Presentation to the Scientific Review Panel on Toxic Air Contaminants

Trimethylbenzenes Reference Exposure Levels (RELs) - Technical Support Document for the Derivation of Noncancer RELs

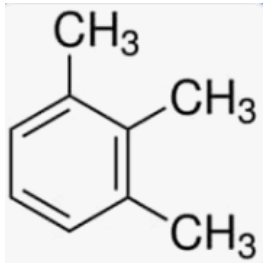
Office of Environmental Health Hazard Assessment

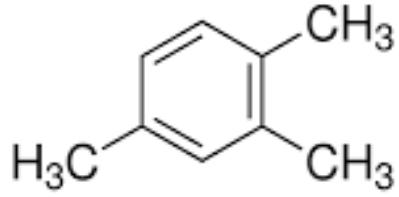
June 16, 2023

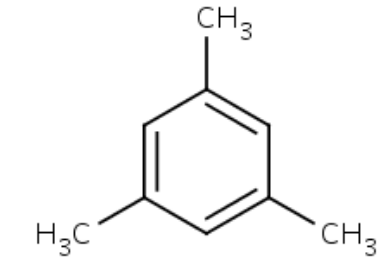
Trimethylbenzenes (TMBs)

Trimethylbenzenes exist in (3) isomeric forms:

- 1,2,3-trimethylbenzene (hemimellitene)
- 1,2,4-trimethylbenzene (pseudocumene)
- 1,3,5-trimethylbenzene (mesitylene)







TMBs: Chemical-Physical Properties

- Molecular formula C_9H_{12}
- Volatile aromatic hydrocarbons
- Clear, colorless liquids at room temp (25°C)
- Nearly insoluble in water (range 48-75 mg/L @ 25°C)
- Boiling points range from 164.7-176.1°C @ 760 mm Hg (torr)
- Vapor pressures range from 1.69 – 2.48 mm Hg (torr) @ 25°C

TMB: Uses and Occurrence

- TMBs occur naturally in petroleum deposits and are common components of petroleum refinery distillation fractions: white spirit, high flashpoint naptha, and gasoline
- Also emitted by steel-making facilities and coal-fired plants
- Other emission sources include construction, cement, paving mixtures, asphalt and metal coatings, as well as other sources
- TMBs are found in printing inks, paint solvents, hydraulic fracturing fluids, and as a pesticide additive
- All (3) TMB isomers are found as constituents of biogas (municipal landfills)

TMB: California Emissions

- Trimethylbenzenes (aggregated) and 1,2,4-TMB stationary point source emissions are reportable to the California Air Resources Board (CARB) under the Hot Spots Program
- For 2020, 1,141 lbs of Trimethylbenzenes (from 34 facilities) and 55,839.5 lbs of 1,2,4-TMB (from 485 facilities) were reported
- This does not necessarily represent every source of TMB emissions in the state; only those applicable to AB 2588 (Air Toxics Hot Spots Information and Assessment Act, 1987)

TMB: Toxicokinetics

- In humans, TMBs are readily absorbed via inhalation (high respiratory uptake)
- Based on their blood/air and oil/air partition coefficients, accumulation in adipose tissue is expected
- In both animals and humans, the 3 TMB isomers demonstrate similar metabolic profiles
- Currently, it is not known which cytochrome P450 isozyme is most responsible for TMB metabolism

TMB: Toxicokinetics (continued)

- All 3 isomers metabolize primarily to dimethylbenzoic and hippuric acids
- In humans, exhalation of the unchanged parent compound is an important route of elimination (20-37% of the absorbed amount, depending on the specific isomer)
- Urinary excretion of unchanged TMBs is very low (< 0.002%)
- In human toxicokinetic studies, following a 4 hr exposure to 25 ppm 1,3,5-TMB, the majority of the absorbed dose was excreted in the first 50 hrs post-exposure; however, urinary levels of metabolites were still detected 160 hrs post-exposure

TMB Acute Effects: Humans

- Paucity of viable human data for an acute REL (≤ 24 hour exposure)
  - Human exposure studies consist only of chamber studies, largely conducted in healthy adult males, that evaluated sensory irritation (25 ppm for up to 4 hrs)
  - No evidence of respiratory irritation, CNS toxicity or other toxicity (self-reported) in human exposure studies
- Effects on the nervous system are seen in acute animal studies - and these form the basis of the Acute TMB REL

TMB Acute Effects: Experimental Animal Exposure

- Acute exposure to TMBs causes primarily respiratory and neurotoxic effects in animals. Exposure duration in most of the acute TMB animal inhalation studies was from 4-6 hours
- There is one animal inhalation developmental study with exposure to TMBs (Saillenfait *et al.,* 2005)
  - Significant decreases in maternal body weight and food consumption @ concentrations of 300 and 600 ppm 1,3,5-TMB and 1,2,4-TMB, respectively
  - Significant dose-dependent decreases in fetal body weights @ 600 (5%) and 900 ppm (11%) 1,2,4-TMB, and 600 (5%) and 1200 ppm (12%) 1,3,5-TMB, compared to control animals
- The Saillenfait et al. (2005) developmental study was not used for the Acute REL because neurotoxicity proved a more sensitive endpoint; Saillenfait did not evaluate neurological/behavioral endpoints

TMB Acute Effects: Experimental Animal Exposure (continued)

- The McKee *et al.* (2010) neurobehavioral inhalation rat study was conducted on 3 consecutive days (up to 8 hrs/day). Rats were exposed to 0, 125, 1250 or 5000 mg/m^3 (0, 25, 250, or 1,000 ppm) 1,2,4-TMB, and tested after each exposure
- Significant increases (latencies) in a number of neurobehavioral tests were seen after a single 8-hour exposure to 5,000 mg/m^3 (1,000 ppm) 1,2,4-TMB
- Significant latencies have been observed in several acute animal studies following exposure to TMBs

Acute REL Derivation for TMBs

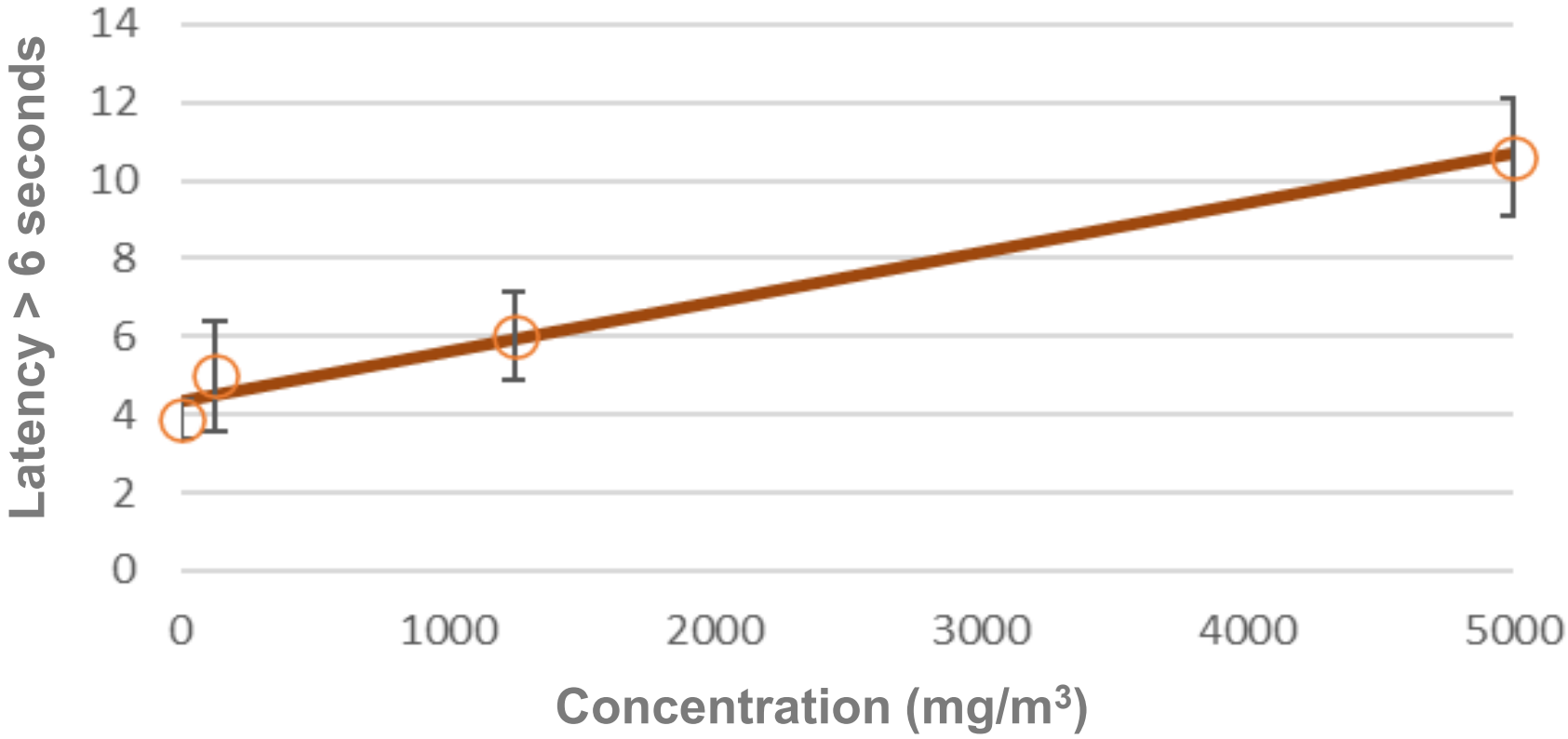
Treatment-Related Neurobehavioral Test Result in Rats Following a Single 8-hour Inhalation Exposure to 1,2,4-TMB (McKee et al., 2010)

Concentration mg/m^3 (ppm) *n* = 8/group	Latency> 6 seconds[a] (mean ± SD)
0	3.88 ± 0.58
125 (25)	5.00 ± 1.69
1250 (250)	6.00 ± 1.34
5000 (1000)	10.63 ± 1.80[b]

[a] = the number of responses taking more than 6 seconds
[b] = p <0.05

Acute REL derivation for TMBs
(drink response latency)

Polynomial Degree 2 Model (BMR_{1SD}) fit to the McKee et al. (2010)
1,2,4-Trimethylbenzene study for neurotoxicity in male rats



Acute REL Derivation for TMBs

- Acute REL intended to protect against infrequent 1-hour exposures
- Benchmark Concentration, 1 SD change from the control mean (BMC_{1SD}) = 970 mg/m^3
- Lower 95% confidence limit on the benchmark concentration, 1 SD change from the control mean ($BMCL_{1SD}$) = 709 mg/m^3
- 709 mg/m^3 = Point of Departure (POD)
- 8-hr exposure adjusted for a 1-hr exposure = 1417 mg/m^3 (288 ppm)
- HEC (Human Equivalent Concentration) adjustment was applied, which accounts for differences in the blood/air concentration in rats vs humans
- In this case, the RGDR (Regional Gas Dose Ratio) used to derive the HEC = 0.98 (rounded to 1) for systemic effects

Acute REL Derivation for TMBs

- Interspecies Uncertainty Factor (UF): 6
  - Toxicokinetic UF = 2, for residual toxicokinetic differences when using the HEC adjustment
  - Toxicodynamic UF = $\sqrt{10}$, for lack of toxicodynamic data on interspecies differences

Acute REL Derivation for TMBs

Intraspecies Uncertainty Factor (UF): 100

- Toxicokinetic UF = 10, due to no information on pharmacokinetic differences for TMBs among adults, infants and children
- Toxicodynamic UF = 10, because TMBs are neurotoxicants and children are potentially more sensitive than adults

Cumulative UF = 600

Acute TMB REL = 2400 µg/m^3 (490 ppb)

TMB Chronic/Subchronic Effects: Humans

- No human controlled chronic/subchronic studies or child-specific toxicity data were identified
- No occupational exposure studies with exposure uniquely to TMBs
- Occupational studies in workers exposed to paint thinners containing > 80% TMBs report CNS effects, including neuropsychological changes, memory deficits, reduced motor speed/coordination, as well as anemia and bronchitis
- In biomonitoring studies of factory workers exposed to solvents containing TMBs, vestibular disorders have been reported

TMB Chronic/Subchronic Effects in Experimental Animals

- No lifetime chronic animal studies were identified for any of the 3 TMB isomers
- Subchronic animal studies show largely respiratory and neurological effects (behavioral alterations)
- Subchronic inhalation studies in rodents also show organ effects (liver, kidneys), hematological (↑ WBC, ↓ RBC, etc), and clinical chemistry effects
- The most sensitive endpoint is neurotoxicity (sensorimotor impairment)

Chronic REL Derivation for the TMBs

- The Korsak and Rydzynski (1996) subchronic neurotoxic inhalation study in rats was used to develop the chronic and 8-hr TMB RELs (lowest POD)
- Concentration-dependent disturbances in pain sensitivity and motor behaviors were seen in male rats following a 6 hr/day, 5 day/week, 3 month exposure to 0, 25, 100, 250 ppm TMBs
  - Significant effects on pain sensitivity @ ≥ 25 ppm 1,2,3-TMB and ≥ 100 ppm 1,2,4-TMB
  - Significant effects on rotarod performance (measures neuromuscular function) @ ≥ 100 ppm 1,2,3-TMB and @ 250 ppm 1,2,4-TMB
- Separately, 1,3,5-TMB has also been found to result in behavioral disturbances (latency of reactions @ 100 ppm) in a related study by same authors

Chronic REL Derivation for TMBs

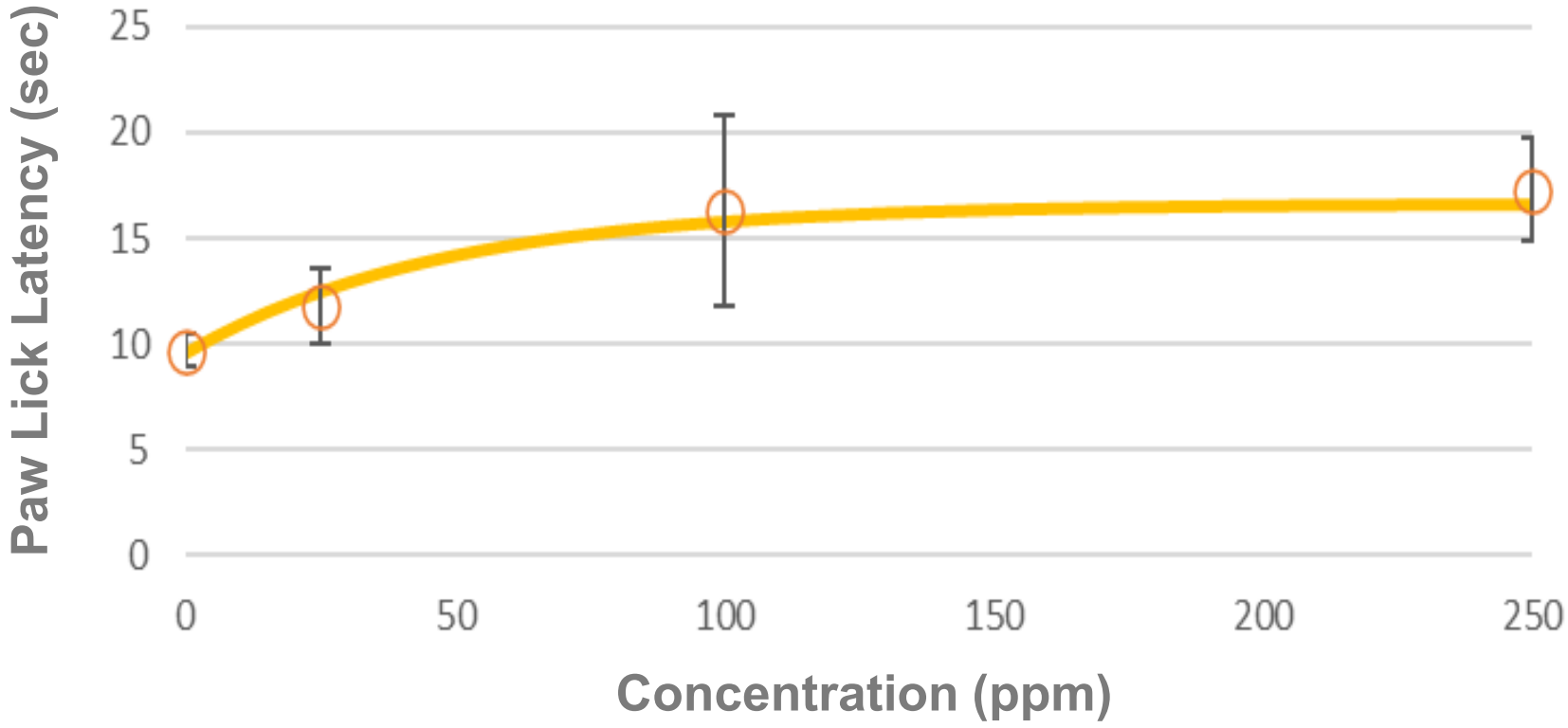
Pain Sensitivity (Latency of the Paw-Lick Response) Results from the Korsak and Rydzynski (1996) Neurotoxicity Study in Rats

TMB Isomer	No Animals/Response (seconds)	Exposure Concentration			
		Control	25 ppm (123 mg/m^3)	100 ppm (492 mg/m^3)	250 ppm (1230 mg/m^3)
1,2,4-TMB	# of Animals	9	10	9	10
	Paw-Lick	15.4 ± 5.8	18.2 ± 5.7	**27.6 ± 3.2***	30.1 ± 7.9*
1,2,3-TMB	# of animals	30	20	10	10
	Paw-Lick	9.7 ± 2.1	**11.8 ± 3.8***	16.3 ± 6.3*	17.3 ± 3.4*

Paw-lick latency values are expressed as mean ± SD
*Statistically significant (at $p < 0.05$ or $p < 0.01$)

Chronic REL Derivation for TMBs
(paw-lick latency)

Exponential 4 Model (BMR_{1SD}) fit to the 90-day 1,2,3-Trimethylbenzene Korsak and Rydzynski (1996) study for neurotoxicity in male rats



Chronic REL Derivation for TMBs

- The 1,2,3-TMB isomer yields the lowest Point of Departure (POD)
- Benchmark Concentration, 1 SD change from the control mean (BMC_{1SD}) = 86 mg/m^3 (18 ppm)
- Lower 95% confidence limit on the benchmark concentration, 1 SD change from the control mean ($BMCL_{1SD}$) = 47 mg/m^3 (10 ppm)
- 47 mg/m^3 = POD
  - The 6 hr/day, 5 day/week exposure adjusted for a continuous 24 hr exposure = $BMCL_{1SD}$ (adj) of 8 mg/m^3 (2 ppm) 1,2,3-TMB
  - Human Equivalent Concentration (HEC): RGDR = 0.98 for systemic effects

Chronic REL Derivation for TMBs

- Chronic REL intended to protect over lifetime, including sensitive subpopulations
- Subchronic UF = $\sqrt{10}$ (13 week study)
- Interspecies Uncertainty Factor (UF): 6
  - Toxicokinetic UF = 2, for residual toxicokinetic differences when using the HEC adjustment
  - Toxicodynamic UF = $\sqrt{10}$, for lack of toxicodynamic data on interspecies differences

Chronic REL Derivation for TMBs

Intraspecies Uncertainty Factor (UF): 100

- Toxicokinetic UF = 10, due to no information on pharmacokinetic differences for TMBs among adults, infants and children
- Toxicodynamic UF = 10, because TMBs are neurotoxicants and children are potentially more sensitive than adults

Cumulative UF = 2000

Chronic TMB REL = 4 µg/m^3 (1 ppb)

8-Hour REL Derivation for TMBs

- Based on same animal study by Korsak and Rydzynski (1996)
- Same POD = 47 mg/m^3 (10 ppm) 1,2,3-TMB
- Time adjustment is different:
  - Adjusted for 8-hr workday and to represent the breathing rate of workers
- All UFs are the same as the chronic REL

8-Hour TMB REL = 8 µg/m^3 (2 ppb)

Proposed TMB RELs: Summary

Acute: 2400 µg/m^3 (490 ppb)

Chronic: 4 µg/m^3 (1 ppb)

8-Hour: 8 µg/m^3 (2 ppb)

Public Comments

- **OEHHA did not receive any public comments on the draft TMB REL document**
- Public comment period: January 27, 2023 – March 13, 2023
- Public Workshops were held on February 23, 2023 in Southern California and on March 2, 2023 in Northern California