ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs)
FOR
CARBONYL SULFIDE
(CAS Reg. No. 463-58-1)

INTERIM

ACUTE EXPOSURE GUIDELINE LEVELS (AEGLs) FOR CARBONYL SULFIDE (CAS Reg. No. 463-58-1)

INTERIM

PREFACE

Under the authority of the Federal Advisory Committee Act (FACA) P. L. 92-463 of 1972, the National Advisory Committee for Acute Exposure Guideline Levels for Hazardous Substances (NAC/AEGL Committee) has been established to identify, review and interpret relevant toxicologic and other scientific data and develop AEGLs for high priority, acutely toxic chemicals.

AEGLs represent threshold exposure limits for the general public and are applicable to emergency exposure periods ranging from 10 minutes to 8 hours. Three levels — AEGL-1, AEGL-2 and AEGL-3 — are developed for each of five exposure periods (10 and 30 minutes, 1 hour, 4 hours, and 8 hours) and are distinguished by varying degrees of severity of toxic effects. The three AEGLs are defined as follows:

AEGL-1 is the airborne concentration (expressed as parts per million or milligrams per cubic meter [ppm or mg/m^3]) of a substance above which it is predicted that the general population, including susceptible individuals, could experience notable discomfort, irritation, or certain asymptomatic, non-sensory effects. However, the effects are not disabling and are transient and reversible upon cessation of exposure.

AEGL-2 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience irreversible or other serious, long-lasting adverse health effects or an impaired ability to escape.

AEGL-3 is the airborne concentration (expressed as ppm or mg/m^3) of a substance above which it is predicted that the general population, including susceptible individuals, could experience life-threatening health effects or death.

Airborne concentrations below the AEGL-1 represent exposure levels that could produce mild and progressively increasing but transient and nondisabling odor, taste, and sensory irritation or certain asymptomatic, non-sensory effects. With increasing airborne concentrations above each AEGL, there is a progressive increase in the likelihood of occurrence and the severity of effects described for each corresponding AEGL. Although the AEGL values represent threshold levels for the general public, including susceptible subpopulations, such as infants, children, the elderly, persons with asthma, and those with other illnesses, it is recognized that individuals, subject to unique or idiosyncratic responses, could experience the effects described at concentrations below the corresponding AEGL

TABLE OF CONTENTS

LIST OF TABLES

SUMMARY

Carbonyl sulfide is a colorless gas. Pure carbonyl sulfide is odorless; however, commercial carbonyl sulfide has a typical sulfur odor. It is produced naturally in soil, marshes, roots and shoots of plants, manure, compost, and by microorganisms. It is found in cheese, horseradish, and brassica vegetables. The natural occurrence of carbonyl sulfide is associated with the occurrence of carbon disulfide and the environmental sulfur cycle (Bartholomaeus and Haritos, 2005). Up to 45 ppm carbonyl sulfide has been reported in mainstream tobacco smoke (Bartholomaeus and Haritos, 2005). It is used as an intermediate in the synthesis of thio-organic compounds and as an intermediate in the production of thiocarbamate herbicides and aliphatic polyureas, and has recently been introduced as a new grain fumigant which has been developed to replace methyl bromide. Carbonyl sulfide, similar to hydrogen sulfide, causes respiratory paralysis. However, the odor warning properties are not as prominent as those of hydrogen sulfide. Carbonyl sulfide also causes neurotoxicity.

Carbonyl sulfide has poor warning properties; it may cause serious effects or lethality at concentrations causing no signs or symptoms. Data were insufficient for deriving AEGL-1 values for carbonyl sulfide. Therefore, AEGL-1 values are not recommended.

A NOEL for clinical signs and brain pathology (300 ppm) in rats exposed to carbonyl sulfide for 6-hours (Morgan et al., 2004) was used as the POD for AEGL-2 values. (Animals exposed to the next highest concentration tested, 600 ppm, exhibited severe clinical signs and brain pathology). Values were scaled across time using the $C^n \times t = k$ equation, where n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points in order to derive values protective of human health (NRC, 2001). The 30-min AEGL-2 value was adopted as the 10-min AEGL-2 value because of the added uncertainty of extrapolating from the 6-hour POD to 10-min. An intraspecies uncertainty factor (UF) of 3 was applied and is considered sufficient due to the steep concentration-response curve, which implies limited intra-individual variability. The steep curve is evidenced in several studies. No mortality was noted in rats exposed to 943 ppm carbonyl sulfide for 4-hours, and 4/10 rats died at 1090 ppm and 10/10 rats died when exposed to 1210 ppm (DuPont, 1981). In another 4-hour rat study (Monsanto, 1985a), no mortality was noted at 993 ppm; whereas, 4/12 rats died at 1060 ppm, and 11/12 rats died at 1147 ppm. Thiess et al. (1968) observed no mortality in rats exposed to 1000 ppm for 75-min and death of 3/6 rats exposed to 1000 ppm for 90-min. An interspecies UF of 3 was also applied. Although the animal data suggest some species variability and the rat is not the most sensitive species [mortality incidences for animals exposed to 1000 ppm carbonyl sulfide for 90 minutes were as follows: 0/6 for guinea pigs, 3/6 for rats, 8/14 for rabbits, and 6/6 for cats (Thiess et al., 1968)], use of the full default interspecies UF of 10 would yield AEGL-2 values that are inconsistent with the overall database. [AEGL-2 values derived using a total UF of 30 would be 23 ppm for 10- and 30-min, 18 ppm for 1-hr, 11 ppm for 4-hr, and 7.7 ppm for 8-hr; no treatment-related effects were noted in rats exposed to 51 ppm 6-hr/day for 11 days (Monsanto, 1985b), or 75, 150, or 300 ppm 6-hr/day for 4 days (Morgan et al., 2004)]. Therefore, the total adjustment is 10.

A 4-hour rat $BMCL_{05}$ and BMC_{01} (both calculated values are equivalent) of 952 ppm (Monsanto, 1985a) was used as the point-of-departure (POD) for AEGL-3 values. Values were scaled across time using the $C^n \times t = k$ equation, where n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points in order to derive values protective of human health (NRC, 2001). The 30-min AEGL-3 value was adopted as the 10-min AEGL-3 value because of the added uncertainty of extrapolating from the 4-hour POD to 10-min. An intraspecies

uncertainty factor (UF) of 3 was applied and is considered sufficient due to the steep concentration-response curve, which implies limited intra-individual variability. The steep curve is evidenced in several studies. No mortality was noted in rats exposed to 943 ppm carbonyl sulfide for 4-hours, and 4/10 rats died at 1090 ppm and 10/10 rats died when exposed to 1210 ppm (DuPont, 1981). In another 4-hour rat study (Monsanto, 1985a), no mortality was noted at 993 ppm; whereas, 4/12 rats died at 1060 ppm, and 11/12 rats died at 1147 ppm. Thiess et al. (1968) observed no mortality in rats exposed to 1000 ppm for 75-min and death of 3/6 rats exposed to 1000 ppm for 90-min. An interspecies UF of 3 was also applied. Although the animal data suggest some species variability and the rat is not the most sensitive species [mortality incidences for animals exposed to 1000 ppm carbonyl sulfide for 90 minutes were as follows: 0/6 for guinea pigs, 3/6 for rats, 8/14 for rabbits, and 6/6 for cats (Thiess et al., 1968)], use of the full default interspecies UF of 10 would yield AEGL-3 values that are inconsistent with the overall database. [AEGL-3 values derived using a total UF of 30 would be 63 ppm for 10- and 30-min, 50 ppm for 1-hr, 32 ppm for 4-hr, and 16 ppm for 8-hr; no treatment-related effects were noted in rats exposed to 51 ppm 6-hr/day for 11 days (Monsanto, 1985b), or 75, 150, or 300 ppm 6-hr/day for 4 days (Morgan et al., 2004). No mortality or clinical signs were present in rats exposed to 200, 300, or 400 ppm 6 hr/day, 5 days/week for 12-weeks; however, significant decreases in brain cholinesterase activity were noted at all three concentrations (Morgan et al., 2004)]. Therefore, the total adjustment is 10.

The calculated values are listed in the table below.

TABLE 1. Summary of AEGL Values for Carbonyl Sulfide

Classification	10-mim	30-min	1-h	4-h	8-h	Endpoint (Reference)
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR	
AEGL-2 (Disabling)	69 ppm (170 mg/m^3)	69 ppm (170 mg/m^3)	55 ppm (130 mg/m^3)	34 ppm (83 mg/m^3)	23 ppm (56 mg/m^3)	NOEL for clinical signs and brain pathology in rats (Morgan et al., 2004)
AEGL-3 (Lethal)	190 ppm (470 mg/m^3)	190 ppm (470 mg/m^3)	150 ppm (370 mg/m^3)	95 ppm (230 mg/m^3)	48 ppm (120 mg/m^3)	4-hour rat $BMCL_{05}$ /BMC_{01}(Monsanto, 1985a)

NR: Not Recommended due to insufficient data. The absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect. Carbonyl sulfide has poor warning properties; it may cause serious effects or lethality at concentrations causing no signs or symptoms

1. INTRODUCTION

Carbonyl sulfide is a colorless gas. Pure carbonyl sulfide is odorless; however, commercial carbonyl sulfide has a typical sulfur odor. It may be made by the reaction of dilute sulfuric acid with ammonium thiocyanate, hydrolysis of ammonium or potassium thiocyanate, by the reaction of carbon monoxide with sulfur, reduction of sulfur dioxide with carbon, or hydrolysis of carbon disulfide (HSDB, 2007). Carbonyl sulfide is produced naturally in soil, marshes, roots and shoots of plants, manure, compost, and by microorganisms. It is found in cheese, horseradish, and brassica vegetables. The natural occurrence of carbonyl sulfide is associated with the occurrence of carbon disulfide and the environmental sulfur cycle (Bartholomaeus and Haritos, 2005). Up to 45 ppm carbonyl sulfide has been reported in mainstream tobacco smoke (Bartholomaeus and Haritos, 2005). It is used as an intermediate in the synthesis of thio-organic compounds and as an intermediate in the production of thiocarbamate herbicides and aliphatic polyureas. Carbonyl sulfide has recently been introduced as a new grain fumigant which has been developed to replace methyl bromide (being phased out) and to supplement phosphine gas (experiencing increased insect resistance). Fumigation of grain products with carbonyl sulfide results in residues that are near to or indistinguishable from natural background levels (HSDB, 2007). Carbonyl sulfide, similar to hydrogen sulfide, causes respiratory paralysis. Carbonyl sulfide also causes neurotoxicity. The warning properties of carbonyl sulfide are not as prominent as those of hydrogen sulfide. Carbonyl sulfide has poor warning properties; it may cause serious effects or lethality at concentrations causing no signs or symptoms (HSDB, 2007). Chemical and physical properties are listed in Table 2.

TABLE 2. Chemical and Physical Properties

Parameter	Value	References
Synonyms	Carbon monoxide monosulfide; carbon oxide sulfide; carbonoxysulfide; oxycarbon sulfide	HSDB, 2007
Chemical formula	COS	HSDB, 2007
Molecular weight	60.1	HSDB, 2007
CAS Reg. No.	463-58-1	HSDB, 2007
Physical state	Colorless gas	HSDB, 2007
Solubility in water	1220 mg/L at 25 °C; may hydrolyze to carbon dioxide and hydrogen sulfide	HSDB, 2007
Vapor pressure	9412 mm Hg at 25 °C	HSDB, 2007
Vapor density	2.1 (air = 1)	HSDB, 2007
Density/Specific Gravity	1.028 g/L at 17 °C	HSDB, 2007
Melting point	-138.8 °C	HSDB, 2007
Boiling point	-50 °C	HSDB, 2007
Flammable range	12-28% (600-1000 °F)	HSDB, 2007
Conversion factors	1 ppm = 2.45 mg/m^3 1 mg/m^3 = 0.41 ppm	

2. HUMAN TOXICITY DATA

Thiess et al. (1968) reported a case study of two workers exposed to carbonyl sulfide in the cellar (6 square meters x 1.6 meters deep) of a "production plant." The workers, ages 56 (mechanic) and 24 years, were exchanging part of a dye pipe. The 56-year old suddenly became very dizzy without noticing any odor. He immediately ran to the staircase and his co-worker followed. He became "really tired" and noticed that he "couldn't really breathe anymore."

Everything was "dancing in front of his eyes" and he collapsed in front of the cellar entrance. When he regained consciousness, he could not immediately remember what had happened. He found the co-worker unconscious and tried to carry him out. However, he again became dizzy and felt a "dull pressure" in his head and chest. He ran back to the escape route and became unconscious for a second time. When he regained consciousness, he was able to call for help. He was administered oxygen and taken to the hospital fully conscious; on admission, the lungs and heart were clinically and radiologically normal. He experienced headaches for 3 days and was discharged on day 4. The 24-year old worker was found dead. Autopsy showed dark brown-red colored blood, lungs filled with blood, blue-red colored kidneys, and moderate brain swelling and edema. No carbonyl sulfide concentration was reported.

Kilburn and Warshaw (1995) reported abnormal neurobehavioral function (two-choice reaction time, balance, color discrimination, digit symbol, immediate recall of a story) in former workers and neighbors living downwind from a coal refinery. Subjects also complained of headaches, nausea, vomiting, depression, personality changes, nose bleeds, and breathing problems. Monitoring outside the desulfurization unit showed 24-hour average concentrations of 0.1 to 21.1 ppm mercaptans, 0 to8.8 ppm hydrogen sulfide, 2.6 to 51.1 ppm carbonyl sulfide, and 6.1 to 70.7 ppm total reduced sulfur gases. The authors attributed the observed effects to exposure to reduced sulfur gases; however, worker exposures were not monitored.

An odor threshold of 0.1 ppm has been reported (U.S. EPA, 1992).

3. ANIMAL TOXICITY DATA

3.1. Acute Toxicity

Groups of ten male Crl:CD rats were exposed to 477, 943, 981, 1050, 1090, 1160, 1210, 1270, or 2180 ppm (analytical concentrations) carbonyl sulfide for 4 hours, followed by a 14-day observation period (DuPont, 1981). The whole-body exposure chambers were constructed of glass and had an internal volume of 20 L. The test atmosphere was generated by metering carbonyl sulfide (as a pressurized gas) through Teflon lines into a mixing flask where dilution air and oxygen were added. The atmosphere was then introduced into the top of the exposure chamber with total airflow of 10 L/min. The test atmospheres were analyzed at half-hour intervals during each exposure by gas chromatography. Clinical signs increased with increasing carbonyl sulfide concentration. Signs observed during exposure (exposure groups not specified) included labored breathing, decreased or no response to sound, lack of coordination, convulsions, pallor, head bobbing, and uncontrolled body movements. Signs noted during the observation period included rapid breathing, pallor, hair loss, cloudy eyes, diarrhea, wet perineal area, lethargy, red ocular discharge, stained nose and mouth, partially closed eyes, lack of righting reflex, and slight to severe weight loss. Animals in the 943 ppm group showed slight to moderate weight loss at 1-2 days post-exposure, followed by normal weight gain. At 981 ppm and above, slight to severe weight loss was noted 1-8 days post-exposure. No other specifics concerning clinical signs were described. A 4-hour LC_{50} value of 1111 ppm (95% CI = 1058-1158 ppm), $BMCL_{05}$ of 969 ppm, and BMC_{01} of 992 ppm were calculated. These calculations included the animal sacrificed *in extremis* at 981 ppm. Mortality data are summarized in Table 3.

TABLE 3. Mortality in rats exposed to carbonyl sulfide for 4-hours*		
Concentration	**Mortality**	
	# Deaths/# Exposed	**Time of Death**
477 ± 21 ppm	0/10	-
943 ± 26 ppm	0/10	-
981 ± 89 ppm	1/10	Sacrificed *in extremis* (day not given)
1050 ± 22 ppm	0/10	-
1090 ± 23 ppm	4/10	2 during exposure; 1 on day 8; 1 on day 9
1160 ± 32 ppm	5/10	1 during exposure; 1 on day 1; 3 on day 9
1210 ± 24 ppm	10/10	3 during exposure; 5 on day 1; 1 on day 7; 1 on day 8
1270 ± 76 ppm	10/10	9 during exposure; 1 on day 1
2180 ± 66 ppm	10/10	10 during exposure
LC_{50}	1111 ppm	
BMC_{01}	992 ppm	
$BMCL_{05}$	969 ppm	

*DuPont, 1981

In another study, groups of six male and six female Sprague-Dawley rats were exposed to 0, 804, 993, 1062, 1096, 1147, or 1189 ppm (analytical concentrations) carbonyl sulfide for 4 hours, followed by a 14-day observation period (Monsanto, 1985a). The whole-body exposure chamber was a 0.3 m^3 Rochester-type stainless steel chamber with a pyramidal top and bottom and a glass window in the door. The test atmosphere was generated by drawing conditioned room air through the chamber at a rate of approximately 50 L/min and metering the carbonyl sulfide gas (by a pressure regulator, needle valve, and rotometer) directly into the chamber inlet. The carbonyl sulfide concentration in the test atmosphere was monitored by infrared analysis continuously during the exposure periods and recorded at hourly intervals. Clinical signs noted during exposure are presented in Table 4, and signs noted immediately after exposure are presented in Table 5. Animals surviving longer than 24-hours post-exposure exhibited few clinical signs; the most prominent was circling. Circling was noted in approximately half of the surviving animals in the 1062 ppm group during the first four days post-exposure; whereas, circling was observed in only one of this group between days 5-7 post-exposure. Four-hour LC_{50} values of 1082 ppm (95% CI = 1059-1102 ppm), 1094 ppm (95% CI = 1055-1136 ppm), and 1070 ppm (95% CI = 1022-1100 ppm) were calculated for both sexes combined, males, and females, respectively. A $BMCL_{05}$ of 951.9 ppm and BMC_{01} of 951.7 ppm were calculated. Mortality data are summarized in Table 6.

TABLE 4. Clinical signs observed during exposure in rats exposed to carbonyl sulfide for 4-hours (incidence/6 animals/sex)

Concentration	Convulsion		Tremor		Hypoactivity		Cyanosis		Breathing difficulty		Nasal bleeding		Lacrimation		Behavioral abnormality	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F	M	F
0 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
804 ppm	0	0	0	0	6	6	0	0	0	0	0	0	0	0	0	0
993 ppm	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
1062 ppm	0	1	0	0	0	0	0	0	1	3	0	0	0	0	1	4
1096 ppm	2	1	2	0	6	6	0	1	0	2	1	0	0	0	0	1
1147 ppm	2	4	2	0	6	6	0	0	6	6	0	0	0	0	6	6
1189 ppm	1	1	0	0	6	6	0	0	6	6	0	0	6	6	0	0

Monsanto, 1985a

TABLE 5. Clinical signs observed immediately post-exposure in rats exposed to carbonyl sulfide for 4-hours (incidence)

Concentration	Convulsion		Tremor		Hypoactivity		Cyanosis		Breathing difficulty		Chromadacryorrhea		Salivation/ Lacrimation	
	M	F	M	F	M	F	M	F	M	F	M	F	M	F
0 ppm	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
804 ppm	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
993 ppm	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6	0/6
1062 ppm	0/6	1/5	1/6	1/5	1/6	2/5	0/6	1/5	0/6	1/5	2/6	0/5	0/6	1/5
1096 ppm	0/3	1/4	0/3	0/4	1/3	1/4	0/3	0/4	0/3	1/4	0/3	1/4	0/3	1/4
1147 ppm	0/5	1/2	0/5	1/2	5/5	2/2	3/5	2/2	2/5	0/2	0/5	0/2	1/5	1/2
1189 ppm	0/1	2/3	0/1	1/3	1/1	3/3	0/1	1/3	0/1	2/3	1/1	0/3	1/1	1/3

Monsanto, 1985a

TABLE 6. Mortality in rats exposed to carbonyl sulfide for 4-hours

Concentration	Mortality		
	Males	Females	Combined
0 ppm	0/6	0/6	0/12
804 ppm	0/6	0/6	0/12
993 ppm	0/6	0/6	0/12
1062 ppm	1/6	3/6	4/12
1096 ppm	4/6	4/6	8/12
1147 ppm	5/6	6/6	11/12
1189 ppm	6/6	5/6	11/12
LC_{50}	1094 ppm	1070 ppm	1082 ppm
BMC_{01}			951.7 ppm
$BMCL_{05}$			951.9 ppm

Monsanto, 1985a

Morgan et al. (2004), exposed groups of five male F344 rats to 0, 75, 150, 300, or 600 ppm carbonyl sulfide for 6-hours, followed by a 2-week follow-up period. Animals were exposed in Hazleton 2000 exposure chambers with an airflow of 400 L/min. Carbonyl sulfide concentrations in the test atmospheres were analytically determined by gas chromatography. No mortality occurred at any test concentration. Animals in the 600 ppm group were lethargic when observed immediately after exposure and the following morning (day 2). By the afternoon of day 2, clinical signs in the 600 ppm group included hypothermia, lethargy, head tilt, and ataxia. The clinical condition improved during the 14-day follow-up; however, several rats continued to exhibit ataxia with head tilt. At necropsy, micropsopic evaluation of brain sections from rats in the 600 ppm group showed necrosis and microgliosis in the cerebellar roof nucleus, internal capsule, and thalamus. Vacuolation of the cerebellar medullary white matter and fifth cranial nerve tract were

also noted. No clinical signs or brain lesions were reported in rats in the 0, 75, 150, or 300 ppm groups. Therefore, 75 and 150 ppm are considered no-effect-levels for all effects, and 300 ppm is a no-effect-level for clinical signs and brain pathology.

In another set of experiments, Thiess et al. (1968), generated carbonyl sulfide from potassium cyanide and dilute sulfuric acid for acute inhalation toxicity tests on rats, cats, rabbits, and guinea pigs. Fresh carbonyl sulfide was produced every 24 hours, and some exposure concentrations were measured via an infrared spectrophotometer.

Clinical signs in rats were described as severe tonic-clonic "cramps." When rats were removed from the test atmosphere immediately at the onset of convulsions (and allowed to breathe clean air), no mortality was noted. Gross examination of deceased rats showed no treatment-related effects. When rats were examined immediately after death, heart function was "still present." Therefore, the authors suggested that death was due to respiratory paralysis.

Clinical signs observed in cats included salivation, followed by respiratory problems, balancing problems, prostration, nausea, and fecal discharge. After exposure for 1-hour, tonic-clonic cramps were noted, followed by shortness of breath and respiratory paralysis. Four cats died during exposure and two died within 24-hours post-exposure. No clinical signs were noted in cats exposed to 300 ppm for 6 hours. Insignificant lung edema was noted in 4/6 cats that died.

Clinical signs in rabbits also included clonic-tonic cramps. Most rabbits died within one hour or several hours after exposure; however, three delayed deaths occurred after 7-18 days. Surviving rabbits quickly recovered after the exposure period. Approximately one-half of the decedent animals showed insignificant lung edema; no abnormalities were noted in the three rats with delayed deaths.

No mortality or clinical signs occurred in guinea pigs. Rat data are summarized in Table 7, and cat, rabbit, and guinea pig data are summarized in Table 8.

TABLE 7. Acute inhalation toxicity of carbonyl sulfide in rats (time saturation test)					
Concentration (ppm)		Exposure duration	Occurrence of tonic-clonic cramps	Mortality incidence	Time to death
Nominal	Analytical				
250,000	-	30 sec	15 sec	6/6	30 sec
50,000	-	13 sec	13 sec	5/6	1 min
10,000	8,000	4 min, 30 sec	2 min, 20 sec	6/6	4 min, 30 sec
10,000	-	3 min	1 min, 15 sec	6/6	3 min
10,000	-	1 min, 15 sec	1 min, 15 sec	0/6	-
3,000	-	9 min	5 min, 30 sec	3/6	8-14 min
1,000	-	75 min	-	0/6	-
1,000	1,400	90 min	59 min	3/6	75 min

Theiss et al., (1968)

TABLE 8. Acute inhalation toxicity of carbonyl sulfide in cats, rabbits, and guinea pigs					
Concentration (ppm)		Exposure duration	Mortality incidence		
Nominal	Analytical		Cats	Rabbits	Guinea pigs
3,000	-	30 min	-	4/4	-
3,000	-	4 min	-	1/4	-
1,000	-	120 min	-	2/4	-
1,000	-	90 min	4/4	8/12	0/4
1,000	1,300	90 min	2/2	0/2	0/2
300	500	6 hr	0/2	0/2	0/2

Theiss et al., (1968)

Nutt et al. (1996) exposed groups of male and female F344 rats nose only to 250-1400 ppm carbonyl sulfide for up to 4-hours, followed by a two week observation period. No lethality was observed below 500 ppm. Time to death was 30-min to 60-min from the start of exposure at 1400 ppm, 2-3 hours at 1000 ppm, 3-4 hours at 750 ppm, and >4 hours at 590 ppm. Exposure to higher concentrations caused an excitation phase followed by a depressive phase with decreased heart rate and body temperature. Lung, liver, kidney, and GI tract were congested at 750-1000 ppm. Rats surviving exposure to > 500 ppm had motor impairment accompanied by swelling of myelin sheaths in the corpus callosum, cerebellum, and and pyramidal tract. Partial to complete resolution of clinical signs occurred during the 14-day observation period. No further information was available (abstract).

3.1.1. Repeated-exposure Studies

Female rabbits (White Danish country breed) were exposed to 0 (17 rabbits) or 50 ppm (mean 54 ppm ± 13 ppm; 18 rabbits) carbonyl sulfide continuously for 7 weeks (Kamstrup and Hugod, 1979; Hugod and Astrup, 1980; Hugod, 1981). Five days after the start of exposure, three carbonyl sulfide-exposed rabbits were found dead and two others showed signs of serious neurological disorders. The dead animals were discarded, whereas the impaired animals were sacrificed and included in the histopathological analysis. There were no gross or microscopic treatment-related effects in the heart, lungs, aorta, or main arteries. Lung sections of exposed rabbits showed no signs of irritation or edema (Kamstrup and Hugod, 1979), and there was no effect on myocardial ultrastructure (Hugod, 1981; Hugod and Astrup, 1980).

Male and female Sprague-Dawley rats (numbers not stated) were exposed to 0, 10, 60, or 182 ppm (analytical concentrations) carbonyl sulfide 6 hr/day, 5 days/week over a 14-week period (Reyna and Ribelin, 1987). There were no clinical signs during exposure and no effects on urinalysis, clinical chemistry, gross pathology, histopathology, or pupillary reflexes. Lymphopenia (no concentration-response) was noted in males in all exposure groups and in high-concentration females. No other details were provided.

Groups of 10 male and 10 female Sprague-Dawley rats were exposed to 0, 51, 151, 253, or 453 ppm (analytical concentrations) carbonyl sulfide 6-hr/day for 11 days in a 2 week period (Monsanto, 1985b). No clinical signs were noted until the second week of exposure when 3 males and 7 females in the 453 ppm group exhibited ataxia, head tilting, circling, prostration, arched backs, tremors, loss of muscle control, convulsions, and bulging and dilated eyes. These animals were sacrificed in extremis after the eighth day of exposure. Concentration-related increases ($p \leq 0.01$) of approximately 68%, 113%, and 175% in methemobgobin were noted in males and females in the 151, 253, and 453 ppm groups, respectively. No treatment-related effects were noted at 51 ppm.

In a range-finding study, Morgan et al. (2004) exposed groups five male F344 rats to 0, 75, 150, 300, or 600 ppm carbonyl sulfide, 6 hours/day for 4 days. The exposure methods were similar to those described in the 6-hour study (Morgan et al., 2004) in section 3.1.1. No mortality, morbidity, or clinical signs of toxicity were noted in rats exposed to 75, 150, or 300 ppm carbonyl sulfide for 4 days. However, some (number not specified) rats in the 600 ppm group were euthanized in a moribund condition after 2 days of exposure. Rats in the 600 ppm group showed clinical signs of hypothermia, lethargy, ataxia, and impaired righting reflex. No microscopic brain lesions were noted in rats exposed to 75, 150, or 300 ppm for 4 days. Microscopic evaluation of brain sections from moribund animals exposed to 600 ppm for 2 days showed extensive bilateral symmetrical necrosis in parietal cortex area 1 and thalamus. Necrosis was also observed in the retrosplenial granular cortex, ptriform cortex, red nucleus, cerebellar roof nucleus, posterior collicular nucleus, and anterior olivary nucleus.

Based on the range-finding study, Morgan et al. (2004) conducted a two-week study. Groups of ten male and ten female F344 rats were exposed to 0, 300, 400, or 500 ppm carbonyl sulfide 6 hr/day, 5 days/week for 12 exposures over a two week period. The exposure methods were similar to those described in the 6-hour study (Morgan et al., 2004) in section 3.1.1. All ten male and 4/10 female rats exposed to 500 ppm were euthanized in moribund condition and removed from the study. Male rats were found moribund after 4 (1/10), 5 (6/10), and 10 (3/10) exposures. Females were found moribund after 5 (2/10) and 11 (2/10) exposures. Moribund animals showed signs of hypothermia, lethargy, ataxia with poor control of front and rear limbs. Rats in the 300 and 400 ppm groups showed no adverse clinical signs. No treatment-related effects on body weight were observed in of animals in the 300 and 400 ppm groups. In a functional operational battery (FOB), surviving females at 500 ppm had decreased forelimb and hindlimb grip strength, hypotonia, and slight gait abnormalities. At 400 ppm, slight gait changes and hypotonia were noted in approximately half the rats. No clear FOB effects were noted at 300 ppm. Bilateral symmetrical malacia of the frontoparietal cortex was observed on gross brain examination from rats exposed to 400 or 500 ppm. Microscopic brain lesions were noted in all early death rats exposed to 500 ppm and in 8/10 males and 9/10 females exposed to 400 ppm. Brain lesions were noted only in one female in the 300 ppm group. Predominant lesions at 400 and 500 ppm included bilateral symmetrical necrosis in parietal cortex area 1 and putamen. At 500 ppm only, necrosis was observed in the retrosplenial cortex, thalamus, and posterior colliculus,

anterior olivary nucleus, and vestibular nucleus. In animals exposed to 500 ppm for 12 days, there was a loss of brain substance within the parietal cortex and retrosplenial cortex, compared to rats exposed to 500 ppm for 5 days.

Based on two-week study, Morgan et al. (2004) conducted a 12-week study. Groups of twenty male and twenty female F344 rats were exposed to 0, 200, 300, or 400 ppm carbonyl sulfide 6 hr/day, 5 days/week for up to 12 weeks. The exposure methods were similar to those described in the 6-hour study (Morgan et al., 2004) in section 3.1.1. Interim sacrifices (5 rats/sex/concentration) were performed at 3 and 6 weeks to measure cytochrome C oxidase activity in the brain. There were no treatment-related deaths, morbidity, clinical signs, or decrease in body weight in animals of any exposure group. Decreases in clinical chemistry parameters were noted in males; however, no concentration-response relationship was present and the findings were not considered treatment-related or toxicologically significant. Mild FOB findings were not concentration-related and were considered incidental to treatment. Concentration-related decreases ($p<0.05$ or $p<0.001$) in cytochrome C oxidase activity, ranging from 90% to 46% of control, were noted the posterior colliculus and parietal cortex of males and females of all treatment-groups at 3, 6, and 12 weeks. The decreases in cytochrome oxidase activity were present in rats exposed to 200 or 300 ppm in the absence of histopathological findings. At 12 weeks, microscopic brain lesions were noted only in male and female rats in the 400 ppm group. Predominant lesions were unilateral and bilateral symmetrical cortical necrosis and cavitation in the parietal cortex, and bilateral symmetrical neuronal loss with microgliosis and hemorrhage in the posterior colliculus (Sills et al., 2004).

3.2. Developmental/Reproductive Toxicity

Groups twelve male albino rats were exposed to 0, 10, 60, or 182 ppm (analytical concentrations) carbonyl sulfide 6 hr/day, 5 days/week over a 13-week period (Reyna and Ribelin, 1987). These males were then mated with untreated females who were allowed to deliver and wean a litter of pups. There were no clinical signs or body weight effects in exposed males. Only 12 of 24 females mated with 182 ppm males became pregnant, compared with 20 of 24 females in the 0, 10, and 60 ppm groups. Reproductive behavior was not affected in the high-concentration males. There were no effects on numbers of pups per litter, pup survival, and histopathology (including reproductive tract). In a follow-up study, the treated males were allowed to recover for 10 weeks and were then mated with new females. There were no treatment-related effects on mating and fertility indices or on gross and histopathology of reproductive organs. Groups of twelve female rats were then exposed to 0, 10, 60, or 180 ppm carbonyl sulfide 6 hr/day, 5 days/week over a 13-week period and mated with unexposed males. No treatment-related effects were noted in dams or pups.

In a pilot teratology study, mated female rats were exposed to 0, 50, 149, 250, 348, or 451 (analytical concentrations) carbonyl sulfide from days 6-15 of gestation (Reyna and Ribelin, 1987). The only treatment-related clinical signs (respiratory problems and prostration) occurred in one 451 ppm female that died on day 14 of gestation. Decreased body weight gain was noted in 451 ppm animals throughout the treatment period and in the other treatment groups from days 10-13 of gestation. No treatment-related gross postmortem findings were noted, and there were no effects on total implantations, litter size, or resorptions. No gross fetal abnormalities were observed. In the subsequent teratology study, mated female Sprague-Dawley rats were exposed to 0, 50, 200, or 400 ppm carbonyl sulfide from days 6-15 of gestation (Reyna and Ribelin, 1987). No maternal toicity was observed at 50 or 200 ppm; at 400 ppm, maternal death and decreased

body weight gain and food consumption were noted from days 6-16 of gestation. Pregnancy rate, reproductive parameters, fetal body weight, and fetal sex distribution were comparable in all groups. No further details were available.

3.3. Genotoxicity

Carbonyl sulfide was negative for *in vivo* spermatoctye chromosome aberrations in mice by both oral and inhalation routes. It was also negative in oral and inhalation bone marrow micronucleus assays in mice. Bacterial reverse mutation assays were generally negative. The exception was a weak positive response with and without metabolic activation in *Salmonella typhimurium* strain TA98 only (Bartholomaeus and Haritos, 2005).

3.4. Chronic Toxicity/Carcinogenicity

No data on chronic toxicity/carcinogenicity were located.

3.5. Summary

Acute inhalation toxicity studies in animals showed clinical signs consistent with neurotoxicity and an extremely steep concentration-response curve. In repeated-exposure studies, clinical signs of neurotoxicity were noted, often in the presence of concurrent histopathological lesions in the brain. Carbonyl sulfide does not appear to be a developmental toxicant; however, data in rats suggest that it may reversibly impair male fertility. Genotoxicity data were generally negative, and no data on chronic toxicity/carcinogenicity were located.

4. SPECIAL CONSIDERATIONS

4.1. Metabolism and Disposition

The major metabolic pathway for carbonyl sulfide is conversion to hydrogen sulfide via carbonic anhydrase (Chengelis and Neal, 1979). Using bovine erythrocyte carbonic anhydrase, the conversion rate of carbonyl sulfide to hydrogen sulfide was shown to be rapid (Bartholomaeus and Haritos, 2005). Chengelis and Neal (1980) showed that administration of the carbonic anhydrase inhibitor, acetazolamide, protected against carbonyl sulfide toxicity in rats. The 1980 study also showed that the hydrogen sulfide metabolite is responsible for carbonyl sulfide toxicity. Rats pre-treated with sodium nitrite to induce 50% methemoglobinemia before carbonyl sulfide administration, were protected from a dose of carbonyl sulfide that killed 75% of non pre-treated rats. (Methemoglobin has been shown to bind sulfide and protect against hydrogen sulfide toxicity). Also, the blood levels of hydrogen sulfide in rats treated with sodium sulfide in slight excess of the LD_{50} (to be comparable to the highest dose of carbonyl sulfide administered) were comparable to levels seen with carbonyl sulfide. Therefore, approximate equally toxic doses of sodium sulfide and carbonyl sulfide resulted in similar blood concentrations of hydrogen sulfide.

Carbonyl sulfide is also a suicide substrate for cytochrome P450. It can be metabolized by cytochrome P450 to produce carbon dioxide and a reactive sulfur species which binds to the heme in the cytochrome P450 and results in inactivation (Bartholomaeus and Haritos, 2005).

4.2. Mechanism of Toxicity

It is thought that the hydrogen sulfide produced from the metabolism of carbonyl sulfide via carbonic anhydrase may be responsible for carbonyl sulfide toxicity (HSDB, 2007) (Section 4.1).

4.3. Structure Activity Relationships

Carbonyl sulfide (S=C=O) is structurally-similar to carbon disulfide (S=C=S) and both are neurotoxic. Carbon disulfide can be metabolized to carbonyl sulfide via the mixed function oxidase system (Sills et al., 2005).

4.4. Other Relevant Information

4.4.1. Species Variability

Results of acute inhalation lethality studies in animals show some species variability. Mortality incidences for animals exposed to 1000 ppm carbonyl sulfide for 90 minutes were as follows: 0/6 for guinea pigs, 3/6 for rats, 8/14 for rabbits, and 6/6 for cats (Thiess et al., 1968).

4.4.2. Susceptible Populations

No information was available on populations especially sensitive to carbonyl sulfide toxicity. However, the extremely steep concentration-response curve implies limited intraspecies variability. The steep curve is evidenced in several studies. No mortality was noted in rats exposed to 943 ppm carbonyl sulfide for 4-hours, and 4/10 rats died at 1090 ppm and 10/10 rats died when exposed to 1210 ppm (DuPont, 1981). In another 4-hour rat study (Monsanto, 1985a), no mortality was noted at 993 ppm; whereas, 4/12 rats died at 1060 ppm, and 11/12 rats died at 1147 ppm. Thiess et al. (1968) observed no mortality in rats exposed to 1000 ppm for 75-min and death of 3/6 rats exposed to 1000 ppm for 90-min.

4.4.3. Time Scaling

The concentration exposure time relationship for many irritant and systemically acting vapors and gases may be described by $C^n \times t = k$, where the exponent ranges from 0.8 to 3.5 (ten Berge et al. 1986). In lieu of a definitive data set allowing empirical derivation of the exponent n, temporal scaling was performed, using n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points using the $C^n \times t = k$ equation (NRC 2001).

5. DATA ANALYSIS FOR AEGL-1

5.1. Summary of Human Data Relevant to AEGL-1

No human data relevant to development of AEGL-1 values were identified.

5.2. Summary of Animal Data Relevant to AEGL-1

No animal data relevant to development of AEGL-1 values were identified.

5.3. Derivation of AEGL-1

Data were insufficient for deriving AEGL-1 values for carbonyl sulfide. Therefore, AEGL-1 values are not recommended (Table 9). Also, carbonyl sulfide has poor warning properties; it may cause serious effects or lethality at concentrations causing no signs or symptoms (HSDB, 2007).

TABLE 9. AEGL-1 Values for Carbonyl Sulfide

10-min	30-min	1-h	4-h	8-h
NR	NR	NR	NR	NR

NR: Not Recommended due to insufficient data. The absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect. Carbonyl sulfide has poor warning properties; it may cause serious effects or lethality at concentrations causing no signs or symptoms

6. DATA ANALYSIS FOR AEGL-2

6.1. Summary of Human Data Relevant to AEGL-2

No human data relevant to development of AEGL-2 values were identified.

6.2. Summary of Animal Data Relevant to AEGL-2

Hypoactivity was noted in rats exposed to 804 ppm carbonyl sulfide for 4-hours (Monsanto, 1985a). Clinical signs (hypothermia, lethargy, head tilt and ataxia) and brain histopathology were noted in rats exposed to 600 ppm for 6-hours; no clinical signs or brain lesions were noted in rats exposed to 75, 150, or 300 ppm carbonyl sulfide for 6-hours (Morgan et al., 2004).

6.3. Derivation of AEGL-2

The NOEL for clinical signs and brain pathology (300 ppm) in rats exposed to carbonyl sulfide for 6-hours (Morgan et al., 2004) will be used as the POD for AEGL-2 values. (Animals exposed to the next highest concentration tested, 600 ppm, exhibited severe clinical signs and brain pathology). Values will be scaled across time using the $C^n \times t = k$ equation, where n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points in order to derive values protective of human health (NRC, 2001). The 30-min AEGL-2 value will be adopted as the 10-min AEGL-2 value because of the added uncertainty of extrapolating from the 6-hour POD to 10-min. An intraspecies uncertainty factor (UF) of 3 will be applied and is considered sufficient due to the steep concentration-response curve (Section 4.4.2), which implies limited intra-individual variability. An interspecies UF of 3 will also be applied. Although the animal data suggest some species variability and the rat is not the most sensitive species [mortality incidences for animals exposed to 1000 ppm carbonyl sulfide for 90 minutes were as follows: 0/6 for guinea pigs, 3/6 for rats, 8/14 for rabbits, and 6/6 for cats (Thiess et al., 1968)], use of the full default interspecies UF of 10 would yield AEGL-2 values that are inconsistent with the overall database. [AEGL-2 values derived using a total UF of 30 would be 23 ppm for 10- and 30-min, 18 ppm for 1-hr, 11 ppm for 4-hr, and 7.7 ppm for 8-hr; no treatment-related effects were noted in rats exposed to 51 ppm 6-hr/day for 11 days (Monsanto, 1985b), or 75, 150, or 300 ppm 6-hr/day for 4 days (Morgan et al., 2004)]. Therefore, the total adjustment is 10. AEGL-2 values are presented in Table 10, and calculations are presented in Appendix A.

TABLE 10. AEGL-2 Values for Carbonyl Sulfide				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
69 ppm (170 mg/m^3)	69 ppm (170 mg/m^3)	55 ppm (130 mg/m^3)	34 ppm (83 mg/m^3)	23 ppm (56 mg/m^3)

The proposed AEGL-2 values are considered protective because no treatment-related effects were noted in rats repeatedly exposed to 51 ppm, 6-hr/day for 11 days (Monsanto, 1985b) and 75 or 150 ppm 6-hr/day for 4 days (Morgan et al., 2004).

7. DATA ANALYSIS FOR AEGL-3

7.1. Summary of Human Data Relevant to AEGL-3

No human data relevant to development of AEGL-3 values were identified.

7.2. Summary of Animal Data Relevant to AEGL-3

Two well-conducted 4-hr rat acute lethality studies support one another. A $BMCL_{05}$ of 969 ppm and BMC_{01} of 992 ppm were calculated from a DuPont (1981) study and a $BMCL_{05}$ of 951.7 ppm and BMC_{01} of 951.9 ppm were calculated from a Monsanto (1985a) study.

7.3. Derivation of AEGL-3

The 4-hour rat $BMCL_{05}$ (951.9) and BMC_{01} (951.7) calculated from Monsanto (1985a) are essentially identical and are slightly more conservative than values calculated from the DuPont (1981) study. A 4-hr concentration of 952 ppm (rounded BMC values; Monsanto, 1985a) will be used as the point-of-departure (POD) for AEGL-3 values. Values will be scaled across time using the $C^n \times t = k$ equation, where n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points in order to derive values protective of human health (NRC, 2001). The 30-min AEGL-3 value will be adopted as the 10-min AEGL-3 value because of the added uncertainty of extrapolating from the 4-hour POD to 10-min. An intraspecies uncertainty factor (UF) of 3 will be applied and is considered sufficient due to the steep concentration-response curve (Section 4.4.2), which implies limited intra-individual variability. An interspecies UF of 3 will also be applied. Although the animal data suggest some species variability and the rat is not the most sensitive species [mortality incidences for animals exposed to 1000 ppm carbonyl sulfide for 90 minutes were as follows: 0/6 for guinea pigs, 3/6 for rats, 8/14 for rabbits, and 6/6 for cats (Thiess et al., 1968)], use of the full default interspecies UF of 10 would yield AEGL-3 values that are inconsistent with the overall database. [AEGL-3 values derived using a total UF of 30 would be 63 ppm for 10- and 30-min, 50 ppm for 1-hr, 32 ppm for 4-hr, and 16 ppm for 8-hr; no treatment-related effects were noted in rats exposed to 51 ppm 6-hr/day for 11 days (Monsanto, 1985b), or 75, 150, or 300 ppm 6-hr/day for 4 days (Morgan et al., 2004). No mortality or clinical signs were present in rats exposed to 200, 300, and 400 ppm 6 hr/day, 5 days/week for 12-weeks; however, significant decreases in brain cholinesterase activity were noted at all three concentrations (Morgan et al., 2004)]. Therefore, the total adjustment is 10. AEGL-3 values are presented in Table 11, and calculations are presented in Appendix A.

TABLE 11. AEGL-3 Values for Carbonyl Sulfide				
10-min	**30-min**	**1-h**	**4-h**	**8-h**
190 ppm (470 mg/m^3)	190 ppm (470 mg/m^3)	150 ppm (370 mg/m^3)	95 ppm (230 mg/m^3)	48 ppm (120 mg/m^3)

The proposed AEGL-3 values are considered protective because no treatment-related effects were noted in rats repeatedly exposed to 75, 150, or 300 ppm 6-hr/day for 4 days (Morgan et al., 2004). No treatment-related clinical signs of FOB effects were noted in male and female rats exposed to 300 ppm, 6 hr/day, 5 days/week for 12 exposures in a two-week period; brain lesions were noted only in 1/5 females in this study (Morgan et al., 2004). No mortality or clinical signs were present in rats exposed to 200, 300, or 400 ppm 6 hr/day, 5 days/week for 12-weeks; however, significant decreases in brain cholinesterase activity were noted at all three concentrations (Morgan et al., 2004).

8. SUMMARY OF AEGLS

8.1. AEGL Values and Toxicity Endpoints

AEGL values are summarized in Table 12. AEGL-1 values are not recommended due to insufficient data and poor warning properties. AEGL-2 values were based on a NOEL for clinical signs of neurotoxicity and brain lesions in rats (Morgan et al., 2004), and AEGL-3 values were based on a 4-hr rat $BMCL_{05}/BMC_{01}$ value (Monsanto, 1985a).

TABLE 12. Summary of AEGL Values					
Classification	**Exposure Duration**				
	10-min	**30-min**	**1-h**	**4-h**	**8-h**
AEGL-1 (Nondisabling)	NR	NR	NR	NR	NR
AEGL-2 (Disabling)	69 ppm (170 mg/m^3)	69 ppm (170 mg/m^3)	55 ppm (130 mg/m^3)	34 ppm (83 mg/m^3)	23 ppm (56 mg/m^3)
AEGL-3 (Lethal)	190 ppm (470 mg/m^3)	190 ppm (470 mg/m^3)	150 ppm (370 mg/m^3)	95 ppm (230 mg/m^3)	48 ppm (120 mg/m^3)

NR: Not Recommended due to insufficient data. The absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect. Carbonyl sulfide has poor warning properties; it may cause serious effects or lethality at concentrations causing no signs or symptoms

8.2. Comparison with Other Standards and Guidelines

There are no other extant standards or guidelines for carbonyl sulfide.

8.3. Data Adequacy and Research Needs

There are no human data, and high-quality animal data are limited to rats. Additional acute inhalation toxicity studies in other animal species would be helpful.

9. REFERENCES

Bartholomaeus, A. R. and Haritos, V. S. 2005. Review of the toxicology of carbonyl sulfide, a new grain fumigant. Food and Chemical Toxicology. 43: 1687-1701.

Chengelis, C. C. and Neal, R. A. 1979. Hepatic carbonyl sulfide metabolism. Biochemical and Biophysical Research Communications. 90: 993-999.

Chengelis, C. C. and Neal, R. A. 1980. Studies of carbonyl sulfide toxicity: metabolism by carbonic anhydrase. Toxicol. Appl. Pharmacol. 55: 198-202.

DuPont. 1981. Initial submission: acute inhalation toxicity of carbon oxide sulfide in rats with cover letter dated 080992. E. I. DuPont de Nemours and Company, Haskell Laboratory for Toxicology and Industrial Medicine, Newark, Delaware. OTS0571009.

HSDB (Hazardous Substances Data Bank). 2007. Carbonyl Sulfide. Online data base, National Library of Medicine: http://toxnet.nlm.nih.gov/cgi-bin/sis.

Hugod, C., and Astrup, P. 1980. Exposure of rabbits to carbon monoxide and other gas phase constituents of tobacco smoke. Munch. Med. Wschr. 122: S18-S24.

Hugod, C. 1981. Myocardial morphology in rabbits exposed to various gas-phase constituents of tobacco smoke. An ultrastructural study. Atherosclerosis. 40: 181-190.

Kamstrup, O., and Hugod, C. 1979. Exposure of rabbits to 50 ppm carbonyl sulfide. Int. Arch. Occup. Environ. Health. 44: 109-116.

Kilburn, K. H. and Warshaw, R. H. 1995. Hydrogen sulfide and reduced-sulfur gases adversely affect neurophysiological functions. Toxicol. Ind. Health. 11:185-197.

Monsanto. 1985a. 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. Monsanto Company, Environmental Health Laboratory, St. Louis, Mo. OTS0534820.

Monsanto. 1985b. Initial submission: two-week study with carbonyl sulfide administered by inhalation to rats with cover letter dated 052892. Monsanto Company, Environmental Health Laboratory, St. Louis, Mo. OTS0540051.

Morgan, D. L., Little, P. B., Herr, D. W., et al. 2004. Neurotoxicity of carbonyl sulfide in F344 rats following inhalation exposure for up to 12 weeks. Toxicology and Applied Pharmacology. 200: 131-145.

NRC (National Research Council). 2001. Standing Operating Procedures for Acute Exposure Guideline Levels for Selected Airborne Chemicals. The National Academies Press, Washington, DC.

Nutt, A. W., Benson, J. M., Barr, E. B., et al. 1996. Acute inhalation toxicity of carbonyl sulfide. Fund. Appl. Toxicol. Supplement. 30:18. (abstract)

Reyna, M. S. and Ribelin, W. E. 1987. One-generation reproduction studies of male albino rats, female albino rats, and previously exposed male Sprague-Dawley rats to carbonyl sulfide by inhalation. Monsanto Technical Laboratory, submitted by E. I. DuPont de Nemours & Co. OTS 0555041.

Sills, R. C., Harry, G. J., Valentine, W. M., and Morgan, D. L. 2005. Interdisciplinary neurotoxicity inhalation studies: carbon disulfide and carbonyl sulfide research in F344 rats. Toxicol. Appl. Pharmacol. 207: S2245-S250.

ten Berge, W.F., Zwart, A., Appelman, L.M. 1986. Concentration-time mortality response relationship of irritant and systemically acting vapours and gases. J. Hazard. Materials: 13: 301-309.

Thiess, A. M., Hey, W., Hofmann, H. T., and Oettel, H. 1968. The toxicity of carbon oxysulfide- illustrated by a case of fatal poisoning. Archiv. Fur Toxikologie. 23: 253-263.

U. S. EPA. 1992. Reference Guide to Odor Thresholds for Hazardous Air Pollutants Listed in the Clean Air Act Amendments of 1990. Air Risk Support Center, U. S. Environmental Protection Agency. Page 2-10. EPA600/R-92-047. March, 1992.

APPENDIX A: Derivation of AEGL Values

Derivation of AEGL-1

AEGL-1 values are not recommended due to insufficient data. The absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect. Carbonyl sulfide has poor warning properties; it may cause serious effects or lethality at concentrations causing no signs or symptoms

Derivation of AEGL-2

Key Study: Morgan et al., 2004
Toxicity endpoint: 300 ppm for 6-hr: NOEL for clinical signs and brain pathology in rats

Time scaling: Values were extrapolated using the relationship $C^n \times t = k$ (ten Berge et al.1986), where n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points in order to derive values protective of human health (NRC, 2001). The 30-min value was adopted as the 10-min value.

30-min, 1-hr, 4-hr
$C^3 \times t = k$
$(300 \text{ ppm})^3 \times 6 \text{ hr} = 162{,}000{,}000 \text{ ppm}^3 \cdot \text{hr}$

8-hr
$(300 \text{ ppm})^1 \times 6 \text{ hr} = 1800 \text{ ppm} \cdot \text{hr}$

Uncertainty factors: 3 for interspecies variability.
3 for intraspecies variability.

10-minute AEGL-2: 69 ppm (30-min value adopted as 10-min value)

30-minute AEGL-2: $C^3 \times 0.5 \text{ hr} = 162{,}000{,}000 \text{ ppm}^3 \cdot \text{hr}$
$C^3 = 324{,}000{,}000 \text{ ppm}$
$C = 687 \text{ ppm}$
AEGL-2 = 687 ppm ÷ 10 = 69 ppm

1-hour AEGL-2: $C^3 \times 1 \text{ hr} = 162{,}000{,}000 \text{ ppm}^3 \cdot \text{hr}$
$C^3 = 162{,}000{,}000 \text{ ppm}$
$C = 545 \text{ ppm}$
AEGL-2 = 545 ppm ÷ 10 = 55 ppm

4-hour AEGL-2: $C^3 \times 4 \text{ hr} = 162{,}000{,}000 \text{ ppm}^3 \cdot \text{hr}$
$C^3 = 40{,}500{,}000 \text{ ppm}$
$C = 343 \text{ ppm}$
AEGL-2 = 343 ppm ÷ 10 = 34 ppm

8-hour AEGL-2: $C^1 \times 8 \text{ hr} = 1800 \text{ ppm} \cdot \text{hr}$
$C = 225 \text{ ppm}$
AEGL-2 = 225 ppm ÷ 10 = 23 ppm

Derivation of AEGL-3

Key Study: Monsanto, 1985a
Toxicity endpoint: 4-hr rat $BMCL_{05}$ and BMC_{01} of 952 ppm ($BMCL_{05}$ and BMC_{01} values are equivalent)

Time scaling: Values were extrapolated using the relationship $C^n \times t = k$ (ten Berge et al.1986), where n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points in order to derive values protective of human health (NRC, 2001). 30-min value was adopted as the 10-min value.

30-min, 1-hr
$C^3 \times t = k$
$(952 \text{ ppm})^3 \times 4 \text{ hr} = 3{,}451{,}205{,}632 \text{ ppm}^3 \cdot \text{hr}$

8-hr
$(952 \text{ ppm})^1 \times 4 \text{ hr} = 3080 \text{ ppm} \cdot \text{hr}$

Uncertainty factors: 3 for interspecies variability.
3 for intraspecies variability.

10-minute AEGL-3: 190 ppm (30-min value adopted as 10-min value)

30-minute AEGL-3: $C^3 \times 0.5 \text{ hr} = 3{,}451{,}205{,}632 \text{ ppm}^3 \cdot \text{hr}$
$C^3 = 6{,}902{,}411{,}264 \text{ ppm}$
$C = 1904 \text{ ppm}$
$\text{AEGL-3} = 1904 \text{ ppm} \div 10 = 190 \text{ ppm}$

1-hour AEGL-3: $C^3 \times 1 \text{ hr} = 3{,}451{,}205{,}632 \text{ ppm}^3 \cdot \text{hr}$
$C^3 = 3{,}451{,}205{,}632 \text{ ppm}$
$C = 1511 \text{ ppm}$
$\text{AEGL-3} = 1511 \text{ ppm} \div 10 = 150 \text{ ppm}$

4-hour AEGL-3: $C = 952 \text{ ppm}$
$\text{AEGL-3} = 952 \text{ ppm} \div 10 = 95 \text{ ppm}$

8-hour AEGL-3: $C^1 \times 8 \text{ hr} = 3808 \text{ ppm} \cdot \text{hr}$
$C = 476 \text{ ppm}$
$\text{AEGL-3} = 476 \text{ ppm} \div 10 = 48 \text{ ppm}$

APPENDIX B: Derivation Summary for Carbonyl Sulfide AEGLs

AEGL-1 Values for Carbonyl Sulfide

10-min	30-min	1-h	4-h	8-h
NR	**NR**	**NR**	**NR**	**NR**
Key Reference:				
Test Species/Strain/Number:				
Exposure Route/Concentrations/Durations:				
Effects:				
Endpoint/Concentration/Rationale:				
Uncertainty Factors/Rationale:				
Modifying Factor: NA				
Animal to Human Dosimetric Adjustment:				
Time Scaling:				
Data Adequacy: NR: Not Recommended due to insufficient data. The absence of AEGL-1 values does not imply that concentrations below AEGL-2 are without effect. Carbonyl sulfide has poor warning properties; it may cause serious effects or lethality at concentrations causing no signs or symptoms				

AEGL-2 Values for Carbonyl Sulfide

10-min	30-min	1-h	4-h	8-h
69 ppm	**69 ppm**	**55 ppm**	**34 ppm**	**23 ppm**

Key Reference: Morgan, D. L., Little, P. B., Herr, D. W., et al. 2004. Neurotoxicity of carbonyl sulfide in F344 rats following inhalation exposure for up to 12 weeks. Toxicology and Applied Pharmacology. 200: 131-145.

Test Species/Strain/Number: rat/F344/5 males/concentration

Exposure Route/Concentrations/Durations: Inhalation/0, 75, 150, 300, 600 ppm/6-hrs

Effects:
No mortality at any concentration.

75, 150 ppm: NOEL for all effects

300 ppm: NOEL for clinical signs and brain pathology

600 ppm: Clinical signs including lethargy, head tilt, hypothermia, and ataxia. Brain lesions including necrosis and microgliosis in the cerebellar roof nucleus, internal capsule, and thalamus. Vacuolation of the cerebellar medullary white matter and fifth cranial nerve tract were also noted.

Endpoint/Concentration/Rationale: No-effect-level for clinical signs and brain pathology/300 ppm

Uncertainty Factors/Rationale:

Intraspecies: 3

Considered sufficient due to the steep concentration-response curve, which implies limited intra-individual variability. The steep curve is evidenced in several studies. No mortality was noted in rats exposed to 943 ppm carbonyl sulfide for 4-hours, and 4/10 rats died at 1090 ppm and 10/10 rats died when exposed to 1210 ppm (DuPont, 1981). In another 4-hour rat study (Monsanto, 1985a), no mortality was noted at 993 ppm; whereas, 4/12 rats died at 1060 ppm, and 11/12 rats died at 1147 ppm. Thiess et al. (1968) observed no mortality in rats exposed to 1000 ppm for 75-min and death of 3/6 rats exposed to 1000 ppm for 90-min.

Interspecies: 3

Although the animal data suggest some species variability and the rat is not the most sensitive species [mortality incidences for animals exposed to 1000 ppm carbonyl sulfide for 90 minutes were as follows: 0/6 for guinea pigs, 3/6 for rats, 8/14 for rabbits, and 6/6 for cats (Thiess et al., 1968)], use of the full default interspecies UF of 10 would yield AEGL-2 values that are inconsistent with the overall database. [AEGL-2 values derived using a total UF of 30 would be 23 ppm for 10- and 30-min, 18 ppm for 1-hr, 11 ppm for 4-hr, and 7.7 ppm for 8-hr; no treatment-related effects were noted in rats exposed to 51 ppm 6-hr/day for 11 days (Monsanto, 1985b), or 75, 150, or 300 ppm 6-hr/day for 4 days (Morgan et al., 2004)].

Modifying Factor: NA

Animal to Human Dosimetric Adjustment:

Time Scaling: $C^n \times t = k$ equation, where n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points in order to derive values protective of human health (NRC, 2001). 30-min value was adopted as the 10-min value because the point-of-departure is 6-hr.

Data Adequacy: The proposed AEGL-2 values are considered protective because no treatment-related effects were noted in rats repeatedly exposed to 51 ppm, 6-hr/day for 11 days (Monsanto, 1985b) and 75 or 150 ppm 6-hr/day for 4 days (Morgan et al., 2004).

1
2

AEGL-3 Values for Carbonyl Sulfide

10-min	30-min	1-h	4-h	8-h
190 ppm	**190 ppm**	**150 ppm**	**95 ppm**	**48 ppm**

Key Reference:
Monsanto. 1985a. 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. Monsanto Company, Environmental Health Laboratory, St. Louis, Mo. OTS0534820.

Test Species/Strain/Number: Rat/Sprague-Dawley/six/sex/concentration

Exposure Route/Concentrations/Durations: Inhalation/ 4-hrs

Effects:

Concentration	Mortality
0 ppm	0/12
804 ppm	0/12
993 ppm	0/12
1062 ppm	4/12
1096 ppm	8/12
1147 ppm	1/12
1189 ppm	11/12

LC_{50}: 1082 ppm
BMC_{01}: 951.7 ppm
$BMCL_{05}$: 951.9 ppm

Endpoint/Concentration/Rationale:
4-hr rat BMC_{01} and $BMCL_{05}$ of 952 ppm, considered a threshold for lethality

Uncertainty Factors/Rationale:

Intraspecies: 3

Considered sufficient due to the steep concentration-response curve, which implies limited intra-individual variability. The steep curve is evidenced in several studies. No mortality was noted in rats exposed to 943 ppm carbonyl sulfide for 4-hours, and 4/10 rats died at 1090 ppm and 10/10 rats died when exposed to 1210 ppm (DuPont, 1981). In another 4-hour rat study (Monsanto, 1985a), no mortality was noted at 993 ppm; whereas, 4/12 rats died at 1060 ppm, and 11/12 rats died at 1147 ppm. Thiess et al. (1968) observed no mortality in rats exposed to 1000 ppm for 75-min and death of 3/6 rats exposed to 1000 ppm for 90-min.

Interspecies: 3

Although the animal data suggest some species variability and the rat is not the most sensitive species [mortality incidences for animals exposed to 1000 ppm carbonyl sulfide for 90 minutes were as follows: 0/6 for guinea pigs, 3/6 for rats, 8/14 for rabbits, and 6/6 for cats (Thiess et al., 1968)], use of the full default interspecies UF of 10 would yield AEGL-3 values that are inconsistent with the overall database. [AEGL-3 values derived using a total UF of 30 would be 63 ppm for 10- and 30-min, 50 ppm for 1-hr, 32 ppm for 4-hr, and 16 ppm for 8-hr; no treatment-related effects were noted in rats exposed to 51 ppm 6-hr/day for 11 days (Monsanto, 1985b), or 75, 150, or 300 ppm 6-hr/day for 4 days (Morgan et al., 2004). No mortality or clinical signs were present in rats exposed to 200, 300, and 400 ppm 6 hr/day, 5 days/week for 12-weeks (Morgan et al., 2004)]

Modifying Factor: NA

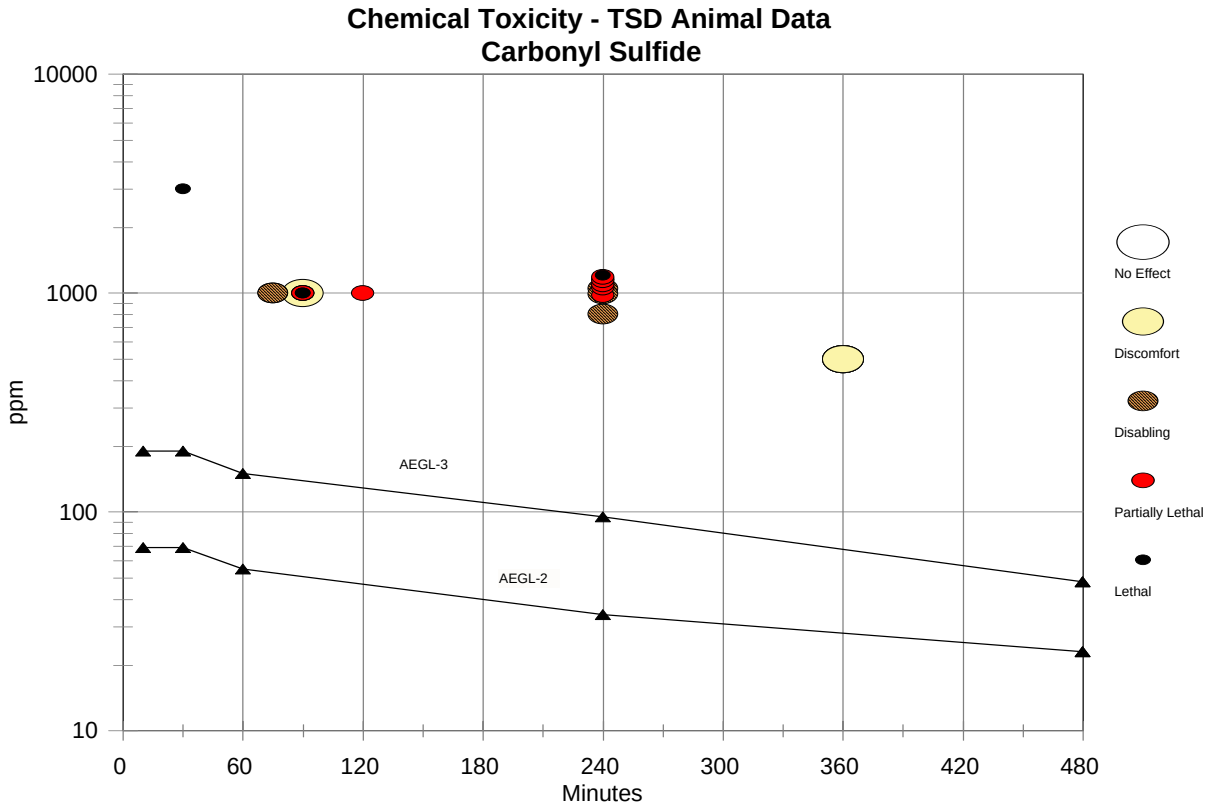
Animal to Human Dosimetric Adjustment:

Time Scaling: $C^n \times t = k$ equation, where n = 3 when extrapolating to shorter time points and n = 1 when extrapolating to longer time points in order to derive values protective of human health (NRC, 2001). 30-min value was adopted as the 10-min value because the point-of-departure is 4-hr.

Data Adequacy:	The proposed AEGL-3 values are considered protective because no treatment-related effects were noted in rats repeatedly exposed to 75, 150, or 300 ppm 6-hr/day for 4 days (Morgan et al., 2004). No treatment-related clinical signs of FOB effects were noted in male and female rats exposed to 300 ppm, 6 hr/day, 5 days/week for 12 exposures in a two-week period; brain lesions were noted only in 1/5 females in this study (Morgan et al., 2004). No mortality or clinical signs were present in rats exposed to 200, 300, and 400 ppm 6 hr/day, 5 days/week for 12-weeks; however, significant decreases in brain cholinesterase activity were noted at all three concentrations (Morgan et al., 2004).

APPENDIX C: Category Plot for Carbonyl Sulfide

1
2


Chemical Toxicity - TSD Animal Data
Carbonyl Sulfide
10000
1000
100
10
ppm
AEGL-3
AEGL-2
0
60
120
180
240
300
360
420
480
Minutes
No Effect
Discomfort
Disabling
Partially Lethal
Lethal

3

APPENDIX D: Benchmark Dose Calculations for Carbonyl Sulfide

```
==============================================================================
      Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
      Input Data File: C:\BMDS\CARBONYL_SULFIDE_MONSANTO.(d)
      Gnuplot Plotting File:  C:\BMDS\CARBONYL_SULFIDE_MONSANTO.plt
                           Fri Sep 14 09:47:57 2007
==============================================================================

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 = COLUMN3
  Independent variable = COLUMN1
  Slope parameter is not restricted

  Total number of observations = 7
  Total number of records with missing values = 0
  Maximum number of iterations = 250
  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 =     -61.2273
                   slope =      8.79468

       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.
```

background	0	NA
intercept	-125.774	0.200664
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)	Deviance	Test DF	P-value
Full model	-22.1604			
Fitted model	-23.4814	2.64201	6	0.8522
Reduced model	-56.6912	69.0616	6	<.0001

AIC: 48.9628

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
1189.0000	0.9536	11.444	11	12	-0.6092
1147.0000	0.8494	10.193	11	12	0.6514
1096.0000	0.5852	7.022	8	12	0.5728
1062.0000	0.3624	4.349	4	12	-0.2096
993.0000	0.0592	0.711	0	12	-0.8692
804.0000	0.0000	0.000	0	12	-0.0007035
0.0000	0.0000	0.000	0	12	0

Chi-square = 1.92 DF = 6 P-value = 0.9266

Benchmark Dose Computation

Specified effect = 0.05

Risk Type = Extra risk

Confidence level = 0.95

BMD = 988.398

BMDL = 951.913

```
 1
 2  ================================================================
 3       Probit Model $Revision: 2.1 $ $Date: 2000/02/26 03:38:53 $
 4       Input Data File: C:\BMDS\CARBONYL_SULFIDE_MONSANTO.(d)
 5       Gnuplot Plotting File:  C:\BMDS\CARBONYL_SULFIDE_MONSANTO.plt
 6                             Fri Sep 14 09:54:53 2007
 7  ================================================================
 8
 9  BMDS MODEL RUN
10  ~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~~
11
12    The form of the probability function is:
13
14    P[response] = Background
15              + (1-Background) * CumNorm(Intercept+Slope*Log(Dose)),
16
17    where CumNorm(.) is the cumulative normal distribution function
18
19
20    Dependent variable = COLUMN3
21    Independent variable = COLUMN1
22    Slope parameter is not restricted
23
24    Total number of observations = 7
25    Total number of records with missing values = 0
26    Maximum number of iterations = 250
27    Relative Function Convergence has been set to: 1e-008
28    Parameter Convergence has been set to: 1e-008
29
30    User has chosen the log transformed model
31
32
33                  Default Initial (and Specified) Parameter Values
34                    background =           0
35                     intercept =     -61.2273
36                        slope =      8.79468
37
38
39            Asymptotic Correlation Matrix of Parameter Estimates
40
41            ( *** The model parameter(s)  -background    -slope
42                 have been estimated at a boundary point, or have been specified by the user,
43                 and do not appear in the correlation matrix )
44
45                intercept
46
47    intercept           1
48
49
```

Parameter Estimates

Variable	Estimate	Std. Err.
background	0	NA
intercept	-125.774	0.200664
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)	Deviance	Test DF	P-value
Full model	-22.1604			
Fitted model	-23.4814	2.64201	6	0.8522
Reduced model	-56.6912	69.0616	6	<.0001

AIC: 48.9628

Goodness of Fit

Dose	Est._Prob.	Expected	Observed	Scaled Size	Residual
1189.0000	0.9536	11.444	11	12	-0.6092
1147.0000	0.8494	10.193	11	12	0.6514
1096.0000	0.5852	7.022	8	12	0.5728
1062.0000	0.3624	4.349	4	12	-0.2096
993.0000	0.0592	0.711	0	12	-0.8692
804.0000	0.0000	0.000	0	12	-0.0007035
0.0000	0.0000	0.000	0	12	0

Chi-square = 1.92 DF = 6 P-value = 0.9266

Benchmark Dose Computation

Specified effect = 0.01

Risk Type = Extra risk

Confidence level = 0.95

BMD = 951.676

BMDL = 906.266