Scientific Review Panel Meeting

Carbonyl Sulfide (COS)
Reference Exposure Levels

March 4, 2016
Sacramento

Carbonyl Sulfide RELs

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Reference Exposure Levels

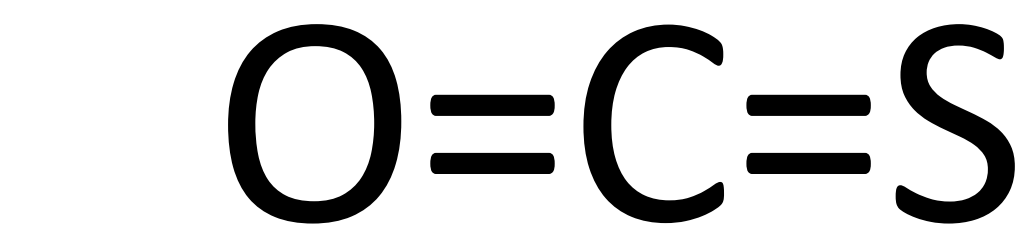
Technical Support Document for the Derivation of Noncancer Reference Exposure Levels

Appendix D1

SRP Review Draft

Revised May 2015

Carbonyl Sulfide



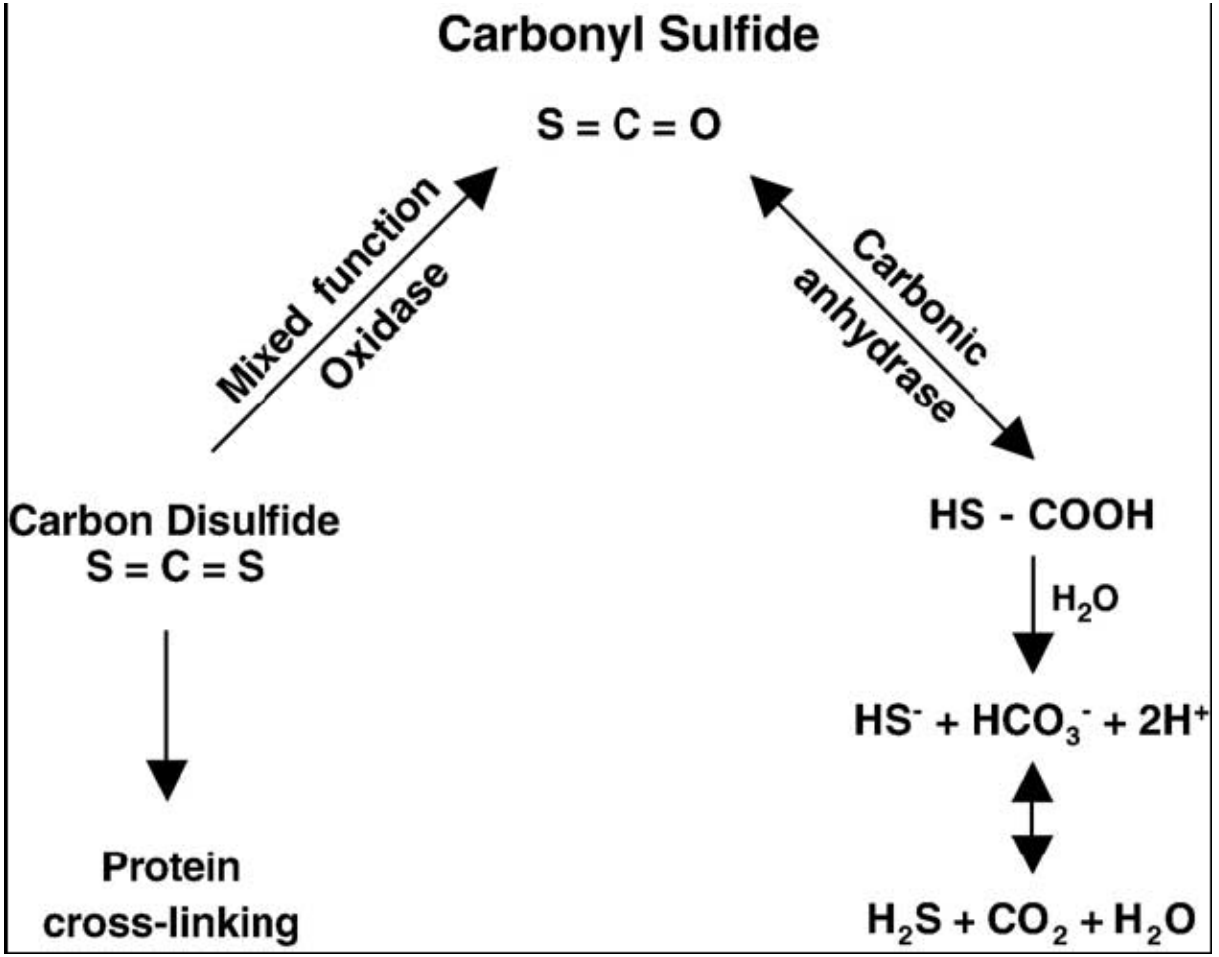
Carbonyl Sulfide

- chemical intermediate
- a byproduct of oil refining
- a potential grain fumigant; not currently registered in CA as fumigant
- Federal Hazardous Air Pollutant - 1990
- Toxic Air Contaminant in CA – 1993

Carbonyl Sulfide

- CA emissions in 2012 = 15,710 lbs (n=56)
- Top CA stationary source = 7,706.2 lbs
- TRI emissions in 2012 = 34,960 lbs (n=15)
- Hot Spots emissions updated every 4 years

Metabolism of COS



Reference Exposure Levels

- Reference Exposure Levels are based on the most sensitive and relevant health effects reported in the medical and toxicological literature.
- They are derived as described in OEHHA (2008). *Air Toxics Hot Spots Risk Assessment Guidelines. Technical Support Document for the Derivation of Noncancer Reference Exposure Levels*. http://www.oehha.ca.gov/air/hot_spots/2008/NoncancerTSD_final.pdf.

Acute REL

- Acute Reference Exposure Levels are levels at which infrequent one-hour exposures are not expected to result in adverse health effects.
- See Section 5 of the Technical Support Document (OEHHA, 2008).

Morgan et al., 2004

In the key study,

- male rats exposed to 600 ppm (1,476 mg/m^3) COS for 6 hours showed ataxia and head tilt, as well as neuropathological lesions in the brain (at 14 day follow-up)
- male rats exposed to 300 ppm (738 mg/m^3) COS did not exhibit these nervous system effects.

Proposed acute REL: NOAEL selection

Key study	Morgan et al., 2004
Study population	groups of 5 male rats
Exposure method	inhalation of 0, 75, 150, 300 or 600 ppm COS
Exposure continuity	single exposure
Exposure duration	6 hours (plus 14 days follow-up)
Critical effects	several CNS effects
LOAEL	600 ppm (1,476 mg/m^3)
NOAEL	300 ppm (738 mg/m^3)
BMCL	not derived
Time adjusted exposure (variant of Haber's Rule)	542 ppm (1,333 mg/m^3) [(300 ppm)^3 x 6 hours = (X ppm)^3 x 1 hour]

Proposed acute REL: REL derivation

Human Equivalent Concentration	542 ppm (RGDR = 1)(systemic effect)
LOAEL uncertainty factor (UF_L)	1
Interspecies uncertainty factor	
Toxicokinetic ($UF_{A\text{-}k}$)	2 (default)
Toxicodynamic ($UF_{A\text{-}d}$)	√10 (default)
Intraspecies uncertainty factor	
Toxicokinetic ($UF_{H\text{-}k}$)	10 (default)
Toxicodynamic ($UF_{H\text{-}d}$)	10 (potential for increased sensitivity of infants and children to neurotoxicants)
Database uncertainty factor	√10 (limited database)
Cumulative uncertainty factor	2,000
Acute Reference Exposure Level	**270 ppb (660 µg/m³)**

Chronic RELs

- The chronic Reference Exposure Level is a concentration at which adverse noncancer health effects would not be expected from continuous chronic exposures.
- See Section 7 in the Technical Support Document (OEHHA, 2008).

Morgan et al., 2004

F344/N rats (10/sex/exposure level)
Discontinuous whole-body inhalation to 0, 200, 300, or 400 ppm COS
6 hours/day, 5 days/week, 12 weeks

- 400 ppm: males and females - increased incidence (1) of necrosis or cavitation in the parietal cortex and (2) of neuronal loss or microgliosis in the posterior colliculus.
- 300 ppm COS: no similar effects.

COS-exposed rat brain pathology data after 12 weeks (Morgan et al., 2004)

CNS region	*Neuropathology*	*Sex*	*Control*	*300 ppm*	*400 ppm*
Parietal cortex area I	Necrosis or cavitation	M	0/10	0/10	5/10*
Parietal cortex area I	Necrosis or cavitation	F	0/10	0/10	4/10*
Posterior colliculus	Neuronal loss or microgliosis	M	0/9	0/9	7/9**
Posterior colliculus	Neuronal loss or microgliosis	F	0/9	0/9	5/9**
Posterior colliculus	Hemorrhage	M	0/9	0/9	2/9
Posterior colliculus	Hemorrhage	F	0/9	0/9	1/9
Thalamus	Necrosis	M	0/10	0/10	1/10
Thalamus	Necrosis	F	0/10	0/10	0/10
* $p < 0.05$; ** $p < 0.01$ vs control by Fisher Exact Test					

Upstream Effects

- Upstream biochemical perturbations may be useful for assessing dose-response relationships.
- For carbonyl sulfide such an upstream effect may be the decrease in cytochrome oxidase levels in certain areas of the brain.

COS-exposed female rat brain parietal cortex cytochrome oxidase activity (Morgan et al., 2004)

Female rats (12 weeks exposure)

COS (ppm)	Cytochrome oxidase[a,b]	% control
0	1,711 ± 125	100
200	1,268 ± 232**	74
300	928 ± 175**	54
400	857 ± 72**	50

[a] µmol cytochrome oxidase/min/mg protein

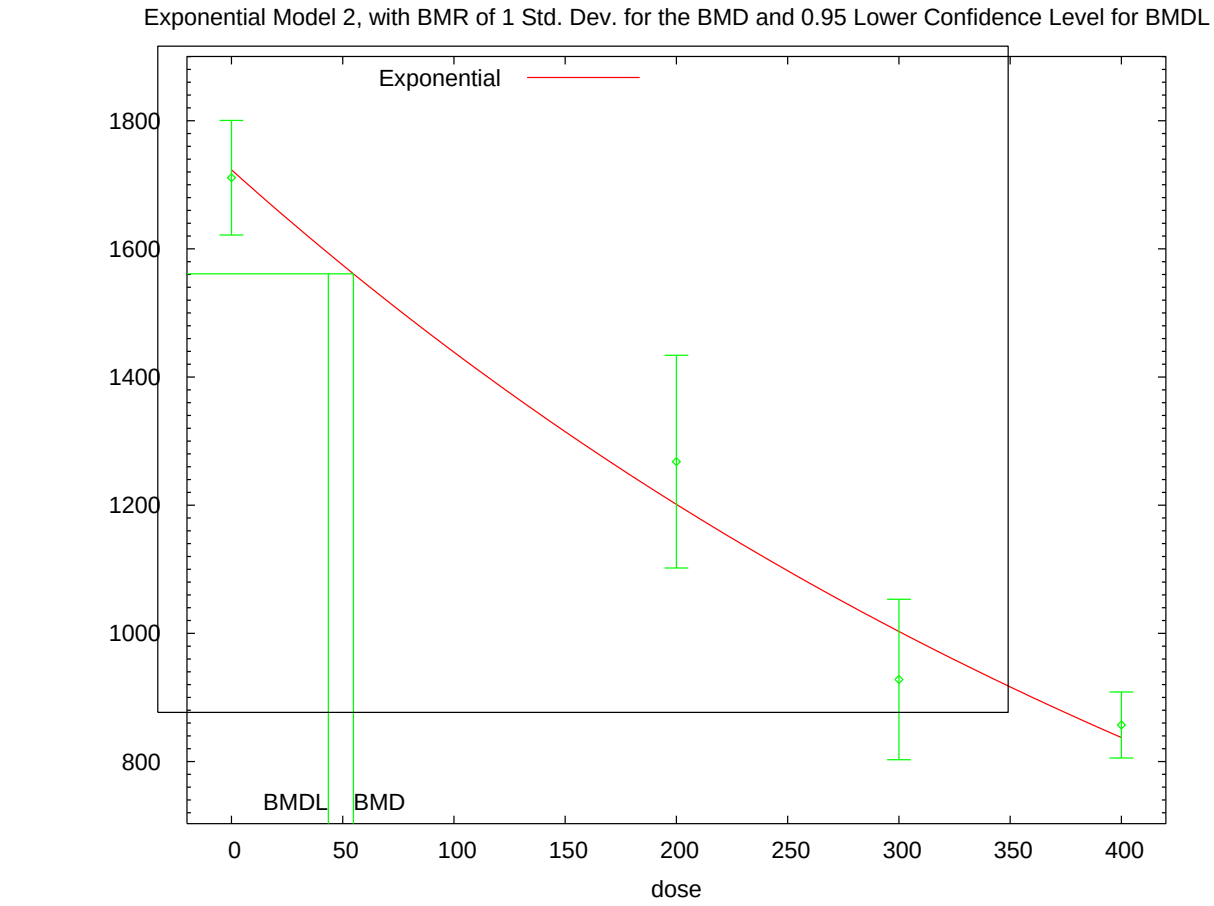
[b] mean ± SD (n=10)

** $p < 0.001$ compared to control (Dunnett's Test)

BMDS analysis of COS-exposed female rat parietal cortex cytochrome oxidase activity (Morgan et al., 2004)

Model	Deviation	BMC	BMCL	p for fit	AIC(fitted)
Hill	1 SD	148	85	NA[3]	452.9006
Hill	0.5 SD	127	56	NA	452.9006
Hill	0.05 relative	130	59	NA	452.9006
Power	1 SD	73	59	0.075	454.0712
Linear	1 SD	73	59	0.075	454.0716
Polynomial (n=2)	1 SD	58	43	0.046	454.8798
Exponential Model 2	**1 SD (normal distribution)**	**55**	**44**	**0.1197**	**453.1459**
Exponential Model 3	1 SD	69	44	0.05139	454.6961
Exponential Model 4	1 SD	55	40	0.1197	453.1459
Exponential Model 5	1 SD	130	78	NA	452.9006

Exponential Model 2 fit to cytochrome oxidase activity (Morgan et al., 2004)



Proposed chronic REL: Point of Departure selection

Study	Morgan et al. (2004)
Study population	F344/N rats (10/sex/exposure level)
Exposure method	Discontinuous whole-body inhalation to 0, 200, 300, or 400 ppm COS
Exposure continuity	6 hours/day, 5 days/week
Exposure duration	12 weeks
Critical effects	Low cytochrome oxidase levels in parietal cortex of female rats
LOAEL	200 ppm (984 mg/m^3)
NOAEL	Not found
$BMCL_{1\ SD}$	44 ppm (Exponential Model 2)

Proposed chronic REL: REL derivation

Time adjusted exposure	7.9 ppm (44 ppm x 6/24 x 5/7)
Human Equivalent Concentration	7.9 ppm (19.4 mg/m^3)(RGDR = 1)
LOAEL uncertainty factor (UF_L)	Not applicable with BMC
Subchronic uncertainty factor (UF_S)	√10 (12 week study)
Interspecies uncertainty factor	
Toxicokinetic (UF_{A-k})	2 (no PBPK model)
Toxicodynamic (UF_{A-d})	√10 (default)
Intraspecies uncertainty factor	
Toxicokinetic (UF_{H-k})	10 (default)
Toxicodynamic(UF_{H-d})	√10 (default)
Database uncertainty factor	√10 (limited database)
Cumulative uncertainty factor	2,000
Chronic Reference Exposure Level	**4 ppb (10 µg/m^3)**

Proposed 8-hour REL

- The 8-hour Reference Exposure Level is a concentration at or below which adverse non-cancer health effects would not be anticipated for repeated 8-hour exposures.
- Because chemicals that have the endpoint of neurotoxicity often have cumulative and sometimes irreversible effects, the 8 hour REL is the same as the chronic REL (4 ppb; 10 $\mu g/m^3$).

Carbonyl Sulfide as a TAC Especially Affecting Infants and Children

- In view of the neurotoxic effects of carbonyl sulfide, exposure may disproportionately impact infants and children. OEHHA recommends that carbonyl sulfide be identified as a toxic air contaminant which may disproportionately impact children pursuant to H&SC, Sec. 39669.5(c).

Public Comments

- No written comments about the Public Review Draft were submitted.

Comments by Dr. Blanc

Comment: US EPA lists 13 refineries with >40,000 pounds total COS emissions. Hot Spots inventory lists 2 or 3, with <8,000 pounds total (e.g. 20% of the EPA estimate). Emissions table is for low year 2008, not the year with 22,000.

Staff Response:

- Document now lists 2012 U.S. EPA Toxic Release Inventory (TRI) and Hot Spots COS California emissions inventories.
- Differences between TRI and ARB COS emission estimates reflect differences in reporting requirements
  - TRI reporting is annual, Hot Spots every 4 years and facilities reports are staggered; any given year does not include all sources.

Comments by Dr. Blanc

Comment: Thiess et al (1968) data discounted based on Bartholomeaus and Haritos (2005) review. Should summarize all the animal experimental data (cats, dogs and guinea pigs, 300-500 ppm).

Staff Response: OEHHA used two independent English translations of the original Thiess study (in German). We added to reporting of Thiess results (page 7): "There were no deaths after 6 hours at 300-500 ppm in cats, rabbits, or guinea pigs (2/species)."

Comments from Dr. Blanc

Comment: May be over emphasizing carbon disulfide as a mechanism. Morgan makes a convincing argument this is not the pathway and rather hydrogen sulfide is the ultimate toxin.

Staff Response:

- A report in the Thiess paper by the Institute for Judicial Medicine and Forensics in Mainz implicated H_2S and CO as candidate poisons.
- The absence of a reaction with lead paper ruled out H_2S.
- From the report it is not clear how CO was ruled out and why COS was implicated.

Comments from Dr. Blanc

Comment: Carbonic anhydrase (CA) activity may be crucial to COS metabolism. How much is known about human carbonic anhydrase polymorphisms?

Staff Response:

- At least 15 polymorphisms of carbonic anhydrase in humans.
- A data gap exists regarding COS metabolism by CA in humans.

Comments by Dr. Blanc

Comment: acute REL $UF_{H\text{-}d}$ = 10, chronic REL $UF_{H\text{-}d}$ = √10. Not convincing that the data justify a chronic REL $UF_{H\text{-}d}$ = √10.

Staff response: used √10 for the chronic REL $UF_{H\text{-}d}$ because an upstream effect was used as REL basis.

Comments by Dr. Blanc

Comment: Suggest more COS dose-response discussion, given steep COS dose response curve. Possibly include discussion of similar toxicants (e.g., hydrogen sulfide (H_2S).

Staff Response:

- Brown and Strickland (2003) H_2S acute toxicity metaanalysis - steep curves for acute lethality for H_2S by inhalation in rats at 8 time points ranging from 5 minutes to 16 hours; were able to perform a meta-analysis on H_2S dose-duration levels because sufficient H_2S inhalation study data existed.
- Limited amount of acute exposure data for COS insufficient for similar metaanalysis.

Comments by Dr. Blanc

Comment: Acute REL for COS (270 ppb) is 50 times higher than the 8 hr and chronic REL (4 ppb), seems out of line with the difference between the acute (30 ppb) and chronic (8 ppb) for H_2S which is thought to be a key pathway for this as a toxicant downstream.

Staff Response:

- The acute REL for H_2S is based on a human study where the adverse effect is a LOAEL for odor perception; chronic REL based on inflammation of nasal mucosa (mice).
- The end points for both are not comparable to those used for COS.
- The COS acute REL is based on an animal study with more severe adverse CNS effects (ataxia, head tilt, necrotic lesions, and vacuolation of myelin) and on a NOAEL.
- Hydrogen cyanide (HCN) also inhibits cytochrome oxidase and has a steep dose-response curve - the acute REL for HCN is 38 times the chronic REL (340 vs. 9 $\mu g/m^3$).

Comments by Dr. Blanc

Comment: A key issue - strict adherence to a 2 week exposure for acute studies, while 3 week exposure data exists that shows 300 PPM to be a LOEL.

Staff Response:

- The OEHHA Noncancer Reference Exposure Level document describes a preference for the use of a single short duration exposure study for acute REL derivations rather than studies with longer exposure durations.
- The Morgan et al. study was preferred for the COS acute REL derivation since it used an acute (6 hour) exposure and had a two-week follow-up.
- This exposure scenario is consistent with the definition of a one-hour REL (protects against infrequent one-hour exposures, not continuing exposures).

Comments by Dr. Blanc

Comment: Why does the 8-hour REL derivation use Morgan (2004) 12-week exposure data since the study also provides 24-day data demonstrating a LOEL of 200 ppm? The intermittent exposure design means that at day 24 the animals have been exposed a maximum of 18 times.

Staff Response:

- The 8-hour REL is applied to repeated 8-hour exposures up to lifetime, and is based on chronic exposures if available.
- The COS 8-hour and chronic RELs are derived from a subchronic study using an 86-day exposure period, which is the longest study available.
- Although cytochrome oxidase activity level decreases tended to be greater with longer exposures, the cytochrome oxidase LOAEL was 200 ppm at 24, 52 and 86 days of exposure.

Comments by Dr. Blanc

Comment: Add expanded data from Benson et. al. (the Nutt abstract cited) in the Lovelace Annual Report.

Staff Response: Added data from Benson et al. on page 8 of the document, used the data to derive a comparison acute REL on page 21.

Comments by Dr. Blanc

Comment: Expand description of COS in natural sources, as a Captan breakdown product, and in environmental tobacco smoke (ETS).

Staff Response: added following information

- COS in ETS
- COS from metam sodium metabolism
- COS from Captan metabolism
- COS from Antabuse metabolism
- Cheng et al (2015): ambient levels and suspected sources of COS in Beijing.