
GSH	glutathione
GST	glutathione-S-transferase
Hb/g-A	animal blood-gas partition coefficient
Hb/g-H	human blood-gas partition coefficient
HEC	human equivalent concentration
HED	human equivalent dose
i.p.	intraperitoneal
IRIS	Integrated Risk Information System
IVF	in vitro fertilization
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LOAEL	lowest-observed-adverse-effect level
MN	micronuclei
MNPCE	micronucleated polychromatic erythrocyte
MOA	mode of action
MTD	maximum tolerated dose
NAG	N-acetyl-β-D-glucosaminidase
NCEA	National Center for Environmental Assessment
NCI	National Cancer Institute
NOAEL	no-observed-adverse-effect level
NTP	National Toxicology Program
NZW	New Zealand white (rabbit breed)
OCT	ornithine carbamoyl transferase
ORD	Office of Research and Development
PBPK	physiologically based pharmacokinetic
PCNA	proliferating cell nuclear antigen
PND	postnatal day
POD	point of departure
POD_{ADJ}	duration-adjusted POD
QSAR	quantitative structure-activity relationship
RBC	red blood cell
RDS	replicative DNA synthesis
RfC	inhalation reference concentration
RfD	oral reference dose
RGDR	regional gas dose ratio
RNA	ribonucleic acid
SAR	structure activity relationship
SCE	sister chromatid exchange
SD	standard deviation
SDH	sorbitol dehydrogenase
SE	standard error
SGOT	glutamic oxaloacetic transaminase, also known as AST
SGPT	glutamic pyruvic transaminase, also known as ALT
SSD	systemic scleroderma
TCA	trichloroacetic acid
TCE	trichloroethylene
TWA	time-weighted average
UF	uncertainty factor
UF_A	interspecies uncertainty factor
UF_H	intraspecies uncertainty factor
UF_S	subchronic-to-chronic uncertainty factor
UF_D	database uncertainty factor
U.S.	United States of America
WBC	white blood cell

PROVISIONAL PEER-REVIEWED TOXICITY VALUES FOR CARBONYL SULFIDE (CARBON OXIDE SULFIDE; CASRN 463 58 1)

BACKGROUND

A Provisional Peer-Reviewed Toxicity Value (PPRTV) is defined as a toxicity value derived for use in the Superfund Program. PPRTVs are derived after a review of the relevant scientific literature using established Agency guidance on human health toxicity value derivations. All PPRTV assessments receive internal review by a standing panel of National Center for Environment Assessment (NCEA) scientists and an independent external peer review by three scientific experts.

The purpose of this document is to provide support for the hazard and dose-response assessment pertaining to chronic and subchronic exposures to substances of concern, to present the major conclusions reached in the hazard identification and derivation of the PPRTVs, and to characterize the overall confidence in these conclusions and toxicity values. It is not intended to be a comprehensive treatise on the chemical or toxicological nature of this substance.

The PPRTV review process provides needed toxicity values in a quick turnaround timeframe while maintaining scientific quality. PPRTV assessments are updated approximately on a 5-year cycle for new data or methodologies that might impact the toxicity values or characterization of potential for adverse human health effects and are revised as appropriate. It is important to utilize the PPRTV database (http://hhpprtv.ornl.gov) to obtain the current information available. When a final Integrated Risk Information System (IRIS) assessment is made publicly available on the Internet (http://www.epa.gov/iris), the respective PPRTVs are removed from the database.

DISCLAIMERS

The PPRTV document provides toxicity values and information about the adverse effects of the chemical and the evidence on which the value is based, including the strengths and limitations of the data. All users are advised to review the information provided in this document to ensure that the PPRTV used is appropriate for the types of exposures and circumstances at the site in question and the risk management decision that would be supported by the risk assessment.

Other U.S. Environmental Protection Agency (EPA) programs or external parties who may choose to use PPRTVs are advised that Superfund resources will not generally be used to respond to challenges, if any, of PPRTVs used in a context outside of the Superfund program.

This document has been reviewed in accordance with U.S. EPA policy and approved for publication. Mention of trade names or commercial products does not constitute endorsement or recommendation for use.

QUESTIONS REGARDING PPRTVs

Questions regarding the contents and appropriate use of this PPRTV assessment should be directed to the EPA Office of Research and Development's National Center for Environmental Assessment, Superfund Health Risk Technical Support Center (513-569-7300).

INTRODUCTION

Carbonyl sulfide is ubiquitous in the atmosphere (HSDB, 2007). This compound occurs naturally in food and is a byproduct of aerobic metabolism of sulfur-containing compounds. Natural emissions of carbonyl sulfide occur from microbes, volcanoes, and the burning of vegetation. Carbonyl sulfide can also be an impurity in natural gas and is a major contributor of sulfur in the atmosphere. Anthropogenic sources of carbonyl sulfide include releases from the manufacture of fuels, refinery gases, and carbon disulfide. Carbonyl sulfide is also a combustion product from sulfur-containing fuels (Weil et al., 2006). Carbonyl sulfide is used as a chemical intermediate for thiocarbamate herbicides and aliphatic polyureas (HSDB, 2007), and as an effective grain fumigant (Bartholomaeus and Haritos, 2005). Anthropogenic sources of carbonyl sulfide are estimated to be less than one-third of that from natural sources (HSDB, 2007). Carbonyl sulfide is listed as a hazardous air pollutant (HAP) under the Clean Air Act as amended in 1990. Carbonyl sulfide has a high vapor pressure and is expected to be present in the atmosphere entirely as a gas. The water solubility indicates that the compound may be found as a water contaminant. The empirical formula for carbonyl sulfide is COS (see Figure 1). A table of physicochemical properties for carbonyl sulfide is provided below (see Table 1).

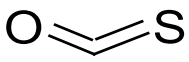

Figure 1. Carbonyl Sulfide Structure (CASRN 463-58-1)

Table 1. Physicochemical Properties of Carbonyl Sulfide (CASRN 463-58-1)[a]

Property (unit)	Value
Boiling point (°C)	−50
Melting point (°C)	−138.8
Density (g/cm^3)	1.028
Vapor pressure (mm Hg at 25°C)	9,034[b]
pH (unitless)	ND
Solubility in water (g/100 mL at 25°C)	1.22
Relative vapor density (air = 1)	2.1
Molecular weight (g/mol)	60.08

[a]HSDB (2007).
[b]Sigma-Aldrich (2014).

ND = no data.

A summary of available toxicity values for carbonyl sulfide from U.S. EPA and other agencies/organizations is provided in Table 2.

Table 2. Summary of Available Toxicity Values for Carbonyl Sulfide (CASRN 463-58-1)

Source/Parameter[a,b]	Value (applicability)	Notes	Reference
Noncancer			
ACGIH (TLV-TWA)	5 ppm (12 mg/m^3)	Based on central nervous system impairment.	ACGIH (2015)
ATSDR	NV	NA	ATSDR (2014)
Cal/EPA	NV	NA	Cal/EPA (2014); Cal/EPA (2015a); Cal/EPA (2015b)
NIOSH	NV	NA	NIOSH (2015)
OSHA	NV	NA	OSHA (2006); OSHA (2011)
IRIS	NV	ND	U.S. EPA (2015)
DWSHA	NV	NA	U.S. EPA (2012a)
HEAST	NV	NA	U.S. EPA (2011)
CARA HEEP	NV	NA	U.S. EPA (1994a)
WHO	NV	NA	WHO (2015)
Cancer			
IRIS	NV	ND	U.S. EPA (2015)
HEAST	NV	NA	U.S. EPA (2011)
DWSHA	NV	NA	U.S. EPA (2012a)
IARC	NV	ND	IARC (2015)
NTP	NV	NA	NTP (2014)
Cal/EPA	NV	NA	Cal/EPA (2015a); Cal/EPA (2011); Cal/EPA (2015b)
ACGIH (WOE)	NV	Sufficient data were not available to recommend a carcinogenicity notation.	ACGIH (2015)

[a]Sources: ACGIH = American Conference of Governmental Industrial Hygienists; ATSDR = Agency for Toxic Substances and Disease Research; Cal/EPA = California Environmental Protection Agency; CARA = Chemical Assessments and Related Activities; DWSHA = Drinking Water Standards and Health Advisories; HEAST = Health Effects Assessment Summary Tables; HEEP = Health and Environmental Effects Profiles; IARC = International Agency for Research on Cancer; IRIS = Integrated Risk Information System; NIOSH = National Institute for Occupational Safety and Health; NTP = National Toxicology Program; OSHA = Occupational Safety and Health Administration; WHO = World Health Organization.
[b]Parameters: TLV-TWA = threshold limit value-time weighted average; WOE = cancer weight of evidence .

NA = not applicable; NV = not available; ND = no data.

Literature searches were conducted through June 2015 for studies relevant to the derivation of provisional toxicity values for carbonyl sulfide (CASRN 463-58-1). Searches were conducted using U.S. EPA's Health and Environmental Research Online (HERO) database of scientific literature. HERO searches the following databases: PubMed, ToxLine (including TSCATS1), and Web of Science. The following databases were searched outside of HERO for health-related values: ACGIH, ATSDR, Cal/EPA, U.S. EPA IRIS, U.S. EPA HEAST, U.S. EPA OW, U.S. EPA TSCATS2/TSCATS8e, NIOSH, NTP, OSHA, and RTECS.

REVIEW OF POTENTIALLY RELEVANT DATA (NONCANCER AND CANCER)

Tables 3A and 3B provide an overview of the relevant database for carbonyl sulfide and include all potentially relevant repeated-dose short-term-, subchronic-, and chronic-duration studies. Principal studies are identified in bold. The phrase "statistical significance," used throughout the document, indicates a p-value of < 0.05, unless otherwise noted.

Table 3A. Summary of Potentially Relevant Noncancer Data for Carbonyl Sulfide (CASRN 463-58-1)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Human								
1. Oral (mg/kg-d)[a]								
ND								
2. Inhalation (mg/m^3)[a]								
ND								
Animal								
1. Oral (mg/kg-d)[a]								
ND								
2. Inhalation (mg/m^3)[a]								
Short-term	10 M/10 F, S-D rat, 6 hr/d, 5 d/wk, 2 wk (whole-body inhalation chamber)	0, 51, 151, 253, or 453 ppm HEC: 0, 22, 66, 111, 199	Methemoglobinemia increased in males and females at concentrations of 66 and above	22	NDr	66	Monsanto (1985)	NPR
Short-term	10 M/10 F, F344 rat, 6 hr/d, 5 d/wk, 2 wk (whole-body chamber)	0, 300, 400, or 500 ppm HEC: 0, 132, 176, 219	Necrotic brain lesions and decreased grip strength	132	NDr	176	Morgan et al. (2004)	PR
Short-term	15 M/0 F, F344 rat, 6 hr/d, 5 d/wk, 2 wk (whole-body chamber)	0, 300, 400 ppm HEC: 0, 132, 176	Decreased amplitudes of BAER peak amplitudes, decreased motor activity and grip strength, slightly abnormal gait, loss of forelimb proprioceptive placing response, and gross brain lesions	132	NDr	176	Herr et al. (2007)	PR

Table 3A. Summary of Potentially Relevant Noncancer Data for Carbonyl Sulfide (CASRN 463-58-1)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Subchronic	Uncertain sex, white Danish rabbit, continuous, 7 wk (whole-body chamber)	0, 54 ppm HEC: 0, 130	On D 5 of exposure, three exposed rabbits died and two rabbits were moribund with signs of severe neurotoxicity	NDr	NDr	NDr	Hugod (1981); Hugod and Astrup (1980); Kamstrup and Hugod (1979) Widely fluctuating concentrations; all rabbits that died did so on the same day.	PR
Subchronic	**10 M/10 F, F344 rat, 6 hr/d, 5 d/wk, 12 wk (whole-body chamber)**	**0, 300, or 400 ppm** **HEC: 0, 132, 176**	**Necrosis of parietal cortex; and neuronal loss and microgliosis in parietal cortex (assessed by light microscopy)**	**132 (male)** **132 (female)**	**125 (male)** **121 (female)** (neuronal loss and microgliosis)	**176 (male)** **176 (female)**	**Morgan et al. (2004)**	**PR, PS**
Subchronic	6 M/6 F, F344 rat, 6 hr/d, 5 d/wk, 4, 8, or 12 wk (whole-body chamber)	0, 200, 300 or 400 ppm HEC: 0, 87.8, 132, 176	Brain lesions in the posterior colliculus, anterior olivary nucleus, and parietal cortex (assessed by magnetic resonance microscopy)	132	NDr	176 (brain lesions)	Sills et al. (2004) Incidence data not reported	PR
Subchronic	16 M/16 F, F344 rat, 6 hr/d, 5 d/wk, 12 wk (whole-body chamber)	0, 200, 300, or 400 ppm HEC: 0, 87.8, 132, 176	Changes in BAER peak amplitudes and SEP peak amplitudes and latencies	132	175	176 (alterations in BAERs and SEPs)	Herr et al. (2007) Responses combined for males and females; only SEP1 responses successfully modeled	PR
Chronic	ND							

Table 3A. Summary of Potentially Relevant Noncancer Data for Carbonyl Sulfide (CASRN 463-58-1)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Reproductive Study 1	0 M/24 F, S-D rat, one-generation study, 6 hr/d, 5 d/wk, ~11 wk, followed by 7 consecutive d before mating, 7 d/wk during mating to unexposed males, and 5 d/wk on GDs 0−19 (total exposure 15−16 wk); litters were delivered naturally and were culled to 8 on PND 4 (4/sex where possible); dams and 10 F1 pups/sex/group sacrificed on PND 21	0, 10, 60 or 182 ppm HEC: 0, 4.6, 27, 84	F0 females: no changes in body weight, ovary weight, reproductive tissue histology, or mating or reproductive indices F1 pups (PND 21): no changes in weight, survival, or histology of 33 organs	Reproductive F0 females: 84 F1 males and females: 84	NDr	Reproductive F0 females: NDr F1 males and females: NDr	Monsanto (1979)	NPR

Table 3A. Summary of Potentially Relevant Noncancer Data for Carbonyl Sulfide (CASRN 463-58-1)

Category	Number of Male/Female, Strain, Species, Study Type, Study Duration	Dosimetry[a]	Critical Effects	NOAEL[a]	BMDL/ BMCL[a]	LOAEL[a]	Reference (comments)	Notes[b]
Reproductive Study 2	24 M/0 F, S-D rat, one-generation study, 6 hr/d, 5 d/wk for ~11 wk, followed by 7 consecutive d before mating and 7 d/wk during mating to unexposed females to produce F1a litter (total exposure ~13 wk). Males were mated with 48 additional females 10 wk later to produce F1b litter; F0 males were sacrificed after F1b mating; half of F1b dams were sacrificed on GD 14 for fertility assessment; the other half of F1b dams and F1a dams were allowed to deliver naturally. Litters were culled to 8 on PND 4 (4/sex where possible); F1a and F1b pups (10/sex/group) were sacrificed on PND 21.	0, 10, 60 or 182 ppm HEC: 0, 4.6, 27, 84	F0 males: no statistically significant changes in body weight, testicular weight, reproductive tissue histology, or reproductive performance F1a generation: no changes in body or organ weights, survival, or histology of 33 organs F1b generation: no changes in body or organ weights, survival, or histology of 33 organs	Reproductive F0 males: 84 F1a pups: 84 F1b pups: 84	NA	Reproductive NDr F1a pups: NDr F1b pups: NDr	Monsanto (1979)	NPR

[a]Dosimetry: The units for inhalation exposure units are expressed as HECs (mg/m^3). Exposure values (2 weeks and longer) are converted from a discontinuous to a continuous (weekly) exposure. Values from animal reproductive studies are not adjusted to a continuous exposure basis.
HEC_{EXRESP} = (ppm × molecular weight [60.08 g/mol] ÷ 24.45) × (hours/day exposed ÷ 24) × (days/week exposed ÷ 7) × ratio of animal:human blood:gas partition coefficients [default value of 1].
[b]Notes: PR = peer reviewed; NPR = not peer reviewed; PS = principal study.

BAER = brainstem auditory evoked response; F = female; FEL = frank effect level; GD = Gestation Day; M = male; NA = not applicable; ND = no data; NDr = not determined; PND = Postnatal Day; S-D = Sprague-Dawley; SD = standard deviation; SEP = sensory evoked potential.

Table 3B. Summary of Potentially Relevant Cancer Data for Carbonyl Sulfide (CASRN 463-58-1)						
Category	**Number of Male/Female, Strain, Species, Study Type, Study Duration**	**Dosimetry**	**Critical Effects**	**BMDL/ BMCL**	**Reference (comments)**	**Notes**
Human						
1. Oral (mg/kg-d)[a]						
ND						
2. Inhalation (mg/m^3)[a]						
ND						
Animal						
1. Oral (mg/kg-d)[a]						
ND						
2. Inhalation (mg/m^3)[a]						
ND						

ND = no data.

HUMAN STUDIES

Oral Exposures

No studies have been identified.

Inhalation Exposures

No studies have been identified.

Three case studies have reported reversible effects potentially attributable to acute inhalation exposure to carbonyl sulfide. Two occupational studies reported illness following acute exposure to gaseous mixtures including carbonyl sulfide [Benson et al. (1996) as cited in ACGIH (2012); Praxair (2003)]. Subjects recovered fully from observed effects, which included respiratory distress, nausea, and intravascular hemolysis with severe anemia and the beginning of acute renal failure. Similarly, a man reported rapid, but transient, dizziness, inability to stand, chest pressure, and ringing in the ears following intentional inhalation of "pure carbonyl sulfide gas" [Klason (1887) as cited in Bartholomaeus and Haritos (2005)]. These studies are included in Appendix C, Table C-2 (Other Studies).

ANIMAL STUDIES

Oral Exposures

No adequate studies have been identified on the oral exposure of carbonyl sulfide to animals. A series of studies by Wang et al. (1999) examined toxicity endpoints in Sprague-Dawley (S-D) rats fed food fumigated with 20,000−500,000 mg/m^3 carbonyl sulfide for 3−24 months. However, the study design and reporting were inadequate for hazard identification or to determine a no-observed-adverse-effect level (NOAEL) or lowest-observed-adverse-effect level (LOAEL) because the concentration of the agent in the feed was not measured (see Appendix C, Table C-2 [Other Studies]).

Inhalation Exposures

Potentially relevant data for noncancer effects include: a series of subchronic-duration studies of general toxicity (lethality, morbidity, body weight) and cardiovascular effects in white Danish rabbits exposed to carbonyl sulfide gas for 7 weeks (Hugod, 1981; Hugod and Astrup, 1980; Kamstrup and Hugod, 1979); a series of subchronic- and short-term-duration studies of neurological effects in rats exposed to carbonyl sulfide gas for 2 or 12 weeks (Herr et al., 2007; Morgan et al., 2004; Sills et al., 2004); a short-term-duration toxicity study of rats exposed to carbonyl sulfide gas for 2 weeks (Monsanto, 1985); and a series of one-generation reproduction toxicity studies in rats exposed to carbonyl sulfide gas for ~11 weeks before mating and during mating (Monsanto, 1979).

Results from these inhalation-exposure animal studies show:

1) A human equivalent concentration LOAEL ($LOAEL_{HEC}$) of 176 mg/m^3 (400 ppm) and a human equivalent concentration NOAEL ($NOAEL_{HEC}$) of 132 mg/m^3 (300 ppm) for neurological effects in rats, including necrotic brain lesions, altered electrophysiology (brainstem auditory evoked responses [BAER], somatosensory evoked potentials [SEP]), and neurobehavioral alterations following exposure for 6 hours/day, 5 days/week for 2 or 12 weeks (Herr et al., 2007; Morgan et al., 2004; Sills et al., 2004).

2) A human equivalent concentration frank effect level (FEL_{HEC}) of 200 mg/m^3 (453 ppm) and a $NOAEL_{HEC}$ of 110 mg/m^3 (253 ppm) for morbidity and clinical signs of neurotoxicity in male and female rats during Week 2 of exposure 6 hours/day, 5 days/week (Monsanto, 1985).
3) A $LOAEL_{HEC}$ of 66 mg/m^3 (151 ppm) and a $NOAEL_{HEC}$ of 22 mg/m^3 (51 ppm) for methemoglobinemia in male and female rats during a 2-week exposure for 6 hours/day, 5 days/week (Monsanto, 1985).
4) A FEL_{HEC} of 130 mg/m^3 (widely fluctuating concentrations averaging 54 ppm; the only concentration tested) for increased mortality and morbidity (severe neurological disorder) in rabbits after the 5th day of exposure during a continuous exposure of carbonyl sulfide for a 7-week exposure period. The 13 rabbits that survived the 7 weeks of exposure showed no exposure-related effects on neurological function, cholesterol levels, or histology of coronary or pulmonary arteries, aortic arch, thoracic aorta, or lungs (Hugod, 1981; Hugod and Astrup, 1980; Kamstrup and Hugod, 1979).
5) A $NOAEL_{HEC}$ of 84 mg/m^3 (the highest concentration tested, 182 ppm 6 hours/day before and during mating to unexposed partners and during Gestation Days [GDs] 0−19) for the absence of statistically significant exposure-related changes in reproductive performance in F0 female rats, weight and survival of F1 pups, and histology of reproductive tissues from F0 rats and histology of 33 tissues in F1 offspring at Postnatal Day (PND) 21 (Monsanto, 1979). At PND 21, F1 male offspring of F0 females (but not female offspring) exposed to 182 or 60 ppm showed decreased absolute and relative liver weight, but no exposure-related histological changes in liver. The liver weight changes are of uncertain toxicological significance in consideration of the inconsistent dose-response relationship, the absence of histological changes, the large functional reserve of the liver, and the absence of liver-weight effects in female offspring or in exposed animals in other studies. Additional support for dismissal of this effect as adverse is provided by a lack of clinical chemistry findings in an unpublished 14-week study (DuPont, 1992).
6) A $NOAEL_{HEC}$ of 84 mg/m^3 (the highest concentration tested, 182 ppm 6 hours/day before and during mating to unexposed partners) for the absence of clear adverse effects on the ability of F0 male rats to impregnate females and produce two litters (F1a and F1b), and no exposure-related histological changes in F0 male reproductive tissue or 33 organ tissues in PND-21 F1 offspring (Monsanto, 1979).

An additional 14-week subchronic-duration inhalation toxicity study of rats was located; however, the report was only available in summary form (DuPont, 1992); therefore, available data are inadequate for independent review of the results or a reliable NOAEL/LOAEL determination (see Table C-2 in Appendix C). Summaries of two developmental toxicity studies were also located (DuPont, 1992), but it is unclear whether these studies are resubmissions of findings previously reported by Monsanto (1985) and Monsanto (1979). Again, available data are inadequate for independent review of the results or a reliable NOAEL/LOAEL determination (see Table C-2 in Appendix C). No chronic-duration/carcinogenicity inhalation studies were located.

Short-Term Tests in Animals

Monsanto (1985)

In a non-peer-reviewed report, groups of S-D rats (10/sex/group) were exposed to nominal concentrations of 0, 50, 150, 250, or 450 ppm (analytical concentrations: 0, 51, 151, 253, or 453 ppm) carbonyl sulfide for 6 hours/day, 5 days/week for 2 weeks in whole-body inhalation chambers. Rats were housed individually and randomly assigned to exposure groups via a computer program on the basis of initial body weight. Male and female rats were 37 and 36 days of age, respectively, at the start of the study. On exposure days, animals were observed before, during, and after exposure periods for mortality and clinical signs of toxicity. Animals were also checked for mortality on nonexposure days. Animal body weights were recorded weekly. Blood was collected just prior to sacrifice at 2 weeks for hematological evaluations including red blood cell (RBC) count, white blood cell (WBC) count, platelets, hematocrit, hemoglobin, mean corpuscular volume, mean corpuscular hemoglobin concentration. Percentages of oxy-, carboxy-, and methemoglobin were determined via spectrophotometry. At sacrifice, animals were examined for gross pathological changes. Organs were not weighed, and tissues were not preserved for histological evaluation.

Clinical signs of neurotoxicity were evident in rats in the 453-ppm group during the second week of exposure, including ataxia, head tilt, circling, pivoting, prostrate and arched back postures, tremors, loss of muscular control, convulsions, and bulging, dilated eyes (see Table B-1). Toxicity led to moribund sacrifice of 2/10 males and 3/10 females after the eighth exposure. Additional signs of toxicity resulting from a viral infection (sialodacryoadenitis) were evenly distributed across exposure groups (e.g., lacrimation, swollen eyes, nasal discharge, salivation, and swollen submaxillary salivary glands). Body weight was significantly reduced in females, but not males, in the 453-ppm group, compared with controls; however, all terminal body weights were within 5% of control values (see Table B-1). When compared to concurrent control values, statistically significantly increased methemoglobin concentrations were observed in blood of rats at ≥151 ppm (see Table B-1), representing a potentially decreased oxygen delivering capacity of the blood. Methemoglobinemia (not in combination with other effects) serves as the critical effect for oral reference dose (RfD) values on IRIS (U.S. EPA, 2015) for nitrate and nitrite (effect observed in humans) and nitrobenzene, where the effect was observed in rats. However, the extent of methemoglobin in humans was 10% (Walton, 1951) and the duration of the rat study was 90 days (NTP, 1983).

The analytical concentrations 0, 51, 151, 253, and 453 ppm in this study were converted to HECs of 0, 22, 66, 111, and 199 mg/m^3 for extrarespiratory effects from a category 3 gas, based on the following equation: $CONC_{HEC} = CONC_{ppm} \times$ (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × blood:air partition coefficient ratio (U.S. EPA, 1994c). The values for the human and rat blood:air partition coefficients are unknown, so the default ratio of 1 was applied. A $LOAEL_{HEC}$ of 66 mg/m^3 (151 ppm) and a $NOAEL_{HEC}$ of 22 mg/m^3 (51 ppm) were identified in male and female rats for increased methemoglobin concentration, compared with controls.

Morgan et al. (2004)

Preliminary to the 12-week study summarized below, Morgan et al. (2004) exposed Fischer 344 rats (10/sex/group) to 0, 300, 400, or 500 ppm 6 hours/day, 5 days/week for 2 weeks. The corresponding HECs are 0, 132, 176, and 219 mg/m^3, respectively. Neurobehavior was assessed with a functional observational battery (FOB) and brain lesions were assessed as

described for the 12-week study. All male rats and 4/10 female rats died or were sacrificed moribund (hypothermia, lethargy, ataxia) in the 500-ppm group; no deaths or clinical signs of toxicity were observed in other dose groups. In the FOB, decreased grip strength was observed in rats exposed to ≥400 ppm, and hypotonia and slight gait abnormalities were observed in surviving females from the 500-ppm group (data not reported by study authors). Significant increases in brain lesion incidence were observed in the parietal cortex and putamen in the 400-ppm group. At 500 ppm, necrotic brain lesions were observed in multiple brain regions of all rats (see Table B-2). No exposure-related findings were observed in the 300-ppm rats. A $LOAEL_{HEC}$ of 176 mg/m^3 (400 ppm) and a $NOAEL_{HEC}$ of 132 mg/m^3 (300 ppm) were identified in male and female rats for exposure-related lesions in multiple brain regions and decreased grip strength, compared with controls.

Herr et al. (2007)

Herr et al. (2007) exposed groups of rats (15 males/group) to 0, 300, or 400 ppm for 6 hours/day, 5 days/week for 2 weeks. The corresponding HECs are 0, 132, and 176 mg/m^3, respectively. The animals were examined using a FOB and response modification audiometry (RMA). No exposure-related effects were found on body weight. Exposure-related changes in the FOB were only observed in the 400-ppm group, including decreased motor activity, decreased grip strength, slightly abnormal gait, and loss of forelimb proprioceptive placing response (data not reported). No changes were observed in the startle response (RMA). Significantly decreased amplitude of BAER peaks were measured in 400-ppm rats, compared with responses in 0- and 300-ppm rats (data reported graphically). Peak-to-peak amplitudes and latencies for cortical and cerebellar SEPs from forelimb stimulation were not significantly changed among the groups, but some qualitative changes in shape and morphology of waveforms were noted in the 400-ppm group. No exposure-related changes were observed for peripheral nerve compound nerve action potentials (CNAPs) or nerve conduction velocity (NCV), or flash-evoked potentials (FEPs). Grossly visible cortical lesions (cavitation) were observed in 11/15 rats in the 400-ppm group, similar to that observed in the earlier study (Morgan et al., 2004). No grossly visible cortical lesions were seen in 0- or 300-ppm rats. A $LOAEL_{HEC}$ of 176 mg/m^3 (400 ppm) and a $NOAEL_{HEC}$ of 132 mg/m^3 (300 ppm) were identified in male rats for gross brain lesions, altered neurobehavior and reflexes (decreased motor activity, decreased grip strength, slightly abnormal gait, loss of forelimb proprioceptive placing response), and decreased BAER peak amplitudes (Herr et al., 2007).

Subchronic-Duration Studies

Hugod (1981); Hugod and Astrup (1980); Kamstrup and Hugod (1979)

In three peer-reviewed studies from the same laboratory, groups of white Danish country breed rabbits were continuously exposed to nominal carbonyl sulfide concentrations (purity and source not reported) of 0 or 50 ppm. Hugod and Astrup (1980) reported that exposure concentrations varied, with a minimum detected value of 40 and a maximum detected value of 75 ppm. The average of detected concentrations was 54 ppm, a HEC of 130 mg/m^3.

While it seems clear from the study design and level of reporting that these studies report results from the same group of exposed rabbits, details of sex and exposure concentration are inconsistently reported. Carbonyl sulfide exposures were described as being to "pure COS" (source and purity not presented) delivered from a gas cylinder and mixed with atmospheric air (Hugod and Astrup, 1980; Kamstrup and Hugod, 1979). While the number of dead (three) and moribund (two) animals is reported on the same study day in reports by both Kamstrup and

Hugod (1979) and Hugod and Astrup (1980), the former study reports groups of $n = 17$ (control) and $n = 18$ (treated) female rabbits and analytical concentrations of 0 and mean concentrations of 54 ppm (range 40−75 ppm), while the latter reports group sizes of 6−24 male animals and no analytic values for measured chamber concentrations. Body weight was monitored at regular intervals throughout exposure (data not reported). Blood samples were collected from a marginal ear vein before exposure and at weekly intervals during exposure to determine serum total (free + esterified) cholesterol and triglyceride levels. After the 7-week exposure period, cholesterol dynamics using injection of labelled cholesterol was measured using two methods. In four rabbits/group, blood samples were collected at intervals over 20 hours following injection of 1α,2α[N]-^{3}H-cholesterol dissolved in ethanol (direct injection method). In three rabbits/group, blood samples were collected at regular intervals for 5 hours following injection with in vivo labelled plasma obtained from two donor rabbits injected with 1α,2α [N]-^{3}H-cholesterol 20 hours prior to bleeding (donor plasma method). Free cholesterol levels were measured in the inner (intima + internal media) and outer (media) layers of the aorta from seven to nine rabbits/group. Eight rabbits/group were sacrificed for histopathological examination of the coronary arteries, aortic arch, thoracic aorta, pulmonary arteries and lungs, and ultrastructural examination of the myocardium of the left ventricle.

As reported in Kamstrup and Hugod (1979) and in Hugod and Astrup (1980), on the fifth day after the initiation of exposure, three exposed animals died and two were sacrificed moribund due to serious (unspecified) neurological disorders (see Table B-3). The three dead animals were excluded from the study; however, the two sacrificed animals were included in the histopathological evaluation. None of the 13 surviving animals demonstrated signs of altered neurological function (Kamstrup and Hugod, 1979). No exposure-related body-weight effects were observed. Overall, no consistent, exposure-related changes in cholesterol levels were found. Significant increases were observed in serum cholesterol levels at Weeks 1, 6, and 7 and serum triglyceride levels at Weeks 4 and 6 (data presented graphically). No exposure-related changes were observed in cholesterol dynamics using either method. Free cholesterol measured in the outer media layer of the aorta was statistically significantly increased by 22% compared with controls; however, no statistically significant effect on free cholesterol levels in the inner intima and internal media aortic layers was observed (see Table B-3). No exposure-related histological changes were observed in the coronary arteries, aortic arch, thoracic aorta, pulmonary arteries, or lungs, and no exposure-related ultrastructural myocardial changes were observed (see Table B-3).

The results of the three rabbit studies are dubious for several reasons. First, the treatment dose that caused mortality and severe neurotoxicity in the rabbits is only moderately above that which produced no or minimal effects in rats (Monsanto, 1985). Second, the studies reported inconsistent sexes. Third, all of the rabbits that died did so on the same day of the exposure regimen. Fourth, the exposure concentrations ranged widely and actual maximum exposure values may have exceeded those reported. And lastly, none of the surviving rabbits demonstrated signs of toxicity. Therefore, no point-of departure (POD) values are estimated due to the lack of confidence in the data from the rabbit studies. Results from these studies will not be further considered for POD derivation.

Herr et al. (2007); Morgan et al. (2004); Sills et al. (2004)

In a series of peer-reviewed National Institute of Environmental Health Sciences (NIEHS) studies, neurobehavior, neurophysiology, and neuroanatomy were evaluated following

inhalation exposure to carbonyl sulfide for 2 or 12 weeks. In all studies, F344 rats were exposed to carbonyl sulfide (<98.1% pure; Tex-La Gases, Houston, TX) at two or three of the following concentrations for 6 hours/day, 5 days/week in whole-body inhalation chambers to target concentrations of 0, 200, 300, 400, or 500 ppm (concentrations were measured but not reported). Rats (6−7-weeks-old) were obtained from Charles River Laboratories (Raleigh, NC) and housed individually at the NIEHS inhalation facility in Hazelton-2000 inhalation exposure chambers. Feed was removed during the 6-hour exposures and for 6 hours/day on nonexposure days. Water was provided ad libitum. Rats were 8−9-weeks-old at the start of exposures.

Morgan et al. (2004) is selected as the principal study for the derivation of the subchronic and chronic provisional reference concentrations (p-RfCs). Morgan et al. (2004) exposed rats (10/sex/group) to 0, 300, or 400 ppm for up to 12 weeks. The corresponding HECs are 0, 132, and 176 mg/m^3, respectively. Rats were observed twice daily for clinical signs of toxicity and morbidity. Individual body weights were recorded the day before the first exposure and weekly thereafter. Immediately after the 12-week exposure, behavioral changes were assessed with a complete functional observation battery (FOB): general appearance (lacrimation, salivation, ptosis, pupil size, piloerection), reaction to handling, 2-minute observation of open-field behavior (activity level, arousal, posture, gait, occurrence of involuntary motor movements), reflex tests (click and tail-pinch response, pupil response, righting reflex), grip strength, and foot-splay. A 30-minute photocell-based assessment of motor activity was also conducted. After behavioral assessment, blood was collected for clinical chemistry from five rats/sex/group (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], sorbitol dehydrogenase [SDH], blood urea nitrogen [BUN], cholesterol, total protein, creatine kinase [CK], creatinine, and glucose). All animals were sacrificed, and brains were harvested and prepared for histological examination of 36 areas from six brain regions (frontal cortex through chiasmi, frontoparietal cortex through the infundibulum, mid-anterior colliculi, posterior colliculi at the level just anterior to the pons, cerebellum and medulla at its midpoint through the cochlear nuclei, and obex at the posterior medulla at the origin of the spinal central canal).

Following 12 weeks of exposure to carbonyl sulfide, there were no exposure-related deaths, morbidity, clinical signs of toxicity, or body-weight effects. Slight, but statistically significant, decreases in serum ALP, SDH, cholesterol, protein, and creatinine were observed in all groups of exposed males (data not reported by the study authors). The toxicological significance of these findings is unclear, as magnitude and pattern of change were not reported. Increased incidence of lesions was observed in several brain regions in male and female rats exposed to 400 ppm, compared with controls (see Table B-4). Findings included necrosis in the parietal cortex and neuronal loss and microgliosis in the posterior colliculus. In male rats, necrosis in the parietal cortex was accompanied by cavitation, a grossly observable absence of cortical tissue. No exposure-related lesions were observed in the brains of rats exposed to 300 ppm. No consistent, concentration-related changes were observed in the FOB or motor activity. The preliminary assessment of BAERs showed decreased amplitudes and increased latencies of peak amplitudes in males exposed to 400 ppm, compared with controls. A more complete analysis of BAERs after 12-week exposures was conducted by Herr et al. (2007) (see below). A $LOAEL_{HEC}$ of 176 mg/m^3 (400 ppm) and a $NOAEL_{HEC}$ of 132 mg/m^3 (300 ppm) were identified in male and female rats for exposure-related necrosis in the parietal cortex and neuronal loss and microgliosis in the posterior colliculus, compared with controls.

Sills et al. (2004) exposed rats to 0, 200, 300, or 400 ppm for up to 12 weeks and examined tissues at end of 12 weeks treatment, as well as tissues from interim sacrifices at 4 and 8 weeks (6/sex/group per time-point) with magnetic resonance microscopy (MRM) to provide a histologic characterization of lesions (neither statistical evaluation nor incidence data reported). The corresponding HECs are 0, 87.8, 132, and 176 mg/m^3, respectively. At sacrifice, rats were injected with the contrast agent Prohance (gadoteridol) prior to MRM. Following MRM, fixed brains were removed and placed in 10% neutral buffered formalin for light microscopy for verification of MRM findings. No exposure-related brain lesions were identified with MRM or light microscopy in 200- or 300-ppm rats. In rats exposed to 400 ppm, altered MRM intensities were identified in the posterior colliculus, anterior olivary nucleus, and parietal cortex after 4, 8, and 12 weeks of exposure. Light microscopy confirmed damage to these areas, including focal areas of gliosis in the posterior colliculus and anterior olivary nucleus and massive loss of neurons within the parietal cortex. Lesion incidence data were not reported; however, the study authors reported that the "most consistent" lesion on MRM was within the posterior colliculus. As with Morgan et al. (2004), a $LOAEL_{HEC}$ of 176 mg/m^3 (400 ppm) and a $NOAEL_{HEC}$ of 132 mg/m^3 (300 ppm) were identified in male and female rats for exposure-related lesions in multiple brain regions. Because of the nature of data presentation, benchmark dose modeling was not possible.

Herr et al. (2007) reported data from electrophysiological measurements and neurobehavioral observations in groups of rats (16/sex/group) exposed to 0, 200, 300, or 400 ppm for 12 weeks. The corresponding HECs are 0, 87.8, 132, and 176 mg/m^3, respectively. At 34−40 days following the last exposure, the rats were surgically implanted with epidural screw electrodes to record electrical potentials from the cortical S1 hindlimb/tail region (sensory evoked potential [$SEP1_{cortex}$]), cortical S1 facial region ($SEP2_{cortex}$), over the cerebellum ($SEP_{cerebellum}$), brainstem (BAER), and posterior to the hairline of the tail (compound nerve action potentials [CNAP]). Following surgery, 4, 0, 1, and 0 males and 3, 2, 4, and 4 females were excluded from the 0, 200-, 300-, and 400-ppm groups, respectively, due to surgical complications. The animals were allowed approximately 1 week to recover prior to neurophysiological testing. All evoked potentials were measured in a single test session in the following order: CNAP, $SEP1_{cortex}$, $SEP2_{cortex}$, $SEP_{cerebellum}$, nerve conduction velocity (NCV), and BAER. Colonic temperature was measured immediately following electrophysiological testing. Electrophysiological data were analyzed using step-down analyses of variance (ANOVAs) with a Greenhouse-Geisser correction factor for degrees of freedom for within-subject effects. The critical α level for peak amplitudes and latencies was calculated to be 0.025 using a Bonferroni correction, and further adjusted based on the number of peak amplitudes, latencies, and step-down ANOVAs (e.g., the level of statistical significance varied among tests and was at most $p < 0.025$). While these adjustments decrease Type I statistical errors, they may also decrease statistical power. Therefore, for the purposes of this review, data are considered statistically significant at $p < 0.05$. Herr et al. (2007) also assessed neurobehavior 5 days after the last exposure by FOB and a motor activity assessment [as described by Morgan et al. (2004)]. Startle response was assessed by reflex modification audiometry (RMA) 11 days after the end of exposure. About 27 days after exposure, electrophysiological tests were conducted: CNAP, NCV, $SEP1_{cortex}$, $SEP2_{cortex}$, $SEP_{cerebellum}$, BAER, and flash-evoked potentials (FEP). Six hours after neurophysiological testing, brains were removed and prepared for histological examination.

Following 12 weeks of exposure, no clinical signs of toxicity or body-weight effects were observed (Herr et al., 2007). Because "no gender related differences were apparent," the study authors combined data from males and females. Statistically significant increases in peak $SEP2_{cortex}$ and $SEP1_{cortex}$ amplitudes were observed in 400-ppm rats, compared with controls (see Table B-5). A significant trend toward increased peak $SEP1_{cortex}$ latency was also reported (see Table B-5). In BAER measurements, significant changes in peak amplitudes were observed in 400-ppm rats following both click and tone pip (4 kHz, 16 kHz) stimuli, but not following stimulus with 64 kHz tone pip (see Table B-5). Graphic presentations of BAER results indicated significant BAER peak amplitude changes in rats exposed to 400 ppm, but not at 300 ppm or lower concentrations. No significant exposure-related effects were noted for peak latencies in BAER waveforms. No exposure-related findings were observed in SEP or BAER tests in 200- or 300-ppm rats, and no exposure-related differences were observed in peripheral nerve electro-physiological measures (CNAP, NCV) in any group. There were also no exposure-related differences in colonic temperature at 12 weeks. A $LOAEL_{HEC}$ of 176 mg/m^3 (400 ppm) and a $NOAEL_{HEC}$ of 132 mg/m^3 (300 ppm) were identified in male and female rats for exposure-related lesions in multiple brain regions, and changes in BAER and SEP peak amplitudes and SEP peak latencies, compared with controls (Herr et al., 2007).

One-Generation Reproduction Studies

Monsanto (1979)

A series of non-peer reviewed one-generation studies were conducted by the Monsanto Agricultural Company. In all studies, S-D rats were obtained from Charles River Breeding Laboratory (Kingston, NY) and quarantined for 2 weeks prior to exposure to carbonyl sulfide (99.1% pure, Matheson, Inc, Gloucester, MA). Rats were approximately 7 weeks at the start of the experiment. Rats were housed separately during whole-body exposure except during mating. Food and water were available ad libitum.

In Study 1, groups of female S-D rats (24/group) were exposed to nominal carbonyl sulfide concentrations of 0, 10, 60, or 180 ppm (analytical concentrations: 0, 10, 60, or 182 ppm), 6 hours/day, 5 days/week for ~11 weeks followed by 7 consecutive exposure days premating, 7 days/week during mating to unexposed males, and 5 days/week during gestation until GD 19 (total exposure 15−16 weeks). Rats were assessed for mortality and morbidity twice daily, with detailed observations once weekly in dams and on days of litter weight measurements in F1 offspring. Body weights were measured weekly in F0 females, litter weights were measured on PNDs 0, 4, 7, and 14, and individual pup weights were measured on PND 21. Dams were allowed to deliver naturally, and all litters were culled to eight pups on PND 4 (four per sex where possible). Reproductive indices evaluated included mating and pregnancy rates, precoital length, pregnancy rate, gestation length, number of live and dead pups, and postnatal survival. F0 females and 10 F1 weanlings/sex in the control and high-dose groups were sacrificed on PND 21. All animals were examined grossly for pathological lesions. Organs weighed included F0 female ovaries and F1 weanling adrenals, brain, heart, kidneys, liver, testes with epididymides, and ovaries. In dams, organs retained for microscopic histology included ovaries, uterus, vagina, and gross lesions. In weanlings, organs retained for microscopic histology included adrenals, bone with marrow, brain, colon, duodenum, esophagus, eyes, heart, ileum, jejunum, kidneys, liver, lung with mainstem bronchi, lymph node (mesenteric and submandibular), muscle (quadriceps femoris), ovaries, pancreas, pituitary, prostate, sciatic nerve, submaxillary salivary gland, skin with mammary tissue, spleen, stomach, testes with epididymides, thymus, thyroid/parathyroid, trachea, uterus (corpus and cervix), vagina, urinary

bladder, seminal vesicles, and all gross lesions. Organs were only microscopically examined in the control and high-dose animals unless grossly evident lesions were observed in the low- and mid-exposure groups. Reproductive organs were examined in all females that failed to produce a litter, regardless of exposure group.

No exposure-related mortalities, clinical signs of toxicity, or body-weight effects were observed in F0 females. No statistically significant, exposure-related changes were observed in mating or pregnancy rates, precoital length, gestational length, or number of live pups (see Table B-6). Differences in pup weight and survival were not statistically significant among groups, and no clinical signs of toxicity were observed. There were no exposure-related effects on ovary weight or reproductive tissue histology in F0 females.

The analytical concentrations 0, 10, 60, and 182 ppm were converted to HECs of 0, 4.6, 27, and 84 mg/m^3 for extrarespiratory effects from a Category 3 gas, based on the following equation: $CONC_{HEC}$ = [(number of weeks exposed 5 days/week × ($CONC_{ppm}$ × (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × (5 days ÷ 7 days) × blood:air partition coefficient ratio) + [(number of weeks exposed 7 days/week × ($CONC_{ppm}$ × (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × blood:air partition coefficient ratio)] ÷ total number of weeks (U.S. EPA, 1994c). The values for the human and rat blood:air partition coefficients are unknown, so the default ratio of 1 was applied. A reproductive $NOAEL_{HEC}$ of 84 mg/m^3 (182 ppm) was identified for F0 females based on a lack of adverse reproductive effects.

In F1 weanlings, no exposure-related histopathological lesions were observed in any of the 33 examined organs, with the exception of extramedullary hematopoiesis observed in the liver of two male and two female rats in the high-dose group and in one control female. In F1 males, but not females, absolute and relative liver weights were significantly decreased by 18−23% in the 60- and 182-ppm groups (HEC values of 27 and 84 mg/m^3 , respectively), but not in the 10-ppm (4.6 mg/m^3 HEC) group (see Table B-7). Several issues complicate a clear understanding of the toxicological significance of this effect. The concentration dependency of the effect is poor, there are no exposure-related histological changes that would account for this effect (see Table B-7), and no clinical chemistry abnormalities are available (DuPont, 1992) (90-day study) to provide additional explanation for weight changes. In addition, no benchmark response level has been established for the decrease in liver weight in adults or in animals exposed in utero. No exposure-related weight changes were observed in any other organs in F1 PND 21 offspring. The highest exposure level (a HEC of 84 mg/m^3 or 182 ppm) is considered to be a NOAEL for all endpoints considered.

In Study 2, groups of male S-D rats (24/group) were exposed to nominal carbonyl sulfide concentrations of 0, 10, 60, or 180 ppm (analytical concentrations: 0, 10, 60, 182 ppm), 6 hours/day, 5 days/week for ~11 weeks followed by 7 consecutive exposure days premating and 7 days/week during mating to unexposed females (total exposure ~13 weeks) which produced the F1a litter. The previously exposed males were allowed 10 weeks without exposure to carbonyl sulfide, and then were mated again with 48 unexposed females which produced the F1b litter. Half of the females were allowed to deliver; the other half were sacrificed "mid-gestation" to obtain fertility data. Reproductive indices measured were as described for Study 1. F0 males were sacrificed after the second mating and 10 F1a and 10 F1b weanlings/sex/group were sacrificed on PND 21. Clinical observations, measures of body weights and weanling organ

weight, and histopathological examinations of 33 organ tissues in PND-21 F1 animals were conducted as described for Study 1. Testes were weighed in F0 males, and organs were retained for histopathology (examined in control and high-dose only) included testes, epididymis, prostate, seminal vesicle, and gross lesions. Reproductive organs were assessed in all males that failed to produce offspring, regardless of exposure group.

No exposure-related mortalities, clinical signs of toxicity, or body-weight effects were observed in F0 males. For the F1a generation, no statistically significant change was observed in the mating rate; however, the pregnancy rate in unexposed females that mated males exposed to 182 ppm was 57%, compared with a pregnancy rate of 87% in controls (see Table B-6). This finding suggests decreased fertility in males; however, the difference did not reach statistical significance after the Bonferroni correction of the Fisher's exact test (as reported by the study authors). A statistically nonsignificant trend toward increased precoital time was also observed, but no statistically significant changes were observed in gestational length or number of live pups (see Table B-6). For the F1b generation, no statistically significant, exposure-related changes were observed in mating or pregnancy rates, precoital length, gestational length, or number of live pups (see Table B-6). Additionally, no exposure-related histopathological findings were observed in F0 male reproductive tissues. The highest exposure level (a HEC of 84 mg/m^3 or 182 ppm) is considered to be a NOAEL for the absence of clear effects on male reproductive performance or reproductive tissues.

No exposure-related changes in pup weight, survival, organ weight, or histology of the 33 organs were observed in PND 21 rats from the F1a or F1b generations of F0 exposed males. Clinical signs of toxicity were not observed in F1a or F1b pups. A developmental $NOAEL_{HEC}$ of 84 mg/m^3 (182 ppm) was identified for F1a and F1b weanling males and females for lack of exposure-related effects.

OTHER DATA (SHORT-TERM TESTS, OTHER EXAMINATIONS)

Tests Evaluating Genotoxicity and/or Mutagenicity

Genotoxicity testing of carbonyl sulfide is limited to a series of in vivo and in vitro studies by (Wang et al., 1999) and an in vitro bacterial mutagenicity study by the NTP (1995) (see Table C-1 in Appendix C for more details). Micronuclei were not induced in mouse bone marrow, and chromosomal aberrations (CA) were not induced in mouse spermatocytes following acute inhalation or oral exposure, and reverse mutations were not induced in *Salmonella typhimurium* or *Escherichia coli* strains Wang et al. (1999). NTP (1995) reported "weakly positive" results for reverse mutation in *S. typhimurium* strain TA97, but not in strains TA98, TA100, or TA1535.

Supporting Human Studies

Three case studies report reversible respiratory and central nervous system effects that could potentially be attributed to acute carbonyl sulfide exposure (see Table C-2).

Supporting Animal Toxicity Studies

A number of inadequately reported animal toxicity studies and short-term studies were identified. Reported findings (see Table C-2 in Appendix C for more details) include:

1) No carcinogenic or exposure-related noncancer effects following subchronic- or chronic-duration oral exposure of S-D rats to feed fumigated with

20,000−500,000 mg/m^3 carbonyl sulfide (actual concentrations of carbonyl sulfide in the feed used for this study were not determined) (Wang et al., 1999).

2) Reduced postnatal growth and survival, but no exposure-related reproductive effects, in rats in one- or two-generation oral exposure studies (feed fumigated with 20,000−500,000 mg/m^3 carbonyl sulfide; actual compound consumption levels were not determined) Wang et al. (1999).
3) Lack of developmental toxicity following gestational exposure of rats to carbonyl sulfide concentrations up to 1,108 mg/m^3 (451 ppm), even at doses that caused maternal toxicity (855−1,108 mg/m^3; 348−451 ppm); results were reported in a study summary only (DuPont, 1992).
4) No exposure-related changes in urinalysis, clinical chemistry, gross or histological pathology, pupillary reflexes, or clinical signs of toxicity in rats exposed to concentrations of carbonyl sulfide up to 447 mg/m^3 (182 ppm) for ~14 weeks; a specific hematological effect (lymphocytopenia) was identified, but potential adversity of effects cannot be determined based on available data, which were reported in a study summary only (DuPont, 1992).
5) Statistically significant increases in methemoglobinemia were reported in a non-peer-reviewed study by Monsanto (1985). The concentrations reached the level of statistical significance at concentrations of 66 mg/m^3 (HEC) and above. There were no effects noted at 22 mg/m^3 (HEC).
6) Short-term LOAELs and NOAELs for neurological effects of 1,474 mg/m^3 (600 ppm) and 737 mg/m^3 (300 ppm), respectively, in rats exposed to carbonyl sulfide for 1−4 days (Morgan et al., 2004; Sills et al., 2004).
7) In a neurotoxicity examination, Herr et al. (2007) demonstrated increased incidences of neuropathology, and altered behavioral endpoints demonstrating a $LOAEL_{HEC}$ of 176 mg/m^3 and a $NOAEL_{HEC}$ of 132 mg/m^3.

Reported acute lethality values for carbonyl sulfide include: rat 4-hour inhalation median lethal concentration (LC_{50}) values ranging from 2,659–2,730 mg/m^3 (1,082−1,111 ppm) (DuPont, 1992; Monsanto, 1982); mouse 35-minute inhalation LC_{50} of 2,940 mg/m^3 (1,196 ppm) [Sax and Lewis (1986) as cited in Bartholomaeus and Haritos (2005)]; mouse inhalation LC_{50} of 2,770 mg/m^3 (1,127 ppm), duration unspecified [RTECS (1997) as cited in Bartholomaeus and Haritos (2005)]; rabbit inhalation LC_{50} of 2,550 mg/m^3 (1,038 ppm), duration unspecified [RTECS (1997) as cited in Bartholomaeus and Haritos (2005)]; and a rat intraperitoneal (i.p.) LD_{50} of 22.5 mg/kg (Chengelis and Neal, 1980). Ninety-minute exposures to 488 ppm (1,200 mg/m^3) caused no deaths in two rats, two rabbits, and two guinea pigs, but exposure to 997 ppm (2,450 mg/m^3) caused deaths in 3/6 rats, 8/14 rabbits, and 0/6 guinea pigs [Thiess et al. (1968) as cited in Bartholomaeus and Haritos (2005)]. The results indicate that guinea pigs may be more resistant to the acute lethality of carbonyl sulfide than rats and rabbits (see Table C-2 in Appendix C for more details).

Metabolism/Toxicokinetic Studies

Toxicokinetic studies have demonstrated that carbonyl sulfide formation in vivo arises through the carbonic anhydrase-catalyzed metabolism of carbon disulfide. The metabolic pathway for carbonyl sulfide is as follows: carbonic anhydrase catalyzes the equilibrium relationship between carbonyl sulfide and monothiocarbonic acid concentrations. Monothiocarbonic acid is hydrolyzed to carbon dioxide (CO_2) and hydrogen sulfide (HS^-) (Dalvi and Neal, 1978); hydrogen sulfide is further oxidized into thiosulfate and sulfate (Chengelis and

Neal, 1987, 1980, 1979). The formation of hydrogen sulfide via this pathway has been shown to be responsible for the toxic action of carbonyl sulfide, as inhibitors of carbonic anhydrase (acetazolamine) and inhibitors of sulfide toxicity (sodium nitrite) have been shown to decrease and/or prevent carbonyl-sulfide mortality in rats (Chengelis and Neal, 1980) and flour beetles (Haritos and Dojchinov, 2005). A study in lactating goats reports that ^{35}S can be transferred to milk following oral exposure to carbonyl sulfide, and that ^{35}S is eliminated from milk in two stages, with a short first half-life (~1 day) and a longer second half-life (>40 days) (Howard et al., 2007). No other absorption, distribution, metabolism, elimination (ADME) studies were identified.

Mode-of-Action/Mechanistic Studies

Mechanistic studies are limited to two studies investigating mechanisms underlying observed neurotoxicity of carbonyl sulfide following short-term inhalation exposure. Morgan et al. (2004) reported decreased levels of brain cytochrome oxidase (a heme-containing enzyme) in the posterior colliculus, a region susceptible to carbonyl sulfide-induced lesions (Morrison et al., 2009; Morgan et al., 2004; Sills et al., 2004). This effect may be due to the parent compound or to the hydrogen sulfide metabolite (Pietri et al., 2011). Inhibition of brain cytochrome oxidase could potentially limit oxidative phosphorylation, contributing to observed neuronal necrosis and death in this and other brain regions following carbonyl sulfide exposure (Morgan et al., 2004). Additionally, significant gene expression changes were observed in the posterior colliculus at time points preceding morphological changes (Morrison et al., 2009). These gene expression changes, including up-regulation of genes involved in deoxyribonucleic acid (DNA) damage and G1/S checkpoint regulation, apoptosis, and vascular mediators, may be predictive of central nervous system (CNS) lesions, and further study may lead to better mechanistic understanding of carbonyl sulfide-induced neurotoxicity (Morrison et al., 2009).

There have been no mechanistic studies specifically directed toward understanding the development of methemoglobinemia by carbonyl sulfide. However, several pieces of information are pertinent and may describe a mode of action for this effect. Binding of carbon- and sulfur-containing functional groups to hemoglobin causes the production of methemoglobin and sulfhemoglobin, respectively. Each of these causes a decrease in the oxygen carrying capacity of hemoglobin, though they are distinguished by the reversibility of methemoglobin by methylene blue administration, whereas the formation of sulfhemoglobin results in a permanent (irreversible change) in hemoglobin. However, when blood is analyzed spectrophotometrically, the shifts in absorbance from that characteristic of oxygenated hemoglobin induced by sulfhemoglobin formation or methemoglobin formation may be indistinguishable (Williams, 2001). Both hydroxylamine and carbonyl sulfide are metabolized to hydrogen sulfide (U.S. EPA, 1994b; Dalvi and Neal, 1978); hydrogen sulfide converts hemoglobin to sulfhemoglobin (Michel, 1938), perhaps via a direct interaction with the ferrous iron component of heme (Pietri et al., 2011). Because of the reporting of sulfhemoglobin (and methemoglobin) in humans exposed to hydroxylamine (Gharahbaghian et al., 2009), it is possible that exposure to carbonyl sulfide results in sulfhemoglobin production in humans.

Carbonyl sulfide is a primary metabolite of carbon disulfide, which is catalyzed by carbonic anhydrase. Inhibition of carbonic anhydrase has been shown to decrease the lethality of carbon disulfide toxicity (Chengelis and Neal, 1987, 1980), presumably by decreasing the formation of carbonyl sulfide. The involvement of sulfhemoglobin formation in toxicity of carbonyl sulfide is supported by the protective effect (against sulfhemoglobin formation) of

methemoglobin-forming compounds prior to administration of carbonyl sulfide (Chengelis and Neal, 1980). While it seems likely that carbonyl sulfide exposure results in the formation of sulfhemoglobin, regardless whether the conversion of hemoglobin is to methemoglobin or sulfhemoglobin, the oxygen carrying capacity of blood may be slightly diminished by carbonyl sulfide exposure.

DERIVATION OF PROVISIONAL VALUES

Tables 4 and 5 present a summary of noncancer reference values and cancer values, respectively, for carbonyl sulfide. IRIS data are indicated in the table, if available.

Table 4. Summary of Noncancer Reference Values for Carbonyl Sulfide (CASRN 463-58-1)

Toxicity Type (units)	Species/Sex	Critical Effect	p-Reference Value	POD Method	POD	UF_C	Principal Study
Subchronic p-RfD	Not derived due to inadequate data						
Chronic p-RfD	Not derived due to inadequate data						
Subchronic p-RfC	Rat/females	Neurotoxicity	1 mg/m^3	BMCL	126 mg/m^3	100	Morgan et al. (2004)
Chronic p-RfC	Rat/females	Neurotoxicity	0.1 mg/m^3	BMCL	126 mg/m^3	1,000	Morgan et al. (2004)

BMCL = benchmark concentration lower confidence limit

Table 5. Summary of Cancer Values for Carbonyl Sulfide (CASRN 463-58-1)

Toxicity Type	Species/Sex	Tumor Type	Cancer Value	Principal Study
Provisional oral slope factor (p-OSF)	Not derived due to inadequate data			
Provisional inhalation unit risk (p-IUR)	Not derived due to inadequate data			

DERIVATION OF PROVISIONAL ORAL REFERENCE DOSES

Human and animal data are inadequate to derive subchronic or chronic p-RfDs for carbonyl sulfide.

The only available information on the oral toxicity of carbonyl sulfide comes from a report of a series of studies of rats in which the concentration of carbonyl sulfide in fumigated feed was not determined (Wang et al., 1999).

DERIVATION OF PROVISIONAL INHALATION REFERENCE CONCENTRATIONS

Derivation of Subchronic Provisional Reference Concentration (p-RfC)

The study of neurological endpoints in rats exposed by inhalation to carbonyl sulfide for 12 weeks is selected as the principal study for the derivation of the subchronic p-RfC.

Neurological effects (brain lesions and altered sensory evoked potentials [SEPs] in hindlimb/tail and facial regions) were considered as potential critical effects based on NOAEL/LOAEL values. Neuronal loss and microgliosis was selected as the critical effect on the basis of the lower BMCL value.

Justification for the Critical Effect

Methemoglobinemia was considered, but dismissed as the critical effect.

1) Some evidence supports the formation of sulfhemoglobin, rather than methemoglobin from the ingestion of carbonyl sulfide. This evidence is from hydroxylamine, which (like carbonyl sulfide) is metabolized to carbon sulfide, and from the finding that carbon sulfide converts hemoglobin to sulfhemoglobin. However, none of the available evidence directly supports the formation of sulfhemoglobin from carbonyl sulfide, primarily due to the lack of specificity of the analytical procedure employed by Monsanto (1985).
2) Statistically significantly increased blood methemoglobin was reported in rats exposed to concentrations ≥151 ppm for 2 weeks 6 hours/day, 5 days/week (Monsanto, 1985) (see Table B-1), but the percentage of methemoglobin was <2.3% in all dose groups (e.g., 2.1 and 2.3% in the highest exposure group [453 ppm, or HEC 219 mg/m^3]). In humans, the normal range of methemoglobin has been reported to be 1.9–3.8% in healthy adults and 3.61–6.44% in healthy children (Rechetzki et al., 2012), and the range of methemoglobin levels in control laboratory rats has been reported to be 0.1−0.4 mg methemoglobin/dL (compared to 16 mg oxyhemoglobin/dL) (approximately 0.6–2.4% as methemoglobin) (Car et al., 2005). No other exposure-related effects on comprehensive hematological endpoints were found in this 2-week study.
3) Humans might be anticipated to tolerate methemoglobin concentrations as high as 10%, but may not tolerate concentrations between 10 and 15% (Coleman and Coleman, 1996).
4) It seems reasonable that humans may tolerate concentrations of methemoglobin that are statistically significantly elevated over controls, and that early symptoms may be mild (Coleman and Coleman, 1996).
5) Methemoglobinemia is biologically reversible through erythrocyte-contained NADPH oxidase systems, as well as by clinical methods.
6) Among the assessments involving methemoglobin on the IRIS database, there appears to be no consensus on the extent of MeHb in humans deemed adverse, and no studies of methemoglobinemia of this duration have been used heretofore to support derivation of reference doses or concentrations.

Neurological effects were chosen as the critical effects for the subchronic p-RfC for carbonyl sulfide because they are the most clearly identified hazard in the short-term- and subchronic-duration studies of animals exposed by inhalation. Several studies observed neurological effects, and data are adequate to describe dose-response relationships (i.e., NOAEL/LOAEL) for brain lesions, changes in evoked potentials, and neurobehavioral endpoints. Several of these data sets were amenable to benchmark dose modeling. Effects observed in studies examining neurological endpoints include:

1) Histological brain lesions (e.g., cortical necrosis or cavitation in parietal cortex area 1 and neuronal loss or microgliosis in posterior colliculus), and changes in evoked potentials (BAER or SEP) in rats exposed to 400 ppm (176 mg/m^3 HEC), but not to concentrations ≤300 ppm (132 mg/m^3 HEC), for 12 weeks, 6 hours/day, 5 days/week (Herr et al., 2007; Morgan et al., 2004; Sills et al., 2004).
2) Altered neurobehavior (e.g., decreased motor activity and grip strength), gross brain lesions, and decreased peak amplitude of BAER in rats exposed to 400 ppm (176 mg/m^3 HEC), but not to concentrations ≤300 ppm (132 mg/m^3 HEC), for 2 weeks, 6 hours/day, 5 days/week (Herr et al., 2007).
3) Clinical signs of neurotoxicity (e.g., ataxia, prostrate and hunched back postures, tremors, loss of muscular control) in rats exposed to 453 ppm (199 mg/m^3 HEC), but not to concentrations ≤253 ppm (111 mg/m^3 HEC), for 2 weeks 6 hours/day, 5 days/week (Monsanto, 1985).
4) Severe neurological symptoms (not otherwise described) in 2/10 rabbits and deaths in 3/10 rabbits exposed continuously to widely varying concentrations which averaged 54 ppm (130 mg/m^3 HEC) for 5 days in a planned 7-week-exposure study (Hugod, 1981; Hugod and Astrup, 1980; Kamstrup and Hugod, 1979); the remaining rabbits survived the full exposure period, but the available reports did not specify whether or not survivors showed clinical signs of neurotoxicity.

The evidence for decreased ability of male rats to impregnate unexposed females observed in a reproductive study (Monsanto, 1979) is not as strong as the evidence for neurological effects. This effect (i.e., decreased pregnancy index) in producing an F1a generation (but not an F1b generation) was reported for male rats exposed to 182 ppm (HEC 84 mg/m^3) 6 hours/day before and during mating (57 versus 87% in controls; see Table B-1 in Appendix B) (Monsanto, 1979). This change was statistically significantly ($p < 0.05$) different from the control value by Fisher's exact test, but not significant ($p > 0.05$, actual p-level not reported) when Bonferroni correction was applied. No exposure-related histological changes in reproductive tissues were found in the exposed male rats. Therefore, it was not selected as critical effects for the subchronic p-RfC.

Justification for the Principal Study

The design, performance and reporting of the 12-week studies reported by Morgan et al. (2004) and Herr et al. (2007) are adequate to describe dose-response relationships for brain lesions and changes in sensory evoked potentials, respectively. Sills et al. (2004) did not present dose-response data but provided a histologic characterization of lesions whose incidence data were reported by Morgan et al. (2004). The results indicate a $NOAEL_{HEC}$ of 132 mg/m^3 and a $LOAEL_{HEC}$ of 176 mg/m^3 for increased incidence of brain lesions (Morgan et al., 2004) and changes in evoked potentials (Herr et al., 2007). Although this series of neurotoxicity studies did not include histological examination of a comprehensive set of tissues, the available database includes two one-generation reproductive toxicity studies reported by Monsanto (1979), which found no exposure-related histological effects in reproductive tissues from F0 male and F0 female rats exposed (before and during mating) to concentrations as high as 182 ppm (HEC 84 mg/m^3) or in 33 tissues in F1 male and female offspring.

Approach for Deriving the Subchronic p-RfC

The most sensitive neurological endpoints showing changes considered to be adverse in the principal study of rats exposed for 12 weeks were increased incidence of necrosis in the

parietal cortex, and neuronal loss or microgliosis in the posterior colliculus (see Table B-4) and altered peak amplitude of SEP in the hindlimb tail region (peak amplitude $SEP1_{cortex}$), the facial region (peak amplitude $SEP2_{cortex}$), and brainstem auditory evoked response (peak amplitude BAER), shown in Table B-5. Data sets for these endpoints were selected to determine potential POD values for the p-RfC values and are summarized in Table 6.

Table 6. Data for the Most Sensitive Neurological Endpoints in the Principal Study of Rats Exposed to Carbonyl Sulfide for 12 Weeks (6 Hours/Day, 5 Days/Week)[a]

Parameter	Exposure Group, ppm Carbonyl Sulfide (HEC in mg/m^3)			
	0	**200 (87.8)**	**300 (132)**	**400 (176)**
Neuronal loss or microgliosis in posterior colliculus Male Female	 0/9[b] 0/9	 NA NA	 0/9 0/9	 7/9* 5/9*
Cortical necrosis or cavitation in parietal cortex area 1 Male Female	 0/10 0/10	 NA NA	 0/10 0/10	 5/10* 4/10*
$SEP1_{cortex}$ (hindlimb/tail region); $P_{14}N_{27}$ peak amplitude (μV)[c]	41.83 ± 4.69	43.33 ± 4.51	41.08 ± 3.38	60.42 ± 6.57*
$SEP2_{cortex}$ (facial region); $P_{16}N_{21}$ peak amplitude (μV)	10.62 ± 0.79	11.83 ± 0.65	10.48 ± 0.98	15.94 ± 1.36*
BAER – click stimulus (80 dB)				
P4 peak amplitude (μV)	20.44	20.81 (+2%)	20.32 (−1%)	12.1* (−41%)
P5 peak amplitude (μV)	14.06	14.62 (+4%)	14.34 (+2%)	10.79* (−23%)
P6 peak amplitude (μV)	7.54	7.09 (−6%)	7.54 (0%)	9.41* (+25%
BAER – 4 kHz tone pip stimulus (80 dB)				
P4 peak amplitude (μV)	7.81	8.42 (+8%)	7.32 (−6%)	4.87* (−38%)
BAER – 16 kHz tone pip stimulus (80 dB)				
P4 peak amplitude (μV)	13.9	13.53 (−3%)	13.29 (−4%)	6.73* (−52%)

[a]Herr et al. (2007); Morgan et al. (2004)
[b]Incidence data are presented as incidence/number of animals examined; Other data are presented as Mean ± standard error of the mean (SEM).
[c]*n* values for combined males and females were control (0 mg/m^3) = 25; 200 mg/m^3 = 30; 300 mg/m^3 = 27; 400 mg/m^3 = 28.
*Statistically significantly different from controls at $p < 0.05$, based on statistics presented by study authors (step-down ANOVA)

NA = not available.

POD values were converted to HEC values by adjusting for duration of exposure and blood:air partition coefficient, for a category 3 gas. Because blood:air partition coefficients for carbonyl sulfide in rats and humans were not available, the default DAF value of 1 was used.

These potential critical effect data sets for neurological effects following subchronic-duration exposure were modeled with BMD models (see details in Appendix D) and results are summarized in Table 7. Of the two neurological lesions observed, neuronal

loss/microgliosis and cortical necrosis, the most sensitive lesions (i.e., neuronal loss or microgliosis) was modeled. Because the standard deviations for BAER responses were not available (Herr et al., 2007), these data could not be modeled.

Table 7. Potential Points of Departure for Neurological Endpoints

Effect	$NOAEL_{HEC}$ (mg/m^3)	$LOAEL_{HEC}$ (mg/m^3)	$BMCL_{HEC}$ (mg/m^3)	POD (mg/m^3)
Neuronal loss or microgliosis in males (Morgan et al., 2004)	132	176	128	128
Neuronal loss or microgliosis in females (Morgan et al., 2004)	**132**	**176**	**126**	**126**
SEP1 peak amplitude* (Herr et al., 2007)	132	176	171	171
SEP2 peak amplitude* (Herr et al., 2007)	132	176	NR	132
BAER peak amplitude* (Herr et al., 2007)	132	176	NA	132

*Data for males and females combined by study authors.

NA = not available (standard deviation values not available, modeling not possible); NR = not reported (models failed to give an acceptable fit to data SEP2).

The $BMCL_{HEC}$ value for brain lesions described as neuronal loss or microgliosis in the posterior colliculus of female rats (126 mg/m^3) is selected as the POD for the p-RfC, because it is the lowest POD, and increased incidence of these effects is considered clearly adverse.

The subchronic p-RfC for carbonyl sulfide is derived as follows:

$$\textbf{Subchronic p-RfC} = BMCL_{HEC} \div UF_C$$
$$= 126\ mg/m^3 \div 100$$
$$= \textbf{1 mg/m}^3$$

Table 8 summarizes the uncertainty factors (UFs) for the subchronic p-RfC for carbonyl sulfide.

Table 8. Uncertainty Factors for the Subchronic p-RfC for Carbonyl Sulfide

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for residual uncertainty associated with extrapolating from animals to humans, using toxicokinetic cross-species dosimetric adjustment for extrarespiratory effects from a category 3 gas, as specified in U.S. EPA (1994c) guidelines for deriving RfCs.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of carbonyl sulfide in humans.
UF_D	3	A UF_D of 3 ($10^{0.5}$) is applied to account for deficiencies and uncertainties in the database. The critical effect is defined in subchronic-duration studies in rats. The database also includes two adequate one-generation reproductive toxicity studies in rats and a limited report of developmental toxicity study. The database lacks a multigenerational reproductive toxicity study and a comprehensive report of a developmental toxicity study.
UF_L	1	A UF_L of 1 is applied because POD is a BMCL value.
UF_S	1	A UF_S of 1 is applied because the POD is derived from a subchronic-duration study of rats.
UF_C	100	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$

The confidence in the subchronic p-RfC for carbonyl sulfide is low as explained in Table 9.

Table 9. Confidence Descriptors for the Subchronic p-RfC for Carbonyl Sulfide

Confidence Categories	Designation[a]	Discussion
Confidence in study	M	Confidence in the principal study is medium. While the principal study (Morgan et al., 2004) contains reasonable numbers of rats of each sex and appears to be a well-conducted study reported in the peer-reviewed literature, the study is restricted to neurological endpoints.
Confidence in database	M	Confidence in the database is medium because it contains several subchronic-duration inhalation studies, and one generation reproductive toxicity studies. However, the database lacks a multigenerational reproductive toxicity study, and an adequate report of developmental toxicity study.
Confidence in subchronic p-RfC	M	The overall confidence in the subchronic p-RfC is medium.

[a]M = medium

Derivation of Chronic Provisional RfC (Chronic p-RfC)

In the absence of studies of toxicity endpoints in humans or animals chronically exposed to carbonyl sulfide by inhalation, a chronic p-RfC for carbonyl sulfide is derived from the subchronic p-RfC.

Justification for selecting the critical effect and principal study are described in the previous section of this document. The selected POD is a $BMCL_{HEC}$ of 126 mg/m^3 for increased incidence of brain lesions in female rats exposed to carbonyl sulfide for 12 weeks.

The chronic p-RfC for carbonyl sulfide, based on a $BMCL_{HEC}$ of 126 mg/m^3 for brain lesions in female rats is derived as follows:

$$\begin{aligned} \textbf{Chronic p-RfC} &= BMCL_{HEC} \div UF_C \\ &= 126 \text{ mg/m}^3 \div 1{,}000 \\ &= \mathbf{1 \times 10^{-1} \text{ mg/m}^3} \end{aligned}$$

Table 10 summarizes the UFs for the chronic p-RfC for carbonyl sulfide.

Table 10. Uncertainty Factors for the Chronic p-RfC for Carbonyl Sulfide

UF	Value	Justification
UF_A	3	A UF_A of 3 ($10^{0.5}$) is applied to account for residual uncertainty associated with extrapolating from animals to humans, using toxicokinetic cross-species dosimetric adjustment for extrarespiratory effects from a category 3 gas, as specified in U.S. EPA (1994c) guidelines for deriving RfCs.
UF_H	10	A UF_H of 10 is applied to account for human variability in susceptibility, in the absence of information to assess toxicokinetic and toxicodynamic variability of carbonyl sulfide in humans.
UF_D	3	A UF_D of 3 ($10^{0.5}$) is applied to account for deficiencies and uncertainties in the database. The critical effect is defined in subchronic-duration studies in rats. The database also includes two adequate one-generation reproductive toxicity studies in rats and a limited report on developmental toxicity study. The database lacks a multigenerational reproductive toxicity study and a comprehensive report of a developmental toxicity study.
UF_L	1	A UF_L of 1 is applied because the POD is a BMCL value.
UF_S	10	A UF_S of 10 is applied to account for uncertainty in deriving the screening chronic p-RfC based on subchronic duration studies.
UF_C	1,000	Composite UF = $UF_A \times UF_H \times UF_D \times UF_L \times UF_S$

The confidence descriptors for the chronic p-RfC are described in Table 11.

Table 11. Confidence Descriptors for the Chronic p-RfC for Carbonyl Sulfide		
Confidence Categories	**Designation[a]**	**Discussion**
Confidence in study	M	Confidence in the principal study is medium. While the principal study (Morgan et al., 2004) contains reasonable numbers of rats of each sex and appears to be a well-conducted study reported in the peer-reviewed literature, the study is restricted to neurological endpoints.
Confidence in database	L	Confidence in the database is low because it contains several subchronic-duration inhalation studies, and one generation reproductive toxicity studies. However, the database lacks an inhalation study of chronic duration, a multigenerational reproductive toxicity study, and an adequate report of developmental toxicity study.
Confidence in chronic p-RfC[b]	L	The overall confidence in the chronic p-RfC is low.

[a]L = low; M = medium.

CANCER WEIGHT-OF-EVIDENCE DESCRIPTOR

Table 12 identifies the cancer weight-of-evidence (WOE) descriptor for carbonyl sulfide.

Table 12. Cancer WOE Descriptor for Carbonyl Sulfide (CASRN 463-58-1)			
Possible WOE Descriptor	**Designation**	**Route of Entry (oral, inhalation, or both)**	**Comments**
"Carcinogenic to Humans"	NS	NA	No human data are available.
"Likely to Be Carcinogenic to Humans"	NS	NA	No adequate chronic-duration animal cancer bioassays are available.
"Suggestive Evidence of Carcinogenic Potential"	NS	NA	No adequate chronic-duration animal cancer bioassays are available.
"Inadequate Information to Assess Carcinogenic Potential"	**Selected**	**NA**	**No adequate chronic-duration animal cancer bioassays are available. No studies are available assessing the carcinogenic potential of carbonyl sulfide in humans or animals.**
"Not Likely to Be Carcinogenic to Humans"	NS	NA	No evidence of noncarcinogenicity is available. No adequate chronic-duration animal cancer bioassays are available.

NA = not applicable; NS = not selected

DERIVATION OF PROVISIONAL CANCER POTENCY VALUES

Derivation of Provisional Oral Slope Factor (p-OSF)

Not derived due to inadequate data.

Derivation of Provisional Inhalation Unit Risk (p-IUR)

Not derived due to inadequate data.

APPENDIX A. SCREENING PROVISIONAL VALUES

No screening values are derived.

APPENDIX B. DATA TABLES

Table B-1. Survival, Clinical Signs, Body Weight, and Methemoglobinemia Findings in Male and Female Rats after Inhalation Exposure to Carbonyl Sulfide for 2 Weeks (6 Hours/Day, 5 Days/Week)[a]

Parameter	Exposure Group, ppm Carbonyl Sulfide (HEC in mg/m^3)[b]				
Male	**0**	**51 (22)**	**151 (66)**	**253 (111)**	**453 (199)**
Sacrificed in moribund condition	0/10	0/10	0/10	0/10	2/10
Clinical signs of neurotoxicity[c]	0/10	1/10	0/10	0/10	3/10
Terminal body weight (g)[d]	237.6 ± 7.78	236.7 ± 12.42 (0%)	235.1 ± 9.60 (−1%)	241.8 ± 10.83 (+2%)	228.5 ± 9.61 (−4%)
Methemoglobinemia (%)[d]	0.8 ± 0.2	1.0 ± 0.1 (+25%)	1.3 ± 0.1* (+63%)	1.6 ± 0.3* (+100%)	2.1 ± 0.2* (+163%)
Female	**0**	**51 (22)**	**151 (66)**	**253 (111)**	**453 (199)**
Sacrificed in moribund condition	0/10	0/10	0/10	0/10	3/10
Clinical signs of neurotoxicity	0/10	0/10	0/10	0/10	7/10[e]
Terminal body weight (g)[d]	162.4 ± 5.13	162.3 ± 4.37 (0%)	164.9 ± 4.72 (+2%)	161 ± 6.27 (−1%)	154 ± 5.97* (−5%)
Methemoglobinemia (%)[d]	1.0 ± 0.2	1.0 ± 0.1 (0%)	1.4 ± 0.1* (+40%)	1.8 ± 0.2* (+80%)	2.3 ± 0.2* (+130%)

[a]Monsanto (1985).

[b]Concentrations have been converted to HECs of 0, 22, 66, 111, and 199 mg/m^3 based on the following equation: $CONC_{HEC} = CONC_{ppm} \times$ (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × blood:air partition coefficient ratio (U.S. EPA, 1994c); molecular weight = 60.08 g/mol. The values for the human and rat blood:air partition coefficients are unknown, so the default ratio of 1 was applied.

[c]Clinical signs were observed during Week 2, and included ataxia, head tilt, circling, pivoting, prostrate and arched back postures, tremors, loss of muscular control, convulsions, and bulging, dilated eyes.

[d]Values are expressed as mean ± SD (percent change compared with control); percent change control = [(treatment mean − control mean) ÷ control mean] × 100.

[e]Statistically significantly different from controls at $p < 0.05$, as calculated for this review (Fisher's exact test).

*Statistically significantly different from controls at $p < 0.05$, as reported by study authors (Dunnett's test).

Table B-2. Necrotic Brain Lesions observed in Male and Female Rats after Inhalation Exposure to Carbonyl Sulfide for 2 Weeks (6 Hours/Day, 5 Days/Week)[a]

Parameter	Exposure Group, ppm Carbonyl Sulfide (HEC in mg/m^3)[b]			
	0	300 (132)	400 (176)	500 (219)
Male				
Parietal cortex area 1	0/10	0/10	5/10*	6/6*
Retrosplenial cortex	0/10	0/10	0/10	4/6*
Putamen	0/10	0/10	5/10*	6/6*
Thalamus (necrosis or vacuolization)	0/10	0/10	0/10	2/6
Posterior colliculus	0/10	0/10	2/7	3/3*
Anterior olivary nucleus	0/10	0/10	0/10	5/6*
Female				
Parietal cortex area 1	0/10	1/10	8/10*	10/10*
Retrosplenial cortex	0/10	0/10	0/10	7/10*
Putamen	0/10	0/10	6/10*	8/9*
Thalamus (necrosis or vacuolization)	0/10	0/10	0/10	6/10*
Posterior colliculus	0/10	0/10	3/9	8/10*
Anterior olivary nucleus	0/8	0/10	0/10	6/10*

[a]Morgan et al. (2004).

[b]Concentrations have been converted to HECs of 0, 132, 176, and 219 mg/m^3 based on the following equation: $CONC_{HEC} = CONC_{ppm} \times$ (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × blood:air partition coefficient ratio (U.S. EPA, 1994c); molecular weight = 60.08 g/mol. The values for the human and rat blood:air partition coefficients are unknown, so the default ratio of 1 was applied.

*Statistically significantly different from controls at $p < 0.05$, as reported by study authors (Fisher's exact test).

Table B-3. Survival, Cholesterol Parameters, and Histological Findings in Female Rabbits After Continuous Inhalation Exposure to Carbonyl Sulfide for 7 Weeks[a]

Parameter	Exposure Group, ppm Carbonyl Sulfide (HEC in mg/m^3)[b]	
	0	54 (130)
Survival		
Animals dead or sacrificed moribund	0/17	5/18[c]
Aortic free cholesterol[d]		
Number of animals examined	7	9
Inner intima and internal media layers (nmole/mg tissue)	2.9 ± 0.2	3.2 ± 0.3 (+10%)
Outer media layer (nmole/mg tissue)	1.8 ± 0.1	2.2 ± 0.2* (+22%)
Cholesterol dynamics[d]		
Number of animals analyzed using direct injection[e]	4	4
Uptake of labelled plasma total cholesterol by the aortic wall (nmole/g tissue/hr)	2.7 ± 0.2	3.8 ± 0.8 (+41%)
Number of animals analyzed using donor plasma injection[f]	3	3
Uptake of labelled plasma total cholesterol by the aortic wall (nmole/g tissue/hr)	1.4 ± 0.3	1.5 ± 0.1 (+7%)
Histology		
Number of animals with abnormal morphology		
Coronary arteries	0/8	0/7
Aortic arch	4/8	2/8
Thoracic aorta	4/8	2/8
Pulmonary arteries	2/8	1/8
Lungs	1/8	0/8
Number of animals with abnormal myocardial ultrastructure	4/8	0/8

[a]Hugod (1981); Hugod and Astrup (1980); Kamstrup and Hugod (1979).
[b]Analytical concentrations have been converted to HECs of 0 and 130 mg/m^3 based on the following equation: $CONC_{HEC} = CONC_{ppm} \times$ (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × blood:air partition coefficient ratio (U.S. EPA, 1994c); molecular weight = 60.08 g/mol. The values for the human and rat blood:air partition coefficients are unknown, so the default ratio of 1 was applied.
[c]Statistically significantly different from controls at $p < 0.05$, as calculated for this review (Fisher's exact test); deaths (three rabbits) or moribund state (two rabbits) occurred within the first 5 days of exposure.
[d]Values are expressed as mean ± SEM (percent change compared with control); percent change control = [(treatment mean − control mean) ÷ control mean] × 100.
[e]Blood samples were collected at intervals over 20 hours following injection of 1α,2α (N)-^{3}H-cholesterol dissolved in ethanol.
[f]Blood samples were collected at regular intervals for 5 hours following injection with in vivo labelled plasma, obtained from two donor rabbits injected with 1α,2α (N)-^{3}H-cholesterol 20 hours prior to bleeding.
*Statistically significantly different from controls at $p < 0.05$, as calculated by study authors (statistical test not reported).

Table B-4. Histological Brain Lesions Observed in Male and Female Rats After Inhalation Exposure to Carbonyl Sulfide for 12 Weeks (6 Hours/Day, 5 Days/Week)[a]

Parameter	Exposure Group, ppm Carbonyl Sulfide (HEC in mg/m^3)[b]		
	0	300 (132)	400 (176)
Male			
Posterior colliculus			
Neuronal loss or microgliosis	0/9	0/9	7/9*
Hemorrhage	0/9	0/9	2/9
Parietal cortex area 1			
Cortical necrosis or cavitation	0/10	0/10	5/10*
Putamen			
Necrosis or cavitation	0/10	0/10	2/10
Thalamus			
Necrosis	0/10	0/10	1/10
Lateral anterior olivary nucleus			
Neuronal loss or microgliosis	0/10	0/9	1/10
Female			
Posterior colliculus			
Neuronal loss or microgliosis	0/9	0/9	5/9*
Hemorrhage	0/9	0/9	1/9
Parietal cortex area 1			
Cortical necrosis	0/10	0/10	4/10*
Putamen			
Necrosis or cavitation	0/10	0/10	0/10
Thalamus			
Necrosis	0/10	0/10	0/10
Lateral anterior olivary nucleus			
Neuronal loss or microgliosis	0/9	0/10	0/9

[a]Morgan et al. (2004).

[b]Concentrations have been converted to HECs of 0, 132, and 176 mg/m^3 based on the following equation: $CONC_{HEC} = CONC_{ppm} \times$ (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × blood:air partition coefficient ratio (U.S. EPA, 1994c); molecular weight = 60.08 g/mol. The values for the human and rat blood:air partition coefficients are unknown, so the default ratio of 1 was applied.

*Statistically significantly different from controls at $p < 0.05$, as reported by study authors (Fisher's exact test).

Table B-5. SEP and BAERs in Male and Female Rats (Combined) After Inhalation Exposure to Carbonyl Sulfide for 12 Weeks (6 Hours/Day, 5 Days/Week)[a]

Parameter	Exposure Group, ppm Carbonyl Sulfide (HEC in mg/m^3)[b]			
	0	**200 (87.8)**	**300 (132)**	**400 (176)**
Animal number	25	30	27	28
SEP1$_{cortex}$ (hindlimb/tail region)[c]				
$P_{14}N_{27}$ peak amplitude (μV)	41.83 ± 4.69	43.33 ± 4.51 (+4%)	41.08 ± 3.38 (−2%)	60.42 ± 6.57* (+44%)
N_{27} peak latency (μV)	23.08 ± 0.39	25.11 ± 0.66 (+9%)	24.71 ± 0.39 (+7%)	25.88 ± 0.72† (+12%)
P_{36} peak latency (μV)	27.57 ± 0.59	29.6 ± 0.66 (+7%)	29.92 ± 0.59 (+9%)	30.84 ± 0.85† (+12%)
SEP2$_{cortex}$ (facial region)[c]				
$P_{16}N_{21}$ peak amplitude (μV)	10.62 ± 0.79	11.83 ± 0.65 (+11%)	10.48 ± 0.98 (−1%)	15.94 ± 1.36* (+50%)
BAER—click stimulus (80 dB)[d]				
P3 peak amplitude (μV)	12.62	12.45 (−1%)	13.04 (+3%)	9.92 (−21%)
P4 peak amplitude (μV)	20.44	20.81 (+2%)	20.32 (−1%)	12.1* (−41%)
P5 peak amplitude (μV)	14.06	14.62 (+4%)	14.34 (+2%)	10.79* (−23%)
P6 peak amplitude (μV)	7.54	7.09 (−6%)	7.54 (0%)	9.41* (+25%)
BAER—4 kHz tone pip stimulus (80 dB)[d]				
P4 peak amplitude (μV)	7.81	8.42 (+8%)	7.32 (−6%)	4.87* (−38%)
BAER—16 kHz tone pip stimulus (80 dB)[d]				
P4 peak amplitude (μV)	13.9	13.53 (−3%)	13.29 (−4%)	6.73* (−52%)
BAER—64 kHz tone pip stimulus (80 dB)[d]				
P4 peak amplitude (μV)	6.75	6.5 (−4%)	5.29 (−22%)	3.59 (−47%)

[a]Herr et al. (2007).

[b]Concentrations have been converted to HECs of 0, 87.8, 132, and 176 mg/m^3 based on the following equation: $CONC_{HEC} = CONC_{ppm} \times$ (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × (days exposed ÷ 7 days) × blood:air partition coefficient ratio (U.S. EPA, 1994c); molecular weight = 60.08 g/mol. The values for the human and rat blood:air partition coefficients are unknown, so the default ratio of 1 was applied.

[c]SEP values were extracted from Figure 2 in the primary report using GrabIt! software. Values are presented as means ± SEM (percent change compared with control); percent change control = [(treatment mean − control mean) ÷ control mean] × 100.

[d]BAER mean values for 80-dB peak sound pressure level intensity were extracted from Figures 4−6 in the primary report using GrabIt! software. Values are presented as means (percent change compared with control); percent change control = [(treatment mean − control mean) ÷ control mean] × 100. SEM values could not be extracted.

*Statistically significantly different from controls at $p < 0.05$, based on statistics reported by study authors (step-down ANOVA).

†Statistically significant concentration-related trend at $p < 0.05$, as reported by study authors (ANOVA).

SEP = sensory evoked potential; BAER = brainstem auditory evoked response.

Table B-6. Reproductive Performance of Male and Female Rats Exposed to Carbonyl Sulfide for 5 Days/Week for ~11 Weeks Followed by 7 Exposure Days (Premating) and Exposure 7 Days/Week during Mating to an Unexposed Partner (6 Hours/Day)[a]

Parameter	Exposure Group, ppm Carbonyl Sulfide (HEC in mg/m^3)[b]			
Study 1: exposed females and unexposed males	**0**	**10 (4.6)**	**60 (27)**	**182 (84)**
Mating index (% copulation)	20/24 (83%)	21/24 (88%)	23/24 (96%)	23/24 (96%)
Pregnancy index of mated females (% pregnant)	16/20 (80%)	17/21 (81%)	17/23 (74%)	19/23 (83%)
Precoital length (d)[c]	3.5 ± 2.8	3.2 ± 2.3 (−9%)	3.3 ± 1.9 (−6%)	3.1 ± 2.0 (−11%)
Gestation length (d)[c]	22.3 ± 0.6	22.2 ± 0.4 (0%)	22.4 ± 0.5 (0%)	22.7 ± 0.7 (+2%)
Live pups/litter[d]	12.5	12.9 (+3%)	13.2 (+6%)	10.6 (−15%)
Study 2: exposed males and unexposed females	**0**	**10 (4.7)**	**60 (28)**	**182 (84)**
F1a generation				
Mating index (% copulation)	23/24 (96%)	23/24 (96%)	23/24 (96%)	21/24 (88%)
Pregnancy index of mated females (% pregnant)	20/23 (87%)	20/23 (87%)	20/23 (87%)	12/21 (57%)[e]
Precoital length (d)[c]	3.6 ± 2.4	3.4 ± 2.4 (−6%)	3.3 ± 2.4 (−8%)	2.9 ± 1.9 (−19%)
Gestation length (d)[c]	22.1 ± 0.4	22.3 ± 0.6 (+1%)	22.1 ± 0.4 (0%)	22.3 ± 0.5 (+1%)
Live pups/litter[d]	12.4	12.6 (+2%)	13.3 (+7%)	11.8 (−5%)
F1b generation				
Mating index (% copulation)	44/48 (92%)	48/48 (100%)	48/48 (100%)	46/48 (96%)
Pregnancy index of mated females (% pregnant)	43/44 (98%)	46/48 (96%)	45/48 (94%)	44/46 (96%)
Precoital length (d)[c]	2.7 ± 1.3	3.0 ± 1.9 (+11%)	2.6 ± 1.3 (−4%)	3.0 ± 1.9 (+11%)
Gestation length (d)[c]	22.0 ± 0.2	22.2 ± 0.4 (+1%)	22.1 ± 0.3 (0%)	22.1 ± 0.3 (0%)
Live pups/litter[d]	13.0	11.7 (−10%)	12.9 (−1%)	13.0 (0%)

[a]Monsanto (1979).

[b]TWA analytical concentrations have been converted to HECs of 0, 4.6, 27, and 84 mg/m^3 based on the following equation: $CONC_{HEC}$ = [(number of weeks exposed 5 days/week × ($CONC_{ppm}$ × (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × (5 days ÷ 7 days) × blood:air partition coefficient ratio) + [(number of weeks exposed 7 days/week × ($CONC_{ppm}$ × (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × blood:air partition coefficient ratio)] ÷ total number of weeks (U.S. EPA, 1994c); molecular weight = 60.08 g/mol. The values for the human and rat blood:air partition coefficients are unknown, so the default ratio of 1 was applied.

[c]Values are presented as means ± SD (percent change compared with control); percent change control = [(treatment mean − control mean)/control mean] × 100.

[d]Values are presented as means (percent change compared with control); percent change control = [(treatment mean − control mean)/control mean] × 100.

[e]Finding is borderline significant (as reported by study authors): it is statistically significantly different from controls at $p < 0.05$ in the uncorrected χ^2 and Fisher's test, but no longer statistically significant following the Bonferroni correction ($p > 0.05$).

SD = standard deviation.

Table B-7. Liver Weights and Histology in F1 Male and Female Weanlings Exposed to Carbonyl Sulfide via Dams on GDs 0−19 (6 Hours/Day, 5 Days/Week)[a]

Parameter[b]	Exposure Group, ppm Carbonyl Sulfide (HEC in mg/m^3)[c]			
	0	**10 (4.6)**	**60 (27)**	**182 (84)**
Males	10	10	10	10
Liver weight				
Absolute (g)	3.792 ± 0.196	3.411 ± 0.191 (−10%)	2.937 ± 0.174* (−23%)	2.980 ± 0.247*† (−21%)
Relative (% body weight)	6.783 ± 0.189	6.502 ± 0.189 (−4%)	5.256 ± 0.242* (−23%)	5.590 ± 0.381* (−18%)
Liver histology				
Number of animals with lesion[d]	0/10	ND	ND	2/10
Females	10	10	10	10
Liver weight				
Absolute (g)	3.604 ± 0.211	3.666 ± 0.198 (+2%)	3.669 ± 0.163 (+2%)	3.510 ± 0.331 (−3%)
Relative (% body weight)	7.419 ± 0.351	7.347 ± 0.374 (−1%)	6.797 ± 0.216 (−8%)	6.842 ± 0.551 (−8%)
Liver histology				
Number of animals with lesion[d]	1/10	ND	ND	2/10

[a]Monsanto (1979).
[b]Values are presented as means ± SEM (% change compared with control); % change control = [(treatment mean − control mean) ÷ control mean] × 100.
[c]TWA analytical concentrations have been converted to HECs of 0, 4.6, 27, and 84 mg/m^3 based on the following equation: $CONC_{HEC}$ = [(number of weeks exposed 5 days/week × ($CONC_{ppm}$ × (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × (5 days ÷ 7 days) × blood:air partition coefficient ratio) + [(number of weeks exposed 7 days/week × ($CONC_{ppm}$ × (molecular weight ÷ 24.45) × (hours exposed ÷ 24 hours) × blood:air partition coefficient ratio)] ÷ total number of weeks (U.S. EPA, 1994c); molecular weight = 60.08 g/mol. The values for the human and rat blood:air partition coefficients are unknown, so the default ratio of 1 was applied.
[d]All animals with liver lesions presented with extramedullary hematopoiesis. No other liver lesions were observed.
*Statistically significantly different from controls at $p < 0.05$, as reported by study authors (Absolute: Dunnett's multiple comparison test; Relative: Mann-Whitney test with Bonferroni inequality procedure).
†Statistically significant concentration-related trend at $p < 0.05$, as reported by study authors (ANOVA).

ND = not determined by study author.

APPENDIX C. SUMMARIES OF SUPPORTING DATA

Table C-1. Summary of Carbonyl Sulfide Genotoxicity

Endpoint	Test System	Dose/ Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Genotoxicity studies in prokaryotic organisms						
Mutation	*S. typhimurium* strain TA97, TA98, TA100, TA1535	0, 0.58, 1.15, 1.73, 2.31, 2.89 µg/plate	(+) TA97 (−) TA98, TA100, TA1535	(+) TA97 (−) TA98, TA100, TA1535	The number of reversions in TA97 was increased 1.5−2-fold at 1.73−2.31 µg/plate. Cytotoxicity occurred at 2.89 µg/plate. Positive controls produced >2-fold more reversion colonies than negative control.	NTP (1995)
Mutation	*S. typhimurium* strain TA97, TA98, TA100, TA102	50,000 mg/m^3	−	−	Positive controls (4QNO, 2-AF) produced >2-fold more reversion colonies than negative control.	Wang et al. (1999)
Mutation	*E. coli* of tryptophan auxotroph (WP_2, WP_{2UVRA}, CMR891), *E. coli* of lactose and VB2 auxotroph (ND_{160} MR_{2-102})	1,000 mg/m^3	−	−	Positive controls (4QNO, 2-AF) produced >2-fold more reversion colonies than negative control.	Wang et al. (1999)
Genotoxicity studies in nonmammalian eukaryotic organisms						
ND						
Genotoxicity studies in mammalian cells—in vitro						
ND						
Genotoxicity studies in mammals—in vivo						
Mouse bone marrow MN test (inhalation)	Mouse (10/group, unspecified strain and sex); 2 inhalation exposures, 2 hr/exposure at 1 and 24 hr; sacrifice 30 hr after second exposure	2,000 mg/m^3	−			Wang et al. (1999)

Table C-1. Summary of Carbonyl Sulfide Genotoxicity

Endpoint	Test System	Dose/ Concentration[a]	Results[b]		Comments	References
			Without Activation	With Activation		
Mouse bone marrow MN test (oral)	Mouse (10/group, unspecified strain and sex); 2 doses via gavage in plant oil at 1 and 24 hr; sacrifice 30 hr after second exposure.	100 mg/kg per dose	−			Wang et al. (1999)
CAs in mouse spermatocytes (inhalation)	Mouse (unspecified number, strain, and sex); inhalation exposure for 2 hr/d for 5 d; sacrifice 13 d postexposure.	1,000 mg/m^3	−			Wang et al. (1999)
CAs in mouse spermatocytes (oral)	Mouse (unspecified number, strain, and sex); once daily exposure via gavage in plant oil for an unspecified number of days; sacrifice 13 d later.	100 mg/kg-d	−			Wang et al. (1999)
Genotoxicity studies in subcellular systems						
No data.						

[a]Highest dose tested for negative results.
[b](+) = weak positive; − = negative.

ND = no data.

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Supporting evidence—cancer effects in humans				
ND				
Supporting evidence—noncancer effects in humans				
Case report	NA	Upon hospitalization, upper respiratory distress, nausea, severe anemia, and the beginning of acute renal failure were noted in a man who was exposed for "seconds to minutes" to a combination of carbonyl sulfide, hydrogen sulfide, and nitrogen gas.	Following hospitalization, rest, and rehydration, the subject recovered fully. Given the apparently short latency between exposure and hospitalization, and the exposure to a mixture of gases, the likelihood that exposure to carbonyl sulfide was involved in the etiology of the effects noted cannot be determined.	Praxair (2003)
Case report	NA	A construction worker became ill following brief exposure to a gaseous mixture of carbonyl sulfide, carbon disulfide, and sulfur dioxide. Specific symptoms were not available. Exposure was estimated to be 1,000 ppm of each gas (2,457 mg/m^3 carbonyl sulfide).	Patient responded to inhaled arynyl nitrite and intravenous sodium; recovery period was not specified. Study authors concluded that the poisoning was due to metabolism of carbonyl sulfide into hydrogen sulfide.	Benson et al (1996) as cited in ACGIH (2012)
Case report	NA	Following acute, intentional exposure to "pure carbonyl sulfide gas," a man reported dizziness, inability to stand, chest pressure, and ringing in the ears after ~10 sec. Symptoms ceased ~2 min after cessation of exposure.	Effects following acute high exposures of a human subject were rapid and transient.	Klason (1887) as cited in Bartholomaeus and Haritos (2005)

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Supporting evidence—cancer in animals				
Carcinogenicity (oral)	In a poorly reported study, weanling S-D rats were fed basal diet fumigated with 0, 20,000, 50,000, 100,000, 200,000, or 500,000 mg/m^3 for 2 yr (25/group; sex unspecified). Details for pathological examination methods were not provided. The amount of compound absorbed by the feed during fumigation was not determined; therefore, compound consumption levels are unknown.	The average life span was significantly decreased in males from the 100,000-, 200,000-, and 500,000-mg/m^3 groups. No compound-related "pathological" or "tumorous" changes were observed.	Carbonyl sulfide was not a carcinogenic compound under the test conditions; however, confidence in this study is low due to inadequate reporting and unknown compound consumption levels.	Wang et al. (1999)

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Supporting evidence—noncancer effects in animals				
Subchronic, chronic, (oral)	In a series of poorly reported studies, weanling S-D rats were fed basal diet fumigated with 0, 20,000, 50,000, 100,000, 200,000, or 500,000 mg/m^3 for various durations Subchronic: 90 d (males and females; number unspecified) Chronic: 12, 18, or 24 mo (4−11/sex/group per time point) Study descriptions were brief and details on reported effects were limited. Endpoints available are in the results column; it is unclear whether other endpoints were assessed. Details for pathological examination methods were not provided. The amount of compound absorbed by the feed during fumigation was not determined; therefore, compound consumption levels are unknown.	Subchronic: No treatment-related changes were observed in body weight or relative organ weights. No pathological abnormality was observed in the "main organs." Food consumption was significantly increased in high-dose females. The percentage of lymphocytes was significantly elevated and the percentage of neutrophils was significantly depressed in male rats in the 200,000- and 500,000-mg/m^3 groups. No other exposure-related hematological changes were observed. Serum albumin levels were significantly elevated in all exposed male rats except the 20,000-mg/m^3 group. Chronic: The only significant, exposure-related findings were decreased hemoglobin in the 100,000-, 200,000-, or 500,000-mg/m^3 females after 6 mo and males after 12 mo. ALP was significantly increased in 500,000-mg/m^3 males. No "special pathological injurions [sic]" were observed in exposed groups.	Subchronic- and chronic-duration studies: No consistent exposure-related effects were found across studies. Reliable NOAEL/LOAEL determinations could not be made due to inadequate reporting and unknown compound consumption levels.	Wang et al. (1999)
Subchronic (inhalation)	Male and female S-D rats (number unspecified) were exposed to 0, 10, 60, or 182 ppm (0, 25, 147, or 447 mg/m^3), 6 hr/d, 5 d/wk for ~14 wk.	Body weight was decreased in all exposed males, but findings were not concentration related. No treatment-related changes in clinical chemistry were observed. Lymphopenia was observed in all exposed males; however, findings in males were not concentration related.	The full report is unavailable. Due to lack of details in the study summary, reliable NOAEL/LOAEL determinations could not be made. The toxicological significance of lymphopenia cannot be determined without review of the magnitude and pattern of response.	DuPont (1992)

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Reproductive/ developmental studies (oral)	Developmental and reproductive toxicity were assessed in S-D rats fed diets fumigated with 0, 20,000, 50,000, 100,000, 200,000, or 500,000 mg/m^3 carbonyl sulfide. The amount of compound absorbed by the feed during fumigation was not determined; therefore, compound consumption levels in these studies are unknown. Developmental study: Gestation (days not specified); 9−12 dams/group; (20,000- and 50,000-mg/m^3 groups were not included). One generation study: Male and female weanlings (10−11/sex/group) were exposed for 90 d prior to within-group mating. It is unclear if carbonyl sulfide exposure continued through mating and gestation. Two generation study: F0 and F1 male and female weanlings (20−24/sex/group per generation) were exposed for 100 d prior to within-group mating. Exposure continued during gestation and lactation.	Developmental study: There were no exposure-related changes in fetal body weight, number of live or dead fetuses, or number of resorptions. No external or skeletal abnormalities were observed. One-generation study: Fetal body weight was statistically significantly lower in the 100,000-, 200,000-, and 500,000-mg/m^3 groups. No significant, exposure-related changes in the number of live or dead fetuses or the number of resorptions were observed. It is not clear if fetuses were examined for external, internal, or skeletal abnormalities. No reproductive indices were reported. Two-generation study: There were no exposure-related changes in mating or pregnancy rate or the number of live pups. The percent survival at weaning was significantly decreased in the F1 500,000-mg/m^3 group and the F2 200,000- and 500,000-mg/m^3 groups. The study authors suggest that this indicates decreased lactation in dams exposed to higher concentrations; however, no data were provided to support this hypothesis. It is not clear whether fetuses were examined for external, internal, or skeletal abnormalities.	Developmental study: Carbonyl sulfide was not a developmental toxicant under the test conditions; however, reliable NOAEL/LOAEL determinations could not be made due to unknown compound consumption levels. One-generation study: Exposure to carbonyl sulfide prior to mating (and potentially during mating and gestation) led to decreased fetal body weight at high concentrations; however, reliable NOAEL/LOAEL determinations could not be made due to unknown compound consumption levels. Two-generation study: Carbonyl sulfide was not a reproductive toxicant under the exposure conditions. Exposure to carbonyl sulfide led to decreased postnatal survival in both the F1 and F2 generations; however, reliable NOAEL/LOAEL determinations could not be made due to unknown compound consumption levels.	Wang et al. (1999)

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Developmental studies (inhalation)	Study 1: Pregnant rats (strain and number not specified) were exposed daily for 6 hr to 50, 149, 250, 348, or 451 ppm (123, 366, 614, 855, or 1,108 mg/m^3) carbonyl sulfide on GDs 6−15. Day of sacrifice was not reported, and it is unclear whether a concurrent control group was used. Study 2: Pregnant S-D rats (number not specified) were exposed to 0, 50, 200, or 400 ppm (0, 123, 491, or 983 mg/m^3) carbonyl sulfide on GDs 6−15 (daily duration not reported). Dams were sacrificed on GD 21.	Study 1: Maternal toxicity was evident in dams exposed to 855 and 1,108 mg/m^3 (decreased weight gain during treatment period). One high-exposure dam died. No exposure-related effects were noted for litter size, live fetuses/litter, or total resorptions. No abnormalities were noted during gross fetal examination. Study 2: Maternal toxicity was evident in dams exposed to 983 mg/m^3 (decreased weight gain and food consumption, maternal death). No exposure-related effects were noted for pregnancy rate, reproductive parameters, fetal body weights, or fetal sex distribution. No exposure-related gross, visceral, or skeletal malformations or variations were attributed to treatment.	The study summary suggests that carbonyl sulfide did not cause developmental toxicity, even at maternally toxic doses. However, because the full report is unavailable, data cannot be independently reviewed and reliable NOAEL/LOAEL determinations cannot be made.	DuPont (1992) (unpublished report summary; full report unavailable)
One-generation reproduction (inhalation)	Male S-D rats (number unspecified) were exposed to 0, 10, 60, or 182 ppm (0, 25, 147, or 447 mg/m^3), 6 hr/d, 5 d/wk for ~14 wk.	Body weight was decreased in all exposed males, but findings were not concentration-related. A 40% reduction in pregnancy rates resulting from male high dose exposure were noted. Lymphopenia was observed in all exposed males; however, findings in males were not concentration-related.	The full report is unavailable. Due to lack of details in the study summary, reliable NOAEL/LOAEL determinations could not be made. The toxicological significance of lymphopenia cannot be determined without review of the magnitude and pattern of response.	DuPont (1992) (unpublished report summary; full report unavailable)

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
One-generation reproduction (inhalation)	Female S-D rats (number unspecified) were exposed to 0, 10, 60, or 182 ppm (0, 25, 147, or 447 mg/m^3), 6 hr/d, 5 d/wk for ~14 wk.	No exposure-related effects were observed in urinalysis, clinical chemistry, gross or histological pathology, pupillary reflexes, or clinical signs of toxicity. "Equivocal decreases in male weanling liver weight" were observed at 60 and 182 ppm accompanying premating exposure of female rats. Lymphopenia was observed in high-exposure females.	The full report is unavailable. Due to lack of details in the study summary, reliable NOAEL/LOAEL determinations could not be made. The toxicological significance of lymphopenia cannot be determined without review of the magnitude and pattern of response. Given the lack of details regarding reduction in liver weight, and the lack of an Agency-established benchmark response level for this effect, it was not given further consideration.	DuPont (1992) (unpublished report summary; full report unavailable)
Short-term-duration studies (inhalation)	S-D rats (10 males/10 females) were exposed to 2,000 mg/m^3, 2 hr/d for 14 d in a whole-body inhalation chamber. A 4 × 5 cm^2 area was clipped free of fur on the back of exposed rats.	No mortality or clinical signs of toxicity were observed. No skin or eye irritation was observed. No other endpoints were examined/reported.	Reliable conclusions cannot be drawn, as it is unclear if a control group was used. Skin and eye irritation were not assessed according to OECD guidelines.	Wang et al. (1999)
Short-term-duration studies (inhalation)	S-D rats (10 males, 10 females per group) were exposed 6 hr/day, 5 d/wk for 2 wk to 0, 51, 151, 253, or 453 ppm carbonyl sulfide.	Central nervous system dysfunction and sacrifice *in extremis* were reported for 2 males and 3 females in the high-dose group. Concentration-related increases in methemoglobinemia were reported at 151 ppm and higher concentrations.	The full report is unavailable. Due to lack of details in the study summary, reliable NOAEL/LOAEL determinations could not be made.	DuPont (1992) [This study seems to be a resubmission of Monsanto (1985)]
Neurotoxicity (inhalation)	F344 rats (5 males/group) were exposed to 0, 75, 150, 300, or 600 ppm (0, 184, 369, 737, or 1,474 mg/m^3), 6 hr/d for 4 d. At sacrifice, brains were removed and prepared for microscopy.	No mortality, morbidity, clinical signs of toxicity, or brain lesions were observed at ≤737 mg/m^3. At 1,474 mg/m^3, rats were moribund after 2 d showing hypothermia, lethargy, head tilt, and ataxia. Necrosis was observed by light microscopy in parietal cortex area 1, thalamus, retrosplenial granular cortex, red nucleus, cerebellar roof nucleus, posterior collicular nucleus, anterior olivary nucleus, and posterior colliculus.	The NOAEL for mortality, morbidity, clinical signs of CNS toxicity, and brain lesions was 737 mg/m^3 for 4 d. At 1,475 mg/m^3, 2 d of exposure produced clinical signs of CNS toxicity and brain lesions.	Morgan et al. (2004)

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Neurotoxicity (inhalation)	F344 rats (5 males/group) were exposed to 0, 75, 150, 300, or 600 ppm (0, 184, 369, 737, or 1,474 mg/m^3) for 6 hr and held for 2 wk without exposure. At sacrifice, brains were removed and prepared for microscopy.	No mortality, morbidity, clinical signs of toxicity or brain lesions were observed at ≤ 737 mg/m^3. At 1,474 mg/m^3, clinical signs during exposure were less severe than those observed with 2 6-hr exposures and diminished during 14 d of recovery, but several rats still showed ataxia and head tilt after 14 d. Brain lesions observed after 14 d in the 1,474 mg/m^3-group included microgliosis in the cerebellar roof nucleus, internal capsule, and thalamus and vacuolation of the cerebellar medullary white matter and 5th cranial nerve tract.	Clinical signs of CNS toxicity from 1,474 mg/m^3 diminished through a 14 d recovery period, but several rats still showed ataxia and head tilt at the end of the recovery period. The persistent signs of toxicity were linked with necrosis in several brain regions.	Morgan et al. (2004)
Neurotoxicity (inhalation)	F344 rats (6 males/group) were exposed to 0 or 600 ppm (0 or 1,475 mg/m^3), 6 hr/d for 2 d and held for 2 wk without exposure. After the 2-wk period, rats were sacrificed and injected with MRI contrast (Prohance). Specimens were evaluated with MRM. After MRM, brains were removed and prepared for light microscopy.	MRM detected lesions in multiple brain regions in the 1,475-mg/m^3 group, including the posterior thalamic nuclear group and zona inserta of the hypothalamus and the posterior colliculus. Light microscopy confirmed neuronal loss and microgliosis in the hypothalamus and neuronal loss, microgliosis, hemorrhage, and accumulation of hemosiderin laden macrophages in the posterior colliculus.	This study is primarily a methods paper, demonstrating that MRM is an effective tool for identifying brain lesions following chemical exposure. This study confirms previous reports that acute exposure to 1,475 mg/m^3 caused brain lesions detected by light microscopy (Morgan et al., 2004).	Sills et al. (2004)
Neurotoxicity (inhalation)	Groups of 15 male rats were exposed to concentrations of 0, 300, or 400 ppm (738 or 983 mg/m^3) carbonyl sulfide 6 hr/day, 5 d/wk for 2 wk. Rats were evaluated via FOB, CNS histopathology, and CNS electrophysiology was measured.	Brainstem and cortical evoked potentials, an increase in grossly observable cortical lesions, and increases in FOB alterations including decreased grip strength, slightly abnormal gait, and decreased motor activity were observed at 983, but not at 738 mg/m^3.	This preliminary investigation identified CNS alterations to be investigated more fully in 12-wk investigations by Morgan et al. (2004), Herr et al. (2007), Sills et al. (2004)	Herr et al. (2007)

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute lethality studies (inhalation)	Groups of 10 male Crl:CD rats were exposed to concentrations of 477, 943, 981, 1,050, 1,090, 1,160, 1,210, 1,270, or 2,180 ppm (1,098, 2,317, 2,411, 2,580, 2,678, 2,850, 2,973, 3,121, or 5,357 mg/m^3) carbonyl sulfide for up to 4 hr. Surviving rats were weighed and observed daily for a 14-d recovery period.	Deaths occurred in groups exposed to all concentrations ≥2,678 mg/m^3. The number of deaths occurring during exposure increased from 2/10 at 2,678 mg/m^3 to 10/10 at 5,357 mg/m^3. All deaths occurred between D 1 and 9 of the observation period. Clinical signs of toxicity increased with increasing exposure concentration. During exposure, these included labored breathing, impaired response to sound, lack of coordination, convulsion, head bobbing, and uncontrolled body movements. Postexposure signs included slight to severe body weight loss, lethargy, stained nose and mouth, partially closed eyes, and lack of righting reflex.	LC_{50} (4-hr) = 1,111 ppm (2,730 mg/m^3); 95% CI 1,058−1,158 ppm (2,600−2,846 mg/m^3).	DuPont (1992)

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute lethality studies (inhalation)	S-D rats (6 males/6 females) were exposed to concentrations of 804, 993, 1,062, 1,096, 1,147, or 1,189 ppm (1,976, 2,440, 2,610, 2,693, 2,818, or 2,922 mg/m^3) carbonyl sulfide for up to 4 hr. Surviving rats were observed for a 14-d period. Necropsy was performed on all animals found dead and rats sacrificed at the end of the observation period.	Deaths occurred in groups exposed to all concentrations ≥2,610 mg/m^3. The number of deaths occurring increased from 1/6 males and 3/6 females in the 2,610-mg/m^3 group to 6/6 males and 5/6 females in the 2,922-mg/m^3 group. All deaths except one occurred during or within 24 hr of exposure. Clinical signs of toxicity were observed during and immediately postexposure in rats exposed to 2,610−2,922 mg/m^3, including breathing difficulties, convulsions, tremors, and behavioral abnormalities. Postexposure signs included slight to severe body weight loss, stained nose and mouth, hypoactivity, and abnormal circling behavior. At necropsy, a concentration-related increase in lung congestion was observed in rats exposed to 2,610−2,922 mg/m^3.	LC_{50} (4-hr) = Combined: 1,082 ppm (2,659 mg/m^3); 95% CI 1,059−1,102 ppm (2,602−2,708 mg/m^3) Males:1,094 ppm (2,688 mg/m^3); 95% CI 1,055−1,136 (2,592−2,791 mg/m^3) Females: 1,070 ppm (2,629 mg/m^3); 95% CI 1,022−1,100 (2,511−2,703 mg/m^3) Slope of lethality curve = Combined: 60.8 Males: 59.2 Females: 71.0	Monsanto (1982)
Acute lethality studies (inhalation)	Lethality was determined in rats, guinea pigs, and rabbits exposed whole-body to 1,200, 2,450, or 3,185 mg/m^3 carbonyl sulfide for 75−120 min.	1,200 mg/m^3 (488 ppm): No deaths in any species (2 animals/species) exposed for 90 min. 2,450 mg/m^3 (997 ppm): Rats: 0/6 dead after 75 min, 3/6 dead after 90 min. Guinea pig: 0/6 dead after 90 min. Rabbit: 8/14 dead after 90 min, 2/4 dead after 120 min. 3,185 mg/m^3 (1,296 ppm): Guinea pig: no deaths after 90 min.	Guinea pigs appeared to be more resistant to the acute lethality of carbonyl sulfide than rats and rabbits.	Theiss et al. (1968) as cited in Bartholomaeus and Haritos (2005)

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Acute lethality studies (inhalation)	Individual white mice were exposed to carbonyl sulfide for various periods of time and observed for clinical signs of neurotoxicity and death.	Concentrations >3,000 mg/m^3 led to convulsions and prostration within a few minutes and death within ~45 min. At 2,200 mg/m^3, no clinical signs of toxicity were observed with exposure up to 16 min.	Data provided by Bartholomaeus and Haritos (2005) are inadequate to make NOAEL/LOAEL determinations; original manuscript is in German.	Klemenc (1943) as cited in Bartholomaeus and Haritos (2005)
Acute lethality studies (inhalation)	Other short-term-duration acute lethality studies with limited reporting of experimental details, as collected, reviewed, and reported by Bartholomaeus and Haritos (2005).	Mouse LC_{50} (35 min) = 2,940 mg/m^3.		Sax and Lewis (1986) as cited in Bartholomaeus and Haritos (2005)
		Mouse LC_{50} (unspecified duration) = 2,770 mg/m^3.		RTECS (1997) as cited in Bartholomaeus and Haritos (2005)
		Rabbit LC_{50} (unspecified duration) = 2,550 mg/m^3.		RTECS (1997) as cited in Bartholomaeus and Haritos (2005)
		Rats: 10-hr exposure to 1,200 mg/m^3 is lethal.		Hayashi et al. (1971) as cited in Bartholomaeus and Haritos (2005)
Acute lethality studies other than oral/inhalation	Male S-D rats (11−18/group) were given single i.p. injections of carbonyl sulfide gas at doses of 20, 25, and 30 mg/kg. It is not clear how long animals were observed following injections.	Death occurred within 10 min of dosing in 1/11, 11/18, and 13/18 rats from the 20-, 25-, and 30-mg/kg groups, respectively. Observed clinical signs of toxicity included ataxia, loss of righting reflex, cyanosis, difficulty breathing, and convulsions. Animals that did not die within 10 min recovered fully.	Rat LD_{50} (i.p.) = 22.5 mg/kg	Chengelis and Neal (1980)

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Studies of absorption, distribution, metabolism, or elimination (ADME)				
ADME	Metabolite formation was determined in rat hepatocyte cultures incubated with carbonyl sulfide gas. Metabolite formation was also measured following coincubation of CYP450 inhibitors (SKF 525-a, 4-methylpyrazole, or metyrapone), the CYP450 substrate carbon disulfide, and the carbonic anhydrase inhibitor acetazolamine. Additional studies measured carbonyl sulfide metabolism by bovine erythrocyte carbonic anhydrase.	Metabolites identified included CO_2, hydrogen sulfide, and thiosulfate. Formation of metabolites was inhibited by acetazolamine, but not carbon disulfide or inhibitors of CYP450. Bovine erythrocyte carbonic anhydrase also metabolized carbonyl sulfide into CO_2, hydrogen sulfide, and thiosulfate.	Findings indicate that carbonyl sulfide is a substrate for carbonic anhydrase. The proposed pathway is as follows: carbonic anhydrase catalyzes the formation of monothiocarbonic acid, which is hydrolyzed to CO_2 and hydrogen sulfide. Hydrogen sulfide is further hydrolyzed into thiosulfate and sulfate.	Dalvi and Neal (1978)
ADME	Mortality and blood levels of carbonyl sulfide and hydrogen sulfide were measured in male S-D rats following i.p. injections of carbonyl sulfide gas (20−30 mg/kg). A separate group of rats were pretreated with the carbonic anhydrase inhibitor acetazolamine or sodium nitrate (to decrease sulfide toxicity).	Animals exposed to 30 mg/kg that died within 10 min had blood hydrogen sulfide levels of 0.3−0.5 µmol/mL. However, animals sacrificed 10 min after exposure to 30 mg/kg that were pretreated with acetazolamine had "barely detectable" blood levels of hydrogen sulfide. Pretreatment with acetazolamine also decreased the carbonyl sulfide-induced mortality by ~40−50%. Pretreatment of rats with sodium nitrate completely protected rats from carbonyl sulfide toxicity (no mortalities).	Findings indicate that carbonyl sulfide is a substrate for carbonic anhydrase and that the metabolite hydrogen sulfide is responsible for observed acute toxicity.	Chengelis and Neal (1980)

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
ADME	The affinity of the bovine carbonic anhydrase II for carbonyl sulfide (0.05−3 mM) was measured using in vitro kinetic metabolism studies. Mortality in the *Tribolium castaneum* (flour beetle) larvae following exposure to carbonyl sulfide gas with and without pretreatment with the carbonic anhydrase inhibitor acetazolamine was also determined.	Carbonic anhydrase II has a high affinity for carbonyl sulfide. The metabolism of carbonyl sulfide to hydrogen sulfide yielded velocity curves used to calculate Michaelis-Menten parameters. Mean parameters for six replicate curves were K_m = 1.86 mM and the maximum turnover number (K_{cat}) = 41 s^{-1} at 25°C. Formation of hydrogen sulfide was inhibited by specific inhibitors of carbonic anhydrase (acetazolamide, ethoxyzolamide, and methazolamide), with IC_{50} values in the 20−50 nM range. Mortality in beetles was reduced 12-fold (at 35 mg/L carbonyl sulfide) following pretreatment with acetazolamine.	Findings indicate that carbonyl sulfide is a high-affinity substrate for carbonic anhydrase and that the metabolite, hydrogen sulfide, is responsible for observed acute toxicity in flour beetles.	Haritos and Dojchinov (2005)
ADME	The transfer of ^{35}S into goat milk was determined in lactating goats following a single feeding of grass contaminated aerially by carbonyl sulfide. ^{35}S transfer was also determined in goats given single oral doses of sulphate or L-methionine or a single feeding of grass contaminated by root uptake from soil contaminated with sulphate.	^{35}S was present in goat milk after all exposures. Concentrations were similar for all sources, except L-methionine, which led to significantly higher transfer levels. Double exponential curves demonstrated 2 phases of elimination, resulting in 2 half-life values ($T_{1/2(1)}$ and $T_{1/2(2)}$). For all sources, $T_{1/2(1)}$ was approximately 1 d. For all sources except grass contaminated with carbonyl sulfide, $T_{1/2(2)}$ was 9−14 d. In contrast, $T_{1/2(2)}$ was 44 d for grass contaminated with carbonyl sulfide.	^{35}S can be transferred to milk in lactating goats following oral exposure to carbonyl sulfide (and other ^{35}S sources). ^{35}S is eliminated from milk in 2 stages, with a short (~1 d) first half-life and a longer (>40 d) second half-life. Elimination of ^{35}S transferred from carbonyl sulfide is slower than ^{35}S transferred from other ^{35}S sources.	Howard et al. (2007)

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Studies of mode of action/mechanism				
Mode of action/mechanistic	F344 rats (5/sex/group) were exposed to 0, 200, 300, or 400 ppm (0, 737, 983, or 1,229 mg/m^3) 6 hr/d, 5 d/wk for 3, 6, or 12 wk in whole-body inhalation chambers. On D 24, 52, and 86, respectively, rats were sacrificed to determine brain cytochrome oxidase activity.	A concentration-dependent decrease in cytochrome oxidase was observed in the posterior colliculus and parietal cortex of exposed rats, brain regions that exhibit lesions and neuronal loss following short-term- and subchronic-duration carbonyl sulfide exposure (Morgan et al., 2004; Sills et al., 2004).	Inhibition of brain cytochrome oxidase could potentially limit oxidative phosphorylation, contributing to observed neuronal death in these brain regions following carbonyl sulfide exposure.	Morgan et al. (2004)

Table C-2. Other Studies

Test	Materials and Methods	Results	Conclusions	References
Mode of action/ mechanistic	Time-course study: F344 rats (15 males/group/time-point) were exposed to 0 or 500 ppm (0 or 1,229 mg/m^3) 6 hr/d for 1, 2, 3, 4, 5, 8, or 10 d. At sacrifice, brains were removed and prepared for microscopy (10/group) or assessed for neuronal degeneration (cupric silver method) and astrocytic response (GFAP immunohistochemistry). Gene expression study: F344 rats (males and females, 3/group per time point) were exposed to 0 or 500 ppm (0 or 1,229 mg/m^3) 6 hr/d for 1 or 2 d. After sacrifice, posterior colliculi were removed and processed for RNA isolation for microarray analysis (Aglient Rat Oligo Microarrays, ~22,000 probes). Significant microarray results (transcripts with a ≥1.3-fold change and a *p*-value ≤ 0.01) were verified with real-time polymerase chain reaction (RT-PCR).	Time-course study: Carbonyl sulfide induced lesions after ≥3 d of exposure. The posterior colliculus was most susceptible to damage. Following appearance of lesions, astrocytic response and neuronal degeneration occurred. Gene expression study: Gene expression in the posterior colliculus was assessed after 1- and 2-d exposures, prior to the onset of morphological change. Analysis indicated upregulation of genes involved in DNA damage and G1/S checkpoint regulation (KLF4, BTG2, GADD45g), apoptosis (TGM2, GADD45g, RIPK3), and vascular mediators (ADAMTS, CTGF, CYR61, VEGFC). Proinflammatory mediators (CCL2, CEBPD) were upregulated prior to increases in GFAP (astrocytic marker) and CSF2rb1 (macrophage marker).	Significant gene expression changes were observed at time points preceding morphological changes. These gene expression changes may be predictive of CNS lesions, and further study may lead to better mechanistic understanding of carbonyl sulfide-induced neurotoxicity.	Morrison et al. (2009)

CI = confidence interval; NA = not applicable; ND = no data; S-D = Sprague-Dawley.

APPENDIX D. BENCHMARK MODELING RESULTS

MODELING PROCEDURE FOR DICHOTOMOUS DATA

The benchmark dose (BMD) modeling of dichotomous data (neuronal loss or microgliosis, the most sensitive histopathological lesions of brain tissue, Table 6) was conducted with the U.S. EPA's Benchmark Dose Software (BMDS) (Version 2.5). For these data, all of the dichotomous models (i.e., Gamma, Multistage, Logistic, Log-logistic, Probit, Log-probit, and Weibull models) available within the software were fit using a default benchmark response (BMR) of 10% extra risk based on the U.S. EPA's *Benchmark Dose Technical Guidance Document* (U.S. EPA, 2012b). Adequacy of model fit was judged based on the χ^2 goodness-of-fit *p*-value ($p > 0.1$), magnitude of scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. Among all models providing adequate fit, the lowest benchmark dose lower confidence limit (BMDL) was selected if the BMDLs estimated from different models varied greater than threefold; otherwise, the BMDL from the model with the lowest Akaike's information criterion (AIC) was selected as a potential point of departure (POD) from which to derive a provisional oral reference dose (p-RfD).

In addition, data from exposures much higher than the study lowest-observed-adverse-effect level (LOAEL) do not provide reliable information regarding the shape of the response curve at low doses. However, such exposures can have a strong effect on the shape of the fitted model in the low-dose region of the dose-response curve in some cases. Thus, if lack of fit is due to characteristics associated with dose-response data for high doses, then the U.S. EPA's *Benchmark Dose Technical Guidance Document* allows for data to be adjusted by eliminating high-dose groups (U.S. EPA, 2012b).

MODELING PROCEDURE FOR CONTINUOUS DATA

The BMD modeling of continuous data (SEP1 and SEP2 evoked potentials, Table 6) was conducted with the U.S. EPA's BMDS (Version 2.5). For these data, all continuous models available within the software were fit using a default BMR of 1 standard deviation (SD) relative risk. For changes in body weight, a BMR of 10% change relative to the control mean was also used. An adequate fit was judged based on the goodness-of-fit *p*-value ($p > 0.1$), magnitude of the scaled residuals in the vicinity of the BMR, and visual inspection of the model fit. In addition to these three criteria for judging adequacy of model fit, a determination was made as to whether the variance across dose groups was constant. If a constant variance model was deemed appropriate based on the statistical test provided in BMDS (i.e., Test 2), the final BMD results were estimated from a constant variance model. If the test for homogeneity of variance was rejected ($p < 0.1$), the model was run again while modeling the variance as a power function of the mean to account for this nonconstant variance. If this nonconstant variance model did not adequately fit the variance data (i.e., Test 3; $p < 0.1$), the data set was considered unsuitable for BMD modeling. Among all models providing adequate fit, the lowest BMDL was selected if the BMDLs estimated from different models varied greater than 3-fold; otherwise, the BMDL from the model with the lowest AIC was selected as a potential POD from which to derive a p-RfD.

The following data sets were selected for BMD modeling:

- incidence data for neuronal loss or microgliosis in male rats (Morgan et al., 2004)
- incidence data for neuronal loss or microgliosis in female male rats (Morgan et al., 2004)
- continuous data for changes in SEP1 evoked potential in combined male and female rats (Herr et al., 2007)
- continuous data for changes in SEP2 evoked potential in combined male and female rats (Herr et al., 2007)

Data describing carbonyl sulfide dependent cortical necrosis (Morgan et al., 2004) were not modeled because this endpoint was less sensitive than neuronal loss of microgliosis. Data describing changes in other measures of central nervous system electrophysiology (Herr et al., 2007) were not modeled because of lack of availability of data describing group variability (e.g., SD or SEM values).

For the male rat neuronal loss or microgliosis data (see Table B-2), the Multistage Models failed due to unacceptable χ^2 goodness-of-fit criteria (see Table D-1). Among the remaining models, BMCL values were within three-fold, and the BMCL for the model with the lowest AIC value (LogProbit) was selected as the POD for this effect (see Table D-1).

Table D-1. Modeling Results for Incidence of Posterior Colliculus Neuronal Loss or Microgliosis—Male Rats Exposed to Carbonyl Sulfide for 12 Weeks[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residuals[c]	AIC	BMC_{10} (HEC mg/m^3)	$BMCL_{10}$ (HEC mg/m^3)
Gamma[d]	2	3.13	0.2092	−1.391	16.3322	120.382	98.4963
Logistic	1	0	0.9998	0.00	13.5347	168.597	126.509
LogLogistic[e]	2	0.18	0.9157	−0.401	11.8691	146.103	125.516
LogProbit[e]	**2**	**0**	**1.00**	**0.00**	**11.5348**	**157.088**	**127.913**
Multistage (1-degree)[f]	2	7.08	0.029	−2.064	21.4945	68.8387	23.9681
Multistage (2-degree)[f]	2	5.5	0.0638	−1.889	19.627	89.8501	39.0493
Probit	1	0	0.9998	0.00	13.5347	162.013	127.19
Weibull[d]	2	0.08	0.9624	0.275	11.6864	151.944	125.201

[a]Morgan et al. (2004)
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals for dose group near BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR: i.e., $_{10}$ = dose associated with 10% extra risk); DF = degrees of freedom.

BMDS outputs for the selected best-fitting model (LogProbit) follow.

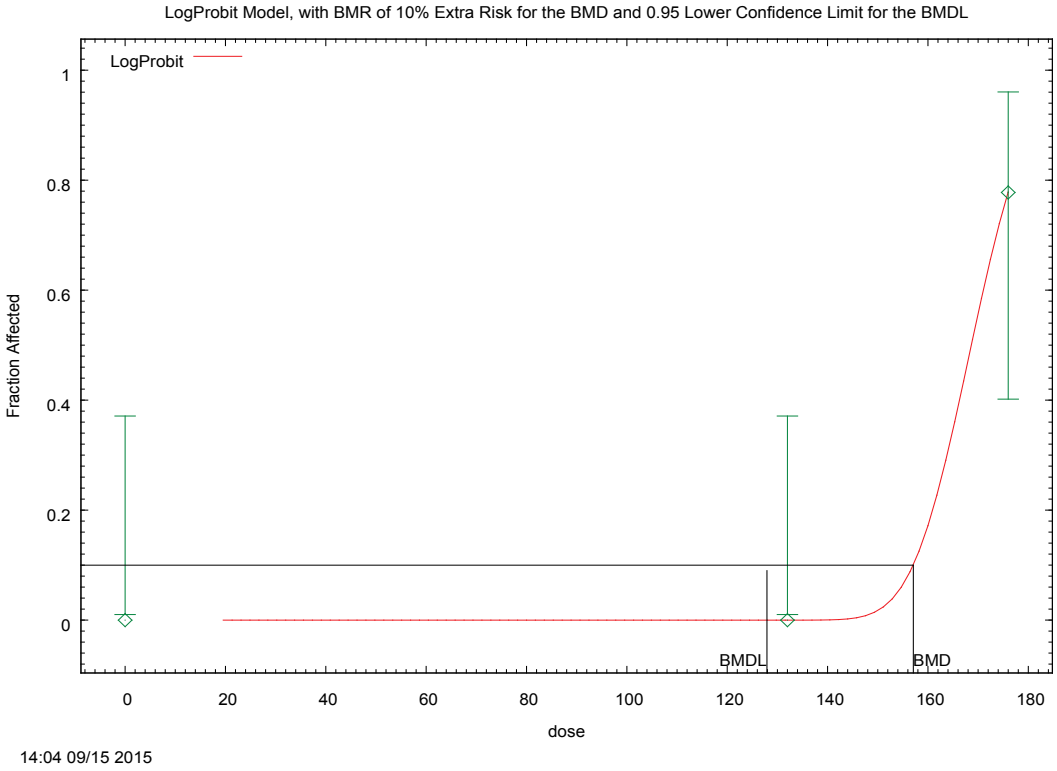

Figure D-1. LogProbit Fit for Incidence of Posterior Colliculus Neuronal Loss or Microgliosis in Male Rats (Morgan et al., 2004).

```
 ================================================================
        Probit Model. (Version: 3.3;  Date: 2/28/2013)
        Input Data File: C:/Users/JLIPSCOM/Desktop/BMDS260/Data/lnp_morgan new
microgliosis male_Lnp-BMR10-Restrict.(d)
        Gnuplot Plotting File:  C:/Users/JLIPSCOM/Desktop/BMDS260/Data/lnp_morgan new
microgliosis male_Lnp-BMR10-Restrict.plt
                                          Tue Sep 15 14:04:34 2015
 ================================================================

 BMDS_Model_Run
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   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 500
```

```
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008


   User has chosen the log transformed model


                 Default Initial (and Specified) Parameter Values
                    background =            0
                     intercept =     -42.5422
                         slope =      8.37579


           Asymptotic Correlation Matrix of Parameter Estimates

           ( *** The model parameter(s)  -background    -slope
                 have been estimated at a boundary point, or have been specified by
the user,
                 and do not appear in the correlation matrix )

              intercept

 intercept            1


                                Parameter Estimates

                                                          95.0% Wald Confidence
Interval
       Variable         Estimate        Std. Err.     Lower Conf. Limit   Upper Conf.
Limit
     background                0              NA
      intercept         -92.3041         0.465292             -93.216            -
91.3921
          slope               18              NA

NA - Indicates that this parameter has hit a bound
     implied by some inequality constraint and thus
     has no standard error.


                        Analysis of Deviance Table

       Model      Log(likelihood)  # Param's  Deviance  Test d.f.   P-value
     Full model         -4.76736         3
   Fitted model          -4.7674         1  9.15034e-005      2              1
  Reduced model         -15.4516         1       21.3684      2         <.0001

           AIC:          11.5348


                                Goodness  of  Fit
                                                                      Scaled
    Dose     Est._Prob.    Expected    Observed     Size       Residual
  ---------------------------------------------------------------------------
    0.0000     0.0000         0.000     0.000       9.000        0.000
  132.0000     0.0000         0.000     0.000       9.000       -0.007
  176.0000     0.7778         7.000     7.000       9.000        0.000

 Chi^2 = 0.00      d.f. = 2        P-value = 1.0000
```

```
   Benchmark Dose Computation

Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        157.088

            BMDL =        127.913
```

For the female rat neuronal loss or microgliosis data (see Table B-2), the Multistage Models failed due to high scaled residuals at the dose response level close to the BMR and poor curve fitting judged by visual inspection (see Table D-2). Among the remaining models, BMCL values were within three-fold, and the BMCL for the model with the lowest AIC value (LogProbit) was selected as the POD for this effect (see Table D-2).

Table D-2. Modeling Results for Incidence of Posterior Colliculus Neuronal Loss or Microgliosis—Female Rats Exposed to Carbonyl Sulfide for 12 Weeks[a]

Model	DF	χ^2	χ^2 Goodness-of-Fit *p*-Value[b]	Scaled Residuals[c]	AIC	BMC_{10} (HEC mg/m^3)	$BMCL_{10}$ (HEC mg/m^3)
Gamma[d]	2	1.45	0.4853	−0.999	16.7022	132.041	100.858
Logistic	1	0	0.9998	0	16.3653	170.419	123.85
LogLogistic[e]	2	0.06	0.9688	0.041	14.49	154.092	123.907
LogProbit[e]	**1**	**0**	**1**	**−1.588**	**14.3653**	**162.638**	**125.808**
Multistage (1-degree)[f]	2	4.09	0.1291	−1.446	20.3043	86.1863	30.1114
Multistage (2-degree)[f]	2	3.12	0.2102	0	19.124	105.05	40.2893
Probit	1	0	0.9998	0.019	16.3653	165.194	124.652
Weibull[d]	2	0.04	0.9796	0	14.4472	157.211	123.311

[a]Morgan et al. (2004)
[b]Values <0.1 fail to meet conventional goodness-of-fit criteria.
[c]Scaled residuals for dose group near BMC.
[d]Power restricted to ≥1.
[e]Slope restricted to ≥1.
[f]Betas restricted to ≥0.

BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR: i.e., $_{10}$ = dose associated with 10% extra risk); DF = degrees of freedom.

BMDS outputs for the selected best-fitting model (LogProbit) follow.

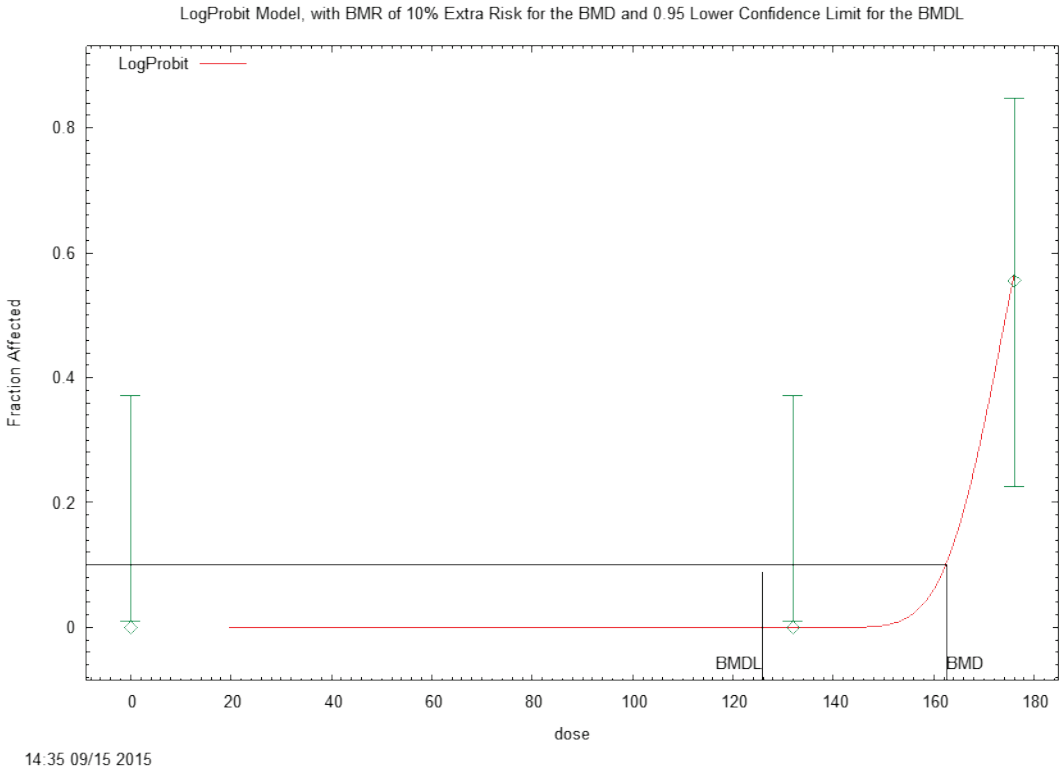

Figure D-1. LogProbit Fit for Incidence of Posterior Colliculus Neuronal Loss or Microgliosis in Female Rats (Morgan et al., 2004).

```
================================================================
        Probit Model. (Version: 3.3;  Date: 2/28/2013)
        Input Data File: C:/Users/JLIPSCOM/Desktop/BMDS260/Data/lnp_morgan new
microgliosis female_Lnp-BMR10-Restrict.(d)
        Gnuplot Plotting File:  C:/Users/JLIPSCOM/Desktop/BMDS260/Data/lnp_morgan new
microgliosis female_Lnp-BMR10-Restrict.plt
                                          Tue Sep 15 14:35:00 2015
 ================================================================

 BMDS_Model_Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the probability function is:

   P[response] = Background
               + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),

   where CumNorm(.) is the cumulative normal distribution function


   Dependent variable = Effect
   Independent variable = Dose
   Slope parameter is restricted as slope >= 1

   Total number of observations = 3
   Total number of records with missing values = 0
   Maximum number of iterations = 500
   Relative Function Convergence has been set to: 1e-008
   Parameter Convergence has been set to: 1e-008
```

User has chosen the log transformed model

Default Initial (and Specified) Parameter Values
background = 0
intercept = -31.9341
slope = 6.20325

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -background -slope
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	intercept
intercept	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
background	0	NA		
intercept	-92.929	0.419254	-93.7507	-92.1073
slope	18	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Analysis of Deviance Table

Model	Log(likelihood)	# Param's	Deviance	Test d.f.	P-value
Full model	-6.18265	3			
Fitted model	-6.18266	1	4.22125e-006	2	1
Reduced model	-12.9375	1	13.5096	2	0.001165

AIC: 14.3653

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Size	Scaled Residual
0.0000	0.0000	0.000	0.000	9.000	0.000
132.0000	0.0000	0.000	0.000	9.000	-0.001
176.0000	0.5556	5.000	5.000	9.000	0.000

Chi^2 = 0.00 d.f. = 2 P-value = 1.0000

Benchmark Dose Computation

```
Specified effect =            0.1

Risk Type        =      Extra risk

Confidence level =           0.95

             BMD =        162.638

            BMDL =        125.808
```

SEP1 amplitude data are presented in Table B-3; to complete BMD modeling, SEM values were converted to SD values by multiplying by the square root of the respective *n* values. For the combined male and female SEP1 amplitude data, all constant variance models failed. Among all the nonconstant models, only Exponential Model 3, Hill Model, and Power Model provide adequate fit to the data. BMCL values from these adequate fitted models varied less than three-fold. The BMCL from the model with the lowest AIC value (Power) was selected as the POD for this effect (see Table D-3).

Table D-3. Modeling Results for SEP1 Hindlimb/Tail Region Peak Amplitude Measurements in Male and Female Rats Exposed to Carbonyl Sulfide for 12 Weeks[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals[d]	AIC	BMC_{1SD} (HEC mg/m^3)	$BMCL_{1SD}$ (HEC mg/m^3)
Constant variance							
Exponential (Model 2)[e]	0.004761	0.004761	0.07	1.27	83.05	255.00	164.34
Exponential (Model 3)[e]	0.004761	0.004761	0.73	0.0008	830.89	178.68	NA
Exponential (Model 4)[e]	0.004761	0.004761	0.02	1.47	836.52	308.12	174.18
Exponential (Model 5)[e]	0.004761	0.004761	NA	0.001	832.89	179.28	173.78
Hill[e]	0.004761	0.004761	0.72	0.001	830.90	179.34	173.73
Linear[f]	0.004761	0.004761	0.06	1.47	834.52	308.12	174.18
Polynomial (2-degree)[f]	0.004761	0.004761	0.18	0.81	831.17	212.06	166.34
Polynomial (3-degree)[f]	0.004761	0.004761	0.34	0.48	830.92	196.37	168.76
Power[e]	0.004761	0.004761	0.94	0.001	828.90	179.28	173.78
Nonconstant variance							
Exponential (Model 2)[e]	0.004761	0.5381	0.001	1.359	832.71	255.36	154.09
Exponential (Model 3)[e]	0.004761	0.5381	0.121	0.001	823.48	177.43	NA
Exponential (Model 4)[e]	0.004761	0.5381	0.0002	1.534	835.28	309.46	NA
Exponential (Model 5)[e]	0.004761	0.5381	NA	0.004	825.49	177.74	171.30
Hill[e]	0.004761	0.5381	0.120	0.004	823.49	177.75	NA
Linear[f]	0.004761	0.5381	0.001	1.53	833.28	309.45	163.38
Polynomial (2-degree)[f]	0.004761	0.5381	0.005	0.962	829.65	209.40	157.38
Polynomial (3-degree)[f]	0.004761	0.5381	0.015	0.639	827.48	193.20	161.14
Power[e]	0.004761	0.5381	**0.298**	**0.004**	**821.49**	**177.74**	**171.30**

[a]Herr et al. (2007)
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals for dose group near the BMC.
[e]Power restricted to ≥1.
[f]Coefficients restricted to be positive.
NA = model failed to indicate value

BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR: i.e., $_{10}$ = dose associated with 10% extra risk); NA = not applicable (BMCL computation failed or the BMC was higher than the highest dose tested).

BMDS outputs for the best-fitting model (Power nonconstant variance) follow.

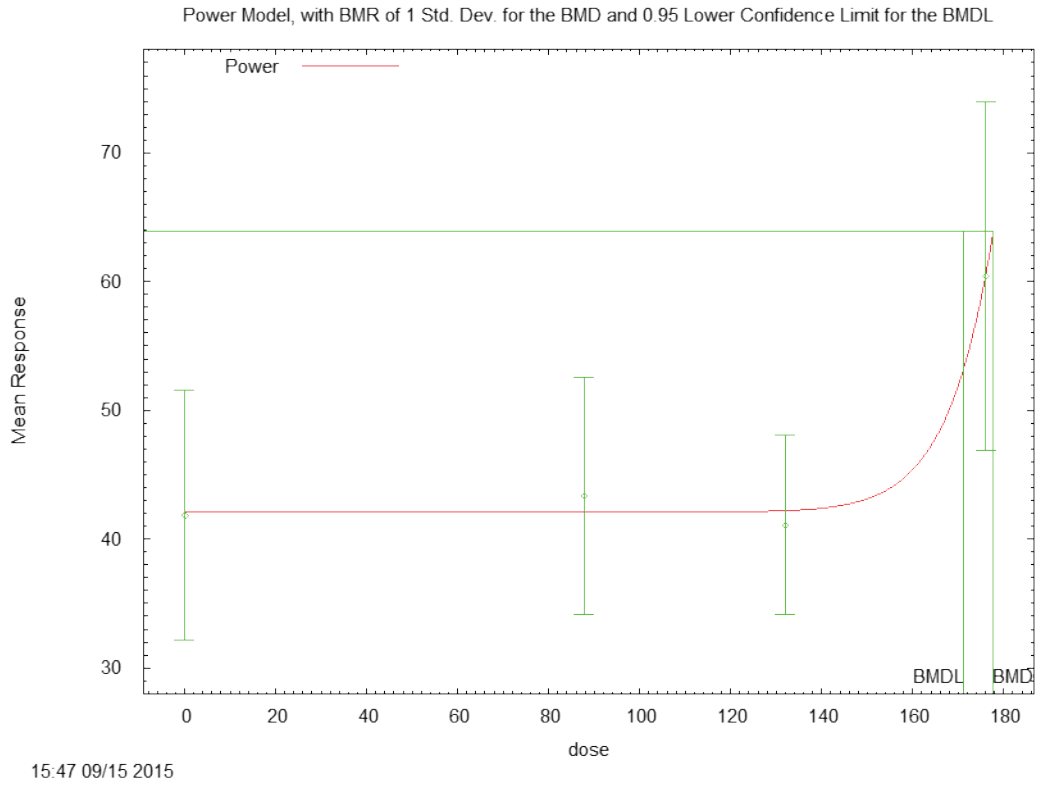

Figure D-3. Power Nonconstant Variance for SEP1 Tail Region Peak Amplitude (Herr et al., 2007)

```
 ======================================================================
        Power Model. (Version: 2.18;  Date: 05/19/2014)
        Input Data File: C:/Users/jzhao/Desktop/pow_COS Herr combined SEP1 _Pow-
ModelVariance-BMR1Std-Restrict.(d)
        Gnuplot Plotting File:  C:/Users/jzhao/Desktop/pow_COS Herr combined SEP1
_Pow-ModelVariance-BMR1Std-Restrict.plt
                                          Tue Sep 15 15:47:12 2015
 ======================================================================

 BMDS Model Run
~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~

   The form of the response function is:

   Y[dose] = control + slope * dose^power


   Dependent variable = Mean
   Independent variable = Dose
   The power is restricted to be greater than or equal to 1
   The variance is to be modeled as Var(i) = exp(lalpha + log(mean(i)) * rho)
```

Total number of dose groups = 4
Total number of records with missing values = 0
Maximum number of iterations = 500
Relative Function Convergence has been set to: 1e-008
Parameter Convergence has been set to: 1e-008

Default Initial Parameter Values

lalpha =	6.51679
rho =	0
control =	41.08
slope =	2.18829e-006
power =	3.09344

Asymptotic Correlation Matrix of Parameter Estimates

(*** The model parameter(s) -power
have been estimated at a boundary point, or have been specified by the user,
and do not appear in the correlation matrix)

	lalpha	rho	control	slope
lalpha	1	-1	-0.36	0.69
rho	-1	1	0.33	-0.69
control	-0.36	0.33	1	-0.35
slope	0.69	-0.69	-0.35	1

Parameter Estimates

Variable	Estimate	Std. Err.	95.0% Wald Confidence Interval Lower Conf. Limit	Upper Conf. Limit
lalpha	-3.10431	4.59022	-12.101	5.89235
rho	2.47867	1.19844	0.12976	4.82757
control	42.1044	2.41708	37.367	46.8418
slope	6.96588e-040	2.62763e-040	1.81582e-040	1.21159e-039
power	18	NA		

NA - Indicates that this parameter has hit a bound
implied by some inequality constraint and thus
has no standard error.

Table of Data and Estimated Values of Interest

Dose	N	Obs Mean	Est Mean	Obs Std Dev	Est Std Dev	Scaled Res.
0	25	41.8	42.1	23.5	21.8	-0.0629
87.8	30	43.3	42.1	24.7	21.8	0.308

132	27	41.1	42.2	17.6	21.9	-0.268
176	28	60.4	60.4	34.8	34.1	0.00403

Model Descriptions for likelihoods calculated

Model A1: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma^2

Model A2: Yij = Mu(i) + e(ij)
Var{e(ij)} = Sigma(i)^2

Model A3: Yij = Mu(i) + e(ij)
Var{e(ij)} = exp(lalpha + rho*ln(Mu(i)))
Model A3 uses any fixed variance parameters that
were specified by the user

Model R: Yi = Mu + e(i)
Var{e(i)} = Sigma^2

Likelihoods of Interest

Model	Log(likelihood)	# Param's	AIC
A1	-411.385922	5	832.771845
A2	-404.914225	8	825.828451
A3	-405.533876	6	823.067752
fitted	-406.744954	4	821.489908
R	-416.548709	2	837.097417

Explanation of Tests

Test 1: Do responses and/or variances differ among Dose levels?
(A2 vs. R)
Test 2: Are Variances Homogeneous? (A1 vs A2)
Test 3: Are variances adequately modeled? (A2 vs. A3)
Test 4: Does the Model for the Mean Fit? (A3 vs. fitted)
(Note: When rho=0 the results of Test 3 and Test 2 will be the same.)

Tests of Interest

Test	-2*log(Likelihood Ratio)	Test df	p-value
Test 1	23.269	6	0.0007112
Test 2	12.9434	3	0.004761
Test 3	1.2393	2	0.5381
Test 4	2.42216	2	0.2979

The p-value for Test 1 is less than .05. There appears to be a
difference between response and/or variances among the dose levels
It seems appropriate to model the data

The p-value for Test 2 is less than .1. A non-homogeneous variance
model appears to be appropriate

The p-value for Test 3 is greater than .1. The modeled variance appears
to be appropriate here

The p-value for Test 4 is greater than .1. The model chosen seems
to adequately describe the data

```
               Benchmark Dose Computation

Specified effect =             1

Risk Type        =     Estimated standard deviations from the control mean

Confidence level =          0.95

             BMD = 177.737


            BMDL = 171.295
```

SEP2 amplitude data are presented in Table B-3; to complete BMD modeling, SEM values were converted to SD values by multiplying by the square root of the respective *n* values. For the combined male and female SEP2 amplitude data, all constant and nonconstant variance models failed. The dataset (SEP2 facial region) was not amenable to BMD analysis; none of the models provided adequate fit with or without the nonconstant variance model applied to the data (see Table D-4).

Table D-4. Modeling Results for SEP2 Facial Region Peak Amplitude Measurements in Male and Female Rats Exposed to Carbonyl Sulfide for 12 Weeks[a]

Model	Test for Significant Difference *p*-Value[b]	Variance *p*-Value[c]	Means *p*-Value[c]	Scaled Residuals[d]	AIC	BMC_{1SD} (HEC mg/m^3)	$BMCL_{1SD}$ (HEC mg/m^3)
Constant variance							
Exponential (Model 2)[e]	<0.0001	0.0006	0.01	1.50	481.88	195.88	140.98
Exponential (Model 3)[e]	<0.0001	0.0006	0.27	0.001	475.90	180.27	172.39
Exponential (Model 4)[e]	<0.0001	0.0006	0.001	1.78	484.75	219.20	141.92
Exponential (Model 5)[e]	<0.0001	0.0006	NA	0.0016	477.90	180.32	172.10
Hill[e]	<0.0001	0.0006	0.27	0.0016	475.90	180.33	172.06
Linear[f]	<0.0001	0.0006	0.006	1.78	482.75	219.20	141.92
Polynomial (2-degree)[f]	<0.0001	0.0006	0.04	0.947	479.05	184.48	152.64
Polynomial (3-degree)[f]	<0.0001	0.0006	0.10	0.55	477.19	181.39	161.02
Power[e]	<0.0001	0.0006	0.54	0.0016	473.90	180.32	172.10
Nonconstant variance							
Exponential (Model 2)[e]	<0.0001	0.08	0.01	1.70	470.87	175.14	116.16
Exponential (Model 3)[e]	<0.0001	0.08	0.56	0.21	464.50	175.02	149.82
Exponential (Model 4)[e]	<0.0001	0.08	0.002	1.92	473.93	194.21	116.69
Exponential (Model 5)[e]	<0.0001	0.08	NA	0.21	466.51	174.86	149.66
Hill[e]	<0.0001	0.08	NA	0.21	466.51	174.85	151.98
Linear[f]	<0.0001	0.08	0.008	1.91	471.93	194.21	116.69
Polynomial (2-degree)[f]	<0.0001	0.08	0.18	1.20	465.58	170.82	133.67
Polynomial (3-degree)[f]	<0.0001	0.08	0.51	0.78	463.49	171.29	143.97
Power[e]	<0.0001	0.08	0.55	0.21	464.51	174.86	149.66

[a]Herr et al. (2007)
[b]Values >0.05 fail to meet conventional goodness-of-fit criteria.
[c]Values <0.10 fail to meet conventional goodness-of-fit criteria.
[d]Scaled residuals for dose group near the BMC.
[e]Power restricted to ≥1.
[f]Coefficients restricted to be positive.

BMC = maximum likelihood estimate of the concentration associated with the selected BMR; BMCL = 95% lower confidence limit on the BMC (subscripts denote BMR: i.e., $_{10}$ = dose associated with 10% extra risk); NA = not applicable (BMCL computation failed or the BMC was higher than the highest dose tested).

No model results follow.

APPENDIX E. REFERENCES

ACGIH (American Conference of Governmental Industrial Hygienists). (2015). 2015 TLVs and BEIs. Based on the documentation of the threshold limit values for chemical substances and physical agents and biological exposure indices [TLV/BEI]. Cincinnati, OH. http://www.acgih.org/forms/store/ProductFormPublic/2015-tlvs-and-beis

ACGIH, ACoGIH. (2012). Carbonyl sulfide. In Documentation of the threshold limit values and biological exposure indices (7th ed.). Cincinnati, OH: American Conference of Governmental Industrial Hygienists.

ATSDR (Agency for Toxic Substances and Disease Registry). (2014). Minimal risk levels (MRLs). Atlanta, GA: Agency for Toxic Substances and Disease Registry, Centers for Disease Control and Prevention. http://www.atsdr.cdc.gov/mrls/pdfs/atsdr_mrls_december_2014.pdf

Bartholomaeus, AR; Haritos, VS. (2005). Review of the toxicology of carbonyl sulfide, a new grain fumigant [Review]. Food Chem Toxicol 43: 1687-1701. http://dx.doi.org/10.1016/j.fct.2005.06.016

Cal/EPA (California Environmental Protection Agency). (2011). Hot spots unit risk and cancer potency values. Appendix A. Sacramento, CA: Office of Environmental Health Hazard Assessment. http://www.oehha.ca.gov/air/hot_spots/2009/AppendixA.pdf

Cal/EPA (California Environmental Protection Agency). (2014). All OEHHA acute, 8-hour and chronic reference exposure levels (chRELs) as of June 2014. Sacramento, CA: Office of Health Hazard Assessment. http://www.oehha.ca.gov/air/allrels.html

Cal/EPA (California Environmental Protection Agency). (2015a). Chemicals known to the state to cause cancer or reproductive toxicity August 14, 2015. (Proposition 65 list). Sacramento, CA: California Environmental Protection Agency, Office of Environmental Health Hazard Assessment. http://oehha.ca.gov/prop65/prop65_list/files/P65single060614.pdf

Cal/EPA (California Environmental Protection Agency). (2015b). OEHHA toxicity criteria database [Database]. Sacramento, CA: Office of Environmental Health Hazard Assessment. Retrieved from http://www.oehha.ca.gov/tcdb/index.asp

Car, BD; Eng, VM; Everds, NE; Bounous, DI. (2005). Clinical pathology of the rat. In MA Suckow; SH Veisboth; CL Franklin (Eds.), The laboratory rat (pp. 127-146). Amsterdam, The Netherlands: Academic Press. http://www.sciencedirect.com/science/book/9780120749034

Chengelis, CP; Neal, RA. (1979). Hepatic carbonyl sulfide metabolism. Biochem Biophys Res Commun 90: 993-999.

Chengelis, CP; Neal, RA. (1980). Studies of carbonyl sulfide toxicity: Metabolism by carbonic anhydrase. Toxicol Appl Pharmacol 55: 198-202. http://dx.doi.org/10.1016/0041-008X(80)90236-7

Chengelis, CP; Neal, RA. (1987). Oxidative metabolism of carbon disulfide by isolated rat hepatocytes and microsomes. Biochem Pharmacol 36: 363-368. http://dx.doi.org/10.1016/0006-2952(87)90295-4

Coleman, MD; Coleman, NA. (1996). Drug-induced methaemoglobinaemia. Treatment issues [Review]. Drug Saf 14: 394-405.

Dalvi, RR; Neal, RA. (1978). Metabolism in vivo of carbon disulfide to carbonyl sulfide and carbon dioxide in the rat. Biochem Pharmacol 27: 1608-1609. http://dx.doi.org/10.1016/0006-2952(78)90494-X

DuPont (E. I. du Pont de Nemours and Company). (1992). Intital submission: letter from EI Dupont de Nemours & Co to USEPA regarding toxicity studies with carbonyl sulfide with cover letter dated 09/01/92. (TSCATS/440041. OTS0555041. Section 8ECP. 88-920008223; 8EHQ-0892-9921). https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0555041

Gharahbaghian, L; Massoudian, B; DiMassa, G. (2009). Methemoglobinemia and sulfhemoglobinemia in two pediatric patients after ingestion of hydroxylamine sulfate. West J Emerg Med 10: 197-201.

Haritos, VS; Dojchinov, G. (2005). Carbonic anhydrase metabolism is a key factor in the toxicity of CO2 and COS but not CS2 toward the flour beetle Tribolium castaneum [Coleoptera: Tenebrionidae]. Comp Biochem Physiol C Toxicol Pharmacol 140: 139-147. http://dx.doi.org/10.1016/j.cca.2005.01.012

Herr, DW; Graff, JE; Moser, VC; Crofton, KM; Little, PB; Morgan, DL; Sills, RC. (2007). Inhalational exposure to carbonyl sulfide produces altered brainstem auditory and somatosensory-evoked potentials in Fischer 344N rats. Toxicol Sci 95: 118-135. http://dx.doi.org/10.1093/toxsci/kfl146

Howard, BJ; Beresford, NA; Mayes, RW; Lamb, CS; Barnett, CL. (2007). The transfer of different forms of 35S to goat milk. J Environ Radioact 98: 177-190. http://dx.doi.org/10.1016/j.jenvrad.2006.08.012

HSDB (Hazardous Substances Data Bank). (2007). Carbonyl sulfide. Available online at http://toxnet.nlm.nih.gov/cgi-bin/sis/search2/f?./temp/~8j9hC5:1:FULL

Hugod, C. (1981). Myocardial morphology in rabbits exposed to various gas-phase constituents of tobacco smoke: An ultrastructural study. Atherosclerosis 40: 181-190. http://dx.doi.org/10.1016/0021-9150(81)90037-X

Hugod, C; Astrup, P. (1980). Exposure of rabbits to carbon monoxide and other gas phase constituents of tobacco smoke. MMW Munch Med Wochenschr 122 Suppl 1: 18-24.

IARC (International Agency for Research on Cancer). (2015). IARC Monographs on the evaluation of carcinogenic risk to humans. Geneva, Switzerland: International Agency for Research on Cancer, WHO. http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php

Kamstrup, O; Hugod, C. (1979). Exposure of rabbits to 50 parts per million carbonyl sulfide: A biochemical and histomorphological study. Int Arch Occup Environ Health 44: 109-116. http://dx.doi.org/10.1007/BF00386744

Michel, HO. (1938). A study of sulfhemoglobin. J Biol Chem 126: 323-348.

Monsanto (Monsanto Company). (1979). A one-generation reproduction fertility study on 2,3-dichloropropene in rats with attached studies, cover sheets and letter dated 022190. (TSCATS/406698. OTS0522997. Section 8E. 88-900000064; 8EHQ-0290-0892). Washington, DC: Bio/Dynamics Inc.

Monsanto (Monsanto Company). (1982). Initial submission: acute toxicity of carbon oxysulfide administered by inhalation to male and female Sprague-Dawley rats (final report) with attachments and letter dated 112791. (TSCATS/420707. OTS0534820. Section 8ECP. 88-920000368). Monsanto Agricultural Company.

Monsanto (Monsanto Company). (1985). Initial submission: Two week study with carbonyl sulfide administered by inhalation to rats with cover letter dated 052892. (TSCATS/427204. OTS0540051. Section 8ECP. 88-920003400; 8EHQ-0692-4757). Washington, DC. https://ntrl.ntis.gov/NTRL/dashboard/searchResults.xhtml?searchQuery=OTS0540051

Morgan, DL; Little, PB; Herr, DW; Moser, VC; Collins, B; Herbert, R; Johnson, GA; Maronpot, RR; Harry, GJ; Sills, RC. (2004). Neurotoxicity of carbonyl sulfide in F344 rats following inhalation exposure for up to 12 weeks. Toxicol Appl Pharmacol 200: 131-145. http://dx.doi.org/10.1016/j.taap.2004.04.013

Morrison, JP; Ton, T; Collins, JB; Switzer, RC; Little, PB; Morgan, DL; Sills, RC. (2009). Gene expression studies reveal that DNA damage, vascular perturbation, and inflammation contribute to the pathogenesis of carbonyl sulfide neurotoxicity. Toxicol Pathol 37: 502-511. http://dx.doi.org/10.1177/0192623309335631

NIOSH (National Institute for Occupational Safety and Health). (2015). NIOSH pocket guide to chemical hazards. Index of chemical abstracts service registry numbers (CAS No.). Atlanta, GA: Center for Disease Control and Prevention, U.S. Department of Health, Education and Welfare. http://www.cdc.gov/niosh/npg/npgdcas.html

NTP (National Toxicology Program). (1983). Report on the subchronic toxicity via gavage of nitrobenzene (C60082) in Fischer 344 rats and B6C3F1 mice [unpublished]. (MRI-NTP08-83-19). Research Triangle Park, NC: Prepared by the EG&G Mason Research Institute, Worcester, MA, for the National Toxicology Program, National Institute of Environmental Health Services, Public Health Service, U.S. Department of Health and Human Services.

NTP (National Toxicology Program). (1995). Chemical Effects in Biological Systems (CEBS); Study information: Carbonyl sulfide; CASRN: 463-58-1. (CEBS Accession Number: 002-01834-0001-0000-9). Research Triangle Park, NC: National Institutes of Environmental Health. http://tools.niehs.nih.gov/cebs3/ntpViews/?activeTab=detail&studyNumber=A35125

NTP (National Toxicology Program). (2014). Report on carcinogens. Thirteenth edition. Research Triangle Park, NC: U.S. Department of Health and Human Services, Public Health Service. http://ntp.niehs.nih.gov/pubhealth/roc/roc13/index.html

OSHA (Occupational Safety & Health Administration). (2006). Table Z-1 limits for air contaminants. Washington, DC: Occupational Safety and Health Administration (OSHA). http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=9992

OSHA (Occupational Safety & Health Administration). (2011). Air contaminants: occupational safety and health standards for shipyard employment, subpart Z, toxic and hazardous substances. (OSHA Standard 1915.1000). Washington, DC: U.S. Department of Labor. http://www.osha.gov/pls/oshaweb/owadisp.show_document?p_table=STANDARDS&p_id=10286

Pietri, R; Roman-Morales, E; Lopez-Garriga, J. (2011). Hydrogen sulfide and hemeproteins: Knowledge and mysteries. Antioxid Redox Signal 15: 393-404.

Praxair (Praxair, Inc.). (2003). Follow-up letter to earlier report of a worker's accidental chemical exposure [TSCA Submission]. (8EHQ-0903-15274 B. DCN: 89030000267). http://yosemite.epa.gov/oppts/epatscat8.nsf/ReportSearchView/5DC548CD29A5858A85256EFC0068DE75

Rechetzki, KF; Henneberg, R; da Silva, PH; Do Nascimento, AJ. (2012). Reference values for methemoglobin concentrations in children. Revista Brasileira de Hematologia e Hemoterapia 34: 14-16. http://dx.doi.org/10.5581/1516-8484.20120007

Sigma-Aldrich. (2014). Carbonyl sulfide 97.5% 463-58-1 [Fact Sheet]. http://www.sigmaaldrich.com/catalog/product/aldrich/295124?lang=en&region=US

Sills, RC; Morgan, DL; Herr, DW; Little, PB; George, NM; Ton, TV; Love, NE; Maronpot, RR; Johnson, GA. (2004). Contribution of magnetic resonance microscopy in the 12-week neurotoxicity evaluation of carbonyl sulfide in Fischer 344 rats. Toxicol Pathol 32: 501-510. http://dx.doi.org/10.1080/01926230490493918

U.S. EPA (U.S. Environmental Protection Agency). (1994a). Chemical assessments and related activities (CARA) [EPA Report]. (600/R-94/904; OHEA-I-127). Washington, DC: U.S. Environmental Protection Agency, Office of Health and Environmental Assessment. http://nepis.epa.gov/Exe/ZyPURL.cgi?Dockey=60001G8L.txt

U.S. EPA (U.S. Environmental Protection Agency). (1994b). Chemical summary for carbonyl sulfide. (EPA 749/F-94/009a). Washington, DC: Office of Pollution Prevention and Toxics, U.S. Environmental Protection Agency. http://www.epa.gov/chemfact/s_carbns.txt

U.S. EPA (U.S. Environmental Protection Agency). (1994c). Methods for derivation of inhalation reference concentrations and application of inhalation dosimetry. (EPA/600/8-90/066F). Research Triangle Park, NC: U.S. Environmental Protection Agency, Environmental Criteria and Assessment Office. http://cfpub.epa.gov/ncea/cfm/recordisplay.cfm?deid=71993

U.S. EPA (U.S. Environmental Protection Agency). (2011). Health effects assessment summary tables (HEAST). Washington, DC: U.S. Environmental Protection Agency, Office of Emergency and Remedial Response. http://epa-heast.ornl.gov/

U.S. EPA (U.S. Environmental Protection Agency). (2012a). 2012 Edition of the drinking water standards and health advisories [EPA Report]. (EPA/822/S-12/001). Washington, DC: Office of Water. http://water.epa.gov/action/advisories/drinking/upload/dwstandards2012.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2012b). Benchmark dose technical guidance. (EPA/100/R-12/001). Washington, DC: Risk Assessment Forum. http://www.epa.gov/raf/publications/pdfs/benchmark_dose_guidance.pdf

U.S. EPA (U.S. Environmental Protection Agency). (2015). EPA's Integrated Risk Information System Program (IRIS). Progress report and report to Congress. Washington, DC: U.S. Environmental Protection Agency, IRIS. http://www.epa.gov/iris/index.html

Walton, G. (1951). Survey of literature relating to infant methemoglobinemia due to nitrate-contaminated water. Am J Public Health 41: 986-996. http://dx.doi.org/doi:10.2105/AJPH.41.8_Pt_1.986

Wang, R; Li, X; Cen, X; Zeng, L; Tan, X. (1999). Report on toxicity test of carbonyl sulfide. In Z Jin; Q Liang; Y Liang; X Tan; L Guan (Eds.), Proceedings of the 7th International Working Conference on Stored-Product Protection (pp. 572-583). Chengdu, China: Sichuan Publishing House of Science and Technology. http://spiru.cgahr.ksu.edu/proj/iwcspp/iwcspp7.html

Weil, ED; Sandler, SR; Gernon, M. (2006). Sulfur compounds. In Kirk-Othmer Encyclopedia of Chemical Technology. New York, NY: John Wiley & Sons. http://dx.doi.org/10.1002/0471238961.1921120623050912.a01.pub2

WHO (World Health Organization). (2015). Online catalog for the Environmental Health Criteria (EHC) monographs. Geneva, Switzerland: World Health Organization (WHO). http://www.who.int/ipcs/publications/ehc/en/

Williams, SR. (2001). Methemoglobin. In LJ Ling; RF Clark; TB Erickson; JH Trestrial (Eds.), Toxicology secrets. Philadelphia, PA: Hanley and Belfus Publishing.