Appendix E

OEHHA Synthetic Turf Study

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Appendix E. Toxicity Criteria

TABLE OF CONTENTS

LIST OF ABBREVIATIONS

ABT	Aminobenzothiazole
AD	Applicability domain
AEGL	Acute Exposure Guideline Levels
AL	Action level
ATSDR	Agency for Toxic Substances and Disease Registry
BEA	Bis(2-ethylhexyl)adipate
BHT	Butylated hydroxy-toluene
BMC	Benchmark concentration
BMCL	Benchmark concentration at lower confidence limit
BMD	Benchmark Dose
BMDL	benchmark dose lower bound
BT	Benzothiazole
BW	Bodyweight
CASRN	Chemical Abstracts Service Registry Number
CBT	Chlorobenzothiazole
CDC	Centers for Disease Control and Prevention
CHO	Chinese Hamster Ovary
CMBT	Chloro–mercaptobenzothiazole
CPP	Cyclopenta(c,d)pyrene
CPSC	Centers for Disease Control and Prevention
$CSF_{(A)}$	Cancer slope factor (for animal)
DART	Developmental and reproductive toxicant (or toxicity)
DNEL	Derived no-effect levels
DNOP	Di-n-octyl phthalate
DPG	1,3-Diphenylguanidine
DPPD	N,N'-Diphenyl-1,4-benzenediamine
ECHA	European Chemicals Agency
ED	Effective dose
EFSA	European Food Safety Authority
EGBE	2-Butoxyethanol
FBT	Fluorobenzothiazole
FDRL	Food and Drug Research Laboratories
GD	Gestational day
GLP	Good laboratory practice
HEAST	Health Effects Assessment Summary Tables
HEC	Human equivalent concentration

HPV	High production volume
IARC	International Agency for Research on Cancer
IC	Inhibitory concentration
IRIS	Integrated Risk Information System
IUR	Inhalation unit risk
LADD	Lifetime average daily dose
LC	Lethal concentration
LD	Lethal dose
LOAEL	Lowest-observed-adverse-effect level
MADL	Maximum Allowable Dose Level
MBT	Mercaptobenzothiazole
MIBK	Methyl isobutyl ketone
MTBT	2-methylthiobenzothiazole
NOAEL	No-observed-adverse-effect level
NOAELHEC	No-observed-adverse-effect level for human equivalent concentration
NOEL	No-observed-effect level
NRC	National Research Council
NSRL	No Significant Risk Level
NTCR	National Center for Toxicological Research
NTP	National Toxicology Program
OECD	Organisation for Economic Co-operation and Development
OECD SIDS	Organisation for Economic Co-operation and Development Screening Information Data Set
OEHHA	Office of Environmental Health Hazard Assessment
OHBT	2-benzothiazolone
PAH	Polycyclic aromatic hydrocarbon
PBPK	Physiologically-based pharmacokinetic modeling
PBT	2-phenyl-benzothiazole
PCBTF	1-Chloro-4-(trifluoromethyl) benzene
PEF	Potency equivalent factor
PND	Postnatal day
POD	Point of departure
PPRTV	Provisional Peer-Reviewed Toxicity Value
QSAR	Quantitative structure-activity relationship
RBC	Red blood cell
REL	Reference exposure level
RGDR	Regional gas dose ratio

TC	Toxicity criteria
TCDD	2,3,7,8-tetrachlorodibenzo-p-dioxin
TCEQ	Texas Commission on Environmental Quality
TXIB	2,2,4-trimethyl-1,3-pentanediol diisobutyrate
UF	Uncertainty factor
UFA	Animal to human (interspecies) extrapolation uncertainty factor
UFD	Database deficiency uncertainty factor
UFH	Human variability in response (intraspecies) uncertainty factor
UFL	LOAEL to NOAEL extrapolation uncertainty factor
UFS	Subchronic to chronic extrapolation uncertainty factor
USEPA	United States Environmental Protection Agency
WHO	World Health Organization

E.1. Non-Cancer Toxicity Criteria for Acute Inhalation Exposure

This appendix lists the values of non-cancer toxicity criteria (TCs) for acute inhalation exposure (Acute TC_{inh}), which are the OEHHA one-hour reference exposure levels (1-Hour RELs) for the most sensitive effects due to acute inhalation exposure. All the Acute TC_{inh} values are chemical-specific. The list of detected chemicals with these 1-Hour RELs and target organ systems are shown in Table E.3.2.2.1-1.

Table E.3.2.2.1-1. Non-Cancer Inhalation Toxicity Criteria for Acute Inhalation Exposure (Acute TC_{inh}, ng per cubic meter) Using the One-Hour Reference Exposure Level (1-Hour REL, µg per cubic meter)(OEHHA Chemicals Library)

Chemical (CASRN)	1-Hour REL	Acute TC_{inh}	Target Organ System
2-Butanone (78-93-3)	1.3E+04	1.3E+07	Respiratory, Sensory
2-Butoxyethanol (111-76-2)	4.7E+03	4.7E+06	Respiratory, Sensory
Acetaldehyde (75-07-0)	4.7E+02	4.7E+05	Respiratory, Sensory
Benzene (71-43-2)	2.7E+01	2.7E+04	Reproductive, Developmental, Immunologic, Hematologic
Formaldehyde (50-00-0)	5.5E+01	5.5E+04	Sensory
m/p-Xylene (106-42-3)	2.2E+04	2.2E+07	Respiratory, Sensory, Nervous
o-Xylene (95-47-6)	2.2E+04	2.2E+07	Respiratory, Sensory, Nervous
Phenol (108-95-2)	5.8E+03	5.8E+06	Respiratory, Sensory
Styrene (100-42-5)	2.1E+04	2.1E+07	Respiratory, Sensory
Tetrachloroethylene (127-18-4)	2.0E+04	2.0E+07	Respiratory, Sensory, Nervous
Toluene (108-88-3)	5.0E+03	5.0E+06	Respiratory, Sensory, Nervous

CASRN: Chemical Abstracts Service Registry Number

E.2. Non-Cancer and Cancer Toxicity Criteria for Various Exposures

This section summarizes the non-cancer TCs for multiple routes of exposure to chemicals, including: TCs for one-day inhalation exposure to sensory irritants (Sensory TC_{inh}), one-day inhalation and oral exposures to developmental and/or reproductive toxicants, DART, (DART TC_{inh} and DART TC_{oral}, respectively), and chronic inhalation and oral exposures to chemicals of other effects (Chronic TC_{inh} and Chronic TC_{oral}, respectively). It also presents the cancer TCs, also known as human cancer slope factors (CSFs) for inhalation (CSF_{inh}) and oral (CSF_{oral}) exposures to carcinogens.

The Sensory TC (Section 0) and DART TC (Section E.2.1) sections summarize the Sensory TC_{inh} and DART TCs each in a single table, whereas the Chronic TCs and CSFs section (Section E.2.2) is organized by chemical group and structure. These summary tables contain:

- Chemical, Symbol, Acronym, and Structure: name of the chemical of which the TC is applied to, a symbol is added for a metal or metalloid, an acronym is given for a chemical with a long name, and the Chemical Abstract Service Registry Number (CASRN) for the chemical; no structure included for chemical with established chemical-specific TC; chemical structure included when the TC is based on a structural analog
- Effect: non-cancer or cancer effects
- Applicable Exposure Route: the route(s) of which receptor categories can be exposed to the chemical on synthetic turf fields
- Analog and Structure: shown as “Chemical-Specific” when established TC available for the chemical; otherwise, name and a drawing of the structural analog used to determine the TC
- Toxicity Criterion: TC established for the listed chemical (chemical-specific), determined from a structural analog, new screening TC developed by OEHHA for the Synthetic Turf Study (the Study); DART TCs and Chronic TCs for oral and dermal routes are expressed as mg per kg per day and for inhalation route as ng per cubic meter; CSFs are expressed as $(\text{mg per kg per day})^{-1}$ for both the oral and inhalation routes (CSF_{oral} and CSF_{inh}, respectively)
- Endpoint: the toxicity endpoint basis for the TC or CSF; generally, the most sensitive endpoint for the chemical (one with the lowest point of departure (POD) for non-cancer effects or with the highest cancer potency for a tumor type)
- Year Derived: the year when the TC was derived
- Reference: the entity that developed the TC or the appendix within this Report for the OEHHA screening values specifically derived for this Study.

Additional information is provided in each subsection or in the table footnotes: (1) source of information by reference to databases or internet website links, when appropriate, (2) additional TCs and the rationale for not selecting them, (3) rationale for structural analog selection, and (4) additional uncertainty factor used for duration extrapolation. For some polycyclic aromatic hydrocarbons (PAHs), OEHHA conducted quantitative structure activity relationship (QSAR) analysis for carcinogenicity potential using Virtual Models for Property Evaluation of Chemicals within a Global Architecture (VEGA). The models are based on structure-activity relationships, which compare the structure of a chemical of concern with a library of carcinogenic structure fragments. Each model may have different sets of data and rules for fragment comparison to

determine the applicability and thus reliability of the prediction. Predictions that are inside the applicability domain are more reliable than those outside the applicability domain.

E.2.1. Non-Cancer Toxicity Criteria for One-Day Exposure to Developmental and/or Reproductive Toxicants

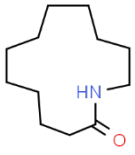
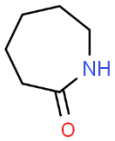
Non-cancer TC for one-day exposure to DARTs via multiple routes (DART TCs) are summarized in this section. Table E.3.2.2.1-1 summarizes the DART TCs for the group of DARTs. These DART TCs are either chemical-specific values, new screening values developed by OEHHA specifically for this Study, or from structural analogs. Inhalation route is the only applicable exposure route for cyclohexylamine and 2-butanone. Oral route is the only applicable exposure route for the three metals and a metalloid. Dermal route is the only applicable exposure route for 2-azacyclotridecanone and 1,3-diphenylguanidine (DPG). Oral and dermal routes are the applicable exposure routes for 1,4-benzenediamine, N,N'-diphenyl-benzenediamine (DPPD), while oral and inhalation routes are the applicable routes for n-caproic acid vinyl ester. All three exposure routes are applicable for the rest of the chemicals. For chemicals with no available TCs for dermal or inhalation exposure (DART TC_{der} or DART TC_{inh}, respectively), the TCs for oral exposure (DART TC_{oral}) are extrapolated (Chapter 4, Section 4.2.3) and used for the dermal or inhalation route.

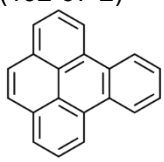
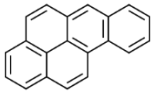
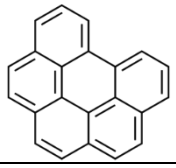
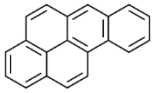
Two metals (lead and nickel) and two metalloids (arsenic and boron) are included as DARTs and the DART TC_{oral} are chemical-specific and route-specific. DART TC_{oral} for lead is developed based on the blood lead level, which has a complex dose-response relationship to the DART effect observed in children. The blood lead level is correlated to continual or continuous oral exposure to lead. Therefore, the DART TC_{oral} for lead is applied in chronic exposure assessment. OEHHA established maximum allowable level (MADL) for lead exposure of 0.5 µg per day (OEHHA Prop 65) and is applied in the one-day exposure assessment (see Chapter 6 for the hazard calculations). The DART TC_{inh} for 2-butanone is chemical-specific and route-specific. The DART TC_{oral} of bis(2-ethylhexyl)adipate (BEA) is an analog value for bis(2,2,6,6-tetramethyl-4-piperidyl)sebacate, methyl stearate; and n-caproic acid vinyl ester. DART TC_{der} or DART TC_{inh} is not available for these chemicals and the DART TC_{oral} of BEA is selected for these exposure routes of these esters. For benzo[a]pyrene (BaP), established chemical-specific values of DART TC_{oral} and DART TC_{inh} are available. The DART TC_{oral} and DART TC_{inh} of BaP are used as analog values for oral and inhalation exposures, respectively, to six PAHs—benzo[e]pyrene, benzo[g,h,i]perylene, chrysene, coronene, cyclopenta[c,d]pyrene, and indeno[1,2,3-cd]pyrene—based on structural similarity as determined by OEHHA. DART TC_{der} is not available for these chemicals, including BaP, and the DART TC_{oral} of BaP is used for the dermal route for all these PAHs. Caprolactam is selected as an analog for 2-azacyclotridecanone based on structural similarity suggested on the USEPA CompTox Chemicals Dashboard. The DART TC_{oral} for caprolactam is also used for the dermal route of 2-azacyclotridecanone.

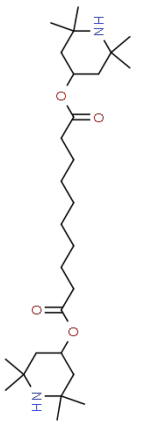
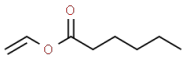
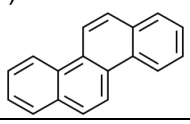
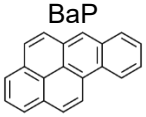
A chemical-specific DART TC_{oral} is available for cyclohexylamine and the chemical is used as an analog for cyclohexanamine, N-cyclohexyl- and N,N-dicyclohexylmethyl- based on structural similarity determined by OEHHA. DART TCs for the non-oral route are not available for these amines so the DART TC_{oral} for cyclohexylamine is used for the dermal and inhalation exposure routes for these amines. There is only an oral subchronic screening oral reference dose (p-RfD_o) of 0.1 mg per kg per day for dimethyl phthalate from USEPA (2007), based on gestational studies of one week or less. OEHHA adopted this p-RfD_o value as DART TC_{oral} for the chemical and used the oral value for the dermal and inhalation exposure routes.

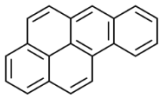
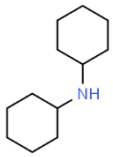
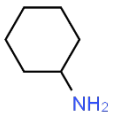
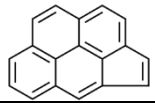
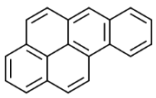
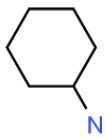
New screening DART TC_{oral} for DPPD and DPG were developed by OEHHA for this Study (Sections 0 and E.3.4). These chemical-specific oral values are used for the dermal exposure route. A new screening DART TC_{oral} for 4-tert-octylphenol (4t-OP) was developed by OEHHA for the Study (Section E.3). This screening DART TC_{oral} also provides an analog value for the other two phenols: phenol, 2,4-bis(1-methyl-1-phenylethyl)- and phenol, 4-(1-phenylethyl)-. DART TC_{der} or DART TC_{inh} are not available for the 4t-OP and the two phenols; the screening DART TC_{oral} for 4t-OP is selected for these exposure routes for these phenols.

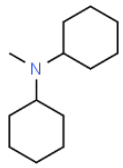
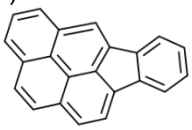
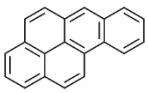
Table E.3.2.2.1-1. Non-Cancer Toxicity Criteria for One-Day Oral Exposure and One-Day Inhalation Exposure (DART TC_{oral} and DART TC_{inh}, respectively) for the Group of Developmental and/or Reproductive Toxicants (DARTs)(OEHHA Chemicals Library; USEPA IRIS; USEPA PPRTV)

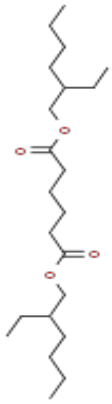
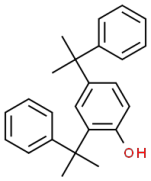
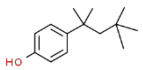
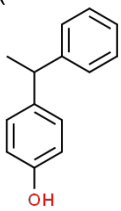
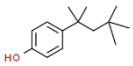
Chemical (Symbol, Acronym, CASRN), Structure	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Arsenic (As)[a]	Oral	Arsenic	DART TC_{oral} = 0.0000035 mg per kg per day[b]	Reduced full-scale intellectual function raw scores in children	2014	OEHHA
2-Azacyclo-tridecanone (947-04-6) 	Dermal	Caprolactam 	DART TC_{oral} = 0.5 mg per kg per day	Reduced offspring bodyweight in rats	1988	USEPA IRIS
1,4-Benzenediamine, N,N'-Diphenyl-1,4- (DPPD, 74-31-7)	Oral or dermal	Chemical-Specific	DART TC_{oral} = 0.008 mg per kg per day	Prolonged gestation period in fetal rats	2023	Section 0
Benzo[a]pyrene (BaP,50-32-8)	Oral or dermal	Chemical-Specific	DART TC_{oral} = 0.0003 mg per kg per day[c]	DART effects, and immunological effects in rats	2017	USEPA IRIS

Chemical (Symbol, Acronym, CASRN), Structure	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Benzo[a]pyrene (50-32-8)	Inhalation	Chemical-Specific	DART TC_{inh} = 2 ng per cubic meter[d] DART TC_{inh} = 400 ng per cubic meter[e]	DART effects in rats	2017	USEPA IRIS/OEHHA
Benzo[e]pyrene (192-97-2) 	Oral or dermal	BaP 	DART TC_{oral} = 0.0003 mg per kg per day	DART, and immunological effects in rats	2017	USEPA IRIS
Benzo[e]pyrene (192-97-2)	Inhalation	BaP	DART TC_{inh} = 2 ng per cubic meter[d] DART TC_{inh} = 400 ng per cubic meter[e]	DART effects in rats	2017	USEPA IRIS/OEHHA
Benzo[g,h,i]-perylene (191-24-2) 	Oral or dermal	BaP 	DART TC_{oral} = 0.0003 mg per kg per day	DART, and immunological effects in rats	2017	USEPA IRIS
Benzo[g,h,i]-perylene (191-24-2)	Inhalation	BaP	DART TC_{inh} = 2 ng per cubic meter[d] DART TC_{inh} = 400 ng per cubic meter[e]	DART effects in rats	2017	USEPA IRIS/OEHHA
Bis(2-ethylhexyl)adipate (BEA, 103-23-1)	Oral, dermal or inhalation	Chemical-Specific	DART TC_{oral} = 0.028 mg per kg per day[f] DART TC_{inh} = 98000 ng per cubic meter	DART effect in rat pups	2003	OEHHA

Chemical (Symbol, Acronym, CASRN), Structure	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Bis(2,2,6,6-tetramethyl-4-piperidyl)sebacate (52829-07-9) 	Oral or dermal	BEA 	DART TC_{oral} = 0.028 mg per kg per day	DART effect in rat pups	2003	OEHHA
Boron (B)[a]	Oral	Boric acid	DART TC_{oral} = 2 mg per kg per day[g]	Reduced bodyweight in fetal rats	2012	USEPA PPRTV
2-Butanone (78-93-3)	Inhalation	Chemical-Specific	DART TC_{inh} = 5000000 ng per cubic meter	DART effect (skeletal variations) in fetal mice	2003	USEPA IRIS
n-Caproic acid vinyl ester (3050-69-9) 	Oral or inhalation	BEA 	DART TC_{oral} = 0.028 mg per kg per day DART TC_{inh} = 98000 ng per cubic meter	DART effect in rat pups	2003	OEHHA
Chrysene (218-01-9) 	Oral or dermal	BaP 	DART TC_{oral} = 0.0003 mg per kg per day	DART effects, and immunological effects in rats	2017	USEPA IRIS

Chemical (Symbol, Acronym, CASRN), Structure	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Chrysene (218-01-9)	Inhalation	BaP	DART TC_{inh} = 2 ng per cubic meter[d] DART TC_{inh} = 400 ng per cubic meter[e]	DART effects in rats	2017	USEPA IRIS/OEHHA
Coronene (191-07-1) 	Oral or dermal	BaP 	DART TC_{oral} = 0.0003 mg per kg per day	DART effects, and immunological effects in rats	2017	USEPA IRIS
Coronene (191-07-1)	Inhalation	BaP	DART TC_{inh} = 2 ng per cubic meter[d] DART TC_{inh} = 400 ng per cubic meter[e]	DART effects in rats	2017	USEPA IRIS/OEHHA
Cyclohexylamine (108-91-8)	Inhalation	Chemical-Specific	DART TC_{inh} = 700000 ng per cubic meter	Testicular damage in rats	1988	USEPA IRIS
Cyclohexanamine, N-cyclohexyl- (101-83-7) 	Oral, dermal or inhalation	Cyclohexylamine 	DART TC_{oral} = 0.2 mg per kg per day DART TC_{inh} = 700000 ng per cubic meter	Testicular damage in rats	1988	USEPA IRIS
Cyclopenta[c,d]-pyrene (27208-37-3) 	Oral, dermal	BaP 	DART TC_{oral} = 0.0003 mg per kg per day	DART effects, and immunological effects in rats	2017	USEPA IRIS
Cyclopenta[c,d]-pyrene (27208-37-3)	Inhalation	BaP	DART TC_{inh} = 2 ng per cubic meter[d] DART TC_{inh} = 400 ng per cubic meter[e]	DART effects in rats	2017	USEPA IRIS/OEHHA
N,N-Dicyclohexyl-methylamine (7560-83-0)	Oral, dermal or inhalation	Cyclohexyl-amine 	DART TC_{oral} = 0.2 mg per kg per day DART TC_{inh} = 700000 ng per cubic	Testicular damage in rats	1988	USEPA IRIS

Chemical (Symbol, Acronym, CASRN), Structure	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
			meter			
Dimethyl phthalate (131-11-3)	Oral, dermal or inhalation	Chemical-Specific	DART TC_{oral} = 0.1 mg per kg per day DART TC_{inh} = 400000 ng per cubic meter	Liver weight and testis effects in rats	2007	USEPA PPRTV
1,3-Diphenylguanidine (DPG, 102-06-7)	Dermal	Chemical-Specific	DART TC_{oral} = 0.005 mg per kg per day	Increased gestation periods, dead litters, pup mortality in rats	2023	Section E.3.4
Indeno[1,2,3-cd]pyrene (193-39-5) 	Oral or dermal	BaP 	DART TC_{oral} = 0.0003 mg per kg per day	DART effects, and immunological effects in rats	2017	USEPA IRIS
Indeno[1,2,3-cd]pyrene (193-39-5)	Inhalation	BaP	DART TC_{inh} = 2 ng per cubic meter[d] DART TC_{inh} = 400 ng per cubic meter[e]	Developmental and reproductive effects in rats	2017	USEPA IRIS/OEHHA
Lead (Pb)	Oral	Lead	DART TC_{oral} = 0.0001 mg per kg per day[h] MADL = 0.5 µg per day[h]	Intelligence deficits in human (child)	2009	OEHHA

Chemical (Symbol, Acronym, CASRN), Structure	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Methyl stearate (112-61-8) 	Oral, dermal or inhalation	BEA 	DART TC_{oral} = 0.028 mg per kg per day DART TC_{inh} = 98000 ng per cubic meter	Developmental and reproductive effect in rat pups	2003	OEHHA
Nickel (Ni)[a]	Oral	Nickel and nickel compounds	0.011 mg per kg per day[i]	Perinatal mortality in rats	2012	OEHHA
Phenol, 2,4-bis(1-methyl-1-phenylethyl)- (2772-45-4) 	Oral, dermal or inhalation	4t-OP 	DART TC_{oral} = 0.04 mg per kg per day DART TC_{inh} = 140000 ng per cubic meter	Bodyweight and uterine weight changes in rats	2023	Section E.3.10
Phenol, 4-(1-phenylethyl)- (1988-89-2) 	Oral, dermal or inhalation	4t-OP 	DART TC_{oral} = 0.04 mg per kg per day DART TC_{inh} = 140000 ng per cubic meter	Bodyweight and uterine weight changes in rats	2023	Section E.3.10
4-tert-Octyphenol (4t-OP, 140-66-9)	Oral, dermal or inhalation	Chemical-Specific	DART TC_{oral} = 0.04 mg per kg per day DART TC_{inh} = 140000 ng per cubic meter	Bodyweight and uterine weight changes in rats	2023	Section E.3.10

[a] CASRN is not applicable for the metals and metalloid as the Study did not determine the exact forms of the metals and metalloid in the samples.
[b] For Arsenic, a higher value of 0.003 mg per kg per day (hyperpigmentation, keratosis and vascular effects in human) is available (ATSDR Toxicological Profiles; USEPA IRIS).

[c] For BaP, there is another value of 0.0017 mg per kg per day (kidney toxicity in rats), derived in 2010 from OEHHA (2001b).
[d] DART TC_{inh} values used to assess third trimester and 11-70 years age groups (see Report Section 4.4.2 for details).
[e] DART TC_{inh} values used to assess 0-11 years age groups. DART TC_{inh} values are extrapolated from DART TC_{oral} value of BaP by multiplying by 70 kg / 20 m^3 and multiplied by 0.40 to account for differences between oral and inhalation absorption (see Report Section 4.4.2 for details).
[f] For Bis(2-ethylhexyl)adipate, there is another value of 0.6 mg per kg per day (developmental, hepatic, urinary, and musculoskeletal effects in rats) derived in 1992, (USEPA IRIS) for BEA.
[g] For boron, this value replaces the lower value of 0.2 mg per kg per day for the same endpoint from an older assessment (USEPA IRIS).
[h] Non-cancer Chronic TC_{oral} is calculated using the point of departure of 2.86 µg per day divides 10 kg child body weight and the total uncertainty factor of 3, then multiplies by a conversion factor of 1 mg per 1000 µg. This TC is used for chronic exposure assessment. The maximum allowable dose level (MADL) of 0.5 µg per day is applied for one-day oral exposure dose assessment (OEHHA, 2009) (see Chapter 6 for details).
[i] For nickel, a higher value of 0.02 mg per kg per day (reduced body and organ weights in rats) is available (USEPA IRIS).
CASRN: Chemical Abstracts Service Registry Number; DART: Developmental and reproductive toxicity; and MADL: maximum allowable dose level.

E.2.2. Non-Cancer Toxicity Criteria for Chronic Inhalation Exposure to Sensory Irritants

Sensory TC_{inh} are the OEHHA chronic reference exposure levels (Chronic RELs) for sensory irritation. The protocol (species, route, and exposure duration) for the toxicity studies as basis for the Chronic RELs are shown in **Error! Not a valid bookmark self-reference.**.

Table E.3.2.2.1-1. Non-Cancer Toxicity Criteria for One-Day Exposure to Sensory Irritants (Sensory TC_{inh}, ng per cubic meter) Using Chronic Reference Effect Levels (Chronic REL, µg per cubic meter)(OEHHA Chemicals Library)

Chemical (CASRN)	Species, Routes, and Exposure Duration	Endpoint	Chronic REL	Sensory TC_{inh}
Acetaldehyde (75-07-0)	Rats, Inhalation, 4 Weeks (6 hours per day, 5 days per week)	Olfactory epithelial degeneration	1.4E+02	1.4E+05[a]
Formaldehyde (50-00-0)	Workers, Inhalation, 1 to 36 years	Nasal obstruction and discomfort, airway discomfort, eye irritation	9.0E+00	9.0E+03[b]
Styrene (100-42-5)	Workers, Inhalation, Average 8.6 years	Poorer scores in sensory and motor function test	9.0E+02	9.0E+05[c]

[a] For formaldehyde, there is another Chronic TC_{inh} of 0.01 mg per cubic meter (10000 ng per cubic meter or 0.008 part per million) based on nasal tissue lesions in rats from ATSDR (derived in 2010).
[b] For acetaldehyde, there is another value of 0.009 mg per cubic meter (9000 ng per cubic meter) based on the same endpoint in rats from USEPA (derived in 1991).

[c] For styrene, there two similar TC values of 1 mg per cubic meter (neurotoxic effects in workers, (USEPA IRIS)) and 0.9 mg per cubic meter (effect on color discrimination in human, (ATSDR Toxicological Profiles)).
CASRN: Chemical Abstracts Service Registry Number

E.2.3. Non-Cancer Chronic Toxicity Criteria for Exposure to Chemicals Based on Other Effects and Cancer Slope Factors for Lifetime Exposure to Carcinogens

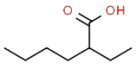
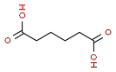
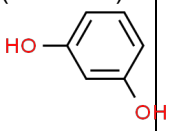
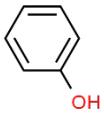
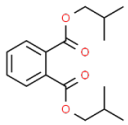
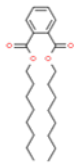
E.2.3.1. Alcohols, Ethers, Acids, and Esters

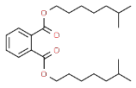
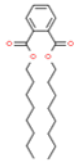
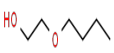
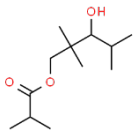
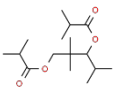
Table E.3.2.2.1-1 summarizes the Chronic TC_{oral} or Chronic TC_{inh} for a group of alcohols (including phenols), ethers (including glycol ethers), acids, and esters (including phthalates). Chronic TCs for these chemicals are either established chemical-specific values, from structural analogs (based on structural similarity as determined by OEHHA, or otherwise specified in the footnotes), or new screening values derived by OEHHA for this Study.

Another new screening Chronic TC_{oral} for 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB) is developed by OEHHA for the Study (Section E.3.7). This new screening Chronic TC_{oral} is also an analog value for texanol. Chronic TC_{inh} is not available for TXIB or texanol and the new screening Chronic TC_{oral} for TXIB is selected for this exposure route for these two chemicals. The Chronic TC_{oral} of di-n-octyl phthalate (DNOP) is an analog for diisobutyl phthalate and diisooctyl phthalate. The Chronic TC_{der} or Chronic TC_{inh} is not available for these phthalates and the chemical-specific Chronic TC_{oral}, or Chronic TC_{oral} from analog is selected for these exposure routes of the phthalates.

Table E.3.2.2.1-1. Non-Cancer Chronic Toxicity Criteria for Oral Exposure (Chronic TC_{oral}) and Inhalation Exposure (Chronic TC_{inh}) for the Group of Alcohols (Including Phenols), Ethers (Including Glycol Ethers), Acids, and Esters (including Phthalates)(OEHHA Chemicals Library; USEPA IRIS; USEPA PPRTV)

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Benzyl butyl phthalate (85-68-7)	Non-cancer	Oral, dermal or inhalation	Benzyl butyl phthalate	Chronic TC_{oral} = 0.2 mg per kg per day Chronic TC_{inh} = 700000 ng per cubic meter	Liver effects in rats	1989	USEPA IRIS
2-Butoxy-ethanol (EGBE, 111-76-2)	Non-cancer	Inhalation	Chemical -Specific	Chroinc TC_{inh} = 80000 ng per cubic meter[a]	Nasal olfactory epithelial degenerati on in rats	2018	OEHHA
Butylated hydroxy-toluene (128-37-0)	Non-cancer	Oral	Chemical -Specific	Chronic TC_{oral} = 0.3 mg per kg per day	Reduced bodyweight in rats	2013	USEPA PPRTV

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
2-Ethyl-1-hexanol (104-76-7)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 400 ng per cubic meter	Olfactory epithelium effect in mice	2019	USEPA PPRTV
Hexanoic Acid, 2-ethyl (149-57-5) 	Non-cancer	Dermal	Hexane-dioic acid 	Chronic TC_{oral} = 2 mg per kg per day	Reduced bodyweight in rats	2006	USEPA PPRTV
Phenol (108-95-2)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 200000 ng per cubic meter	Neurotoxicity, or increased liver enzymes in rats, mice, or monkeys	2000	OEHHA
Resorcinol (108-46-3) 	Non-cancer	Inhalation	Phenol 	Chronic TC_{inh} = 200000 ng per cubic meter	Neurotoxi-city, or increased liver enzymes in rats, mice, or monkeys	2000	OEHHA
Dibutyl phthalate (84-74-2)	Non-cancer	Oral or inhalation	Dibutyl phthalate	Chronic TC_{oral} = 0.1 mg per kg per day Chronic TC_{inh} = 350000 ng per cubic meter	Increased mortality in rats	1987	USEPA IRIS
Diethyl phthalate (84-66-2)	Non-cancer	Oral, dermal or inhalation	Diethyl phthalate	Chronic TC_{oral} = 0.8 mg per kg per day Chronic TC_{inh} = 2800000 ng per cubic meter	Reduced bodyweight gain, food consumpt-ion and altered organ weights in rats	1987	USEPA IRIS
Diisobutyl phthalate (84-69-5) 	Non-cancer	Oral, dermal or inhalation	DNOP 	Chronic TC_{oral} = 0.01 mg per kg per day Chronic TC_{inh} = 35000 ng per cubic meter	Liver effects in rats	2012	USEPA PPRTV
Diisooctyl phthalate (27554-26-3)	Non-cancer	Oral, dermal or inhalation	DNOP	Chronic TC_{oral} = 0.01 mg per kg per day	Liver effects in rats	2012	USEPA PPRTV

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
				Chronic TC_{inh} = 35000 ng per cubic meter			
Di-n-octyl phthalate (DNOP, 117-84-0)	Non-cancer	Oral, dermal or inhalation	Chemical-Specific	Chronic TC_{oral} = 0.01 mg per kg per day Chronic TC_{inh} = 35000 ng per cubic meter	Liver effects in rats	2012	USEPA PPRTV
Triethylene glycol monobutyl ether (143-22-6) 	Non-cancer	Oral or dermal	EGBE[b] 	Chronic TC_{oral} = 0.1 mg per kg per day	Hemosiderin deposition in the liver of rats	2010	USEPA IRIS
2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (TXIB, 6846-50-0)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 10500 ng per cubic meter	Increased relative liver weight in rats	2023	Section E.3.7
2,2,4-Trimethyl-1,3-pentanediol monoisobutyrate (Texanol, 25265-77-4) 	Non-cancer	Inhalation	TXIB 	Chronic TC_{inh} = 10500 ng per cubic meter	Increased relative liver weight in rats	2023	Section E.3.7

[a] For EGBE, there are other Chronic TC_{inh} of 1.6 mg per cubic meter (liver effects in rats and mice) from USEPA (derived in 2010) and 1 mg per cubic meter (0.2 part per million, blood effects in workers) from ATSDR (derived in 1998).
[b] OEHHA selected EGBE as an analog chemical because it is a similar chemical in the USEPA CompTox Chemicals Dashboard
CASRN: Chemical Abstracts Service Registry Number

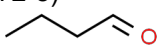
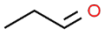
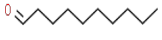
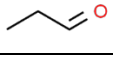
E.2.3.2. Carbonyls

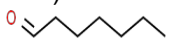
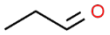
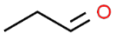
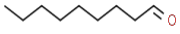
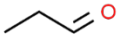
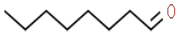
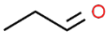
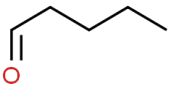
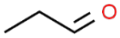
Aldehydes and ketones are carbonyls. Based on the structure of carbon chain of the

carbonyls, the chemicals can be divided into two classes: aliphatic and aromatic carbonyls. The aliphatic carbonyls contain open carbon chain (saturated or unsaturated), while the aromatic carbonyls contain unsaturated and conjugated carbon ring structure (e.g., benzene ring). Chronic TCs for these chemicals are either established chemical-specific values, from structural analog based on structural similarity as determined by OEHHA, or screening values derived by OEHHA for this Study. All CSFs are chemical-specific.

Table E.3.2.2.1-1 summarizes Chronic TC_{inh} and CSF_{inh} for a group of aliphatic aldehydes. Inhalation route is the only applicable exposure route for the group of aliphatic aldehydes. Among the nine (9) aldehydes in this group, propionaldehyde is the only chemical with established chemical-specific Chronic TC_{inh} available, whereas a screening value of Chronic TC_{inh} of methacrolein is developed by OEHHA for this Study (details in Section E.3). Propionaldehyde is used as an analog for the other seven aliphatic aldehydes based on structural similarity and toxicity comparison as determined by OEHHA. The comparison of toxicity showed that the shorter-chain aldehydes are more toxic than the longer-chain ones, thus the use of propionaldehyde as the analog for the TCs of these seven aliphatic aldehydes are health protective. Formaldehyde and acetaldehyde are included as carcinogens via inhalation, while their non-cancer effects are addressed in Sections E.1 and 0. Both chemicals have established chemical- and route-specific CSF_{inh}.

Table E.3.2.2.1-1. Non-Cancer Chronic Inhalation Toxicity Criteria (Chronic TC_{inh}) and Lifetime Inhalation Cancer Slope Factors (CSF_{inh}) for the Group of Aliphatic Aldehydes (OEHHA Chemicals Library; USEPA IRIS)

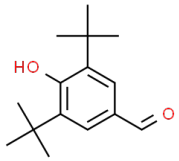
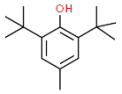
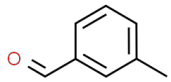
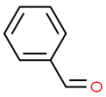
Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Acetaldehyde (75-07-0)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.01 (mg per kg per day)$^{-1}$	Nasal tumors in rats	2009	OEHHA
Formaldehyde (50-00-0)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.021 (mg per kg per day)$^{-1}$	Nasal tumors in rats	2009	OEHHA
Butanal (123-72-8) 	Non-cancer	Inhalation	Propion-aldehyde 	Chronic TC_{inh} = 8000 ng per cubic meter	Olfactory epithelial atrophy in rats	2008	USEPA IRIS
Decanal (112-31-2) 	Non-cancer	Inhalation	Propion-aldehyde 	Chronic TC_{inh} = 8000 ng per cubic meter	Olfactory epithelial atrophy in rats	2008	USEPA IRIS

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Heptanal (111-71-7) 	Non-cancer	Inhalation	Propion-aldehyde 	Chronic TC_{inh} = 8000 ng per cubic meter	Olfactory epithelial atrophy in rats	2008	USEPA IRIS
Hexanal (66-25-1) 	Non-cancer	Inhalation	Propion-aldehyde 	Chronic TC_{inh} = 8000 ng per cubic meter	Olfactory epithelial atrophy in rats	2008	USEPA IRIS
Methacrolein (78-85-3)	Non-cancer	Inhalation	Chemical -Specific	Chronic TC_{inh} = 1400 ng per cubic meter	Nasal olfactory and larynx lesions in rats	2023	Section E.3
Nonanal (124-19-6) 	Non-cancer	Inhalation	Propion-aldehyde 	Chronic TC_{inh} = 8000 ng per cubic meter	Olfactory epithelial atrophy in rats	2008	USEPA IRIS
Octanal (124-13-0) 	Non-cancer	Inhalation	Propion-aldehyde 	Chronic TC_{inh} = 8000 ng per cubic meter	Olfactory epithelial atrophy in rats	2008	USEPA IRIS
Propion-aldehyde (123-38-6)	Non-cancer	Inhalation	Chemical -Specific	Chronic TC_{inh} = 8000 ng per cubic meter	Olfactory epithelial atrophy in rats	2008	USEPA IRIS
Valeraldehyde (110-62-3) 	Non-cancer	Inhalation	Propion-aldehyde 	Chronic TC_{inh} = 8000 ng per cubic meter	Olfactory epithelial atrophy in rats	2008	USEPA IRIS

CASRN: Chemical Abstracts Service Registry Number

Table E.3.2.2.1-2 summarizes the Chronic TC_{inh} for a group of three aromatic aldehydes. Inhalation route is the only applicable exposure route for benzaldehyde and m-tolualdehyde, whereas multiple exposure routes are applicable for 3,5-di-tert-butyl-4-hydroxy-benzaldehyde. Benzaldehyde has established Chronic TC_{oral}. For the other two aromatic aldehydes, analogs are selected based on structural similarity as determine by OEHHA. Established values of Chronic TC_{der} or Chronic TC_{inh} are not available for this group of chemicals. The established chemical-specific Chronic TC_{oral} or Chronic TC_{oral} from the structural analogs are selected for these applicable exposure routes. The Chronic TC_{oral} are converted to the inhalation unit (ng per cubic meter) by multiplying the Chronic TC_{oral} (mg per kg per day) with a default adult bodyweight of 70 kg and a conversion factor of 1000000 mg per ng, and then dividing with a default inhalation volume of 20 cubic meter per day.

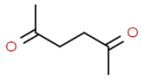
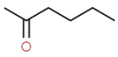
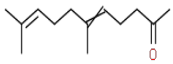
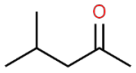
Table E.3.2.2.1-2. Non-Cancer Chronic Oral Toxicity Criteria (Chronic TC_{oral}) and Non-Cancer Chronic Inhalation Toxicity Criteria (Chronic TC_{inh}) for the Group of Aromatic Aldehydes (USEPA IRIS; USEPA PPRTV)

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Benzaldehyde (100-52-7)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 350000 ng per cubic meter	Fore-stomach and kidney toxicity in rats	1988	USEPA IRIS
3,5-di-tert-Butyl-4-hydroxy-benzaldehyde (BHT-CHO, 1620-98-0) 	Non-cancer	Oral, dermal or inhalation	Butylated hydroxy-toluene 	Chronic TC_{oral} = 0.3 mg per kg per day Chronic TC_{inh} = 1050000 ng per cubic meter	Bodyweight change in rats	2013	USEPA PPRTV
m-Tolualdehyde (620-23-5) 	Non-cancer	Inhalation	Benz-aldehyde 	Chronic TC_{inh} = 350000 ng per cubic meter	Fore-stomach and kidney toxicity in rats	1988	USEPA IRIS

CASRN: Chemical Abstracts Service Registry Number; and TC: Toxicity Criterion

Table E.3.2.2.1-3 summarizes the Chronic TCs and CSF_{inh} for a group of aliphatic ketones. There are no aromatic ketones evaluated in this section. Inhalation route is the only applicable exposure route for most of the ketones, except for 5,9-undecadien-2-one, 6,10-dimethyl- of which all three exposure routes were applicable. Among the four ketones in this group, only acetone have established chemical-specific non-cancer TCs available. An established Chronic TC_{inh} for acetone is not available and the chemical-specific Chronic TC_{oral} is selected for the inhalation route and converted to the inhalation unit (ng per cubic meter) as previously described in the section above. Screening values of Chronic TC_{inh} and CSF_{inh} for MIBK are developed by OEHHA for this Study (details in Section E.3.8). Established value of Chronic TC_{oral} or Chronic TC_{der} of 5,9-undecadien-2-one, 6,10-dimethyl- is not available. MIBK is used as an analog for chronic non-cancer oral exposure to 5,9-undecadien-2-one, 6,10-dimethyl- and this Chronic TC_{oral} for MIBK established by OEHHA (is also applied for the dermal route of 5,9-undecadien-2-one, 6,10-dimethyl-. 2-Hexanone is used as analog for 2,5-hexanedione based on structural similarity between the two chemicals determined by OEHHA.

Table E.3.2.2.1-3. Non-Cancer Chronic Toxicity Criteria for Oral Exposure (Chronic TC_{oral}), Non-Cancer Chronic Toxicity Criteria for Inhalation Exposure (Chronic TC_{inh}), and Lifetime Cancer Inalation Cancer Slope Factor (CSF_{inh}) for the Group of Aliphatic Ketones (OEHHA Chemicals Library; USEPA IRIS)

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Acetone (67-64-1)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 3150000 ng per cubic meter	Kidney toxicity in rats	2003	USEPA IRIS
2,5-Hexane-dione (110-13-4) 	Non-cancer	Inhalation	2-Hexanone 	Chronic TC_{inh} = 30000 ng per cubic meter	Effect on sciatic-tibial nerve in monkeys	2009	USEPA IRIS
Methyl isobutyl ketone (MIBK, 108-10-1)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 160000 ng per cubic meter	Kidney effects in rats	2023	Section E.3.8
Methyl isobutyl ketone (MIBK, 108-10-1)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.0039 (mg per kg per day)$^{-1}$	Liver tumors in mice	2023	Section E.3.8
5,9-Undecadien-2-one, 6,10-dimethyl- (689-67-8) 	Non-cancer	Oral dermal, or inhalation	MIBK 	Chronic TC_{oral} = 0.017 mg per kg per day Chronic TC_{inh} = 160000 ng per cubic meter	Kidney and liver weights, nephron-pathy in rats	1999	OEHHA

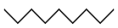
CASRN: Chemical Abstracts Service Registry Number

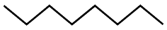
E.2.3.3. Alkanes and Alkenes

Table E.3.2.2.1-1 summarizes the Chronic TCs for a group of unsubstituted alkanes and alkenes. Multiple exposure routes were applicable for this group of hydrocarbons. Two of the 10 chemicals (n-hexane and n-heptane) have established chemical-specific Chronic TC_{inh}. n-Nonane is used as an analog for Chronic TC_{inh} of the other six (6) alkanes and two (2) alkenes Chronic TC_{inh} (C8 to C35) and Chronic TC_{oral} for 1-Octadecene (C18), as recommended by USEPA Provisional Peer-Reviewed Toxicity Values, PPRTV, (USEPA, 2009a) for hydrocarbons in the medium range (C9 to C18). The use of mineral oil as an analog for Chronic TC_{oral} of 17-pentatriacontene (C35) is

recommended by USEPA (2009a) for hydrocarbons in the high carbon range aliphatic C19 to C32 hydrocarbon fraction. Chronic TC_{der} is not available for 1-Octadecene, the only chemical in this group that can be exposed via the dermal route, and Chronic TC_{oral} from the analog is selected for the dermal exposure for this chemical.

Table E.3.2.2.1-1. Non-Cancer Chronic Toxicity Criteria for Oral Exposure (Chronic TC_{oral}) and Inhalation Exposure (Chronic TC_{inh}) for the Group of Unsubstituted Alkanes and Alkenes (USEPA IRIS; USEPA PPRTV)

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Decane (C10, 124-18-5) 	Non-cancer	Inhalation	n-Nonane 	Chronic TC_{inh} = 20000 ng per cubic meter	Salivation, lacrimation, and reduced bodyweight in rats	2009	USEPA PPRTV
Dodecane (C12, 112-40-3) 	Non-cancer	Inhalation	n-Nonane 	Chronic TC_{inh} = 20000 ng per cubic meter	Salivation, lacrimation, and reduced bodyweight in rats	2009	USEPA PPRTV
n-Heptane (142-82-5)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 400000 ng per cubic meter	Loss of hearing sensitivity in rats	2016	USEPA PPRTV
Hexadecane (C16, 544-76-3) 	Non-cancer	Oral or Inhalation	n-Nonane 	Chronic TC_{oral} = 0.0003 mg per kg per day Chronic TC_{inh} = 20000 ng per cubic meter	Oral: Salivation, lacrimation, and reduced bodyweight in rats Inhalation: Salivation, lacrimation, and reduced bodyweight in rats	2009	USEPA PPRTV
n-Hexane (110-54-3)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 700000 ng per cubic meter[a]	Peripheral neuropathy in rats	2005	USEPA IRIS

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
1-Octa-decene (C18, 112-88-9) 	Non-cancer	Oral, dermal, or Inhalation	n-Nonane 	Chronic TC_{oral} = 0.0003 mg per kg per day Chronic TC_{inh} = 20000 ng per cubic meter	Oral: Forestomach lesions in mice Inhalation: Salivation, lacrimation, and reduced bodyweight in rats	2009	USEPA PPRTV
Octane (C8, 111-65-9) 	Non-cancer	Inhalation	n-Nonane 	Chronic TC_{inh} = 20000 ng per cubic meter	Salivation, lacrimation, and reduced bodyweight in rats	2009	USEPA PPRTV
17-Penta-triacontene (C35, 6971-40-0) 	Non-cancer	Oral	Oral: Mineral oil Inhalation: n-Nonane 	Chronic TC_{oral} = 3 mg per kg per day Chronic TC_{inh} = 20000 ng per cubic meter	Oral: Laxative in human Inhalation: Salivation, lacrimation, and reduced bodyweight in rats	2009	USEPA PPRTV
Tetradecane (C14, 629-59-4) 	Non-cancer	Inhalation	n-Nonane 	Chronic TC_{inh} = 20000 ng per cubic meter	Salivation, lacrimation, and reduced bodyweight in rats	2009	USEPA PPRTV
Undecane (C11, 1120-21-4) 	Non-cancer	Inhalation	n-Nonane 	Chronic TC_{inh} = 20000 ng per cubic meter	Salivation, lacrimation, and reduced bodyweight in rats	2009	USEPA PPRTV

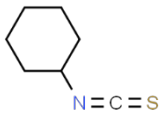
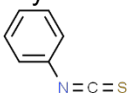
[a] For n-hexane, there are other TC_{inh} of 7 mg per cubic meter (electrophysiological alterations in mice, derived by OEHHA in 2000) and 2.1 mg per cubic meter (0.6 part per million, reduced motor nerve conduction velocity in workers, derived by ATSDR in 1999)
CASRN: Chemical Abstracts Service Registry Number

E.2.3.4. Substituted Alkane and Alkenes

Table E.3.2.2.1-1 summarizes Chronic TC_{inh} and CSF_{inh} for a group of substituted alkane (including a cycloalkane) and alkenes. Inhalation route is the only applicable exposure route for this group of chemicals, except cyclohexyl isothiocyanate. All three halogenated chemicals have established chemical-specific Chronic TC_{inh} and CSF_{inh}. For trichloroethylene, an inhalation unit risk (IUR) of 4 $x10^{-6}$ (µg per cubic meter)$^{-1}$ was derived in 2011 (USEPA IRIS), and the IUR was converted to CSF_{inh} (mg per kg per day)$^{-1}$ by multiplying a 70 kg bodyweight, a conversion factor of 1000 µg per mg, and

dividing by an inhalation volume of 20 cubic meter per day in 2012 (OEHHA Chemicals Library). Chronic TC_{oral} for cyclohexyl isothiocyanate is from phenyl isothiocyanate based on structural similarity as determined by OEHHA. Oral and dermal exposure routes were applicable for this chemical. Chronic TC_{der} or Chronic TC_{inh} is not established for these chemicals, thus, chemical-specific Chronic TC_{oral} or Chronic TC_{oral} from structural analog is selected for the dermal or inhalation exposure route.

Table E.3.2.2.1-1. Non-Cancer Chronic Toxicity Criteria for Inhalation Exposure (Chronic TC_{inh}) and Lifetime Inalation Cancer Slope Factors (CSF_{inh}) for the Group of Halogenated Alkane and Alkenes (OEHHA Chemicals Library; USEPA IRIS; USEPA PPRTV)

Chemical (Acronym, CASRN)	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Cyclohexyl isothio-cyanate (1122-82-3) 	Non-cancer	Oral or dermal	Phenyl isothio-cyanate 	Chronic TC_{oral} = 0.0002 mg per kg per day	Thyroid function in rats	2009	USEPA PPRTV
Tetrachloro-ethylene (127-18-4)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 40000 ng per cubic meter[a]	Neuro-toxicity in workers	2012	USEPA (2009a); USEPA IRIS
Tetrachloro-ethylene (127-18-4)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.021 (mg per kg per day)$^{-1}$	Liver and mono-nuclear cell leukemia in rats	2016	OEHHA
Trichloro-ethylene (79-01-6)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 2000 ng per cubic meter[b]	Decreased thymus weight in mice and heart effect in fetal rats	2011	USEPA IRIS
Trichloro-ethylene 79-01-6)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.014 (mg per kg per day)$^{-1}$	Kidney, liver, and non-Hodgkin lymphoma in human	2012	OEHHA
Trichloro-methane (Chloroform, 67-66-3)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 300000 ng per cubic meter[c]	Liver and kidney effects in rats	2000	OEHHA

Chemical (Acronym, CASRN)	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Trichloro-methane (Chloroform, 67-66-3)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.014 (mg per kg per day)$^{-1}$	Liver and kidney tumors in rodents	2020	OEHHA

[a] For tetrachloroethylene, a value of 0.006 ppm (0.04 mg per cubic meter) was derived in 2019 (ATSDR Toxicological Profiles). OEHHA has a similar value of 0.035 mg per cubic meter (liver and kidney effects in rats) derived in 1991 (OEHHA Chemicals Library).
[b] For trichloroethylene, a value of 0.0004 ppm (0.002 mg per cubic meter) was derived in 2019 (ATSDR Toxicological Profiles). There is another value of 0.6 mg per cubic meter (drowsiness, fatigue, headache, and eye irritation in workers, OEHHA (2000b).
[c] For trichloromethane, there is another value of 0.1 mg per cubic meter (0.02 ppm, liver effects in workers) derived in 1997 (ATSDR Toxicological Profiles). The OEHHA value is more recent and included a determination of developmental toxicity.
CASRN: Chemical Abstracts Service Registry Number

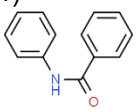
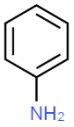
E.2.3.5. Amines, Amide, and Ureas

Table E.3.2.2.1-1 summarizes the Chronic TC_{inh}, Chronic TC_{oral}, and CSF_{inh} for a group of amines and amide. All chemicals have established chemical-specific TCs, except for N-phenylbenzamide. All three exposure routes were applicable for all the chemicals in this group.

Aniline is the only chemical that is included as a carcinogen via the multiple exposure routes. The chemical-specific CSF_{oral} and CSF_{inh} are available, thus, the CSF_{oral} is applied for the dermal route. The chemical also has established chemical-specific Chronic TC_{oral} and Chronic TC_{inh}. Chronic TC_{der} is not available for aniline and the Chronic TC_{oral} are used for the dermal route. Aniline is selected as analog for N-phenylbenzamide based on structure similarity as determined by OEHHA. The Chronic TC_{oral} for aniline is used for oral and dermal exposure of N-phenylbenzamide, whereas the Chronic TC_{inh} for aniline is used for the inhalation exposure route for this chemical. New screening Chronic TC_{oral} for 6PPD is developed by OEHHA for this Study (Section E.3). Chronic TC_{der} or Chronic TC_{inh} is not available for 6-PPD. The screening Chronic TC_{oral} is selected for the dermal and inhalation exposure routes for this chemical. Chronic TC_{oral} is converted to the inhalation unit (ng per cubic meter) as previously described in this section.

N,N-dicyclohexylurea, diphenylurea, and phenoxazine can be exposed via oral route. There are no established toxicity criteria for these chemicals, as well as lack of toxicity to derive a new value and suitable analog chemicals. Therefore, these three chemicals are not included in Table E.3.2.2.1-1.

Table E.3.2.2.1-1. Non-Cancer Chronic Toxicity Criteria for Oral and Inhalation Exposures (Chronic TC_{oral} and Chronic TC_{inh}, respectively), and Lifetime Oral and Inhalation Cancer Slope Factors (CSF_{oral} and CSF_{inh}, respectively) for the Group of Amines and Amide (OEHHA Chemicals Library; USEPA PPRTV)

Chemical (Acronym, CASRN) Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Aniline (62-53-3)	Non-cancer	Oral, dermal, or inhalation	Chemical-Specific	Chronic TC_{oral} = 0.007 mg per kg per day Chronic TC_{inh} = 1000 ng per cubic meter	Oral: Blood and spleen effects in rats Inhalation: Increased methemoglobin level and spleen toxicity in rats	Oral: 2017 Inhalation: 1990	USEPA PPRTV
Aniline (62-53-3)	Cancer	Oral or Inhalation, dermal	Chemical-Specific	CSF_{oral} and CSF_{inh} = 0.0057 $(mg\ per\ kg\ per\ day)^{-1}$	Splenic sarcoma in male rats	2009	OEHHA
1,4-Benzenediamine, N-(1,3-dimethyl-butyl)-N'-phenyl- (6PPD, 793-24-8)	Non-cancer	Oral, dermal or inhalation	Chemical-Specific	Chronic TC_{oral} = 0.003 mg per kg per day Chronic TC_{inh} = 10500 ng per cubic meter	Reduced bodyweight and food consumption in rats	2023	Section E.3.2
N-Phenyl-benzamide (93-98-1) 	Non-cancer	Oral, dermal, or inhalation	Aniline 	Chronic TC_{oral} = 0.007 mg per kg per day Chronic TC_{inh} = 1000 ng per cubic meter	Blood and spleen effects in rats	Oral: 2017 Inhalation: 1990	USEPA PPRTV

CASRN: Chemical Abstracts Service Registry Number

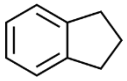
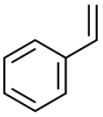
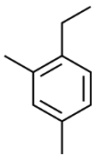
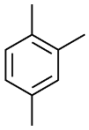
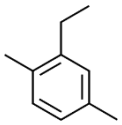
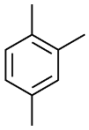
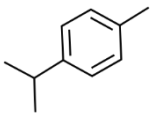
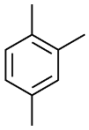
E.2.3.6. Benzene and Alkylbenzenes

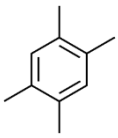
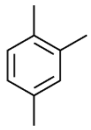
Table E.3.2.2.1-1 summarizes the Chronic TC_{inh}, Chronic TC_{oral}, and CSF_{inh} for benzene, 13 alkyl derivatives of benzene and a mixture of structural isomers of xylene (dimethylbenzene). TCs for these chemicals are either established chemical-specific values or from structural analog based on structural similarity as determined by OEHHA. All three exposure routes was applicable for n-butylbenzene (benzene, n-

butyl), whereas only inhalation exposure route was applicable for all other chemicals in the group. Only Chronic TC_{oral} was estabilised for n-butylbenzene and this Chronic TC_{oral} was applied for the inhalation and dermal exposure routes. USEPA , IRIS, recommended the use of a single value for each of the trimethylbenzene structural isomers—1,2,4-trimethylbenzene, 1,3,5-trimethylbenzene, and 1,2,3-trimethylbenzene—because of similar neurotoxic effects and pharmacokinetics among these isomers. This recommendation is more recent than the USEPA PPRTV reports for individual trimethylbenzenes (USEPA PPRTV). 1,2,4-trimethylbenzene is used as structural analog for 1-methyl-4-(1-methylethyl) benzene, 1-ethyl-2,4-dimethyl-benzene, 2-ethyl-1,4-dimethyl-benzene, and 1,2,4,5-tetramethylbenzene based on structural similarity as determined by OEHHA. The Chronic TC_{inh} for xylenes is established as a mixture and is used for each of the xylene isomers. The Chronic TC_{inh} of 1000000 ng per cubic meter chosen here is more health protective compared to the Sensory TC_{inh} of 700000 ng per cubic meter. One-day exposure to xylenes for sensory hazard (using the Sensory TC_{inh} of 700000 ng per cubic meter) and chronic exposure to xylenes for the other endpoint are evaluated and compared (see Chapter 6). Benzene, ethylbenzene, and styrene were included as carcinogens via inhalation exposure. All three chemicals have established chemical- and route-specific CSF_{inh}.

Table E.3.2.2.1-1. Non-Cancer Chronic Toxicity Criteria for Oral and Inhalation Exposures (Chronic TC_{oral} and Chronic TC_{inh}, respectively) and Lifetime Cancer Slope Factors for Inhalation Exposure (CSF_{inh}) for the Group of Benzene and Alkylbenzenes (OEHHA Chemicals Library)

Chemical (Acronym, CASRN) Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Benzene (71-43-2)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 3000 ng per cubic meter[a]	Reduced peripheral blood cells in workers	2014	OEHHA
Benzene (71-43-2)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.1 (mg per kg per day)$^{-1}$ [b]	Leukemia in workers	2009	OEHHA
Benzene, n-butyl (104-51-8)	Non-cancer	Oral, dermal, or inhalation	Chemical-Specific	Chronic TC_{oral} = 0.05 mg per kg per day Chronic TC_{inh} = 50000 ng per cubic meter	Hepato-cellular hypertrophy in rats	2010	USEPA PPRTV

Chemical (Acronym, CASRN) Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Benzo-cyclopentane (496-11-7) 	Non-cancer	Inhalation	Styrene 	Chronic TC_{inh} = 900000 ng per cubic meter	Memory and sensory/ motor deficits in workers	2000	OEHHA
Ethylbenzene (100-41-4)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 300000 ng per cubic meter[c]	Kidney effects in rats	2010	ATSDR Toxicological Profiles
Ethylbenzene (100-41-4)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.0087 (mg per kg per day)$^{-1}$	Kidney tumors in rats	2008	OEHHA
1-Ethyl-2,4-dimethyl-benzene (874-41-9) 	Non-cancer	Inhalation	1,2,4-Trimethyl-benzene 	Chronic TC_{inh} = 60000 ng per cubic meter	Reduced pain sensitivity in rats	2016	USEPA IRIS
2-Ethyl-1,4-dimethyl-benzene (1758-88-9) 	Non-cancer	Inhalation	1,2,4-Trimethyl-benzene 	Chronic TC_{inh} = 60000 ng per cubic meter	Reduced pain sensitivity in rats	2016	USEPA IRIS
1-Methyl-4-(1-methylethyl) benzene (99-87-6) 	Non-cancer	Inhalation	1,2,4-Trimethyl-benzene 	Chronic TC_{inh} = 60000 ng per cubic meter	Reduced pain sensitivity in rats	2016	USEPA IRIS
1,2,3-Trimethyl-benzene (526-73-8)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 60000 ng per cubic meter	Reduced pain sensitivity in rats	2016	USEPA IRIS

Chemical (Acronym, CASRN) Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
1,2,4-Trimethyl-benzene (95-63-6)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 60000 ng per cubic meter	Reduced pain sensitivity in rats	2016	USEPA IRIS
1,3,5-Trimethyl-benzene (108-67-8)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 60000 ng per cubic meter	Reduced pain sensitivity in rats	2016	USEPA IRIS
1,2,4,5-Tetramethylbenzene (95-93-2) 	Non-cancer	Inhalation	1,2,4-Trimethyl-benzene 	Chronic TC_{inh} = 60000 ng per cubic meter	Reduced pain sensitivity in rats	2016	USEPA IRIS
Styrene (100-42-5)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.026 (mg per kg per day)$^{-1}$	Bronchiolar-alveolar tumors in mice	2010	OEHHA
Toluene (108-88-3)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 420000 ng per cubic meter[d]	Acquired color vision impairment in workers	2020	OEHHA
Xylenes mixture (1330-20-7): m-Xylene (108-38-3), p-Xylene (106-42-3), and o-Xylene (95-47-6)	Non-cancer	Inhalation	Xylene mixture[e]	Chronic TC_{inh} = 100000 ng per cubic meter[f]	Impaired motor coordination in rats	2003	USEPA IRIS

[a] For benzene, there are other values of 0.03 mg per cubic meter (reduced lymphocyte count in workers, derived in 2003 (USEPA IRIS)) and 0.01 mg per cubic meter (0.003 ppm, hematotoxicity in workers, derived in 2007 (ATSDR Toxicological Profiles)).
[b] For benzene, there are other values: 0.05 (mg per kg per day)-1 (with 50% absorption factor applied, leukemia in workers, OEHHA (2001a); (2003)) and 0.008 to 0.027 (mg per kg per day)-1 (leukemia in workers, derived in 2000 (USEPA IRIS)). The unit risks of 2.2E-06 (µg per cubic meter)-1 to 7.8E-06 (µg per cubic meter)-1 were converted to (mg per kg per day)-1 basis using factors of 1 day per 20 cubic meters and 70 kg bodyweight.
[c] For ethylbenzene, there are other values of 2 mg per cubic meter (effects in the kidney, pituitary gland, and liver in rats and mice (OEHHA Chemicals Library)) and 1 mg per cubic meter (developmental toxicity in rats (USEPA IRIS)).
[d] For toluene, there are other values of 5 mg per cubic meter (neurological effects in workers (USEPA IRIS)) and 3.8 mg per cubic meter (neurological effects in workers (ATSDR Toxicological Profiles)).
[e] There is only one value for the toxicity criteria for xylenes as a mixture.

[f] There are other values for the xylenes: Sensory TC_{inh} of 0.7 mg per cubic meter (eye irritation, sore throat, floating sensation, and poor appetite in workers (OEHHA Chemicals Library)) and 0.2 mg per cubic meter (0.05 ppm, neurological and respiratory effects in workers (ATSDR Toxicological Profiles)). The Chronic TC_{inh} of 1000000 ng per cubic meter chosen here is more health protective.
CASRN: Chemical Abstracts Service Registry Number

E.2.3.7. Halogenated Benzene and Halogenated Alkylbenzene

Table E.3.2.2.1-1 summarizes the Chronic TC_{inh} and CSF_{inh} for a halogenated benzene and a halogenated alkylbenzene. Inhalation route is the only applicable exposure route for these chemicals. Both chemicals have established chemical- and route-specific Chronic TC_{inh} and CSF_{inh}.

Table E.3.2.2.1-1. Non-Cancer Chronic Toxicity Criteria for Inhalation Exposure (Chronic TC_{inh}) and Lifetime Cancer Slope Factors for Inhalation Exposure (CSF_{inh}) for a Halogenated Benzene and a Halogenated Alkylbenzene (OEHHA Chemicals Library; USEPA PPRTV)

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
1-Chloro-4-(trifluoromethyl) benzene (PCBTF, 98-56-6)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 300000 ng per cubic meter	Liver effects in rats	2007	USEPA PPRTV
1-Chloro-4-(trifluoromethyl) benzene (PCBTF, 98-56-6)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.03 (mg per kg per day)$^{-1}$	Liver tumors in mice	2020	OEHHA
1,4-Dichloro-benzene (106-46-7)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 60000 ng per cubic meter[a]	Nasal lesions in rats	2006	OEHHA
1,4-Dichloro-benzene (106-46-7)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.04 (mg per kg per day)$^{-1}$	Liver tumors in mice	1988	OEHHA

[a] For 1,4-Dichlorobenzene, there are other values as 0.8 mg per cubic meter from two sources (nasal and ocular discharge, reduced bodyweight and food consumption, increased liver and kidney weights in rats (OEHHA Chemicals Library); and increased liver weight in rats (USEPA IRIS)).
CASRN: Chemical Abstracts Service Registry Number

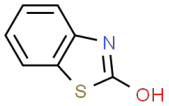
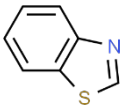
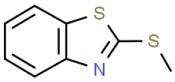
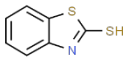
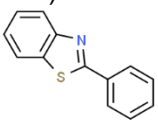
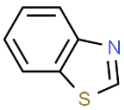
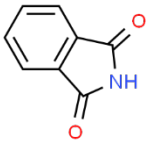
E.2.3.8. Heterocyclic Aromatic Chemicals

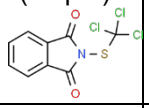
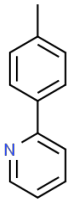
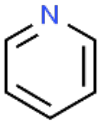
Table E.3.2.2.1-1 summarizes the Chronic TCs and CSF_{oral} for a group of heterocyclic aromatic chemicals. The group contains five benzothiazoles (BT), dibenzothiophene, 2-methylfuran, phthalimide, and 2-(4-methylphenyl)-pyridine. Chronic TCs for these chemicals are either established chemical-specific values, from structural analog based

only on structural similarity as determined by OEHHA (or otherwise specified), or new screening values derived by OEHHA for this Study. For most of the chemicals in the group, multiple exposure routes were applicable. Chronic TC_{der} or TC_{inh} are not available for these chemicals and chemical-specific Chronic TC_{oral}, new screening Chronic TC_{oral}, or Chronic TC_{oral} from structural analog are selected for the dermal or inhalation exposure route. Pyridine is used as analog for pyridine, 2-(4-methylphenyl)- based on structural similarity and toxicity. New screening Chronic TC_{oral} for BT and furan, 2-methyl (2-methylfuran) are developed by OEHHA for this Study (Sections E.3.5 and E.3.6). The use of BT as an analog for 2-benzothiazolone and 2-phenyl-benzothiazole is discussed in Section E.3.5. 1,3-benzothiazole-2-thiol (also known as 2-mercaptobenzothiazole or 2-MBT) has established chemical-specific Chronic TC_{oral} and CSF_{oral}. Dermal is the only applicable exposure pathway for the chemical. It is also the only chemical that is included as a carcinogen. The chemical-specific Chronic TC_{der} and CSF_{der} are not available for 2-MBT, thus, the Chronic TC_{oral} and CSF_{oral} are selected for the dermal exposure.

Table E.3.2.2.1-1. Non-Cancer Chronic Toxicity Criteria for Oral and Inhalation Exposures (Chronic TC_{oral} and Chronic TC_{inh}, respectively) and Lifetime Cancer Slope Factor for Oral Exposure (CSF_{oral}) for the Group of Heterocyclic Aromatic Chemicals (USEPA IRIS; USEPA PPRTV)

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Benzothiazole (BT, 95-16-9)	Non-cancer	Oral, dermal, or inhalation	Chemical-Specific	Chronic TC_{oral} = 0.0005 mg per kg per day Chronic TC_{inh} = 1750 ng per cubic meter	No adverse effects in rats[a]	2023	Section E.3.5
1,3-benzothiazole-2-thiol (2-mercapto-benzothiazole, 2-MBT; 149-30-4)	Non-cancer	Dermal	Chemical-Specific	Chronic TC_{oral} = 0.004 mg per kg per day	Increased relative liver weight in rats	2016	USEPA PPRTV
1,3-benzothiazole-2-thiol (2-mercapto-benzothiazole, 2-MBT; 149-30-4)	Cancer	Dermal	Chemical-Specific	CSF_{oral} = 0.01 $(mg\ per\ kg\ per\ day)^{-1}$	Adrenal gland and pituitary gland tumors in female rats	2016	USEPA PPRTV

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
2-Benzo-thiazolone (2-hydroxybenothiazole, 2-OHBT, benzothiazolone; 934-34-9) 	Non-cancer	Oral, dermal, or inhalation	BT 	Chronic TC_{oral} = 0.0005 mg per kg per day Chronic TC_{inh} = 1750 ng per cubic meter	No adverse effects in rats[a]	2023	Section E.3.5
Dibenzo-thiophene (132-65-0)	Non-cancer	Oral, dermal or inhalation	Chemical-Specific	Chronic TC_{oral} = 0.01 mg per kg per day Chronic TC_{inh} = 35000 ng per cubic meter	Increased relative liver weight and fatty liver in rats	2013	USEPA PPRTV
Furan, 2-methyl (534-22-5)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 350 ng per cubic meter	Liver lesions in rats	2023	Section E.3.6
2-(Methylthio)-benzothiazole (2-MTBT, 615-22-5) 	Non-cancer	Oral or Dermal	2-MBT 	Chronic TC_{oral} = 0.004 mg per kg per day	Increased relative liver weight in rats	2016	USEPA PPRTV
2-Phenyl-benzothiazole, (2-PBT, 883-93-2) 	Non-cancer	Oral, dermal, or inhalation	BT 	Chronic TC_{oral} = 0.0005 mg per kg per day Chronic TC_{inh} = 1750 ng per cubic meter	No adverse effects in rats[a]	2023	Section E.3.5
Phthalimide (85-41-6) 	Non-cancer	Oral or dermal	1H-Isoindole-1,3(2H)-dione, 2-[(trichloromethyl)-thio]-	Chronic TC_{inh} = 0.1 mg per kg per day	Reduced bodyweight gain, altered serum chemistry in dogs	1987	USEPA IRIS

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
			(Folpet) 				
Pyridine, 2-(4-methylphenyl)-(4467-06-5) 	Non-cancer	Oral, dermal or inhalation	Pyridine 	Chronic TC_{oral} = 0.001 mg per kg per day Chronic TC_{inh} = 3500 ng per cubic meter	Liver effects in rats	1987	USEPA IRIS

[a] Chronic TC_{oral} derived from a repeated dose toxicity study with no effect observed in the exposed rats.
CASRN: Chemical Abstracts Service Registry Number

E.2.3.9. Polyaromatic Hydrocarbons, and Their Derivatives

Table E.3.2.2.1-1 summarizes the Chronic TC_{oral} and CSF_{oral} for a group of polyaromatic hydrocarbons (containing two or more conjugated aromatic rings, PAHs), and their derivatives. Toxicity criteria for these chemicals are either established chemical-specific values, from structural analog based only on structural similarity as determined by OEHHA (unless otherwise specified), or new screening values derived by OEHHA for this Study. For most of the chemicals in the group, multiple exposure routes were applicable.

Naphthalene has chemical-specific and route-specific Chronic TC_{oral} and Chronic TC_{inh}. Naphthalene is used as a structural analog for its 1,2-dimethyl, 1,6-dimethyl, 2,3-dimethyl, and 2-bromomethyl derivatives. Chronic TC_{der} is not available for naphthalene and its derivatives. The Chronic TC_{oral} is used for the dermal route for these chemicals. The two methyl-naphthalenes have chemical-specific Chronic TC_{oral}. These chemical-specific Chronic TC_{oral} are used for the inhalation and dermal route for each of the chemical.

Chemical-specific Chronic TC_{oral} are used as the structural analog values for these chemicals:

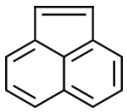
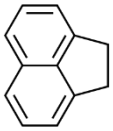
- acenaphthene for acenaphthylene.
- anthracene for anthracene, 2-methyl-; anthracene, 9,10-dimethyl; anthracene, 9-phenyl; anthracene, 9,10-diphenyl-; benz[a]anthracene; dibenz[a,h]anthracene; and phenanthrene; phenanthrene, 2-methyl.
- pyrene for 1-hydroxypyrene.
- fluorene for 7H-benzo[c]fluorene, benzo[k]fluoranthene.
- fluoranthene for benzo[b]fluoranthene.

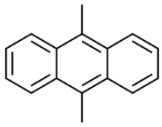
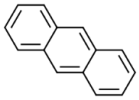
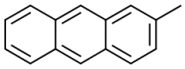
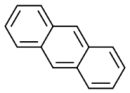
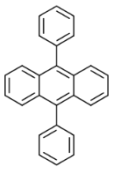
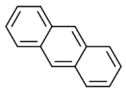
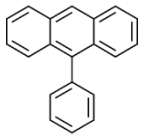
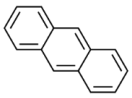
These chemical-specific or analog values of Chronic TC_{oral} are used for inhalation and dermal routes.

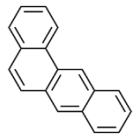
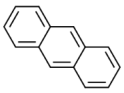
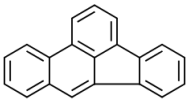
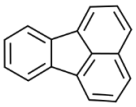
Chronic TC_{der} or Chronic TC_{inh} are not established for some of the chemicals and chemical-specific Chronic TC_{oral}, new screening Chronic TC_{oral}, or Chronic TC_{oral} from structural analog are selected for the dermal or inhalation route. Several PAHs are considered as DART and their DART TCs are presented in Section E.2.1.

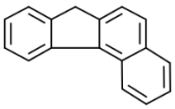
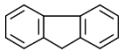
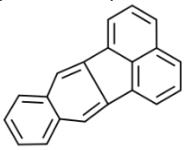
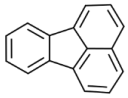
Naphthalene is included as a carcinogen via multiple exposure routes. The chemical has established chemical- and route-specific CSF_{inh} and the CSF_{inh} is selected for all exposure routes. Benz[a]anthracene, BaP, cyclopenta[c,d]pyrene, indeno[1,2,3-cd]pyrene, chrysene, benzo[b]fluoranthene, and benzo[k]fluoranthene are included as carcinogens via multiple exposure routes. CSF_{oral} and CSF_{inh} for BaP are used as analogs for cyclopenta[c,d]pyrene and the rationale is provided in Section E.3.9. All these chemicals, except dibenz[a,h]-anthracene, only have established chemical-specific CSF_{oral} and CSF_{inh}, or CSF_{oral} and CSF_{inh} from structural analog; thus, the chemical-specific or analog CSF_{oral} are selected for the dermal exposure. Dibenz[a,h]-anthracene only has established CSF_{oral} and the CSF_{oral} is selected for the dermal and inhalation routes.

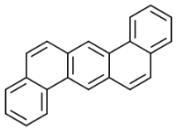
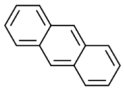
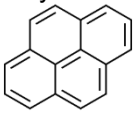
Table E.3.2.2.1-1. Non-Cancer Toxicity Criteria for Chronic Oral and Inhalation Exposures (Chronic TC_{oral} and Chronic TC_{inh}, respectively) and Lifetime Cancer Slope Factors for Oral and Inhalation Exposure (CSF_{oral} and CSF_{inh}, respectively) for the Group of Polyaromatic Hydrocarbons and Their Derivatives (ATSDR Toxicological Profiles; OEHHA Chemicals Library; USEPA IRIS; USEPA PPRTV)

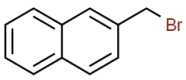
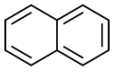
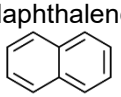
Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Ace-naphthylene (208-96-8) 	Non-cancer	Oral, dermal or inhalation	Ace-naphthene 	Chronic TC_{oral} = 0.06 mg per kg per day [a] Chronic TC_{inh} = 210000 ng per cubic meter	Increased liver weight and cellular hyper-trophy in mice	1990	USEPA IRIS
Anthracene (120-12-7)	Non-cancer	Oral, dermal or inhalation	Chemical-Specific	Chronic TC_{oral} = 0.3 mg per kg per day [b] Chronic TC_{inh} = 1050000	No adverse effect in mice[c]	1990	USEPA IRIS

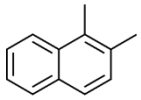
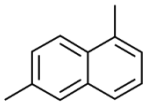
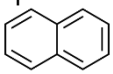
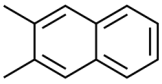
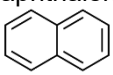
Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
				ng per cubic meter			
Anthracene, 9,10-dimethyl (781-43-1) 	Non-cancer	Oral, dermal or inhalation	Anthracene 	Chronic TC_{oral} = 0.3 mg per kg per day Chronic TC_{inh} = 1050000 ng per cubic meter	No adverse effect in mice[c]	1990	USEPA IRIS
Anthracene, 2-methyl- (613-12-7) 	Non-cancer	Oral, dermal or inhalation	Anthracene 	Chronic TC_{oral} = 0.3 mg per kg per day Chronic TC_{inh} = 1050000 ng per cubic meter	No adverse effect in mice[c]	1990	USEPA IRIS
Anthracene, 9,10-diphenyl- (1499-10-1) 	Non-cancer	Oral, dermal or inhalation	Anthracene 	Chronic TC_{oral} = 0.3 mg per kg per day Chronic TC_{inh} = 1050000 ng per cubic meter	No adverse effect in mice[c]	1990	USEPA IRIS
Anthracene, 9-phenyl (602-55-1) 	Non-cancer	Oral, dermal or inhalation	Anthracene 	Chronic TC_{oral} = 0.3 mg per kg per day Chronic TC_{inh} = 1050000 ng per cubic meter	No adverse effect in mice[c]	1990	USEPA IRIS

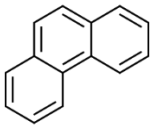
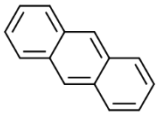
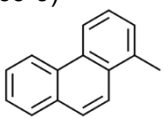
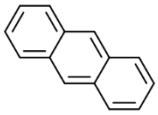
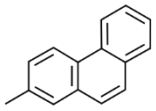
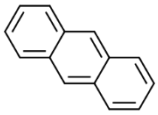
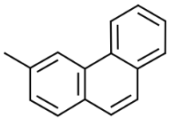
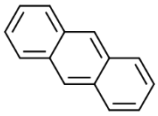
Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Benz[a]-anthracene (56-55-3) 	Non-cancer	Oral, dermal or inhalation	Anthracene 	Chronic TC_{oral} = 0.3 mg per kg per day Chronic TC_{inh} = 1050000 ng per cubic meter	No adverse effect in mice[c]	1990	USEPA IRIS
Benz[a]-anthracene (56-55-3)	Cancer	Oral or dermal	Chemical-Specific	CSF_{oral} = 1.2 (mg per kg per day)$^{-1}$ [d]	Gastric tumors in mice	2015	OEHHA
Benz[a]-anthracene (56-55-3)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.39 (mg per kg per day)$^{-1}$ [d]	Respirat-ory tract tumors in hamsters	2015	OEHHA
Benzo[a]-pyrene (BaP, 50-32-8)	Cancer	Oral or dermal	Chemical-Specific	CSF_{oral} = 12 (mg per kg per day)$^{-1}$	Gastric tumor in mice	2015	OEHHA
Benzo[a]-pyrene (50-32-8)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 3.9 (mg per kg per day)$^{-1}$	Respirat-ory tract tumors in hamsters	2015	OEHHA
Benzo[b]-fluoranthene (205-99-2) 	Non-cancer	Oral, dermal or inhalation	Fluor-anthene 	Chronic TC_{oral} = 0.04 mg per kg per day Chronic TC_{inh} = 140000 ng per cubic meter	Kidney, urinary and blood systems effects in mice	1990	USEPA IRIS
Benzo[b]-fluoranthene (205-99-2)	Cancer	Oral or dermal	Chemical-Specific	CSF_{oral} = 1.2 (mg per kg per day)$^{-1}$ [e]	Gastric tumors in mice	2015	OEHHA
Benzo[b]-fluoranthene (205-99-2)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.39 (mg per kg per day)$^{-1}$ [l]	Respirat-ory tract tumors in hamsters	2015	OEHHA

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
7H-Benzo[c]-fluorene (205-12-9) 	Non-cancer	Oral, dermal or inhalation	Fluorene 	Chronic TC_{oral} = 0.04 mg per kg per day Chronic TC_{inh} = 140000 ng per cubic meter	Decreased RBC, packed cell volume and hemo-globin in mice	1990	USEPA IRIS
Benzo[k]-fluoranthene (207-08-9) 	Non-cancer	Oral, dermal or inhalation	Fluor-anthene 	Chronic TC_{oral} = 0.04 mg per kg per day Chronic TC_{inh} = 140000 ng per cubic meter	Kidney, urinary and blood systems effects in mice	1990	USEPA IRIS
Benzo[k]-fluoranthene (207-08-9)	Cancer	Oral or dermal	Chemical-Specific	CSF_{oral} = 1.2 (mg per kg per day)$^{-1}$ [e]	Gastric tumors in mice	2015	OEHHA
Benzo[k]-fluoranthene (207-08-9)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.39 (mg per kg per day)$^{-1}$ [e]	Respirat-ory tract tumors in hamsters	2015	OEHHA
Chrysene (218-01-9)	Cancer	Oral or dermal	Chemical-Specific	CSF_{oral} = 0.12 (mg per kg per day)$^{-1}$ [f]	Gastric tumors in mice	2015	OEHHA
Chrysene (218-01-9)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.039 (mg per kg per day)$^{-1}$ [f]	Respirat-ory tract tumors in hamsters	2015	OEHHA
Cyclopenta[c,d]pyrene (27208-37-3)	Cancer	Oral, dermal	BaP	CSF_{oral} = 12 (mg per kg per day)$^{-1}$	Gastric tumor in mice	2023	Section E.3.9
Cyclopenta[c,d]pyrene (27208-37-3)	Cancer	Inhalation	BaP	CSF_{inh} = 3.9 (mg per kg per day)$^{-1}$	Respirat-ory tract tumors in hamsters	2023	Section E.3.9

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Dibenz[a,h]-anthracene (53-70-3) 	Non-cancer	Oral, dermal or inhalation	Anthracene 	Chronic TC_{oral} = 0.3 mg per kg per day Chronic TC_{inh} = 1050000 ng per cubic meter	No adverse effect in mice[c]	1990	USEPA IRIS
Dibenz[a,h]-anthracene (53-70-3)	Cancer	Oral, dermal or inhalation	Chemical-Specific	CSF_{oral} and CSF_{inh} = 4.1 (mg per kg per day)$^{-1}$	Alveolar cell carcinoma in mice	2015	OEHHA
Fluoranthene (206-44-0)	Non-cancer	Oral, dermal or inhalation	Chemical-Specific	Chronic TC_{oral} = 0.04 mg per kg per day Chronic TC_{inh} = 140000 ng per cubic meter	Kidney, urinary and blood systems effects in mice	1990	USEPA IRIS
Fluorene (86-73-7)	Non-cancer	Oral, dermal or inhalation	Chemical-Specific	Chronic TC_{oral} = 0.04 mg per kg per day Chronic TC_{inh} = 140000 ng per cubic meter	Decreased RBC, packed cell volume and hemo-globin in mice	1990	USEPA IRIS
1-Hydroxy-pyrene (5315-79-7) 	Non-cancer	Oral, dermal	Pyrene[g] 	Chronic TC_{oral} = 0.03 mg per kg per day Chronic TC_{inh} = 1050000 ng per	Kidney effects in mice	1990	USEPA IRIS

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
				cubic meter			
Indeno[1,2,3-cd]pyrene (193-39-5)	Cancer	Oral or dermal	Chemical-Specific	CSF_{oral} = 1.2 (mg per kg per day)$^{-1}$ [h]	Gastric tumors in mice	2015	OEHHA
Indeno[1,2,3-cd]pyrene (193-39-5)	Cancer	Inhalation	Chemical-Specific	CSF_{inh} = 0.39 (mg per kg per day)$^{-1}$ [gh]	Respiratory tract tumors in hamsters	2015	OEHHA
Naphthalene (91-20-3)	Non-cancer	Oral or dermal	Chemical-Specific	Chronic TC_{oral} = 0.02 mg per kg per day [i]	Reduced body-weight in rats	2000	OEHHA
Naphthalene (91-20-3)	Non-cancer	Inhalation	Chemical-Specific	Chronic TC_{inh} = 3000 ng per cubic meter[i,j]	Nasal, olfactory, and respiratory effects in rats	2005	ATSDR Toxicological Profiles
Naphthalene (91-20-3)	Cancer	Oral, dermal or inhalation	Chemical-Specific	CSF_{oral} and CSF_{inh} = 0.12 (mg per kg per day)$^{-1}$	Nasal respiratory epithelial adenoma and nasal olfactory epithelial neuro-blastoma in rats	2015	OEHHA
Naphthalene, 2-(bromomethyl) - (939-26-4) 	Non-cancer	Oral or dermal	Naphthalene 	Chronic TC_{oral} = 0.02 mg per kg per day	Reduced body-weight in rats	2000	OEHHA
Naphthalene, 2-(bromomethyl) - (939-26-4)	Non-cancer	Inhalation	Naphthalene	Chronic TC_{inh} = 3000 ng per cubic meter	Nasal, olfactory, and respiratory effects in rats	2005	ATSDR Toxicological Profiles
Naphthalene, 1,2-dimethyl- (573-98-8)	Non-cancer	Oral or dermal	Naphthalene 	Chronic TC_{oral} = 0.02 mg per kg per day	Reduced bodyweight in rats	2000	OEHHA

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
							
Naphthalene, 1,2-dimethyl- (573-98-8)	Non-cancer	Inhalation	Naphthalene	Chronic TC_{inh} = 3000 ng per cubic meter	Nasal, olfactory, and respiratory effects in rats	2005	ATSDR Toxicological Profiles
Naphthalene, 1,6-dimethyl- (575-43-9) 	Non-cancer	Oral or dermal	Naphthalene 	Chronic TC_{oral} = 0.02 mg per kg per day	Reduced body-weight in rats	2000	OEHHA
Naphthalene, 1,6-dimethyl- (575-43-9)	Non-cancer	Inhalation	Naphthalene	Chronic TC_{inh} = 3000 ng per cubic meter	Nasal, olfactory, and respiratory effects in rats	2005	ATSDR Toxicological Profiles
Naphthalene, 2,3-dimethyl- (581-40-8) 	Non-cancer	Oral or dermal	Naphthalene 	Chronic TC_{oral} = 0.02 mg per kg per day	Reduced body-weight in rats	2000	OEHHA
Naphthalene, 2,3-dimethyl- (581-40-8)	Non-cancer	Inhalation	Naphthalene	Chronic TC_{inh} = 3000 ng per cubic meter	Nasal, olfactory, and respiratory effects in rats	2005	ATSDR Toxicological Profiles
Naphthalene, 1-methyl (1-MN, 90-12-0)	Non-cancer	Oral, dermal or inhalation	Chemical-Specific	Chronic TC_{oral} = 0.007 mg per kg per day[k] Chronic TC_{inh} = 24500 ng per cubic meter	Pulmonary alveolar proteinosis in mice	2008	USEPA PPRTV
Naphthalene, 2-methyl (2-MN, 91-57-6)	Non-cancer	Oral, dermal or inhalation	Chemical-Specific	Chronic TC_{oral} = 0.004 mg per kg per day[l]	Pulmonary alveolar proteinosis in mice	2003	USEPA IRIS

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
				Chronic TC_{inh} = 14000 ng per cubic meter			
Phenanthrene (85-01-8) 	Non-cancer	Oral, dermal or inhalation	Anthracene 	Chronic TC_{oral} = 0.3 mg per kg per day Chronic TC_{inh} = 1050000 ng per cubic meter	No adverse effect in mice[c]	1990	USEPA IRIS
Phenanthrene, 1-methyl (832-69-9) 	Non-cancer	Oral, dermal or inhalation	Anthracene 	Chronic TC_{oral} = 0.3 mg per kg per day Chronic TC_{inh} = 1050000 ng per cubic meter	No adverse effect in mice[c]	1990	USEPA IRIS
Phenanthrene, 2-methyl (2531-84-2) 	Non-cancer	Oral, dermal or inhalation	Anthracene 	Chronic TC_{oral} = 0.3 mg per kg per day Chronic TC_{inh} = 1050000 ng per cubic meter	No adverse effect in mice[c]	1990	USEPA IRIS
Phenanthrene, 3-methyl (832-71-3) 	Non-cancer	Oral, dermal or inhalation	Anthracene 	Chronic TC_{oral} = 0.3 mg per kg per day Chronic TC_{inh} = 1050000 ng per cubic meter	No adverse effect in mice[c]	1990	USEPA IRIS

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Pyrene (129-00-0)	Non-cancer	Oral, dermal or inhalation	Chemical-Specific	Chronic TC_{oral} = 0.03 mg per kg per day Chronic TC_{inh} = 1050000 ng per cubic meter	Kidney effects in mice	1990	USEPA IRIS

[a] For acenaphthene, the reference dose (RfD, (USEPA IRIS)) was restated (USEPA PPRTV).
[b] For anthracene, there is another value of 10 mg per kg per day (liver effect in mice (ATSDR Toxicological Profiles)).
[c] For anthracene, the Chronic TC_{oral} was derived based on a 90-day multi-dose oral toxicity study on mice (USEPA IRIS). No treatment-related effects were observed in all dosed animals.
[d] For benz[a]anthracene, Oral and inhalation CSFs are expressed as 0.1 (PEF) of BaP CSF, which are 1.2 and 3.9 (mg per kg per day)-1, for oral and inhalation exposure, respectively.
[e] Oral and inhalation CSFs are expressed as 0.1 (PEF) of BaP CSF, which are 12 and 3.9 (mg per kg per day)-1, for oral and inhalation exposure, respectively.
[f] Oral and inhalation CSFs are expressed as 0.01 (PEF) of BaP CSF, which are 12 and 3.9 (mg per kg per day)-1, for oral and inhalation exposure, respectively.
[g] The use of pyrene as an analog is determined by OEHHA and is based on structural similarity and 1-hydroxypyrene is a metabolite of pyrene.
[h] Oral and inhalation CSFs are expressed as 0.1 (PEF) of BaP CSF, which are 12 and 3.9 (mg per kg per day)-1, for oral and inhalation exposure, respectively.
[i] For naphthalene, the same value is available from USEPA (.
[j] For inhalation exposure to naphthalene, a value of 0.0007 ppm (3000 ng per cubic meter) is available (ATSDR Toxicological Profiles). There is another value of 0.009 mg per cubic meter (nasal, olfactory, and respiratory effects in mice) derived in 2000 from OEHHA (2000a). The more recent and more health protective ATSDR value is chosen for this Study.
[k] For 1-methyl-naphthalene, there is another value of 0.07 mg per kg per day (pulmonary alveolar proteinosis in mice (ATSDR Toxicological Profiles)).
[l] For 2-methyl-naphthalene, there is a higher value of 0.04 mg per kg per day (pulmonary alveolar proteinosis in mice, (ATSDR Toxicological Profiles)).
CASRN: Chemical Abstracts Service Registry Number

Table E.3.2.2.1-2 presents the VEGA model results for selected PAHs and derivatives. For carcinogenicity potential, the prediction is either a carcinogen or not a carcinogen. The reliability scores are: low, moderate, or good (or based on experimental data). PAHs predicted to be carcinogens are those with good reliability and inside the application domain.

Acenaphthylene has not been classified as a carcinogen and none of the models showed reliable carcinogenicity prediction. Anthracene and 2-methyl-anthracene have not been classified as carcinogens, but the VEGA cancer model results showed one

model with reliable prediction for carcinogenicity for anthracene and 2-methyl-anthracene, as shown in the following table. Anthracene, 9-phenyl and anthracene, 9,10-diphenyl- have not been classified as carcinogens. Two to three VEGA cancer models showed reliable prediction of these anthracenes as carcinogens. Benzo[e]pyrene and benzo[g,h,i]perylene have not been classified as carcinogens, but three VEGA cancer models showed reliable prediction for both chemicals as carcinogens. Pyrene has not been classified as a carcinogen, but two of the cancer prediction models in VEGA showed reliable prediction of pyrene as a carcinogen. Coronene has not been classified as a carcinogen, but three VEGA cancer models showed reliable prediction for coronene as a carcinogen. Fluorene and 7H-benzo[c]fluorene have not been identified as carcinogens. All the VEGA cancer models showed unreliable prediction for fluorene to be a non-carcinogen. Two cancer models showed reliable prediction for 7H-benzo[c]fluorene to be a carcinogen. Fluoranthene has not been identified as a carcinogen, but two VEGA cancer prediction models showed reliable prediction for fluoranthene to be a carcinogen. Phenanthrene, 1-methyl-phenanthrene, 2-methyl-phenanthrene, and 3-methyl-phenanthrene have not been classified as carcinogens. One VEGA cancer model (IRFMN/ISSCAN-CGX) showed reliable prediction for these phenanthrenes to be carcinogens. An additional model (IRFMN/Antares) predicted 1-methyl-phenanthrene to be a carcinogen.

Table E.3.2.2.1-2. VEGA Model Results for Selected Polyaromatic Hydrocarbons and Derivatives

Chemical	Carcinogenicity Potential	CAESAR 2.1.9	ISS 1.0.2	IRFMN/ Antares 1.0.0.	IRFMN/ ISSCAN-CGX 1.0.0.
Acenaphthylene	Prediction	Non-Carcinogen	Non-Carcinogen	Carcinogen	Carcinogen
Acenaphthylene	Reliability	Low	Low	Low	Moderate
Acenaphthylene	AD Index	Outside	Outside	Outside	Could be outside
Anthracene	Prediction	Non-Carcinogen	Carcinogen	Non-Carcinogen	Carcinogen
Anthracene	Reliability	Low	Low	Low	Good
Anthracene	AD Index	Outside	Outside	Outside	Into
Anthracene, 2-methyl	Prediction	Carcinogen	Carcinogen	Possible Non-Carcinogen	Carcinogen
Anthracene, 2-methyl	Reliability	Low	Moderate	Moderate	Good
Anthracene, 2-methyl	AD Index	Outside	Could be outside	Could be outside	Into
Anthracene, 9,10-dimethyl	Prediction	Carcinogen	Carcinogen	Carcinogen	Carcinogen
Anthracene, 9,10-dimethyl	Reliability	Low	moderate	Good	Good

Chemical	Carcinogenicity Potential	CAESAR 2.1.9	ISS 1.0.2	IRFMN/ Antares 1.0.0.	IRFMN/ ISSCAN-CGX 1.0.0.
Anthracene, 9,10-dimethyl	AD Index	Outside	Could be outside	Into	Into
Anthracene, 9-phenyl	Prediction	Carcinogen	Carcinogen[d]	Non-Carcinogen	Carcinogen
Anthracene, 9-phenyl	Reliability	Good	Good	Low	Good
Anthracene, 9-phenyl	AD Index	Into	Into	Outside	Into
Anthracene, 9,10-diphenyl	Prediction	Carcinogen	Carcinogen	Possible Non-Carcinogen	Carcinogen[f]
Anthracene, 9,10-diphenyl	Reliability	Good	Good	Low	Good
Anthracene, 9,10-diphenyl	AD Index	Into	Into	Outside	Into
Benzo[e]pyrene	Prediction	Carcinogen	Carcinogen	Non-Carcinogen	Carcinogen
Benzo[e]pyrene	Reliability	Good	Good	Good	Good
Benzo[e]pyrene	AD Index	Into	Into	Into	Into
Benzo[g,h,i]perylene	Prediction	Carcinogen	Carcinogen	Non-Carcinogen	Carcinogen
Benzo[g,h,i]perylene	Reliability	Good	Good	Good	Good
Benzo[g,h,i]perylene	AD Index	Into	Into	Into	Into
Pyrene	Prediction	Carcinogen	Carcinogen	Possible Non-Carcinogen	Carcinogen
Pyrene	Reliability	Good	Low	Moderate	Good
Pyrene	AD Index	Into	Outside	Could be outside	Into
Coronene	Prediction	Carcinogen	Carcinogen	Possible Non-Carcinogen	Carcinogen
Coronene	Reliability	Good	Good	Moderate	Good
Coronene	AD Index	Into	Into	Could be outside	Into
Fluorene	Prediction	Non-Carcinogen	Non-Carcinogen	Possible Non-Carcinogen	Possible Non-Carcinogen
Fluorene	Reliability	Low	Low	Moderate	Low
Fluorene	AD Index	Outside	Outside	Could be outside	Outside
7H-benzo[c]fluorene	Prediction	Carcinogen	Carcinogen	Possible Non-Carcinogen	Carcinogen

Chemical	Carcinogenicity Potential	CAESAR 2.1.9	ISS 1.0.2	IRFMN/ Antares 1.0.0.	IRFMN/ ISSCAN-CGX 1.0.0.
7H-benzo[c]fluorene	Reliability	Low	Good	Low	Good
7H-benzo[c]fluorene	AD Index	Outside	Into	Outside	Into
Fluoranthene	Prediction	Carcinogen	Carcinogen	Carcinogen	Carcinogen
Fluoranthene	Reliability	Low	Moderate	Good	Good
Fluoranthene	AD Index	Outside	Could be outside	Into	Into
Phenanthrenes	Prediction	Carcinogen	Carcinogen	Possible Non-Carcinogen	Carcinogen
Phenanthrenes	Reliability	Low	Low	Good	Good
Phenanthrenes	AD Index	Into	Outside	Into	Into
Phenanthrene, 1-methyl	Prediction	Carcinogen	Carcinogen	Carcinogen	Carcinogen
Phenanthrene, 1-methyl	Reliability	Low	Moderate	Good	Good
Phenanthrene, 1-methyl	AD Index	Outside	Could be outside	Into	Into
Phenanthrene, 2-methyl	Prediction	Carcinogen	Carcinogen	Possible Non-Carcinogen	Carcinogen
Phenanthrene, 2-methyl	Reliability	Low	Moderate	Moderate	Good
Phenanthrene, 2-methyl	AD Index	Outside	Could be outside	Could be outside	Into
Phenanthrene, 3-methyl	Prediction	Carcinogen	Carcinogen	Possible Non-Carcinogen	Carcinogen
Phenanthrene, 3-methyl	Reliability	Low	Moderate	Moderate	Good
Phenanthrene, 3-methyl	AD Index	Outside	Could be outside	Could be outside	Into

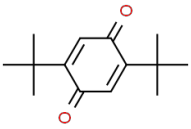
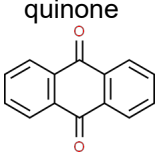
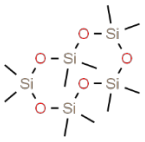
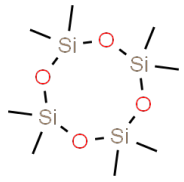
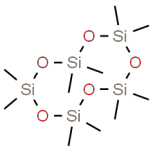
For mutagenicity potential, the mutagenicity prediction is either a mutagen or not a mutagen. Reliability score: low, moderate, good reliability (or based on experimental data).
Applicability domain (AD) of the model: Could be outside = could be outside of the AD, Into = inside the AD, Outside = outside the AD.

E.2.3.10. Benzoquinone and Siloxanes

Table E.3.2.2.1-1 summarizes the Chronic TCs and CSF_{oral} for a benzoquinone and three siloxanes. Inhalation was the only applicable route for the three siloxanes, while multiple routes were applicable for 2,5-di-tert-butyl-1,4-benzoquinone. Decamethyl-cyclopentasiloxane (D5) has established chemical-specific Chronic TC_{inh}. Chronic TCs for the other three chemicals are from structural analog based only on structural similarity as determined by OEHHA. Chronic TC_{oral} from 9,10-anthraquinone is selected

as an analog for the multiple route exposures to the benzoquinone. Chronic TC_{inh} from D5 is selected as an analog for the inhalation exposure to the other two siloxanes.

Table E.3.2.2.1-1. Non-Cancer Chronic Toxicity Criteria for Oral and Inhalation Exposures (Chronic TC_{oral} and Chronic TC_{inh}) for a Benzoquinone and Three Siloxanes

Chemical (Acronym, CASRN), Structure	Effect	Applicable Exposure Route	Analog, Structure	Toxicity Criterion	Endpoint	Year Derived	Reference
Decamethyl-cyclopenta-siloxane (D5, 541-02-6)	Non-cancer	Inhalation	Chemical-Specific	TC_{inh} = 700000 ng per cubic meter	Spleen and liver changes in rats	2007	OEHHA (2007)
2,5-di-tert-Butyl-1,4-benzoquinone (2460-77-7) 	Non-cancer	Oral, dermal or inhalation	9,10-anthra-quinone 	Chronic TC_{oral} = 0.002 mg per kg per day Chronic TC_{inh} = 7000 ng per cubic meter	Liver, kidney, and spleen effects in rats	2011	USEPA PPRTV
Hexamethyl-cyclotrisiloxane (D3, 541-05-9) 	Non-cancer	Inhalation	D5 	TC_{inh} = 700000 ng per cubic meter	Spleen and liver changes in rats	2007	OEHHA (2007)
Octamethyl-cyclotetra-siloxane (D4, 556-67-2) 	Non-cancer	Inhalation	D5 	TC_{inh} = 700000 ng per cubic meter	Spleen and liver changes in rats	2007	OEHHA (2007)

CASRN: Chemical Abstracts Service Registry Number

E.2.3.11. Metals and Metalloids

Assessment of exposure to metals and metalloids is by the oral route only for OEHHA the Study. Although some of the metals or metalloids have been classified as carcinogens, the established lifetime CSF_{inh} are not applicable to the oral route, and were not used as explained below. For each chemical, the summary table contains:

- Chemical (Symbol, CASRN): Name of the metal or metalloid, symbol of the

element

- Effect: non-cancer and cancer
- Compound Tested: the TC established for the listed chemical form
- Endpoint: the toxicity endpoint basis for TC, or the most sensitive endpoint
- Year Derived: the year that the Chronic TC_{oral} was derived
- Reference: the entity which developed the Chronic TC_{oral}

Table E.3.2.2.1-1 summarizes the Chronic TC_{oral} and CSF_{oral} for metals and metalloids. For antimony, antimony trioxide is classified as a 2B International Agency for Research on Cancer (IARC) carcinogen. Antimony trisulfide is classified as a 2B carcinogen by IARC. Antimony and antimony trioxide are not assessed by USEPA IRIS. Antimony trioxide is listed under Proposition 65 for cancer (OEHHA Prop 65), but no CSF or no significant risk level (NSRL) is available. Since the basis of the carcinogenic classification is from inhalation exposure and the target organ is the lung, it is not applicable for oral exposure in this Study. For arsenic, the human CSF_{oral} of 9 (mg per kg per day)$^{-1}$ is calculated from a drinking water unit risk of 0.00027 liter per µg multiplying with 70 kg bodyweight, and 1000 µg per mg conversion factor, and dividing by 2 liter per day water consumption rate. Beryllium is classified as a human carcinogen by IARC and USEPA for lung cancer in workers exposed to beryllium via inhalation. Beryllium is also listed under Proposition 65 for cancer, but the CSF_{inh} for lung cancer from inhalation exposure is not applicable for oral exposure in this Study. Cadmium is considered as a B1 (USEPA IRIS) and class 1 (IARC) carcinogen. It is also listed under Proposition 65 for cancer via inhalation. The CSF_{inh} is derived from occupational inhalation exposure and thus not applicable for oral exposure in this Study. Cobalt is classified as carcinogen by IARC. Cobalt and cobalt compounds are listed under Proposition 65 for cancer. Established CSF_{inh} are for inhalation exposure and finding of lung tumors in rats and mice. These CSF_{inh} are not applicable for oral exposure. Some nickel and nickel compounds are classified as carcinogens by IARC and USEPA, and listed under Proposition 65 for cancer from inhalation to nickel dust resulting in lung cancer in workers. The inhalation CSF_{inh} are not applicable for oral exposure in this Study. USEPA (USEPA IRIS) classified selenium sulfide as a B2 carcinogen (probably human carcinogen, based on sufficient evidence of carcinogenicity in animals). Selenium sulfide given orally resulted in liver tumors in both sexes of F344 rats and female B6C3F1 mice and alveolar/bronchiolar carcinomas or adenomas in female mice. Selenium sulfide is listed under Proposition 65 by the labor code, but not CSF has been developed. Vanadium compounds are classified as a 2B (IARC) carcinogen. Vanadium pentoxide is listed under Proposition 65 for cancer based on a Nation Toxicology Program, NTP, report (OEHHA). In the NTP report (NTP, 2002), rats and mice were exposed to vanadium pentoxide by inhalation for two years. Treated male and female rats showed increased incidences of alveolar/bronchiolar tumors. They also showed non-neoplastic lesions related to the respiratory system (lung, larynx, and nose). A CSF

for vanadium has not been established.

Table E.3.2.2.1-1. Metals and Metalloids: Oral Non-Cancer Chronic Toxicity Criteria and Cancer Slope Factors

Chemical (Symbol)	Effect	Compound tested	Toxicity Criterion	Endpoint	Year Derived	Reference
Aluminum (Al)	Non-cancer	Aluminum lactate	Chronic TC_{oral} = 0.018 mg per kg per day[a]	Increased serum aluminum in human	2001	OEHHA
Antimony (Sb)	Non-cancer	Antimony potassium tartrate	Chronic TC_{oral} = 0.00014 mg per kg per day[b]	Liver nuclear anisokaryosis in rats	2016	OEHHA
Arsenic (As)	Cancer	Arsenic	CSF_{oral} = 9 (mg per kg per day)$^{-1}$[1, c]	Lung and urinary bladder cancers in human	2004	OEHHA
Barium (Ba)	Non-cancer	Barium	Chronic TC_{oral} = 0.07 mg per kg per day[d]	Cardiovascular toxicity in human	2003	OEHHA
Beryllium (Be)	Non-cancer	Beryllium sulfate tetrahydrate	Chronic TC_{oral} = 0.002 mg per kg per day[e]	Ulcerative and inflammatory lesions of the intestine in dogs	2003	OEHHA
Cadmium (Cd)	Non-cancer	Cadmium	Chronic TC_{oral} = 0.00006 mg per kg per day[f]	Kidney toxicity in human	2006	OEHHA
Chromium (Cr)	Non-cancer	Sodium dichromate ($Na_2Cr_2O_7$) (Cr VI)	Chronic TC_{oral} = 0.0002 mg per kg per day[g]	Liver chronic inflammation and fatty changes in rats	2011	OEHHA
Chromium (Cr)	Cancer	Chromium VI	CSF_{oral} = 0.5 (mg per kg per day)$^{-1}$	Intestinal tumors in mice	2011	OEHHA
Cobalt (Co)	Non-cancer	Cobalt	Chronic TC_{oral} = 0.0003 mg per kg per day	Decreased iodine uptake in human	2008	USEPA PPRTV
Copper (Cu)	Non-cancer	Copper	Chronic TC_{oral} = 0.14 mg per kg per day	Gastrointestinal effect in human	2008	OEHHA
Lead (Pb)	Cancer	Lead	CSF_{oral} = 0.0057 (mg per kg per day)$^{-1}$ [h]	Kidney tumors in rats	2009	OEHHA
Manganese (Mn)	Non-cancer	Manganese	Chronic TC_{oral} = 0.14 mg per kg per day	Weakness, fatigue, gait disturbances tremors, and dystonia in human	1995	USEPA IRIS
Molybdenum (Mo)	Non-cancer	Molybdenum	Chronic TC_{oral} = 0.005 mg per kg per day	Increased uric acid level in human	1992	USEPA IRIS

Chemical (Symbol)	Effect	Compound tested	Toxicity Criterion	Endpoint	Year Derived	Reference
Selenium (Se)	Non-cancer	Selenium	Chronic TC_{oral} = 0.005 mg per kg per day[i]	Clinical selenosis (garlic odor, nail effects, hair loss), decreased hemoglobin levels, mottled teeth, skin lesion and central nervous system abnormalities in human	2010	OEHHA
Strontium (Sr)	Non-cancer	Strontium carbonate ($SrCO_3$)	Chronic TC_{oral} = 0.6 mg per kg per day	Rachitic bone in rats	1992	USEPA IRIS
Thallium (Tl)	Non-cancer	Thallium sulfate (Tl_2SO_4)	Chronic TC_{oral} = 0.00001 mg per kg per day[j]	Hair loss and liver damage in rats	2004	OEHHA
Tin (Sn)	Non-cancer	Tin	Chronic TC_{oral} = 0.03 mg per kg per day[k,l]	Hematological effects in rats	2022	OEHHA
Vanadium (V)	Non-cancer	Sodium metavanadate ($NaVO_3$)	Chronic TC_{oral} = 0.00007 mg per kg per day[m]	Kidney pathology in rats	2009	USEPA PPRTV
Zinc (Zn)	Non-cancer	Zinc supplement	Chronic TC_{oral} = 0.3 mg per kg per day[n]	Reduced red blood cell cupper-zinc-superoxide dismutase in human	2005	USEPA IRIS

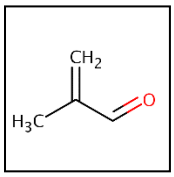
[a] A higher value of 1 mg per kg per day (neurotoxicity in offspring of mice) is available in (ATSDR Toxicological Profiles; USEPA PPRTV).
[b] A higher value of 0.0004 mg per kg per day (longevity, and altered blood glucose and cholesterol levels in rats) is available (USEPA IRIS).
[c] A lower human CSF of 1.5 (mg per kg per day)-1 (skin cancer in human) is available (USEPA IRIS).
[d] A Higher value of 0.2 mg per kg per day (renal lesions in mice) is available (ATSDR Toxicological Profiles; USEPA IRIS).
[e] For beryllium, other sources have the same toxicity criteria (ATSDR Toxicological Profiles; USEPA IRIS).
[f] Higher values of 0.0005 mg per kg per day and 0.001 mg per kg per day, both for kidney toxicity, are available (ATSDR Toxicological Profiles; USEPA IRIS).
[g] Higher values are available for Cr III (1.5 mg per kg per day) and K2CrO4 (Cr VI) (0.003 mg per kg per day)(USEPA IRIS). A value of 0.0009 mg per kg per day for Na2Cr2O7 (Cr VI) is also available (ATSDR Toxicological Profiles).
. [h] There is another cancer potency factor for kidney tumors from OEHHA (2002).
[i] Other sources have the same toxicity criteria (ATSDR Toxicological Profiles; OEHHA Chemicals Library; USEPA IRIS).
[j] Other values of 0.00002 mg per kg per day for insoluble thallium and 0.00001 mg per kg per for soluble thallium, both for hair follicle atrophy, are available (USEPA PPRTV).
[k] An intermediate-duration oral exposure (15 to 364 days) of 0.3 mg per kg per day for inorganic tin is available (ATSDR Toxicological Profiles).
[l] OEHHA applied an uncertainty factor of 10 for extrapolation from subchronic to chronic exposure,

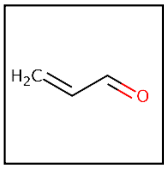
resulting in 0.03 mg per kg per day.
[m] A higher value of 0.002 mg per kg per day (developmental effects in rats) from OEHHA (2000c).
[n] Same value and endpoint available (ATSDR Toxicological Profiles).

E.3. De Novo Derivation of Toxicity Criteria for Tire-Related Chemicals

E.3.1. Methacrolein (CASRN 78-85-3)

E.3.1.1. Introduction



(a)


(b)

Figure E.3.2.2.1-1. Structures of (a) methacrolein (methacrylaldehyde, CASRN 78-85-3) and (b) acrolein (CASRN 107-02-8)

OEHHA derived a chemical-specific screening non-cancer Chronic TC for methacrolein (Figure E.3.2.2.1-1a) because there were no established Chronic TC_{inh} from OEHHA, USEPA, or Agency for Toxic Substances and Disease Registry (ATSDR). Since the database for this compound was limited, the evaluation was supplemented with data for acrolein (Figure E.3.2.2.1-1b).

E.3.1.2. Toxicity of Methacrolein

A literature search on methacrolein conducted in 2020 yielded limited toxicity information. There are Acute Exposure Guideline Levels (AEGLs) from the National Advisory Committee of the National Research Council (NRC, 2015)(Table E.3.2.2.1-1). AEGLs are intended for emergency response to once-in-a-lifetime, or rare, exposure to airborne chemicals. There are three levels from mild to lethal effects: 1 (discomfort, irritation, or certain asymptomatic non-sensory effects which are transient and reversible), 2 (irreversible or other serious, long-lasting adverse health effects, and 3 (life-threatening health effects of death).

Table E.3.2.2.1-1. Acute Exposure Guideline Levels (AEGLs) for Methacrolein by Effect Level (NRC, 2015)

Effect Level	1-Hour AEGL, ppm (mg per cubic meter)	4-Hour AEGL, ppm (mg per cubic meter)	8-Hour AEGL, ppm (mg per cubic meter)
1	0.2 (0.58)	0.2 (0.58)	0.2 (0.58)
2	0.33 (0.96)	0.33 (0.96)	0.33 (0.96)
3	3.5 (10)	2.2 (6.4)	1.4 (4.1)

In the AEGL report, two repeated dose studies sponsored by BG Chemie (Germany) were cited as the basis for the AEGLs (NRC, 2015). In the first study, Sprague-Dawley rats (5 per sex per group) were exposed to methacrolein (5 and 19 parts per million,

ppm) for 6 hours per day, 5 days per week for 2 weeks (Coombs *et al.*, 1992). The 19 ppm group showed clinical signs (closed eyes and hunched position during exposure) and minimal hyperplasia of the respiratory epithelium of the nasal turbinates and laryngeal epithelia were observed. No effect was reported for the 5 ppm group (14.5 mg per cubic meter).

OEHHA reviewed the second study in depth for use in the derivation of TC. Sprague-Dawley rats (10 per sex per group) were exposed to methacrolein (0, 1, 4.9, or 15.3 ppm) for 6 hours per day, 5 days per week for 13 weeks (Coombs *et al.*, 1994). The 4.9 and 15.3 ppm groups showed clinical signs (closed eyes) and salivation (15.3 ppm only, "occasional"). The eye effect was transient as it was observed from exposures 1 to 6 ppm. At 15.3 ppm for both sexes, there were reduced weight gain and food consumption (Table E.3.2.2.1-2 and Table E.3.2.2.1-3). There were no effects on other parameters measured, including hematology and organ weights. Microscopic examination showed changes only for the high dose group and with lesions limited to the nasal and larynx tissues (Table E.3.2.2.1-4 and Table E.3.2.2.1-5). To simplify, Table E.3.2.2.1-4 and Table E.3.2.2.1-5only shows data for Level A section; although the report also provides data for Levels B and C. There were no histological changes with the lungs or other tissues. The no-observed-adverse-effect levels (NOAELs) were 1 ppm for eye irritation and 4.9 ppm for effect in the nasal tissues.

Table E.3.2.2.1-2. Effects on Bodyweight Gain and Food Consumption of Male Rats Exposed to Methacrolein (Dose, in parts per million, ppm) by Inhalation for 13 Weeks (Coombs *et al.*, 1994)

Effect	Dose			
	0	1	4.9	15.3
Mean bodyweight gain in grams	252	257	254	208*
Mean cumulative food consumption in grams	2607	2586	2594	2475

Statistical significance from the report: * p<0.01 compared with control values using Williams' test. No standard deviation given in the report.

Table E.3.2.2.1-3. Effects on Bodyweight Gain and Food Consumption of Female Rats Exposed to Methacrolein (Dose, parts per million, ppm) by Inhalation for 13 Weeks (Coombs *et al.*, 1994)

Effect	Dose			
	0	1	4.9	15.3
Mean bodyweight gain in grams	98	100	103	71*
Mean cumulative food consumption in grams	1811	1795	1832	1654*

Statistical significance from the report: * p<0.01 compared with control values using Williams' test. No

standard deviation given in the report.

Table E.3.2.2.1-4. Effects and Incidences on the Respiratory Tract Tissues of Male Rats Exposed to Methacrolein (Dose, parts per million, ppm) by Inhalation for 13 Weeks (Coombs *et al.*, 1994)

Effect	Dose			
	0	1	4.9	15.3
Nasal atrophic olfactory epithelium (Level A)	0/10**	0/10	0/10	7/10**
Nasal squamous metaplasia of respiratory/olfactory epithelium (Level A)	0/10**	0/10	0/10	5/10*
Nasal erosion/ inflammation of olfactory epithelium (Level A)	0/10	0/10	0/10	1/10
Larynx epithelial hyperplasia ventral aspect (Level A)	0/10**	0/10	0/10	10/10**
Larynx epithelial hyperplasia arytenoid cartilages	0/10**	0/10	0/10	7/10**
Larynx squamous metaplasia of ventral epithelium	0/10**	0/10	0/10	4/10*
Lung aggregation of alveolar macrophages	1/10	0/10	0/10	0/10
Alveolitis	0/10	0/10	0/10	1/10

The incidences are expressed as number of animals with effect over number of total animals examined. The results for the treated groups were compared with the control group using the Fisher Exact test. The dose-response trend was calculated using the Cochran-Armitage trend test, and the p-value is noted at the control incidence. Statistical significance p-values are noted with * for $p<0.05$ and ** for $p<0.01$.

Table E.3.2.2.1-5. Effects and Incidences on the Respiratory Tract Tissues of Female Rats Exposed to Methacrolein (Dose, parts per million, ppm) by Inhalation for 13 Weeks (Coombs *et al.*, 1994)

Effect	Dose			
	0	1	4.9	15.3
Nasal atrophic olfactory epithelium (Level A)	0/10**	0/10	0/10	4/10*
Nasal squamous metaplasia of respiratory/olfactory epithelium (Level A)	0/10	0/10	0/10	4/10*
Nasal erosion/ inflammation of olfactory epithelium (Level A)	0/10	0/10	0/10	0/10
Larynx epithelial hyperplasia ventral aspect (Level A)	0/10**	0/10	0/10	8/10**
Larynx epithelial hyperplasia arytenoid cartilages	0/10**	0/10	0/10	3/10

Effect	Dose			
	0	1	4.9	15.3
Larynx squamous metaplasia of ventral epithelium	0/10**	0/10	0/10	6/10**
Lungs aggregation of alveolar macrophages	0/10	0/10	0/10	1/10
Alveolitis	0/10	0/10	0/10	0/10

The incidences are expressed as number of animals with effect over number of total animals examined. The results for the treated groups were compared with the control group using the Fisher Exact test. The dose-response trend was calculated using the Cochran-Armitage trend test, and the p-value is noted at the control incidence. Statistical significance p-values are noted with * for $p<0.05$ and ** for $p<0.01$.

E.3.1.3. Toxicity of Acrolein

Acrolein is structurally similar to methacrolein, although acrolein is more acutely toxic than methacrolein (Table E.3.2.2.1-1) by the inhalation and oral exposure routes.

Table E.3.2.2.1-1. Acute Lethality of Acrolein (ECHA Acrylaldehyde) and Methacrolein (ECHA Methacrylaldehyde)

Chemical	Inhalation 4-Hour LC_{50}, mg per cubic meter (species)	Oral LD_{50}, mg per kg (species)	Dermal LD_{50}, mg per kg (species)
Acrolein	17-20 (rat)	13.9 (rat)	NA
Methacrolein	500-600 (rat)	140 (rat)	364 (rabbit)

The lethality values are from key studies (highest reliable rating) from European Chemicals Agency (ECHA) registration dossier for methacrolein.
Lethal concentration (LC) or lethal dose (LD); LC_{50} or LD_{50} concentration or dose which resulted in the death of 50% of the animals; and NA: not available

There were established Acute TC_{inh} and Chronic TC_{inh} for acrolein as shown in Table E.3.2.2.1-2. It is an eye irritant and affects the respiratory tract. When reported as ppm, the TCs is converted with 1 ppm = 2.3 mg per cubic meter.

Table E.3.2.2.1-2. Established Acute and Chronic Non-Cancer Toxicity Criteria for Inhalation Exposure to Acrolein (ATSDR Toxicological Profiles; OEHHA Chemicals Library)

Exposure Route and Duration	Toxicity Criterion	Endpoint	Reference
Acute 1-hour Inhalation	Reference Exposure Level = 0.0025 mg per cubic meter	Subjective ocular irritation in human	OEHHA
Acute Inhalation, ≤14 days	Minimal Risk Level = 0.007 mg per cubic meter (0.003 ppm)	Nasal and respiratory effects in human	ATSDR Toxicological Profiles

Exposure Route and Duration	Toxicity Criterion	Endpoint	Reference
Chronic Inhalation	Reference Exposure Level = 0.00035 mg per cubic meter	Respiratory epithelium lesions in in rats	OEHHA

E.3.1.4. Supplemental Information

The Texas Commission on Environmental Quality, TCEQ, report (2014) used the results of Coombs *et al.* (1994) to establish a health-based chronic value for evaluation of ambient air monitoring data (chronic ReV). Both endpoints (eye irritation and lesions in the nasal and olfactory tract) were considered with NOAELs of 1 ppm and 4.9 ppm, respectively. The time adjusted NOAEL for eye irritation remained 1 ppm because it was considered an acute effect. The time adjusted NOAEL for nasal and olfactory tract tissues were time adjusted to 0.875 ppm (4.9 ppm times 6 hours per 24 hours times 5 days per 7 days). Since the effects are considered extrathoracic respiratory tract effects, the regional gas dose ratio (RGDR) is a value of 1, resulting in a NOAEL for human equivalent concentration ($NOAEL_{HEC}$) of 0.875 ppm (2.45 mg per cubic meter). TCEQ applied a total uncertainty factor (UF) of 300, from subchronic to chronic duration UF_S = 3, animal to human extrapolation (interspecies) UF_A = 3, human variability (intraspecies) UF_H = 10, and database deficiency UF_D = 3 to calculate the chronic ReV of 2.9 ppb (0.008 mg per cubic meter or 8.1 µg per cubic meter with 1 ppm = 2.8 mg per cubic meter). There were inadequate data to evaluate the carcinogenic potential of methacrolein.

E.3.1.5. OEHHA Derived Screening Toxicity Criteria for Methacrolein

OEHHA evaluated the NOAELs from the study by Coombs *et al.* (1994), and selected the NOAEL of 4.9 ppm (2.9 mg per cubic meter) for effects on the nasal olfactory and larynx tissues as the basis for the Chronic TC_{inh} (Table E.3.2.2.1-4 and Table E.3.2.2.1-5). The time adjusted NOAEL is 0.876 ppm (2.45 mg per cubic meter), as shown in the TCEQ report (TCEQ, 2014). Since the effects are extrathoracic, the RGDR is a value of 1 and the $NOAEL_{HEC}$ is 2.45 mg per cubic meter. Using the OEHHA guidance for UFs (OEHHA, 2008), the combined UF is 1800 (subchronic to chronic UF_S = $\sqrt{10}$, interspecies UF_A = 6, intraspecies UF_H = 100). The interspecies factor UF_A is 6, derived from a value of 2 for residual toxicokinetic differences in studies of non-primate species using the human equivalent concentration (HEC) approach, and a value of 3 for non-primate studies with no data on toxicodynamic interspecies differences. The intraspecies factor $UF_{H\text{-}k}$ (pharmacokinetics) is 10 to allow for diversity, including infants and children, with no human kinetic data, and the $UF_{H\text{-}d}$ (pharmacodynamics) is 10 for additional susceptibility of children (e.g., exacerbation of asthma from a chemical irritant), for a UF_H of 100. A database UF is not applied because the toxicity of methacrolein appears to be mainly at the upper respiratory tract without systemic effects. The calculated screening Chronic TC_{inh} to methacrolein is 0.0014 mg per cubic meter (or 1400 ng per cubic meter) (Table E.3.2.2.1-1).

Table E.3.2.2.1-1. OEHHA Synthetic Turf Study-Specific Screening Chronic Non-Cancer Toxicity Criterion for Inhalation Exposure to Methacrolein (Chronic TC_{inh}, ng per cubic meter)

Species, Route, and Duration	Toxicity Endpoint	Point of Departure	Uncertainty Factors	Chronic TC_{inh}	Reference
Rat, Inhalation,13 weeks	Effects on nasal olfactory and larynx tissues	$NOAEL_{HEC}$ = 2.45 mg per cubic	$UF_S = \sqrt{10}$ $UF_A = 6$ $UF_H = 100$ Combined UF = 1800	1400	Coombs *et al.* (1994)

Chronic TC_{inh} was calculated as the value for point of departure divided by the value for combined uncertainty factors.
HEC: human equivalent concentration; NOAEL: no-observed-adverse-effect level; UF: uncertainty factor; UF_S: subchronic to chronic extrapolation UF; UF_A: animal to human (interspecies) extrapolation UF; UF_H: human variability (intraspecies) in response

E.3.2. N-(1,3-dimethylbutyl)-N'-phenyl-p-benzenediamine (6PPD, CASRN 793-24-8)

E.3.2.1. Introduction

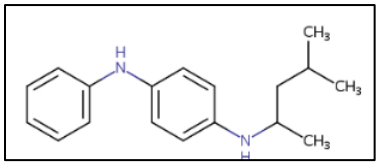


Figure E.3.2.2.1-1. Structure of N-(1,3-dimethylbutyl)-N'-phenyl-p-benzenediamine (6PPD)

OEHHA derived a chemical-specific screening Chronic TC_{oral} for N-(1,3-dimethylbutyl)-N'-phenyl-p-benzenediamine (6PPD, Figure E.3.2.2.1-1) because there were no established TC from OEHHA, USEPA, or ATSDR.

6PPD is degraded in the environment (Organisation for Economic Co-operation and Development Screening Information Data Set, OECD SIDS (2004)). It is rapidly photodegraded in the air. In water, it is also degraded to several degradates which can leach into the groundwater and aquatic environment. One degradates from reaction with ozone, 6PPD-quinone, has been detected in storm-water and is recently implicated in causing acute lethality to coho salmon (Tian *et al.*, 2021).

E.3.2.2. Toxicity of 6PPD

There were no published studies on the disposition of 6PPD in mammals. From the literature search, there was one comprehensive review of 6PPD conducted by Bayer AG (Germany) under the OECD High Production Volume (HPV) Chemicals Programme (OECD SIDS, 2004). The review included environmental fate and detailed description of the toxicology studies with data summaries. The toxicology studies, which include reproductive and chronic toxicity studies, were registrant reports and some were

conducted under OECD guidelines; they have not been published.

E.3.2.2.1. Developmental and Reproductive Toxicity

No developmental effects were reported in developmental toxicity studies conducted with rats or rabbits (Table E.3.2.2.1-1). For reproductive toxicity (Table E.3.2.2.1-1), the lowest NOAEL is 6 mg per kg per day for liver and adrenal effects in parental rats (Table E.3.2.2.1-2 and Table E.3.2.2.1-3 Ref123632261). In this study, Crj:CD(SD) rats (12 per sex per group) were given 6PPD (0, 6, 25, or 100 mg per kg per day) by gavage. Male rats were exposed for 48 days before mating and females were exposed from 14 days before mating to day 3 of lactation. There were no effects on reproduction parameters (organ weight, estrus cycle, copulation, and fertility), and the reproductive toxicity NOAEL was 100 mg per kg per day. Increased vacuolation was noted in male rat livers, but no incidences were provided for the control and lowest dose groups.

Table E.3.2.2.1-1. Developmental and Reproductive Toxicity Studies of 6PPD (OECD SIDS, 2004)

Study Type	Species, Route, Dose, and Duration	Parental NOAEL, mg per kg per day	Parental Effects at LOAEL	Offspring NOAEL, mg per kg per day	Offspring Effects at LOAEL
Reproductive toxicity	Crj:CD(SD) rats, (12 per sex per group), gavage doses: 0, 6, 25, or 100 mg per kg per day, for 48 days in males 14 days before mating until day 3 of lactation in females	6	Liver and adrenal organ absolute and relative weight effect	100	No effect on reproduction or development
Developmental toxicity	Rabbits (animals per group unknown), oral capsules: 0, 10 or 30 mg per kg per day, from gestation days 6 to 18	>30	No adverse effects at the highest dose tested	>30	No adverse effects at the highest dose tested
Developmental toxicity	Female rats (animals per group unknown), gavage dose: 0, 50, 100 or 250 mg per kg per day, from gestation days 6 to 15	50	Maternal: Clinical signs (salivation, diarrhea)	250	No adverse effects

LOAEL: lowest-observed-adverse-effect level; and NOAEL: no-observed-adverse-effect level

Table E.3.2.2.1-2. Effects in Male Rats Exposed to 6PPD by Gavage (Dose, mg per kg per day) in a Reproductive Toxicity Study (OECD SIDS, 2004)

Effect	Dose			
	0	6	25	100
Absolute adrenal weight in grams (Relative to bodyweight in percent)	0.051 (0.010)	0.051 (0.010)	0.053 (0.011)	0.060** (0.012*)

Effect	Dose			
	0	6	25	100
Absolute liver weight in grams (Relative to bodyweight in percent)	16.03 (3.35)	17.70 (3.59)	17.84 (3.69*)	22.15** (4.51**)
Vacuolar liver degeneration incidence (number of animals affected per examined)	NA	NA	2/12	9/11

Statistical significance at *p<0.05, **p<0.01 from OECD SIDS (2005). Only mean values were given in the report.
NA: incidence data not available in report

Table E.3.2.2.1-3. Effects in Female Rats Exposed to 6PPD by Gavage (Dose, mg per kg per day) in a Reproductive Toxicity Study (OECD SIDS, 2004)

Effect	Dose			
	0	6	25	100
Absolute adrenal weight in grams (Relative to bodyweight in percent)	0.073 (0.026)	0.067 (0.023)	0.071 (0.024)	0.079 (0.026)
Absolute liver weight in grams (Relative to bodyweight in percent)	11.14 (3.98)	12.11 (4.19)	13.12 (4.43**)	15.24** (5.16**)

Statistical significance at *p<0.05, **p<0.01 from OECD SIDS (2005). Only mean values were given in the report. NA: incidence data not available in report

E.3.2.2.2. Subchronic and Chronic Toxicity

Summaries of subchronic and chronic toxicity are presented in Table E.3.2.2.2-1 _Ref123632244.

Table E.3.2.2.2-1. Subchronic and Chronic Toxicity Studies of 6PPD (OECD SIDS, 2004)

Study Type	Species, Route, Doses, and Duration	NOAEL, mg per kg per day	Effects at LOAEL
Subchronic (28 days)	Rats (5 per sex per group), gavage dose: 0, 4, 20, or 100 mg per kg per day for 28 days followed by 14 days of recovery	4 for females	Periportal fatty change
Subchronic (13 weeks)	Rat (25 per sex per group), in diet at 0, 15.7, 62.3, or 153.8 mg per kg per day for males and 0, 18.5, 75.0, or 172.2 mg per kg per day for females for 13 weeks	15.7 for males 18.5 for females	Anemia

Study Type	Species, Route, Doses, and Duration	NOAEL, mg per kg per day	Effects at LOAEL
Chronic and carcinogenicity Study 1	Charles River rats (CD outbred) (50 per sex per dose), in diet at 0, 8, 23 or 75 mg per kg per day for 24 months	23	Bodyweight, organ weight, and blood chemistry
Chronic and carcinogenicity Study 2	Rat (no data on strain per sex), in Diet at 0, 2.6 to 3.2, 13.5 to 16.5 or 84.8 to 109.6 mg per kg per day for 2 years	3.2	Bodyweight and food consumption

LOAEL: lowest-observed-adverse-effect level; and NOAEL: no-observed-adverse-effect level.

For chronic exposure, there were two chronic and carcinogenicity studies (Table E.3.2.2.2-1 Ref123632244). The first study (Study 1) is cited in OECD SIDS (2004) as Monsanto Chemical Company undated and Stevens et al. 1981. The European Chemicals Agency (ECHA) database (ECHA N-1,3-dimethylbutyl-N'-phenyl-p-phenylenediamine) cited this as Monsanto Chemical Company 1978. From the OECD SIDS (2004) report, Charles River rats (CD outbred) (50 per sex per dose) were exposed to 6PPD in the diet (0, 100, 300, or 1000 ppm; 0, 8, 23 or 75 mg per kg per day) for 24 months. The survival rate was low for males but was considered comparable with controls (Table E.3.2.2.2-2). At 100 or 300 ppm, there were no effects on organ weights, or gross or microscopic pathology. At 1000 ppm, there were several effects reported; but no data were provided. They included: reduced bodyweight gain, erythrocyte counts, hemoglobin concentration, and hematocrit levels at some interim measurements but not at the end of the study. Increased kidney and spleen weights at terminal sacrifice was reported for females (Table E.3.2.2.2-2). Histopathological results for gross lesions or tissue masses showed no treatment-related effects. Microscopic examination was limited to "the chest and abdominal regions", and from the central nervous system of all high dose and control rats. No lesions were reported only for the high dose group. The NOAEL was 23 mg per kg per day for effects on bodyweight gain, hematology, and organ weights at 75 mg per kg per day.

Table E.3.2.2.2-2. Effects in Charles River Rats Exposed to 6PPD in the Diet (Dose, mg per kg per day) for 2 Years from Monsanto Chemical Company (undated)

Sex, Effect	Dose			
	0	8	23	75
Male Survival rate, percent	24	28	26	28
Female Survival rate, percent	56	52	46	52

Sex, Effect	Dose			
	0	8	23	75
Female Other effects	NR	NR	NR	Effect on bodyweight gain, hematology, and kidney and spleen weight

NR: not reported.

Another chronic toxicity study conducted by the Monsanto Chemical Company in 1993 was cited in the OECD SIDS (2004) report, but no data were provided (Study 2 in Table E.3.2.2.2-1). More details on this study were found in the ECHA online database and this study was conducted under OECD guidelines (ECHA N-1,3-dimethylbutyl-N'-phenyl-p-phenylenediamine). In this study, Sprague-Dawley rats (70 per sex per group, with 20 per sex per group for interim sacrifice) were given 6PPD in the diet (0, 50, 250, or 1500 ppm). The mean 6PPD intakes (male or female) for the study duration were: 0, 2.6, 13.5, and 84.8 mg per kg per days for males and 0, 3.2, 16.5, and 109.5 mg per kg per day for females. The results were presented mainly in the text without group-specific numerical data. There were no differences in survival or early deaths between groups. For non-cancer effects, the significant findings were changes in bodyweight, food consumption, and liver weight (Table E.3.2.2.2-3 and Table E.3.2.2.2-4 _Ref123632332). The effect on hematology was considered slightly (<15 percent change from control) affecting the high dose group of males (at 3, 6 and 12 months) and females (all time points). Platelet counts increased between 8 and 30 percent when measured at 3, 6, 12, and 24 months. Data for individual time points were not included in the review.

There were increased incidences (not statistically significant) of thyroid follicular cell hyperplasia and of carcinoma (male rats) (Table E.3.2.2.2-3 _Ref123632332). ECHA suggested that these thyroid effects were secondary to the liver effects. The ECHA no-observed-effect level (NOEL) was 50 ppm. OEHHA established the NOAEL at 3.2 mg per kg per day and the lowest-observed-adverse-effect level (LOAEL) at 16.5 mg per kg per day for effects on bodyweight and food consumption in the female rats (Table E.3.2.2.2-4).

Table E.3.2.2.2-3. Effects in Male Sprague-Dawley Rats Exposed to 6PPD in the Diet (Dose, mg per kg per day) for 2 Years by Monsanto Chemical Company (1993)

Effect	Dose			
	0	2.6	13.5	84.8
Bodyweight (percent of control)	NA	NA	NA	-9.9%
Food consumption (percent of control)	NA	NA	NA	+5.5%

Effect	Dose			
	0	2.6	13.5	84.8
Liver weight (absolute and relative)	NA	NA	NA	Increased
Liver histopathology	NA	NA	No effect	No effect
Thyroid adenoma (number affected per total examined)	3/70	2/69	3/70	3/69
Thyroid carcinoma (number affected per total examined)	0/70	0/69	2/70	3/69

NA: no data available

Table E.3.2.2.2-4. Effects in Female Sprague-Dawley Rats Exposed to 6PPD in the Diet (Dose, mg per kg per day) for 2 Years by Monsanto Chemical Company (1993)

Effect	Dose			
	0	3.2	16.5	109.5
Mean bodyweight (percent of control)	NA	NA	-5.4%	-18.4%
Food consumption (percent of control)	NA	NA	+4.1%	+17.3%
Liver weight (absolute and relative)	NA	NA	NA	Increased
Thyroid adenoma (number affected per total examined)	0/69	1/70	0/69	1/69
Thyroid carcinoma (number affected per total examined)	1/69	2/70	1/69	1/69

NA: no data available

E.3.2.2.3. Genotoxicity and Carcinogenicity

6PPD is not genotoxic in the studies reviewed in OECD SIDS (2004) (Table E.3.2.2.3-1 Ref123632320). For potential carcinogenicity of 6PPD, there were two lifetime studies with no significant treatment-related tumors were detected (Table E.3.2.2.1-3 Ref123632244). However, the database is limited and inadequate for carcinogenicity assessment.

Table E.3.2.2.3-1. Genotoxicity Studies for 6PPD (OECD SIDS, 2004)

Study	Test System	Results
Bacteria mutation assay (Zeiger *et al.*, 1987)	*Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537 were exposed to 6PPD (0, 0.1 to 200 µg per plate) and ± S9 Aroclor-1254 induced liver.	No induction at non-cytotoxic dose

Study	Test System	Results
Bacterial mutation assay (Rannug *et al.*, 1984)	*Salmonella typhimurium* strains TA 98, TA100, TA1535, TA1537, TA1538 were exposed to 6PPD (µg per plate not specified) and ± S9 activation system	No induction
Chromosome aberration and micronuclei (George and Kuttan, 1996)	Micronuclei test, Swiss albino male mice (5 per group) were given 0, 100, 150 or 200 mg per kg 6PPD by 2 intraperitoneal injections in 24 hours.	No increased micronuclei in the polychromatic or normochromatic erythrocytes in bone marrow cells
Chromosome aberration and micronuclei (George and Kuttan, 1996)	Chromosome aberration, Swiss albino male mice (4 per group) were given 0, 100, or 200 mg per kg 6PPD by 2 intraperitoneal injections in 24 hours.	No induction of chromosomal abnormalities in bone marrow cells

OEHHA conducted QSAR analysis for carcinogenicity potential of 6PPD using (Table E.3.2.2.3-2 Ref123632423). No conclusion regarding the potential carcinogenicity of 6PPD can be made because the predictions for either case are unreliable, ranged from low to moderate reliability and were all outside of the applicability domain. This is likely due to the lack of chemicals with similar structure and carcinogenicity information in the models.

Table E.3.2.2.3-2. Carcinogenicity Prediction for 6PPD Using VEGA QSAR Models

Carcinogenicity Potential	CAESAR 2.1.9	ISS 1.0.2	IRFMN/Antares 1.0.0	IRFMN/ISSCAN -CGX 1.0.0
Prediction	Carcinogen	Non-Carcinogen	Carcinogen	Carcinogen
Reliability	Low	Moderate	Moderate	Low
AD Index	Outside	Outside	Outside	Outside

For carcinogenicity potential, the prediction is either a carcinogen or not a carcinogen. Reliability score: low, moderate, or good (or based on experimental data).
Applicability domain (AD) of the model: Inside= into the AD, Outside= outside of the AD

E.3.2.3. OEHHA Derived Screening Toxicity Criteria for 6PPD

The review of the chronic toxicity of 6PPD relied upon a review conducted by OECD and supplemented with OEHHA review of data summaries for the same studies in the ECHA database (ECHA N-1,3-dimethylbutyl-N'-phenyl-p-phenylenediamine). Overall, OEHHA considered there was sufficient information provided in these reviews to evaluate the chronic and lifetime toxicity of 6PPD and develop a screening Chronic TC_{oral} for non-cancer effect.

The POD is the NOAEL of 3.2 mg per kg per day for effects in the chronic toxicity study conducted by Monsanto Chemical Company, 1993 (Table E.3.2.2.2-3 Ref123632320,

Table E.3.2.2.3-1 _Ref123632494). The combined UF is 1000-fold with animal to human extrapolation UF (UF_A) of 10-fold, human variability UF (UF_H) of 30-fold, and database deficiency UF (UF_D) of √10 for uncertainty associated with the use of summarized data from reviews. The Chronic TC_{oral} is applicable for the dermal and inhalation exposure routes.

Table E.3.2.2.3-1. OEHHA Synthetic Turf Study-Specific Screening Chronic Non-Cancer Toxicity Criteria for Oral Exposure (Chronic TC_{oral}, mg per kg per day) to 6PPD

Species, Route and Duration	Toxicity Endpoint	NOAEL	Uncertainty Factors	Chronic TC_{oral}	Reference
Rat, in diet for 2 years	Effects on bodyweight and food consumption	3.2 mg per kg per day	UF_A = 10 UF_H = 30 UF_D = √10 Combined UF = 1000	0.003	(ECHA)

Chronic TC_{oral} was calculated as the value for NOAEL divided by the value for combined uncertainty factors.
NOAEL: no-observed-adverse-effect level; UF: uncertainty factor; UF_A: animal to human (interspecies) extrapolation UF; UF_H: human variability in response (intraspecies) UF; and UF_D: database deficiency UF.

E.3.3. 1,4-benzenediamine, N,N'-Diphenyl- (DPPD, CASRN 74-31-7)

E.3.3.1. Introduction

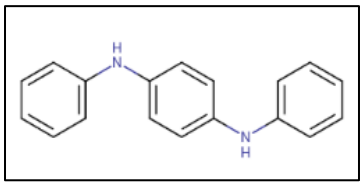


Figure E.3.2.2.3-1. Structure of 1,4-benzenediamine, N,N'-Diphenyl- (DPPD)

OEHHA derived a chemical-specific screening non-cancer DART TC for N,N-diphenyl-benzenediamine (DPPD, Figure E.3.2.2.3-1) after a reassessment of the USEPA screening provisional reference dose (p-RfD) for DPPD (USEPA, 2009b). The main reason was the availability of a well-conducted recent study (Matsumoto *et al.*, 2013). Based on the reproductive effects of DPPD via oral exposure, the chemical is considered a DART (discussed in Section 0E.2.1).

In its 2009 review, the USEPA found the database for DPPD to be too limited to develop p-RfD. Instead, USEPA derived a screening p-RfD based on studies conducted by Draper et al. (1956, 1958 as cited in USEPA (2009b)) with the purpose to determine whether DPPD would ameliorate the adverse reproductive effects of vitamin E deficiency. The screening subchronic and chronic p-RfD was 0.0003 mg per kg per day based on a NOAEL of 0.3 mg per kg per day for increased stillbirths in rats given DPPD at 2.5 mg per kg per day in the diet deficient in vitamin E (during growth and

reproductive period), and a total UF of 1,000. USEPA assigned low confidence to the value because of numerous deficiencies in the toxicity studies.

E.3.3.2. Toxicity of DPPD

OEHHA reviewed the studies described in USEPA (2009b) and conducted a literature search for any additional published studies. The literature search yielded one published report with two studies (Matsumoto *et al.*, 2013). Both studies were conducted under the Organisation for Economic Co-operation and Development (OECD) guidelines.

E.3.3.2.1. Subchronic and Reproductive Toxicity

In the first study of Matsumoto *et al.* (2013), Crl:CD(SD) rats (5 per sex per dose) were given DPPD (0, 100, 300, or 1000 mg per kg per day) by gavage for 28 days. There were no effects on clinical observations, sensory function, motor activity, bodyweight, or blood chemistry. Food consumption was reduced only in the 4th week for the 300 mg per kg per day group and 3rd and 4th weeks of the 1000 mg per kg per day males (Table E.3.3.2.1-1 and Table E.3.3.2.1-2). The only significant effect with serum chemistry was an increase in total bilirubin in male treated groups, about 60 percent higher than the control group. The slight increase in the female treated groups were not statistically significant. The authors showed that the presence of DPPD can interfere with the bilirubin assay. Thus, the significance of this finding is uncertain. Relative and/or absolute organ weighs of the thyroid (male only) and kidneys (female only) were increased only in the 100 mg per kg per day group, but no data were provided. No significant treatment-related changes were observed in histopathology examination. The NOAEL is 100 mg per kg per day for reduction of food consumption in males.

Table E.3.3.2.1-1. Effects in Male Crl:CD(SD) Rats Given DPPD by Gavage (Dose, mg per day) for 28 Days (Matsumoto *et al.*, 2013)

Effect	Dose			
	0	100	300	1000
Food consumption, g per day: Week 3	34±3	36±2	34±2	32±2*
Food consumption, g per day: Week 4	41±4	38±3	35±3*	31±3**
Serum bilirubin, mg per dL	0.33±0.05	0.53±0.05**	0.60±0.10**	0.61±0.09**

Values are mean plus/minus deviation (not specified in the report). Statistical significance from the report using Kruskal-Wallis followed by the Dunnett test: *, $p<0.05$; **, $p<0.01$.

Table E.3.3.2.1-2. Effects in Female Crl:CD(SD) Rats Given DPPD by Gavage (Dose, mg per day) for 28 Days (Matsumoto *et al.*, 2013)

Effect	Dose			
	0	100	300	1000
Food consumption, g per day: Week 3	23±2	24±4	22±4	22±3
Food consumption, g per day: Week 4	24±3	24±5	24±1	23±2
Serum bilirubin, mg per dL	0.26±0.05	0.26±0.01	0.29±0.03	0.29±0.04

Values are mean plus/minus deviation (not specified in the report).

The second study examined the reproductive toxicity of DPPD (Matsumoto *et al.*, 2013). Crl:CD(SD) rats (13 per sex per dose) were exposed to DPPD (0, 8, 150, or 300 mg per kg per day) by gavage. The exposure of the males to DPPD started 14 days before mating (total exposure of 42 days). Female exposure also started 14 days before mating, through mating and gestation, and to day 4 of lactation (total exposure 42 to 46 days). The study NOAEL was 8 mg per kg per day for increased gestation lengths at 150 and 300 mg per kg per day (Table E.3.3.2.1-3). Other reproductive effects showed dose-related decreases in birth indices and number of live pups, but none of these changes achieved statistical significance. Some females in the 300 mg per kg per day treatment group showed clinical signs and pathological/histopathological changes in multiple organs. One female in the 300 mg per kg per day group died on day 23 of pregnancy. The data were not amenable for benchmark dose modeling.

Table E.3.3.2.1-3. Reproductive and Developmental Effects in Pregnant Crl:CD(SD) Rats Exposed to DPPD by Gavage (Dose, mg per kg per day) in a Reproductive Toxicity Study (Matsumoto *et al.*, 2013)

Effect	Dose			
	0	8	150	300
Gestation length, days	22.4±0.5 (13)	22.8±0.5 (12)	23.0±0.0** (12)	23.0±0.4** (11)
Number of pups born	14.8±2.1 (13)	14.8±3.1 (12)	14.3±1.5 (12)	13.7±3.1 (11)
Delivery index	92.5±7.5 (13)	90.7±8.2 (12)	88.3±8.7 (12)	86.7±16.1 (11)
Number of live pups	14.7±2.1 (13)	14.4±2.7 (12)	13.8±1.5 (12)	12.8±4.1 (11)
Birth index	92.1±7.9 (13)	88.4±7.1 (12)	85.8±10.1 (12)	81.2±24.7 (11)
Live birth index	99.5±1.7 (13)	97.7±5.4 (12)	97.2±5.3 (12)	92.0±20.7 (11)

Values are mean ± deviation (not specified in the report). Numbers in parentheses are the number of dams in the group.

Significantly different from the control group (**, p<0.01, Kruskal-Wallis followed by the Dunnett type test), provided in the report.

E.3.3.2.2. Genotoxicity

Genotoxicity tests showed mixed positive and negative results in *in vitro* mutation assays (USEPA, 2009b). No *in vivo* genotoxicity studies were cited.

E.3.3.2.3. Chronic Toxicity and Carcinogenicity

In addition to the vitamin E studies used by the USEPA for the screening p-RfD, there were two chronic toxicity studies, with no tumors found in either study (Table E.3.3.2.3-1). Both studies were conducted with high doses (>100 mg per kg per day) and with other limitations. In the Hasegawa *et al.* (1989) study, measurements (blood chemistry, organ weights, and histology) were done 8 weeks after treatment. This may have affected the results. The study by Bionetics Research Laboratories *et al.* (1968) is a single dose study. USEPA concluded that the available data were inadequate to assess the carcinogenicity potential of DPPD.

Table E.3.3.2.3-1. Chronic Toxicity Studies of DPPD Reviewed by USEPA (2009b)

Species, Route, Dose, and Duration	NOAEL	Effects at LOAEL	Reference
F344 rats (50 per sex per group), in diet of 0, 194, or 857 mg per kg per day in males and 0, 259, or 1024 mg per kg per day in females, for 104 weeks	<194 mg per kg per day	Absolute weight (heart, liver, adrenal, kidney, and testis); relative organ weights; blood chemistry; and calcium deposit in male kidney	Hasegawa *et al.* (1989)
B6C3F1 and B6AKF1 mice (18 per sex per dose), in diet of 0, or 1000 mg per kg per day for 2 years	1000 mg per kg per day	No treatment-related increase in tumor incidences	Bionetics Research Laboratories *et al.* (1968)

LOAEL: lowest-observed-adverse-effect level; NOAEL: no-observed-adverse-effect level.

OEHHA conducted QSAR analysis for carcinogenicity potential of 6PPD using VEGA (Table E.3.3.2.3-2). Models with good prediction reliability and within the applicability domain indicate the DPPD is not a carcinogen.

Table E.3.3.2.3-2. Carcinogenicity Prediction for DPPD Using VEGA QSAR Models

Carcinogenicity Potential	CAESAR 2.1.9	ISS 1.0.2	IRFMN/Antares 1.0.0	IRFMN/ISSCAN-CGX 1.0.0
Prediction	Non-Carcinogen	Non-Carcinogen	Possible Non-Carcinogen	Carcinogen
Reliability	Low	Good	Good	Low
AD Index	Outside	Into	Into	Outside

For carcinogenicity potential, the prediction is either a carcinogen or not a carcinogen. Reliability score: low, moderate, or good (or based on experimental data). Applicability domain (AD) of the model: Into= into the AD, Outside= outside of the AD.

E.3.3.3. OEHHA Derived Screening Toxicity Criteria for DPPD

OEHHA considered the data from Matsumoto *et al.* (2013) subchronic and DART studies (Table E.3.3.2.1-1, Table E.3.3.2.1-2, and Table E.3.3.2.1-3) appropriate for the derivation of a screening chemical-specific TC_{oral} (Table E.3.3.2.3-1). These studies followed governmental testing guidelines using animals fed normal diets (not deficient in vitamin E) and provided comprehensive evaluations of toxicity. The screening TCs from both studies are shown in Table E.3.3.2.3-1. The combined UF consisted of factors for UF_S, UF_A, UF_H, and UF_D. The lower DART TC_{oral} of 0.008 mg per kg per day based on the DART study is selected because it is slightly lower than that (0.01 mg per kg per day) based on the subchronic study, and it has a lower uncertainty value. This DART TC_{oral} is applicable for dermal and inhalation exposure.

Table E.3.3.2.3-1. OEHHA Synthetic Turf Study-Specific Screening Toxicity Criteria for Oral (TC_{oral}) Exposure to DPPD

Species, Route, and Duration	Toxicity Endpoint	NOAEL, mg per kg per day	Uncertainty Factors	Toxicity Criterion	Reference
Rat, gavage for 28 days	Reduced food consumption	100	UF_S = 10 UF_A = 10 UF_H = 30 UF_D = √10 Combined = 10,000	Chronic TC_{oral} = 0.01 mg per kg per day	Matsumoto *et al.*, 2013
Rat, gavage for >40 days	Prolonged gestation period	8	UF_A = 10 UF_H = 30 UF_D = √10 Combined = 1,000	DART TC_{oral} = 0.008 mg per kg per day	Matsumoto *et al.*, 2013

Chronic TC_{oral} was calculated as the NOAEL divided by the value for combined uncertainty factors.

NOAEL: no-observed-adverse-effect level; UF=uncertainty factor; UF_S: subchronic to chronic extrapolation UF; UF_A: animal to human (interspecies) extrapolation UF; UF_H: human variability in response (intraspecies) UF; and UF_D: database deficiency UF.

E.3.4. 1,3-Diphenylguanidine (DPG, CASRN 102-06-7)

E.3.4.1. Introduction

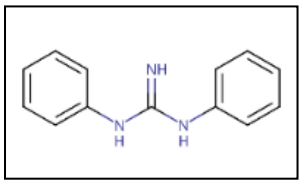


Figure E.3.3.2.3-1. Structure of 1,3-diphenylguanidine (DPG)

There were no established TCs from OEHHA, US EPA, or ATSDR for 1,3-diphenylguanidine (DPG, Figure E.3.3.2.3-1). OEHHA conducted a literature search in August 2021, which yielded a toxicology review by the NTP (1995) and repeated-dosing toxicology studies. Based on the reproductive effects of DPG via oral exposure, the chemical is considered a DART (discussed in Section 0E.3.4.3). OEHHA used these studies to derive a chemical-specific screening DART TC_{oral} for DPG. Other published papers focused on allergic contact dermatitis from the presence of DPG in latex gloves (for example, Dejonckheere *et al.* (2019) and references cited within). The symptoms range from contact urticarial to anaphylactic shock.

E.3.4.2. Pharmacokinetics of DPG

Shah *et al.* (1985) studied the dermal absorption, distribution, and metabolism of ^{14}C-radiolabeled DPG in acetone applied to the clipped back skin of adult female Sprague-Dawley rats. DPG was poorly absorbed through the skin of rats, as only 10 percent of the dose penetrated the skin in 5 days. Once absorbed, DPG was retained in the body (13 percent of the absorbed dose after 5 days) and detected in the skin, muscle, liver, intestine, and fat. The primary route of excretion was via the urine (61 percent of absorbed dose) and less in the feces (27 percent of absorbed dose). Three metabolites were detected in the excreta and/or skin, but they were not identified.

Ioannou and Matthews (1984) studied the disposition of DPG in male Fischer rats after oral and intravenous administrations. DPG was rapidly absorbed and distributed to the tissues by either route. Most of the dose was excreted in the urine and feces within 3 days. Equal amount of radioactivity was found in the urine and feces. Three metabolites were detected in the urine, but they were not identified. Radioactivity was found in the bile, indicating enterohepatic recirculation.

E.3.4.3. Toxicity of DPG

E.3.4.3.1. Subchronic and Chronic Toxicity

There were only oral toxicity studies with DPG. Table E.3.4.3.1-1 is a summary of DPG oral toxicity studies in reviewed by NTP (1995) as well as the 2-week and 13-week feeding studies conducted by NTP. The common endpoints are reduced food consumption and body weight (gain) in rats and mice, and effects on the sperm of mice.

Table E.3.4.3.1-1. Subchronic and Chronic Toxicity Studies of DPG Cited in NTP (1995)

Species, Route, Doses, and Duration	NOAEL	Effects at LOAEL
F344/N Rat (5 per sex per group), in diet at 0, 250, 500, 750, 1500, or 3000 ppm for 2 weeks	500 ppm	Effect on food consumption and mean body weight. No gross lesions.
B6C3F1 Mouse (5 per sex per group), in diet at 0, 250, 500, 750, 1500, or 3000 ppm for 2 weeks	1500 ppm	Effect on body weight
S-D rats (5 per sex per group), in diet at 0, 300, 500, 800, 1500, or 3000 ppm for 2 weeks	<300 ppm	Effects on food consumption, body weight, and body weight gain
S-D rats (15 per sex per group), in diet at 0, 50, 150, or 500 ppm for 2 weeks	150 ppm	Effects on food consumption, body weight, and body weight gain
F344/N Rat (10 per sex per group) in diet at 0, 250, 500, 750, 1500, or 3000 ppm for 13 weeks	<250 ppm	See Table E.3.4.3.1-2 and Table E.3.4.3.1-3
B6C3F1 Mouse (10 per sex per group), in diet at 0, 250, 500, 750, 1500, or 3000 ppm for 13 weeks	500 ppm	Effect on body weight

LOAEL: lowest-observed-adverse-effect level; and NOAEL: no-observed-adverse-effect level.

Since there were no chronic toxicity studies, the effects from the two 13-week dietary studies are relevant for the derivation of DART TC_{oral}. The NOAEL in rats (<17 mg per kg per day) was lower than that for mice (75 mg per kg per day), so the rat study was reviewed in detail. F344/N rats were given DPG (0, 250, 500, 750, 1500 or 3000 ppm) in diet. These doses estimated by NTP were: 0, 17, 32, 50, 100, or 181 mg per kg per day for males, and 0, 17, 32, 49, 95, or 184 mg per kg per day for females. There were excess mortality at the highest dose (3000 ppm); thus the data for this group are not shown in Table E.3.4.3.1-2. All gross and microscopic changes were observed in the 1500 and 3000 ppm groups and they were in multiple organs (bone marrow, thymus, uterus, testes, prostate gland/seminal vesicle, and salivary gland). At 250 ppm (17 mg per kg per day), the effects were increased alkaline phosphatase activity for both male and female rats and bile acids for male rats, while increased alkaline phosphatase activity was seen at 500 ppm (32 mg per kg per day) in female rats (Table E.3.4.3.1-2 and Table E.3.4.3.1-3). In the absence of pathology, these were attributed to lower nutrient and water intake. The NOAEL for these effects (increased alkaline phosphatase and bile acid levels) was <250 ppm (<17 mg per kg per day). Other effects were observed at higher doses (≥ 750 ppm, ≥ 49 mg per kg per day). They included reduced final necropsy body weight; reduced kidney, tests, and thymus relative weights; decreased sperm motility; and increased estrous cycle length.

Table E.3.4.3.1-2. Effects in Male Rats Given DPG in the Diet (Dose, mg per kg per day) for 13 Weeks (NTP, 1995)

Effect	Dose				
	0	17	32	50	100
Mean body weight, g	368	351	350	340	290
Necropsy body weight, g	374±6	362±7	358±5	347±4**	300±7**
Food consumption, g per day	17.3	17.0	16.7	16.4	14.8
Alkaline phosphatase, IU per L	199±7	258±8**	282±7**	291±9**	359±11**
Bile acids, µmol per L	5.1±0.8	12.0±1.9**	13.8±2.4**	11.1±2.5*	22.8±3.0**
Right kidney relative weight, mg organ weight per g body weight	3.52±0.05	3.51±0.04	3.61±0.06	3.41±0.03	3.84±0.08**
Right testis relative weight, mg organ weight per g body weight	4.05±0.06	4.06±0.05	4.20±0.06	4.18±0.08	4.74±0.07**
Thymus relative weight, mg organ weight per g body weight	0.89±0.05	0.91±0.03	0.86±0.04	0.81±0.02	0.72±0.04**
Epididymis sperms activity, percent motility	94.76±1.42	NA	92.30±1.76	87.34±3.75	83.69±2.77**

When indicated, values are mean ± standard error with n =10 for most groups.
Statistical significance: * p<0.05, ** p<0.01 from the report.
NA: not available

Table E.3.4.3.1-3. Effects in Female Rats Given DPG in the Diet (Dose, ppm and mg per kg per day) for 13 Weeks (NTP, 1995)

Effect	Dose				
	0	17	32	49	95
Mean body weight, g	202	195	191	187	174
Necropsy body weight, g	204±4	200±3	195±3	191±3**	177±2**

Effect	Dose				
	0	17	32	49	95
Food consumption, g per day	11.4	11.2	10.6	10.4	9.5
Alkaline phosphatase, IU per L	164±6	185±4**	249±5**	251±11**	254±11**
Bile acids, µmol per L	14.6±2.1	12.3±2.0	18.3±2.8	17.8±3.0	51.9±4.1**
Right kidney relative weight, mg organ weight per g body weight	3.64±0.07	3.66±0.07	3.71±0.08	3.62±0.04	3.89±0.09*
Estrous cycle length, day	4.95±0.05	NA	5.00±0.00	6.00±0.33**	5.67±0.44[a]

[a] Estrous cycle was longer than 12 days or unclear in 1 of 10 animals.
Values are mean ± standard error with n = 10 for most groups.
Statistical significance: * p<0.05, ** p<0.01 from the report.
NA: not available

E.3.4.3.2. Reproductive and Developmental Toxicity

In addition to the effects on sperm and estrous cycle of rats in the 13-week NTP (1995), other studies showed DPG have DART effects. The most complete evaluation of the DART of DPG is the one-generation reproductive toxicity conducted from 2019 to 2020, and reported in 2021 (European Chemistry Agency, ECHA (2021)). This study was conducted following the OECD Guideline 443 (Extended One-Generation Reproductive Toxicity Study). While the study report is not publicly available, the protocol and results are well described in the ECHA registration dossier for DPG (ECHA, 2021). Sprague-Dawley rats were given DPG (0, 5, 15, or 25 mg per kg per day) by gavage. For the parents (P) (24 animals per sex per dose), they were treated with DPG, 2 weeks before mating and during the mating period (up to 14 days). The P females continued to be exposed during gestation and during lactation until days 21 to 23 post parturition (p.p.). Females with no evidence of mating or no delivery were sacrificed 25 to 26 days after the last day of the mating period. The first generation (F1) were divided into two cohorts (1A and 1B, 20 animals per sex per dose). Cohort 1A (both sexes) which were exposed to DPG during *in utero* and via lactation, were given DPG during weaning (day 22 p.p.) to euthanasia (from day 90 p.p. to day 93 p.p. maximum). Cohort 1B were designed to produce an F2 generation. F1 males were treated from weaning for at least 10 weeks before mating, during mating, and after euthanasia of F2 pups. Cohort 1B females were also treated at weaning and mating, with additional exposures during gestation, during lactation, and until sacrifice. The animals were observed daily for morbidity, mortality, and clinical signs. Body weight, food consumption, hematology, clinical chemistry, urinalysis, and thyroid hormone were measured. Effects on the reproductive systems

were monitored for P and Cohort 1A group; they included: estrous cycle and sperm parameters (such as testis weight, sperm count, sperm motility and morphology). Observations on the pups included litter size, survival, clinical signs, and sexual development. Postmortem examinations were performed using both gross necropsy and histopathology.

Data tables were not provided in the ECHA study summary to verify the basis for the report established NOAELs. For general toxicity, the NOAEL was 15 mg per kg per day for clinical signs and mortality. The clinical signs were reported for Cohort 1B at 25 mg per kg per day and included clonic/tonic convulsion, loss of balance and/or staggering gait. The Cohort 1B also had unscheduled deaths at 3 of 10 (control), 0 of 10 (5 mg per kg per day), 2 of 10 (15 mg per kg per day) and 5 of 10 animals (25 mg per kg per day), with the deaths in the 15 and 25 mg per kg per day groups attributed to treatment. For DART, there were no effects on the estrous cycle or sperm parameters. However, there were effects on the reproductive performance with the NOAEL at <5 mg per kg per day for increased gestation periods at all dose levels, reproductive problems (dead litters and delivery difficulties) in females resulting in high pup mortality at birth and early lactation for the 5 mg per kg per day group.

Reproductive effects were also reported in published studies (Bempong and Hall, 1983; Yasuda and Tanimura, 1980). Bempong and Hall (1983) reported studies from two experiments (15 weeks and reproductive toxicity). In the subchronic toxicity study, male hybrid mice (C57BL/J6 x DBA_2) were given DPG in the drinking water ad libitum up to 15 weeks (Table E.3.4.3.2-1). The doses were reported to be 0, 4.0, or 8.0 mg per kg per day; however. the report did not provide information on water consumption or how the doses were calculated under the *ad libitum* scenario. Testicular weight and sperm count were reduced for both dose groups. The report also included histopathological results, which showed the treated mice had more germinal cells than spermatozoa in the epididymis. Effects in the testes were described as irregularly shaped seminiferous tubules, loss of interstitial cells, and “limited numbers” of spermatids and spermatozoa in the tubular lumen. The authors set the LOAEL for this study at 4 mg per kg per day.

Table E.3.4.3.2-1. Sperm and Testicular Effects in Male Mice Given DPG in the Drinking Water (Dose, mg per kg per day)(Bempong and Hall, 1983)

Effect	Dose		
	0	4	8
Testis weight (mg), Week 3	301	285	269
Testis weight (mg), Week 5	289	147* (51%)	131* (45%)
Testis weight (mg), Week 15	293	139* (47%)	112* (38%)
Sperm number (in million per milliliter sample), Week 3	17.62	19.43	16.75

Effect	Dose		
	0	4	8
Sperm number (in million per milliliter sample), Week 5	17.10	12.84 (75%)	9.63 (56%)
Sperm number (in million per milliliter sample), Week 15	17.16	7.45* (43%)	3.19* (19%)

Data for Weeks 1, 7 and 9 were provided in the report, but not included here. Only mean values were provided in the report. There were 8 mice each for Week 3 and 5, and10 mice for Week 15.
Results were noted "*" as "significantly different from controls."
Values in parenthesis are percent of control values.

In the reproductive toxicity portion of Bempong and Hall (1983), male hybrid mice (C57BL/J6 x DBA_2) were given either water or DPG in drinking water (at a final concentration of 0.025 percent acetic acid for both control and treated groups) *ad libitum* at 1 week before mating, and continuously to 16 weeks of mating (90 days of exposure). The doses were stated to be 0, 4.0, or 8.0 mg per kg per day, with no information on water consumption. The mice were mated with untreated females each week, and the females were sacrificed on day 13 of pregnancy. The fertility indices and implants, and number of dead fetuses were noted as significant at $p<0.02$ after 5 weeks of exposure for the treated groups compared to the control. Furthermore, the differences between the 2 treated groups were evident on week 7 (Table E.3.4.3.2-2). However, no details on the statistical analysis were included in the report. The authors stated that treatment-related effects continued to the 16th week of DPG exposure, but they did not provide the data. The combined results of the two Bempong and Hall studies with male mice indicate a LOAEL of 4 mg per kg per day for reproductive toxicity effects.

The NTP (1995) included an assessment of the Bempong and Hall (1983) study. The NTP noted that since water consumption data were not provided, it was unclear whether the effects on the testis and sperm may be associated with reduced water consumption. Additionally, the difference in response compared to the dietary study (NTP, 1995) may be attributed to route of exposure, diet versus drinking water.

Table E.3.4.3.2-2. Fertility Index and Dominant Lethality in Male C57BL/J6 x DBA_2 Mice Given DPG in the Drinking Water (Dose, mg per kg per day) in a Reproductive Toxicity Study (Bempong and Hall, 1983)

Effect	Dose		
	0	4	8
Number of pregnant mice, Week 1	20/20	18/20	12/20
Number of pregnant mice, Week 3	19/20[a]	16/20	14/20
Number of pregnant mice, Week 5	19/20	16/20	11/20

Effect	Dose		
	0	4	8
Number of pregnant mice, Week 7	20/20	17/20	8/20
Implants per female, Week 1	11.8	10.3	9.8
Implants per female, Week 3	12.4	11.1	10.6
Implants per female, Week 5	12.2	10.9	9.3
Implants per female, Week 7	11.3	10.4	9.6
Dead fetuses per pregnancy, Week 1	0.54/0.35	0.44/0.39	0.67/0.33
Dead fetuses per pregnancy, Week 3	0.40/0.35	0.05/0.44	0.64/0.43
Dead fetuses per pregnancy, Week 5	0.53/0.37	0.75/0.69	0.91/0.73
Dead fetuses per pregnancy, Week 7	0.45/0.25	1.35/1.06	2.13/1.88

Incidences for number of pregnant mice was number of pregnant per total number of females mated.
Number of dead fetuses per pregnancy was shown as those from early death/late death.

Yasuda and Tanimura (1980) studied the developmental toxicity in ICR pregnant mice given DPG (0, 0.25, 1, 4, or 10 mg per kg per day) by gavage from gestation days 0 to 18. The only significant effect was reduced implantation (Table E.3.4.3.2-3). The NOAEL for this study was 4 mg per kg per day.

Table E.3.4.3.2-3. Developmental Toxicity in ICR Mice Given DPG by Gavage (Dose, mg per kg per day) (Yasuda and Tanimura, 1980)

Effect	Dose				
	0	0.25	1.0	4.0	10.0
Number of pregnant mice	20	19	20	20	7
Total number of implants	253	229	266	261	79
Average implant per mouse	12.7±0.3	12.1±0.7	13.3±0.5	13.7±0.3	11.3±0.4*

Average implant per mouse ± standard error of the mean.
Significant different from control with * for $p<0.05$, from report.

E.3.4.3.3. Genotoxicity

NTP (1995) reported that the *in vitro* Ames assay showed DPG as weakly mutagenic in the presence of hamster liver S9, and negative in the presence of rat liver S9. DPG was also negative in *in vitro* mammalian cells (HGPRT activity in Chinese hamster V79 cells) with or without liver S9 fraction (NTP, 1995).

E.3.4.3.4. Carcinogenicity

The carcinogenicity of DPG could not be assessed because there was no lifetime carcinogenicity bioassay for DPG. *In vitro* genotoxicity studies showed mostly negative results; although there were no *in vivo* studies. OEHHA conducted QSAR analysis for carcinogenicity potential of DPG using VEGA (Table E.3.4.3.4-1). The models showed mixed results on whether DPG is a carcinogen with moderate to low reliability and mostly outside of the applicability domain. One model (IRFMN/ISSCAN-CGX 1.0.0) predicted DPG to be a carcinogen because of structural similarity to aniline, a carcinogen (Figure E.3.4.3.4-1).

Table E.3.4.3.4-1. Carcinogenicity Predictions for Diphenylguanidine Using VEGA QSAR Models

Carcinogenicity Potential	CAESAR 2.1.9	ISS 1.0.2	IRFMN/Antares 1.0.0.	IRFMN/ISSCAN-CGX 1.0.0.
Prediction	Carcinogen	Non-Carcinogen	Possible Non-Carcinogen	Carcinogen
Reliability	Low	Low	Moderate	Low
AD Index	Outside	Outside	Could be Outside	Outside

For carcinogenicity potential, the prediction is either a carcinogen or not a carcinogen.
The reliability scores are: low, moderate, or good (or based on experimental data).
Applicability domain (AD) of the model: Outside = outside of the AD.

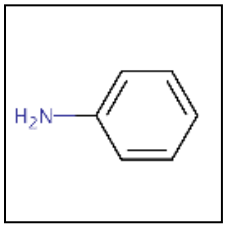


Figure E.3.4.3.4-1. Structure of Aniline (CASRN 62-53-3)

E.3.4.4. OEHHA Derived Screening Toxicity Criteria for DPG

For chronic exposure to DPG, the critical endpoint was reproductive toxicity as shown by several studies (Bempong and Hall, 1983; ECHA, 2021; Yasuda and Tanimura, 1980) with low LOAELs at 4 or 5 mg per kg per day. There were uncertainties in the use of these studies, mainly the limited data available presented in the reports, and the concern expressed by NTP about the dose in the drinking water experiments by Bempong and Hall (1983). Nevertheless, the ECHA study was the strongest study as the basis for OEHHA to develop a screening DART TC_{oral} because it was the most recently conducted study, followed the OECD guideline for the study type, and was conducted under Good Laboratory Practices. The other studies were older studies and are supportive of the LOAEL of 5 mg per kg per day (ECHA, 2021).

Using the LOAEL of 5 mg per kg per day as the POD, OEHHA derived screening DART TC_{oral} is 0.005 mg per kg per day for reproductive toxicity (Table E.3.4.3.4-1). The combined UF was 1,000 with UF_H reduced from 30 (for early life sensitivity) to 10 since the POD is based on an early life effect (fetal death). The other uncertainty factors included: LOAEL to NOAEL extrapolation (UF_L), UF_A, and UF_H. The use of this DART TC_{oral} for dermal exposure might need to be adjusted for dermal absorption, which is 13 percent in rats (Shah *et al.*, 1985).

Table E.3.4.3.4-1. OEHHA Synthetic Turf Study-Specific Screening Chronic Non-Cancer Toxicity Criteria for Oral Exposure (DART TC_{oral}) to DPG (ECHA, 2021) Based on Developmental and/or Reproductive Toxicity (DART)

Species, Route, and Duration	Toxicity Endpoint	LOAEL	Uncertainty Factors	DART TC_{oral}	Reference
Rat, Gavage, and One-generation	Increased gestation periods, dead litters, pup mortality	5 mg per kg per day	UF_L = 10 UF_A = 10 UF_H = 10 Combined UF = 1000	0.005 mg per kg per day	ECHA (2021)

The TC was calculated as the value for point of departure divided by the value for combined uncertainty factors.
LOAEL: lowest-observed-adverse-effect level; UF: uncertainty factor; UF_A: interspecies (animal to human) extrapolation factor; UF_H : intraspecies variability factor; UF_L : LOAEL to NOAEL extrapolation factor.

E.3.5. Benzothiazole (BT, CASRN 95-16-9), 2-Benzothiazolone (2-OHBT, CASRN 934-34-9), and 2-Phenylbenzothiazole (2-PBT, CASRN 883-93-2)

E.3.5.1. Introduction

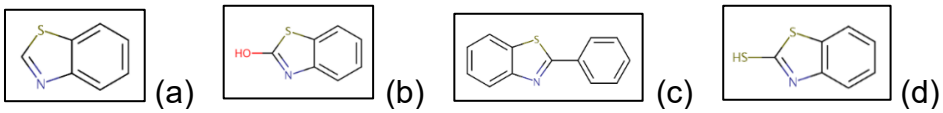


Figure E.3.4.3.4-1. Structures of benzothiazoles (a) benzothiazole (BT), (b) 2-benzothiazolone (2-hydroxybenzothiazole, 2-OHBT), (c) 2-phenylbenzothiazole (2-PBT), and (d) 1,3-benzothiazole-2-thiol (2-mercaptobenzothiazole, 2-MBT; CASRN 149-30-4).

For the three benzothiazoles detected in the synthetic turf study, benzothiazole (BT), benzothiazolone (2-OHBT) and 2-phenylbenzothiazole (2-PBT) (Figure E.3.4.3.4-1a, b, and c), the abbreviations for benzothiazolone and 1,3-benzothiazole-2-thiol (2-OHBT and 2-MBT) are based on their common names used in published toxicity studies. There were no established TCs from OEHHA, USEPA, or ATSDR. OEHHA evaluated the toxicity database of the benzothiazoles and derived a chemical-specific screening non-cancer TC_{oral} for BT, and selected BT as an analog for 2-OHBT and 2-PBT. While

the database was very limited, it was necessary to derive a value because benzothiazoles are common components of crumb rubber.

In 2004, USEPA concluded that the lack of oral and inhalation toxicity data for BT precluded the derivation of p-RfD and provisional reference concentration (p-RfC) values (USEPA, 2004). In addition, USEPA decided not to use the toxicity data of 2-MBT (Figure E.3.4.3.4-1d) as the basis to evaluate the toxicity of BT. 2-MBT is classified as probable carcinogen (Group 2A) by IARC (2016). The rationales were (1) there was no known pathway for the metabolism of BT to 2-MBT, while 2-MBT could be metabolized to BT; and (2) the carcinogenicity of 2-MBT might be due to the mercapto-group, which is absent in BT.

E.3.5.2. Pharmacokinetics and Metabolism of Benzothiazoles

Wilson *et al.* (1991) studied the metabolism of BT in guinea pigs given a dose of 30 mg per kg by intraperitoneal (ip) injection. BT was metabolized with the cleavage of the thiazole ring and five products were identified in the urine: 2-methylmercaptoaniline, 2-methylsulphinylaniline, 2-methylsulphonylaniline, 2-methylsulphinylphenyl-hydroxylamine, and 2-methylsulphonyl-phenylhydroxylamine. The first three metabolites were detected as conjugated and unconjugated forms. The latter two were identified after hydrolysis with sulfatase. A subsequent study showed that aldehyde oxidase may be involved in the cleavage of ring in BT (Fowler *et al.*, 1995).

Asimakopoulos *et al.* (2013) collected human urine samples from seven countries (including the United States) and analyzed them for various chemicals. For benzothiazoles, the results showed detections of BT, 2-morpholin-4-yl-benzothiazole, 2-OHBT, 2-methythiobenzo-thiazole, 2-aminobenzothiazole, and 2-thiocyanomethythiol-benzothiazole. The authors discussed the potential source of 2-OHBT, citing the work of Reddy and Quinn (1997), from bacterial degradation of BT in pond water.

E.3.5.3. Toxicity of Benzothiazoles

There was limited information on the disposition and toxicity of three benzothiazoles (BT, 2-OHBT and 2-PBT). The toxicology database showed only one *in vivo* toxicity study with BT, but none with 2-OHBT or 2-PBT. There were several *in vitro* studies on the comparative toxicity of the benzothiazoles.

E.3.5.3.1. Acute Toxicity

A summary of acute lethality values in laboratory animals is presented in Table E.3.5.3.1-1. Rats and rabbits were more sensitive to the lethality of BT given by the oral and dermal routes, respectively. In a brief report on the rat lethality study, Reddy and Mayhew (1992) gave F-344 rats (5 per sex per group) a single dose of BT at 398, 501, or 631 mg per kg by gavage. Clinical signs were reportedly observed in all dose groups, but no incidences were provided. They included lethargy, ataxia, prostration, lacrimation, and others. While bodyweights were measured for 14 days, the only result presented was a note that bodyweight gain observed for the 398 and 501 mg per kg

group. Deaths were reported within 2 days after dosing; total deaths for each group were: 2/10 for 398 mg per kg, 5/10 for 501 mg per kg, and 10/10 for 631 mg per kg. The mean oral dose which resulted in the death of 50 percent of the animals (LD_{50}) for both sexes was 479 mg per kg. Necropsy of animals found dead showed damages to multiple organs (gastrointestinal tract, liver, lungs, and urinary bladder). The incidences and severity were not in the report.

For nonlethal inhalation exposure, the US Consumer Product Safety Commission (CPSC, 1996) exposed Swiss-Webster mice (4 per group, sex not specified) to BT by whole-body inhalation and measured respiratory rate change. A respiratory depression of 12 percent (RD_{12}) was considered a no-observed-effect level (NOEL). For BT, the RD_{12} and RD_{50} (50 percent depression) were 21 mg per cubic meter and 235 mg per cubic meter, respectively.

Table E.3.5.3.1-1. Acute Toxicity of Benzothiazole in Laboratory Animals

Species and Route	Toxicity Value	Reference
Rat Oral	LD_{50} = 380 mg per kg to 479 mg per kg	a, b, and c
Mouse Oral	LD_{50} = 900 mg per kg	a
Rat Dermal	LD_{50} = 933 mg per kg	c
Rabbit Dermal	LD_{50} = 126 to 200 mg per kg	a and b
Rat Inhalation	4-hour LC_{50} = 5000 mg per cubic meter	b and c
Mouse Inhalation	RD_{12} and RD_{50} = 21 mg per cubic meter and 235 mg per cubic meter	d

References: a = NTP (1997), b = ThermoFisher Scientific (2018), c = DC Fine Chemicals (2021), d = CPSC (1996)
LC_{50}: lethal concentration that resulted in the death of 50% of the treated animals; LD_{50}: lethal dose that resulted in the death of 50% of the treated animals; NA = not available; RD: respiratory depression with RD_{12} at 12% depression and RD_{50} at 50% depression.

E.3.5.3.2. Subchronic Toxicity

There was only one subchronic toxicity study conducted in 1971 by Food and Drug Research Laboratories (FDRL)(FDRL, 1971). The report was submitted by the US Flavor and Extract Manufacturers' Association to the World Health Organization (WHO) as a part of the application for approval of using BT as a food flavoring agent. Rats (15 per sex per group) were given BT (0 or 5.1 mg per kg per day) in the diet for 90 days and observed for clinical signs of toxicity. Food consumption and bodyweights were measured weekly. At 6 and 12 weeks, blood and urine samples were taken for hematology and urinary analyses, respectively. Necropsy was performed on all animals by gross and microscopic examination. No significant differences between the control and treated groups were observed for parameters measured. OEHHA considered the dose of 5.1 mg per kg per day dose as the NOAEL.

E.3.5.3.3. Genotoxicity

BT had been tested only in *in vitro* systems and was considered not genotoxic. USEPA (1989) concluded that BT was not mutagenic to *Salmonella typhimurium* strains (TA 98, 100, 1535, 1537, and 1538) in the presence or absence of S9 fraction.

NTP reported BT as "negative" for genetic toxicity (NTP, 2020). BT was tested with several strains of *S. typhimurium* (TA97, TA98, TA100, TA102, TA104, TA1535, TA1537, and TA1538) in the absence and presence of liver metabolic enzymes from rat, hamster, or mouse liver enzymes (S9 mix).

Ye *et al.* (2014) studied DNA damage by BT and BT-related compounds with (1) SOS/umu test in *S. typhimurium* TA 1535/pSK1002 for change in β-galactosidase activity and induction ratio, and (2) chromosomal damage with *in vitro* micronucleus test with human lung and gastric carcinoma epithelial cells (A549 and MGC-803) measured by number of cells with micronuclei. For both *in vitro* assays, BT was negative with and without S9 liver fraction (Table E.3.5.3.3-1 and Table E.3.5.3.3-2). BT showed similar lethal concentration that resulted in the death of 50% of the treated animals (LC_{50}) values in the three cell systems (Table E.3.5.3.3-3). In comparison, 2-OHBT appeared to be more genotoxic than BT showing positive results in 2 of the 3 *in vitro* assays (Table E.3.5.3.3-1 and Table E.3.5.3.3-2), and more toxic with lower LC_{50} in mg per L (milligram per liter) than BT (Table E.3.5.3.3-3). 2-PBT was not tested in this study. It is worth noting that 2-MBT, a carcinogen, is also negative in the *in vitro* assays in this report.

Table E.3.5.3.3-1. Genotoxicity of Benzothiazole-Related Compounds Using *in vitro* SOS/umu Assay with *Salmonella typhimurium* TA 1535/pSK1002 Strain (Ye *et al.*, 2014)

Chemical Name	No rat liver S-9 fraction	With rat liver S-9 fraction for metabolic activation
Benzothiazole (BT)	-	-
2-Hydroxybenzothiazole (2-OHBT)	+	+
2-Aminobenzothiazole (2-ABT)	-	+
2-Bromobenzothiazole (2-BrBT)	-	-
2-Chlorobenzothiazole (2-CBT)	-	-
2-Fluorobenzothiazole (2-FBT)	-	-
1,3-Benzothiazole-2-thiol (2-Mercaptobenzothiazole, 2-MBT)	-	-
2-Methylbenzothiazole (2-MeBT)	-	-
2-Methythiobenzothiazole (2-MTBT)	-	-

"+": positive result or the chemical is mutagenic and "-": negative result or the chemical is not mutagenic.

Table E.3.5.3.3-2. Genotoxicity of Benzothiazole-related Compounds Using *in vitro* Micronucleus Test with Two Human Cell Types (Ye *et al.*, 2014)

Chemical Name	Gastric epithelial cells (MGC-803)	Lung epithelial cells (A549)
Benzothiazole (BT)	-	-
2-Hydroxybenzothiazole (2-OHBT)	+	-
2-Aminobenzothiazole (2-ABT)	+	-
2-Bromobenzothiazole (2-BrBT)	+	-
2-Chlorobenzothiazole (2-CBT)	+	+
2-Fluorobenzothiazole (2-FBT)	-	-
1,3-Benzothiazole-2-thiol (2-Mercaptobenzothiazole, 2-MBT)	-	-
2-Methylbenzothiazole (2-MeBT)	-	+
2-Methythiobenzothiazole (2-MTBT)	+	-

"+": positive result or the chemical is genotoxic and "-": negative result or the chemical is not genotoxic.

Table E.3.5.3.3-3. Acute Lethality of Benzothiazole-related Compounds Using Bacterial Strain TA1535 and Human Cell Lines (Ye *et al.*, 2014)

Chemical Name	TA1535 LC_{50}, mg per L	Human MGC-803 LC_{50}, mg per L	Human A549 LC_{50}, mg per L
Benzothiazole (BT)	219-182	160	267
2-Hydroxybenzothiazole (2-OHBT)	85-24	135	102
2-Aminobenzothiazole (2-ABT)	123-29	138	138
2-Bromobenzothiazole (2-BrBT)	48-62	103	246
2-Chlorobenzothiazole (2-CBT)	43-79	165	270
2-Fluorobenzothiazole (2-FBT)	100-155	17	40
1,3-Benzothiazole-2-thiol (2-Mercaptobenzothiazole, 2-MBT)	19-20	>100	>100
2-Methylbenzothiazole (2-MeBT)	59-95	146	231
2-Methythiobenzothiazole (2-MTBT)	48-53	197	203

LC_{50}: concentration which kills 50% of the cells. . For TA1535, the values are presented as a range for assays without rat liver S9 fraction and with S9 fraction.

The only positive mutagenic response of BT was that reported by Ginsberg *et al.*

(2011a) citing the result of Kinae *et al.* (1981), which is a one-page report from a meeting proceeding. Kinae et al. collected sea water from an estuary and extracted with organic solvents (diethylether and methanol). The solvent extracts were tested using *S. typhimurium* TA 1527 in the presence or absence of S-9 fractions and found to show mutagenic activity. Gas chromatograph-mass spectrometry analysis of the extracts identified a mixture of compounds, including BT. OEHHA considered the conclusion on BT mutagenicity questionable because BT along with other chemicals in the extracts were tested in the bacterial mutagenicity assay.

E.3.5.3.4. Chronic Toxicity and Carcinogenicity

There was no chronic toxicity or lifetime cancer studies with BT, 2-OHBT, or 2-PBT. BT was nominated in 1987 and 1997 to the NTP for testing of its carcinogenic potential, but no study had been conducted (NTP, 2020). In the 1997 nomination (NTP, 1997), the rationale included its presence in food and environment, in particular leachate from tires; and lack of chronic toxicity data.

To evaluate the carcinogenicity potential of BT, OEHHA (1) used cancer prediction models, (2) compared the metabolism of BT and 2-MBT, (3) compared BT and 2-MBT biological activities, and (4) examined structural similarity. OEHHA concluded that there was insufficient evidence to assess BT as a carcinogen.

(1) Cancer Prediction Models

OEHHA investigated the mutagenicity and carcinogenicity potential of BT using the models in VEGA. The models are based on QSAR, which compare the structure of the chemical of concern with a set of known mutagenic or carcinogenic structure fragments (training set). Each model may have different sets of data and rules for fragment comparison to determine the applicability and thus reliability of the prediction.

BT was predicted as not a mutagen from mutagenicity model (Consensus model 1.0.3) with good reliability and within the applicability domain Table E.3.5.3.4-1). This prediction was consistent with the negative mutagenicity results discussed already (NTP, 2020; USEPA, 1989; Ye *et al.*, 2014). The carcinogenicity model predictions for BT were either could be or are outside of the applicability domain; and thus, were not reliable (Table E.3.5.3.4-2). The lack of reliability was due several factors including: insufficient number of structurally similar carcinogens in the dataset, some fragments of this compound were not in the training set of chemicals in the model, or they were rare fragments in the structure which had not been characterized with respect to carcinogenicity.

Table E.3.5.3.4-1. Mutagenicity Prediction for Benzothiazole Using VEGA QSAR Models

Mutagenicity Potential	CONSENSUS model 1.0.3	CAESAR 2.1.13	SarPy/IRFMN 1.0.7	ISS 1.0.2
Prediction	Non-Mutagen	Non-Mutagen	Non-Mutagen	Non-Mutagen
Reliability	Good	Moderate	Moderate	Low
AD Index	Into	C_Outside	C_Outside	Outside

For mutagenicity potential, the mutagenicity prediction is either a mutagen or not a mutagen. Reliability score: low, moderate, good reliability (or based on experimental data).
Applicability domain (AD) of the model: C_Outside = could be outside of the AD, Into = inside the AD, Outside = outside the AD

Table E.3.5.3.4-2. Mutagenicity and Carcinogenicity Prediction for Benzothiazole Using VEGA QSAR Models

Carcinogenicity Potential	CAESAR 2.1.9	ISS 1.0.2	IRFMN/Antares 1.0.0	IRFMN/ISSCAN-CGX 1.0.0
Prediction	Carcinogen	Non-Carcinogen	Carcinogen	Carcinogen
Reliability	Low	Low	Moderate	Low
AD Index	Outside	Outside	C_Outside	Outside

For carcinogenicity potential, the prediction is either a mutagen or not a mutagen under mutagenicity, and either a carcinogen or not a carcinogen under carcinogenicity. Reliability score: low, moderate, good reliability (or based on experimental data).
Applicability domain (AD) of the model: C_Outside = could be outside of the AD, Outside = outside the AD

(2) BT and 2-MBT Metabolism

The difference in the metabolic pathways between BT and 2-MBT implies that it was unlikely for BT to be metabolized to 2-MBT resulting in carcinogenicity. The USEPA assessment concluded that there was no metabolic pathway for BT to form 2-MBT (USEPA, 2004). Ginsberg *et al.* (2011a) also reported a difference in metabolism of these two compounds. They noted that BT metabolites were ring scission products. In contrast, the ring structure of 2-MBT remained intact, and the metabolites were from conjugation of the sulfhydryl moiety. Whittaker *et al.* (2004) gave rats 2-MBT by gavage and detected unchanged 2-MBT and 2,2'-dibenzothiazole disulfide (Figure E.3.5.3.4-1) as major metabolites. Other metabolites in the urine were MBT-sulfate, MBT-glucuronide, and 2-benzothiazole mercapturic acid. The detection of conjugation products as metabolites of 2-MBT by oral and other routes in laboratory animals had also been reported (el Dareer *et al.*, 1989).

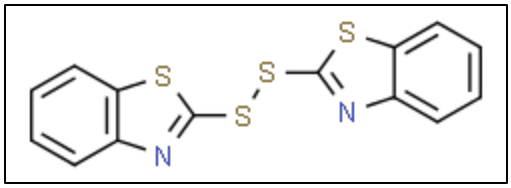


Figure E.3.5.3.4-1. Structure of 2,2'-dibenzothiazole disulfide, a metabolite of 2-MBT

(3) BT and 2-MBT Biological Activities

As described in the genotoxicity section, BT was negative in *in vitro* assays, but had not been tested with *in vivo* assays. In comparison, there was some evidence of 2-MBT causing genotoxicity. Ginsberg *et al.* (2011a) and Whittaker *et al.* (2004) concluded that 2-MBT was negative in *Salmonella* assays and an *in vivo* mouse micronucleus test in two different mouse strains. However, 2-MBT was mutagenic *in vitro* in two different mouse lymphoma assays and was positive in the Chinese hamster ovary chromosomal aberration assay. After these two reports were published, Ye *et al.* (2014) showed that 2-MBT was not genotoxic in two *in vitro* assays (Table E.3.5.3.3-1., Table E.3.5.3.3-2.).

BT and 2-MBT have different effects on receptors and hormone activities (He *et al.*, 2011; Hornung *et al.*, 2015). He *et al.* (2011) compared the effects of BT-related compounds on the aryl hydrocarbon receptor (AhR). The induction of AhR-dependent luciferase reporter gene expression was measured after 4-hour or 24-hour incubation in recombinant mouse hepatoma cells. The stimulated AhR transformation and DNA binding were measured after incubation for 2 hours in guinea pig hepatic cytosol. AhR DNA binding results were estimated from Figure 4 of the report; luciferase activity was expressed as percent of TCDD activity. 2-MBT and 2-OHBT stimulated luciferase activity, and thus were considered AhR agonist, while BT and 2-methylthio-benzothiazole (2-MTBT) were considered weak agonists. The results for BT-related compounds are shown in Table E.3.5.3.4-3. 2-PBT was not tested in this study.

Table E.3.5.3.4-3. Effects of Benzothiazole Compounds (Dose at 10 µM) on Aryl Hydrocarbon Receptor (He *et al.*, 2011)

Chemical	Induction of AhR-Dependent Gene Expression in Mouse Hepatoma Cells	AhR DNA Binding in Guinea Pig Hepatic Cytosol, percent of TCDD activity
Benzothiozole (BT)	$>10^{-4}$ M	15-20%
2-Hydroxybenzothiazole (2-OHBT)	$5x10^{-6}$ M	40-50%
1,3-Benzothiazole-2-thiol (2-Mercaptobenzothiazole, 2-MBT)	10^{-4} M	40-50%
2-Methythiobenzothiazole (2-MTBT)	$>10^{-4}$ M	15-20%

AhR: aryl hydrocarbon receptor; and TCDD: 2,3,7,8-tetrachlorodibenzo-p-dioxin.

Hornung *et al.* (2015) measured the thyroid hormone modulating activity of BT and BT-related compounds using *in vitro*, *ex vivo*, and *in vivo* bioassays at various concentrations. Thyroid peroxidase activity was measured in pig thyroid glands, *in vitro*. Thyroxine release was studied using *Xenopus laevis* thyroid gland explant. Thyroid hormone activities (thyroid gland T3 and T4, blood T4) were measured in *Xenopus laevis* tadpoles. Results using *Xenopus* are not shown here since it is not a mammalian system. Inhibition was calculated as concentration that caused 50 percent reduction in enzyme activity, IC_{50}, values (Table E.3.5.3.4-4). BT, 2-OHBT and 2-MBT inhibited pig thyroid peroxidase activity, with 2-MBT as the most potent inhibitor. 2-PBT was not tested.

Table E.3.5.3.4-4. Effects of Benzothiazole Compounds on Pig Thyroid Peroxidase Activity (Hornung *et al.*, 2015)

Chemical	Concentration (percent of Inhibition)
Benzothiazole (BT)	10 mM (highest dose tested, 40%)
2-Hydroxybenzothiazole (2-OHBT)	600 µM (highest dose tested, 16%)
1,3-Benzothiazole-2-thiol (2-Mercaptobenzothiazole, 2-MBT)	12 µM (50%)
2-Aminobenzothiazole (2-ABT)	1200 µM (50%)
5-Chloro–mercaptobenzothiazole (5-CMBT)	13 µM (50%)
2-Methythiobenzothiazole (2-MTBT)	1 mM (highest dose tested, no effect)

(4) Structural Similarity

The USEPA CompTox Chemistry Dashboard was used to identify structural analogs defined by similarity score of ≥ 0.8 (Table E.3.5.3.4-5, USEPA (2023b)). Higher scores mean closer structural similarity to BT. The analogs with an intact thiazole ring had higher similarity scores (from 0.9 to 0.97). Analogs with modification to the thiazole ring had lower similarity scores, at 0.8; they were 2-methylbenzothiazole, 2-MBT, and 2-chlorobenzothiazole. Neither 2-OHBT nor 2-PBT were included in the similar structure list.

Table E.3.5.3.4-5. Structural Analogs of Benzothiazole from USEPA (2023)

Chemical	Similarity Score
Benzothiazole (BT)	1.0
1,3-Benzothiazole-2-thiol (2-Mercaptobenzothiazole, 2-MBT)	0.8
2-Methylbenzothiazole (2-MeBT)	0.8
2-Chlorobenzothiazole (2-CBT)	0.8

E.3.5.4. Benzothiazole Toxicity Criteria in Published Reports

OEHHA also reviewed published human health risk assessments of BT exposure from activities on synthetic turf fields (Ginsberg *et al.*, 2011b; Pronk *et al.*, 2020; Schneider *et al.*, 2020) and from BT in food (Api *et al.*, 2018). While these sources were not part of the established sources (OEHHA, USEPA, and ATSDR) designated for this project, they provided supplemental toxicity information for comparison. These studies are discussed below and listed in Table E.3.5.4.3-1.

E.3.5.4.1. Acute Toxicity

Ginsberg *et al.* (2011a) and Ginsberg *et al.* (2011b) derived screening values for BT for use in the Connecticut synthetic turf field human health risk assessment. The acute inhalation screening value was 0.11 mg per cubic meter based on the 50 percent reduction in respiration rate in mice exposed to BT by inhalation for 60 minutes (CPSC, 1996) and extrapolated by comparing the toxicity (in terms of the dose for RD_{50}) with that for formaldehyde, and its indoor air value.

E.3.5.4.2. Non-cancer Chronic Toxicity

Ginsberg *et al.* (2011a) derived a chronic inhalation screening value for BT based on the 90-day dietary rat toxicity study (FDRL, 1971), as discussed previously in this assessment). The dose of 5.1 mg per kg per day was considered the oral NOAEL. The calculated value was 0.018 mg per cubic meter, assuming an oral absorption efficiency of 100 percent, an inhalation rate of 20 cubic meters per day, 70 kg bodyweight, and a total UF of 1,000 (Table E.3.5.3.4-4).

In the Dutch synthetic turf risk assessment, Pronk *et al.* (2020) used the derived no-effect levels (DNELs) for 2-MBT to calculate the risk for soccer players exposed to all BT-related compounds detected (including BT and 2-MBT). The assumption was that all BT-related compounds have the same toxicological metabolite. The DNELs of 2-MBT were: 0.31 mg per kg per day (oral), 0.94 mg per kg per day (dermal), and 1.09 mg per cubic meter (inhalation).

In the Europe-wide synthetic turf risk assessment, Schneider *et al.* (2020) calculated reference values for BT were 26 µg per kg per day (oral or dermal) and 44 µg per cubic meter (inhalation). These values were based on the NOAEL of 5.1 mg per kg per day from the 90-day dietary rat study (FDRL, 1971) and European Chemicals Agency (ECHA, 2012) methodology for derivation of DNELs.

Api *et al.* (2018) used a Threshold of Toxicological Concern value of 1.5 µg per kg per day (0.0015 mg per kg per day) for chronic systemic effects for Cramer structural class III chemical determined by Kroes *et al.* (2007). Class III chemicals have the highest toxicity potential.

E.3.5.4.3. Carcinogenicity

The potential carcinogenicity of BT was not assessed in three published studies (Api *et al.*, 2018; Pronk *et al.*, 2020; Schneider *et al.*, 2020). On the other hand, Ginsberg *et al.*

(2011a) considered BT a possible carcinogen and calculated a human CSF_{oral} using the kidney tumor data from the 2-MBT study by NTP (1988). Ginsberg et al. noted that the human CSF_{oral} value was intended as a screening-level assessment of BT carcinogenicity.

Table E.3.5.4.3-1. Published Toxicity Criteria (TC) Used to Evaluate Benzothiazole

Chemical Basis	TC	Toxicity Study or Derivation Method	Reference
Benzothiazole	Acute TC_{inh}: 0.11 mg per cubic meter[a]	Respiratory depression ratio	Ginsberg *et al.* (2011a)
Benzothiazole	Chronic TC_{oral}: 0.005 mg per kg per day Chronic TC_{inh}: 0.018 mg per cubic meter[b]	FDRL (1971)	Ginsberg *et al.* (2011a)
Class III Chemicals	Chronic TC_{oral}: 0.0015 mg per kg per day	Threshold of Toxicological Concern	Api *et al.* (2018)
2-Mercaptothiazole	Chronic TC_{oral}: 0.31 mg per kg per day Chronic TC_{der}: 0.94 mg per kg per day Chronic TC_{inh}: 1.09 mg per cubic meter	Studies cited in Pronk *et al.* (2020)	Pronk *et al.* (2020)
Benzothiazole	Chronic TC_{oral} or TC_{der}: 0.026 mg per kg per day Chronic TC_{inh}: 0.044 mg per cubic meter	FDRL (1971)	Schneider *et al.* (2020)
2-Mercaptothiazole	CSF: 0.000634 (mg per kg per day)$^{-1}$	NTP (1988)	Ginsberg *et al.* (2011a)

[a] Point of Departure = 1.1 mg per cubic meter from the ratio of RD_{50} benzothiazole 235.4 mg per cubic meter. Acute inhalation screening value = 1.1 mg per cubic meter divided by an uncertainty factor of 10 resulting in a value of 0.11 mg per cubic meter.

[b] Chronic inhalation screening value of 0.018 mg per cubic meter is calculated based on a point of departure of 5.1 mg per kg per day converted to 18 mg per cubic meter using 70 kg bodyweight and breathing volume of 20 cubic meters per day. The inhalation level of 18 mg per cubic meter is divided by a total uncertainty factor of 1000-fold, resulting in an inhalation reference value of 0.018 mg per cubic meter.

E.3.5.5. OEHHA Derived Screening Toxicity Criteria for Benzothiazoles

OEHHA derived Chronic TC_{oral} for BT using the NOAEL of 5.1 mg per kg per day from the only repeated-dose toxicity study (FDRL, 1971) (Table E.3.5.4.3-1). Given the limitation of the study and the database, OEHHA applied the maximum uncertainty factor of 10,000 for screening values, resulting in Chronic TC_{oral} of 0.0005 mg per kg per day. This oral value is lower than any of the published chronic oral values shown in

Table E.3.5.4.3-1.

OEHHA selected the Chronic TC_{oral} of BT as an analog to evaluate the oral exposures of 2-OHBT and 2-PBT due to lack of *in vivo* toxicity data for the derivation of new chemical-specific TCs of these two chemicals. Although it might be appropriate to consider using relative molecular weights to extrapolate across these two chemicals, this would affect the TC magnitude by less than a factor of two. The molecular weights for BT, 2-OHBT, and 2-PBT are 135.19, 151.19, and 211.28 grams per mole, respectively. This refinement was not applied in view of the choice to use the maximum UF value of 10,000.

In addition, the Chronic TC_{oral} of 0.0005 mg per kg per day would also be the value to assess the inhalation and dermal exposure of BT, 2-OHBT, and 2-PBT, using route-to-route extrapolation.

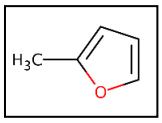
Table E.3.5.4.3-1. OEHHA Synthetic Turf Study-Specific Screening Chronic Non-Cancer Toxicity Criteria for Oral Exposure (Chronic TC_{oral}, mg per kg per day) to Benzothiazole, Benzothiazolone, and 2-Phenylbenzothiazole

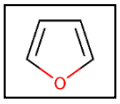
Species, Route, and Duration	Toxicity Endpoint	Point of Departure	Uncertainty Factors	Chronic TC_{oral}	Toxicity Study Reference
Rat Diet 90 days	No effects	5.1 mg per kg per day (NOAEL for Benzothiazole)	Combined UF = 10,000	0.0005	FDRL (1971)

The toxicity criterion was calculated as the value for point of departure divided by the value for combined UF.
NOAEL: no-observed-adverse-effect level; and UF: uncertainty factor

E.3.6. 2-Methylfuran (CASRN 534-22-5)

E.3.6.1. Introduction



(a)


(b)

Figure E.3.5.4.3-1. Structures of (a) 2-methyl furan and (b) furan (CASRN 110-00-9)

OEHHA derived a chemical-specific screening Chronic TC_{oral} for 2-methylfuran (Figure E.3.5.4.3-1a) because there were no established TCs from OEHHA, USEPA, or ATSDR. Since the database for this compound was limited, the evaluation was supplemented with data for furan, a structural analog (Figure E.3.5.4.3-1b).

E.3.6.2. Toxicity of 2-Methyl Furan

There were no chronic studies or lifetime bioassays available to evaluate the non-cancer toxicity or the potential carcinogenicity of 2-methylfuran. There was only one subchronic toxicity study (Gill *et al.*, 2014) available. While this study had limited data,

OEHHA considered it adequate for derivation of a screening toxicity criterion.

In Gill *et al.* (2014), male Fischer 344 rats (10 per group) were given 2-methylfuran (0, 0.4, 1.5, 3.0, 6.0, 12.0, or 25.0 mg per kg per day) by gavage daily for 28 days. The liver was the target organ showing increased relative liver weights at ≥ 3.0 mg per kg per day, and histological changes (necrosis, inflammation, and fibrosis) at ≥ 1.5 mg per kg per day (Table E.3.5.4.3-1). The report stated that histological lesions were observed starting at the 1.5 mg per kg per day dose group, but incidences and severity data were not provided. The authors noted that the liver microscopic lesions found were similar to those they had reported for furan. The NOAEL for liver histopathology was 0.4 mg per kg per day.

Table E.3.5.4.3-1. Liver Effects in Male Rats Exposed to 2-Methylfuran by Gavage (Dose, mg per kg per day) for 28 Days (Gill *et al.*, 2014)

Effect	Dose						
	0	0.4	1.5	3.0	6.0	12.0	25
Liver percent of bodyweight[a]	3.91± 0.11	3.99± 0.13	4.05± 0.14	4.11± 0.19*	4.6± 0.12*	4.98± 0.10*	5.54± 0.14*
Liver histopathology[b]	no	no	yes	yes	yes	yes	yes

[a] Values for liver as percent of bodyweight are mean ± standard deviation. Statistical analysis from the report with * significance at $p<0.05$ using Tukey's multiple comparison tests.
[b] Histopathology data are shown as yes or no, indicating presence or absence, respectively, of lesions.

Nasrullah *et al.* (2014) used *in silico* methods to conduct hazard identification and characterization of food additives. They showed that 2-methylfuran had no structural alert for *S. typhimurium* mutagenicity, and all models (T.E.S.T., VEGA, CAESAR, and SARPy) predicted it to be a non-mutagen. They reported VEGA predicted 2-methylfuran to be non-carcinogenic, while CAESAR predicted it to be carcinogenic.

OEHHA investigated the carcinogenicity potential of 2-methylfuran using the models in VEGA. The models are based on QSAR, which compare the structure of the chemical of concern with a library of carcinogenic structure fragments. Each model may have different sets of data and rules for fragment comparison to determine the applicability and thus reliability of the prediction. Predictions that are inside the applicability domain are more reliable than those outside the applicability domain. For 2-methylfuran, two models (IRFMN/Antares and IRFMN/ISSCAN-CGX) predicted it to be a carcinogen and the prediction was considered reliable (Table E.3.5.4.3-2). This result was based on the structural alert fragment similarity with that for furan, which is a carcinogen. The predications from the other two models (CAESAR and ISS) are not useful because they may not be reliable.

Table E.3.5.4.3-2. Carcinogenicity Prediction for 2-Methyl Furan Using VEGA QSAR Models

Carcinogenicity Potential	CAESAR 2.1.9	ISS 1.0.2	IRFMN/Antares 1.0.0	IRFMN/ISSCAN -CGX 1.0.0
Prediction	Carcinogen	Non-Carcinogen	Carcinogen	Carcinogen
Reliability	Moderate	Low	Good	Good
AD Index	Outside	Outside	Into	Into

For carcinogenicity potential, the prediction is either a carcinogen or not a carcinogen. Reliability score: low, moderate, good or reliability (or based on experimental data).
Applicability domain (AD) of the model: Into = into the AD, Outside = outside of the AD.

E.3.6.3. Toxicity of Furan

USEPA (1987) developed the reference dose for furan using the results from 13-week subchronic toxicity studies of furan in rats and mice. These studies were reported by the NTP, but they were conducted by the Southern Research Institute under contract. This NTP report is not available online.

F344/N Rats and B6C3F$_1$ mice (10 animals per sex per group) were given furan by gavage at (0, 4, 8, 15, 30, or 60 mg per kg per day for rats and mice, and an additional group of 2 mg per kg per day for mice) by gavage 5 days per week for 13 weeks. In treated rats, there were lesions observed in the liver, kidney, thymus, testes, and ovaries of treated rats. The most sensitive endpoint was liver effects found in all treated groups (≥4 mg per kg per day with statistical significance) in rats, and a NOAEL of <4 mg per kg per day. For mice, USEPA established a NOAEL of 2 mg per kg per day for “toxic hepatitis” (USEPA, 1987). This subchronic NOAEL for mice was used by the USEPA in the development of a chronic oral reference dose (RfD); chronic exposure results were not yet available.

In the lifetime exposure of the NTP (1993) study, rats and mice (50 animals per sex per group) were given furan (0, 2, 4, or 8 mg per kg per day for rats, and 0, 8, or 15 mg per kg per day for mice) by gavage for two years. In the rat, the results for liver lesions showed high incidences (some at 90 percent or more) for all treated groups (≥ 2 mg per kg per day with statistical significance). The lesions included chronic inflammation, cyst, fibrosis, hyperplasia and metaplasia of the biliary tract; cytoplasmic vacuolization, degeneration, hyperplasia, and necrosis of hepatocytes; as well as pigmentation in the Kupffer cells. The LOAEL was 2 mg per kg per day. The incidences for some of the effects are shown in Table E.3.5.4.3-1 and Table E.3.5.4.3-2. Liver effects were also reported in the mice of both dose groups with a LOAEL of 8 mg per kg per day.

Table E.3.5.4.3-1. Incidences of Liver Effects in Male Rats Exposed to Furan by Gavage (Dose, mg per kg per day) for 2 Years (NTP, 1993)

Effect	Dose			
	0	2	4	8
Biliary tract: focal hyperplasia	0/50	44/50**	48/50**	49/50**
Biliary tract: metaplasia	0/50	44/50**	48/50**	49/50**
Hepatocyte: degeneration	0/50	33/50**	46/50**	49/50**
Hepatocyte: hyperplasia	0/50	30/50**	46/50**	49/50**
Hepatocyte: necrosis	0/50	32/50**	46/50**	49/50**
Kupffer cell: focal pigmentation	0/50	44/50**	48/50**	49/50**

Incidence is expressed as overall rates with number of animals with lesion/number of animals examined microscopically.
Statistical significance ** at $p<0.01$ by pair-wise comparisons from the report.

Table E.3.5.4.3-2. Incidences of Liver Effects in Female Rats Exposed to Furan by Gavage (Dose, mg per kg per day) for 2 Years (NTP, 1993)

Effect	Dose			
	0	2	4	8
Biliary tract: focal hyperplasia	0/50	49/50**	50/50**	49/50**
Biliary tract: metaplasia	0/50	49/50**	50/50**	49/50**
Hepatocyte: degeneration	0/50	35/50**	49/50**	47/50**
Hepatocyte: hyperplasia	0/50	32/50**	47/50**	46/50**
Hepatocyte: necrosis	0/50	18/50**	46/50**	47/50**
Kupffer cell: focal pigmentation	0/50	49/50**	50/50**	48/50**

Incidence is expressed as overall rates with number of animals with lesion/number of animals examined microscopically.
Statistical significance ** at $p<0.01$ by pair-wise comparisons from the report.

The NTP (1993) concluded that there was clear evidence of carcinogenic activity of furan in both sexes of rats based on bile duct cancers (i.e., cholangiocarcinoma), hepatocellular neoplasms, and mononuclear cell leukemia. There was also clear evidence of carcinogenic activity of furan in mice based on hepatocellular neoplasms and benign pheochromocytoma of the adrenal gland.

The National Center for Toxicological Research (NTCR; Von Tungeln *et al.* (2017)) in collaboration with NTP, conducted a 2-year study with male rats given lower doses of furan to better define the dose-response relationship for liver effects, which were

observed in all treated groups (≥2 mg per kg per day) in the NTP (1993) study. Male F344/N rats were given furan (0, 0.02, 0.044, 0.092, 0.2, 0.44, 0.92, and 2.0 mg per kg per day) by gavage 5 days per week for 2 years. The most sensitive endpoint was cholangiofibrosis with the severity increased with the dose (Table E.3.5.4.3-3). The severity was noted as minimal-to-mild at 0.2 mg per kg per day to moderate-to-marked at 2 mg per kg per day.

Table E.3.5.4.3-3. Incidences of Cholangiofibrosis in Male Rats Exposed to Furan by Gavage, (Dose, mg per kg per day) Von Tungeln *et al.* (2017)

Duration	Dose							
	0	0.014	0.031	0.066	0.14	0.31	0.66	1.4 mg
36 weeks	0/20	0/20	0/20	0/20	0/20	6/20*	17/20**	19/20**
60 weeks	0/20	0/10	0/10	0/10	0/10	10/10**	10/10**	8/10**
2 years	0/149	0/150	0/99	1/100	38/50**	49/49**	47/50**	49/49**

Daily dose is derived from administered dose by adjusting with a 5 days/7 days factor.
Incidence is expressed as the number of animals with lesion/number of animals examined.
Statistical significance *, ** at $p<0.05$, $p<0.01$, respectively, by pair-wise comparisons using a Fisher's Exact test from the report.

Furan has been listed since 1998 as *reasonably anticipated to be a carcinogen* by the NTP in its Report on Carcinogens, based primarily on its 1993 carcinogenicity studies by the oral route wherein it caused liver tumors and other tumor sites in rats and mice of both sexes. These results formed the basis for its listing as a carcinogen under Proposition 65 in 1993. The IARC (1995) classified furan as a Group 2B carcinogen. The USEPA did not assess the carcinogenicity of furan when it conducted its assessment in 1987; the results from the chronic toxicity study by the NTP (1993) were not available when that assessment was conducted. OEHHA has not developed a CSF or NSRL for furan.

E.3.6.4. Comparison of Toxicity

A comparison of the doses for liver effects in rodents given 2-methyl furan and furan is shown in Table E.3.5.4.3-1. Both compounds showed similar LOAELs for liver effects for subchronic exposure (3 to 4 mg per kg per day); although the specific endpoints are different. For furan, the 2-year results of NTP (1993) study showed rats, with lower NOAELs, to be more sensitive than mice. The comparison also showed that the difference between the subchronic and chronic LOAELs and NOAELs for furan is only 2-fold.

Table E.3.5.4.3-1. Comparison of Subchronic and Chronic Toxicity (Liver Lesions) of 2-Methyl Furan and Furan in Rats and Mice

Chemical	Species, Route, Duration	LOAEL mg per kg per day	NOAEL mg per kg per day	Reference
2-Methyl furan	Rat, gavage, 28 days	1.5	0.4	Gill *et al.* (2014)
Furan	Mouse, gavage, 13 weeks	4	2	NTP (1993)
Furan	Rat, gavage, 13 weeks	4	0.4[a]	NTP (1993)
Furan	Mouse, gavage, 2 years	8	0.8[a]	NTP (1993)
Furan	Rat, gavage, 2 years	2	0.2[a]	NTP (1993)
Furan	Male rat, gavage, 2 years	0.2	0.092	Von Tungeln *et al.* (2017)

[a] Preliminary estimated NOAEL determined by OEHHA using a 10-fold uncertainty factor for LOAEL to NOAEL extrapolation.
LOAEL: lowest-observed-adverse-effect level; and NOAEL: no-observed-adverse-effect level.

In addition to furan, OEHHA reviewed the toxicity data for other alkylated furans in the European Food Safety Authority assessment of furans (EFSA, 2017). The alkylated furans evaluated were: 3-methylfuran, 2-ethylfuran, 3-ethylfuran, and 3-pentyfuran. All studies were conducted by intraperitoneal (ip) injection, except those for 3-methyfuran which also included inhalation and gavage administrations. With 3-methylfuran, the studies conducted by ip injections or by 1-hour inhalation exposures were not considered relevant by OEHHA to inform the repeated inhalation toxicity of the chemical of concern, 2-methylfuran. There was one subchronic inhalation toxicity study (344 µmol per L, 2-hours daily over 10 weeks) with hamsters, but no pulmonary effects were reported. There were no repeated-dose inhalation toxicity studies with rodents. There were two gavage toxicity studies with rats exposed to 3-methylfuran. Liver lesions were reported in rats given 3-methylfuran after subchronic exposure of either 28 days daily exposure (Gill *et al.*, 2014) or 90 days of 5 days per week exposure (cited as Gill et al. 2017 in preparation in the EFSA report). In the EFSA report, the NOAEL for histological changes in the liver were 0.3 mg per kg per day (LOAEL was 1.5 mg per kg per day) from the 28-day study, and 0.075 mg per kg per day (LOAEL was 0.25 mg per kg per day) for the 90-day study.

E.3.6.5. OEHHA Derived Screening Toxicity Criteria for 2-Methyl Furan

E.3.6.5.1. Noncancer Toxicity Criteria

OEHHA derived a Chronic TC_{oral} for 2-methylfuran using the Gill *et al.* (2014) data with a subchronic NOAEL of 0.4 mg per kg per day via gavage (Table E.3.5.4.3-1), or daily dose of 0.3 mg per kg per day adjusted for 7 days of dosing (5 days per 7 days) (Table E.3.6.5.1-1). The Chronic TC_{oral} was 0.0001 mg per kg per day using a combined UF of

3,000 (UF_S = √10, UF_A = 10, UF_H = 30, and UF_D = √10). A UF_S of √10 was applied because there was only a factor of 2 difference between subchronic and chronic NOAELs for furan (Table E.3.5.4.3-1). This Chronic TC_{oral} was to be applied for inhalation exposure, using route-to-route extrapolation.

Table E.3.6.5.1-1. OEHHA Synthetic Turf Study-Specifc Screening Chronic Toxicity Criterion for Oral Exposure (Chronic TC_{oral}, mg per kg per day) to 2-Methlyl Furan

Species, Route, Duration	Toxicity Endpoint	Point of Departure	Uncertainty Factors	Chronic TC_{oral}	Reference
Rat, Gavage, 28 days	Liver lesions	0.3 mg per kg per day (NOAEL)	UF_S = √10 UF_A = 10 UF_H = 30 UF_D = √10 Combined UF = 3000	0.0001	Gill *et al.* (2014)

The toxicity criterion was calculated as the value for point of departure divided by the value for combined uncertainty factors. .
NOAEL: no-observed-adverse-effect level; UF; uncertainty factor; UF_S: subchronic to chronic extrapolation UF; UF_A: animal to human (interspecies) extrapolation UF; UF_H: human variability in response (intraspecies) UF; and UF_D: database deficiency UF.

As a comparison, OEHHA also calculated a screening value for furan using the NOAELs listed in Table E.3.5.4.3-1 based on the NTP (1993) and Von Tungeln *et al.* (2017) chronic toxicity data for rats (Table E.3.6.5.1-2). The Chronic TC_{oral} would be 0.0005 mg per kg per day and 0.0002 mg per kg per day, respectively. Both of these screening values derived by OEHHA for furan are lower than the USEPA oral RfD of 0.001 mg per kg per day for furan based on the subchronic toxicity data of the NTP (1993).

Table E.3.6.5.1-2. OEHHA Screening Chronic Non-Cancer Toxicity Criteria for Oral Exposure (Chronic TC_{oral}) and the USEPA Oral Reference Dose (oral RfD) for Furan (USEPA, 1993) Based on Liver Lesions

Species, Route, and Duration	Point of Departure[a], mg per kg per day	Uncertainty Factors	Toxicity Criteria	Reference
Rat, Gavage, 2 years	1.4	UF_L = 10 UF_A = 10 UF_H = 30 Combined = 3000	Chronic TC_{oral} = 0.0005 mg per kg per day	NTP (1993)
Rat, Gavage, 2 years	0.066	UF_A = 10 UF_H = 30 Combined = 300	Chronic TC_{oral} = 0.0002 mg per kg per day	Von Tungeln *et al.* (2017)
Rat, Gavage, 13 weeks	1.4	UF_S = 10 UF_A = 10 UF_H = 10 Combined = 1000	USEPA RfD = 0.001 mg per kg per day (USEPA, 1993)	NTP (1993)

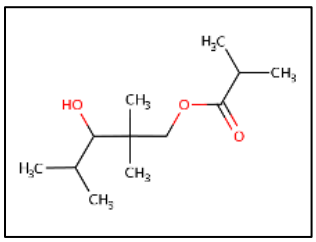
[a] For the point of departure, the administered dose was adjusted with a 5 day over 7 day factor to derive the daily dose.
[b] The toxicity criterion was calculated as the value for point of departure as daily dose divided by the value for combined uncertainty factors.
LOAEL: lowest-observed-adverse-effect level; NOAEL: no-observed-adverse-effect level; UF: uncertainty factor; UF_L: LOAEL to NOAEL extrapolation; UF_S: subchronic to chronic extrapolation UF; UF_A: animal to human (interspecies) extrapolation UF; and UF_H: human variability in response (intraspecies) UF.

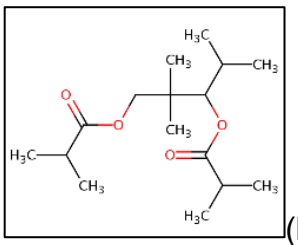
E.3.6.5.2. Cancer Toxicity Criteria

2-Methyfuran has been predicted to be a carcinogen by structure-activity relationship models because of its structural similarity to furan (Table E.3.5.4.3-2). However, OEHHA could not assess the carcinogenicity of 2-methylfuran quantitatively due to lack of human or animal bioassay data from lifetime exposure.

E.3.7. 2,2,4-Trimethyl-1,3-pentanediol monoisobutyrate (Texanol, CASRN 25265-77-4) and 2,2,4-Trimethyl-1,3-pentanediol diisobutyrate (TXIB, CASRN 6846-50-0)

E.3.7.1. Introduction



(a)


(b)

Figure E.3.6.5.2-1. Structures of (a) 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate (Texanol) and (b) 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB)

OEHHA evaluated the toxicology data for 2,2,4-trimethyl-1,3-pentanediol monoisobutyrate (Texanol, Figure E.3.6.5.2-1a) and 2,2,4-trimethyl-1,3-pentanediol diisobutyrate (TXIB) (Figure E.3.6.5.2-1b) because there were no established TCs from OEHHA, USEPA, or ATSDR for these compounds. Texanol has been detected as a metabolite in rats given TXIB (Eastman, 2007). OEHHA derived a chemical-specific screening Chronic TC_{oral} for TXIB because of an adequate toxicity database. This value is to be used as an analog for Texanol, for which the database was too limited.

E.3.7.2. Toxicology of Texanol

A report from the OECD SIDS (1994) on Texanol contained two repeated dose toxicology studies (Faber and Hosenfeld, 1992; O'Donoghue, 1984) and they are presented in Table E.3.6.5.2-1. The studies were noted in the report to have been conducted following OECD guidelines with Good Laboratory Practice (GLP).

Table E.3.6.5.2-1. Toxicity Studies for Texanol Reviewed (OECD SIDS, 1994)

Study	Species, Route, Doses, Duration	NOAEL	Effects at LOAEL
Reproductive Toxicity (Faber and Hosenfeld, 1992)	Sprague-Dawley rat, Gavage dose: 0, 100, 300, or 1000 mg per kg per day Male: 51 days Female: premating, mating, pregnancy, and lactation	100 mg per kg per day	Enlarged hepatocytes, and accumulation of hyaline droplets in kidney in males only. No effect on reproduction.
Short-term (O'Donoghue, 1984)	Sprague-Dawley rat, Gavage dose: 0, 100, or 1000 mg per kg per day, for 11 treatments over 15 days	1000 mg per kg per day	Effect on liver weight, hyaline droplets in kidney of males only.

LOAEL: lowest-observed-adverse-effect level; and NOAEL: no-observed-adverse-effect level.

There were no lifetime carcinogenicity studies on Texanol. Texanol is not genotoxic in two genotoxicity studies: (1) Ames' assay using *Salmonella typhimurium* strains TA 1535, 1537, 1538, 98 and 100; and (2) Micronucleus test with Swiss CD-1 mice (OECD SIDS, 1994). OEHHA used carcinogenicity models in VEGA predict if Texanol is a potential carcinogen (Table E.3.6.5.2-2). The predictions are based on structure-activity relationships, which compare the structure of the chemical of concern with a set of carcinogenic structure fragments (training set). Each model may have different sets of data and rules for fragment comparison to determine the applicability and thus reliability of the prediction. For Texanol, the structural alert is the substituted n-alkylcarboxylic acid. Two of the carcinogenicity models predict Texanol to be a carcinogen. However, these predictions are outside of the applicability domain and thus are not reliable because there was a limited number of similar compounds with known experimental results in the training set.

Table E.3.6.5.2-2. Carcinogenicity Prediction for Texanol Using VEGA QSAR models

Carcinogenicity Potential	CAESAR 2.1.9	ISS 1.0.2	IRFMN/Antares1.0.0	IRFMN/ISSCAN-CGX 1.0.0
Prediction	Non-carcinogen	Carcinogen	Possible Non-carcinogen	Carcinogen
Reliability	Moderate	Moderate	Moderate	Moderate
AD Index	Outside	C_Outside	C_Outside	C_Outside

For carcinogenicity potential, the prediction is either a carcinogen or not a carcinogen. Reliability score: low, moderate, or good reliability (or based on experimental data).
Applicability domain (AD) of the model: C_Outside = could be outside of the AD, Out = outside the AD.

The USEPA CompTox Chemicals Dashboard showed eight POD records for Texanol with the lowest NOAEL of 750 mg per kg per day in rats after oral exposure, as reported in the ECHA IUCLID database.

E.3.7.3. Toxicology of TXIB

A literature search yielded one toxicology review by Eastman (2007). Table E.3.6.5.2-1 shows the repeated dose studies of TXIB cited in Eastman (2007). The NOAEL was 30 mg per kg per day for liver effects at 150 mg per kg per day from a DART study. Most of the studies have not been published.

Table E.3.6.5.2-1. Toxicity Studies for TXIB Reviewed in Eastman (2007)

Study	Species, Route, Doses, and Duration	NOAEL	Effects at LOAEL
Repeat Dose (Astill *et al.*, 1972)	Dogs (Beagle), Diet dose: 0.1, 0.35, or 1% (w/w) for 90 days	1%	No adverse effects at any dose level
Repeat Dose (Unpublished)	Rats (Crl:CD(SD)), Diet dose: 30, 150, or 750 mg per kg per day for 90 days	150 mg per kg per day	Chronic progressive nephropathy in males
Repeat Dose (Astill *et al.*, 1972)	Rats (Albino, Holtzman), Diet dose: 0, 0.1, 1% (772 mg per kg per day) for 100 days	772 mg per kg per day	No adverse effects at any dose level
Reproductive and Developmental Toxicity (Unpublished)	Rats (unspecified), Gavage dose: 0, 30, 150, or 750 mg per kg per day Pre-mating, mating. Females exposed also at gestation to lactation	30 mg per kg per day	Effect on liver weight in males. No developmental toxicity at any dose

Study	Species, Route, Doses, and Duration	NOAEL	Effects at LOAEL
Reproductive and Developmental Toxicity (Unpublished)	Male Rats (Sprague-Dawley), Diet dose: 0, 91, 276, or 905 mg per kg per day Premating and mating	276 mg per kg per day	Effect on sperms. No developmental toxicity at any dose

LOAEL: lowest observed-adverse-effect level and NOAEL: no-observed-adverse-effect level.

The USEPA CompTox Chemicals Dashboard (USEPA, 2023b) showed the lowest oral POD of 30 mg per kg per day for TXIB reproductive developmental effects in rats after oral exposure. There were no inhalation POD values. This is consistent with the information in Table E.3.6.5.2-1 where 30 mg per kg per day is the lowest NOAEL.

As with Texanol, the carcinogenicity of TXIB also cannot be assessed due to the lack of lifetime toxicity studies. TXIB is negative in genotoxicity studies. *In vitro* mutagenicity studies using the Ames assay, hypoxanthine-guanine phosphoribosyltransferase (HGPRT) activity in Chinese Hamster Ovary (CHO) cells and chromosomal aberration studies with CHO cells showed negative genotoxicity for TXIB (Eastman, 2007). The carcinogenicity predictions for TXIB from the VEGA models are outside of the applicability domain and thus are not reliable (Table E.3.6.5.2-2). Thus, an assessment on the carcinogenicity of TXIB is also not conducted.

Table E.3.6.5.2-2. Carcinogenicity Prediction for TXIB Using VEGA QSAR Models

Carcinogenicity Potential	CAESAR 2.1.9	ISS 1.0.2	IRFMN/Antares1.0.0	IRFMN/ISSCAN-CGX 1.0.0
Prediction	Non-carcinogen	Carcinogen	Possible Non-carcinogen	Carcinogen
Reliability	Low	Moderate	Moderate	Moderate
AD Index	Outside	C_Outside	C_Outside	C_Outside

For carcinogenicity potential, the prediction is either a carcinogen or not a carcinogen. Reliability score: low, moderate, or good reliability (or based on experimental data).
Applicability domain (AD) of the model: C_Outside = could be out of the AD, Outside = outside the AD.

E.3.7.4. OEHHA Derived Screening Toxicity Criterion for Texanol and TXIB

OEHHA derived a Chronic TC_{oral} for Texanol using the results from TXIB (Table E.3.6.5.2-1). While Texanol appeared to be less toxic than TXIB, the toxicity database for Texanol is limited (Table E.3.6.5.2-1). This value is applicable for both Texanol and TXIB, and is applicable for inhalation exposure using route-to-route extrapolation.

The lowest POD was 30 mg per kg per day of TXIB for increased liver weight from a reproductive toxicity study in rats reviewed by Eastman (2007) (Table E.3.6.5.2-1). For uncertainties associated with this POD, the uncertainty factors were: UF_S of because the male rat exposure was only 44 days or 6 percent of the lifetime, UF_A of 10, UF_H of

30, and UF_D of 3. These would lead to a combined UF of 10,000, resulting in a Chronic TC_{oral} of 0.003 mg per kg per day. Although it might be appropriate to consider using relative molecular weight to extrapolate across chemicals, this would affect the Chronic TC_{oral} magnitude by only a factor of 1.3, based on the molecular weight difference of the two compounds.

Table E.3.6.5.2-1. OEHHA Synthetic Turf Study-Specific Screening Chronic Non-Cancer Toxicity Criteria for Oral Exposure (Chronic TC_{oral}) to Texanol and TXIB

Species, Route, and Duration	Toxicity Endpoint	Point of Departure	Uncertainty Factors	Chronic TC_{oral}	Reference
Rat, 44 days, gavage	Increased relative liver weight	30 mg per kg per day (NOAEL for TXIB)	$UF_S = 10$ $UF_A = 10$ $UF_H = 30$ $UF_D = \sqrt{10}$ Combined UF = 10000	0.003 mg per kg per day	Eastman, 2007

The Chronic TC_{oral} was calculated as the value for NOAEL divided by the value for combined UF. NOAEL: no-observed-adverse-effect level; U: uncertainty factor; UF_S: subchronic to chronic extrapolation UF; UF_A: animal to human (interspecies) extrapolation UF; UF_H: human variability in response (intraspecies) UF; and UF_D: database deficiency UF.

E.3.8. Methyl Isobutyl Ketone (MIBK, CASRN 108-10-1)

E.3.8.1. Introduction

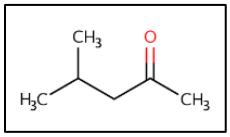


Figure E.3.6.5.2-1. Structure of methyl isobutyl ketone (MIBK)

OEHHA reassessed the established Chronic TC_{inh} and developed chemical-specific screening Chronic TC_{inh} and human CSF_{inh} for methyl isobutyl ketone (MIBK, Figure E.3.6.5.2-1).

For human exposure to MIBK in the air above synthetic turf fields, OEHHA determined that TCs for the following effects and duration for inhalation exposure are needed:

1. Chronic non-cancer: There were established Chronic TC_{oral} (OEHHA, 1999) and Chronic TC_{inh} (USEPA, 2003) for MIBK. However, both values need to be reassessed because, after their releases, significant findings in a NTP inhalation chronic/carcinogenicity study (NTP, 2007) became available.
2. Cancer potency: MIBK is listed under Proposition 65 for cancer under the Labor Code because of IARC's determination (OEHHA, 2011a). IARC (2013) classified MIBK as possibly carcinogenic to humans (Group 2B) based on the finding of liver and kidney tumors from the NTP (2007) study. OEHHA has not yet

developed a CSF or a NSRL for MIBK.

E.3.8.2. Pharmacokinetics of MIBK

IARC (2013) reviewed the pharmacokinetics of MIBK, which also included a physiologically-based pharmacokinetic (PBPK) model. MIBK is rapidly absorbed, distributed, and metabolized following oral and inhalation routes of exposure. The available metabolism data are from experimental animals exposed to MIBK by the oral or inhalation route. With inhalation in rats, the hydroxylation of MIBK resulted in the detection of 4-hydroxymethyl isobutyl ketone and 4-methyl-2-pentanol in the plasma, liver, and lung, in addition to the parent compound. With oral exposure in rats, only the parent and 4-hydroxymethyl isobutyl ketone were detected in the tissues. The metabolism was via alcohol dehydrogenase and cytochrome P450 mono-oxygenases. Studies with guinea pigs indicated that 4-methyl-2-pentanol may be further transformed to sulfate- or glucuronic acid-conjugates.

E.3.8.3. Toxicity of MIBK

The review of the toxicity of MIBK relied upon published reviews (IARC, 2013; USEPA, 2003) and focused on study types to address the TCs needed (chronic non-cancer and cancer).

E.3.8.3.1. Developmental and/or Reproductive Toxicity

MIBK has been listed as a DART under California's Proposition 65 Program since 2014 (OEHHA, 2014). The listing was based on the identification of USEPA, an authoritative body, that MIBK caused DART effect (developmental endpoint) in a rodent study. USEPA selected the developmental endpoint as the basis for the IRIS reference concentration (RfC) calculation (USEPA, 2003). A Maximum Allowable Dose Level (MADL) has not been established for the Proposition 65 Program by OEHHA. The following are key studies describing the DART effects of MIBK.

Tyl *et al.* (1987) exposed pregnant F344 rats (35 per group) and CD-1 mice (30 per group) to MIBK (0, 300, 1000, and 3000 ppm) by inhalation for 6 hours per day on gestational day (GD) 6 through 15. The average bodyweights for pregnant rats and mice were 0.23 kg and 0.036 kg, respectively.

At 3000 ppm, the critical effects were increased skeletal variations and decreased fetal bodyweight in rats and mice, as well as increased fetal death in mice. At this same dose, the rat dams showed significant reduction of bodyweight, bodyweight gain, and food consumption in some of the days during the gestation period. They also showed clinical signs (loss of coordination, negative tail and/or toe pinch, paresis and muscular weakness of the hindlimbs, piloerection, lacrimation, and red perioral encrustation.

For mouse dams at 3000 ppm, there were no treatment-related changes in maternal bodyweight, but there was a significant increase in bodyweight gain from GD 6 to 9. Clinical signs were also observed at this dose, and they were similar to those observed in the rats.

Nemec *et al.* (2004) conducted a two-generation reproductive toxicity study in rats (cited as WIL Research Laboratories 2000 in USEPA (2003)). Sprague-Dawley rats (parental F0, 30 per sex per group) were given MIBK by whole-body inhalation (0, 500, 1000, or 2000 ppm) for 6 hours per day for 70 days prior to mating and throughout mating for each generation in a two-generation reproductive toxicity study. F0 and F1 females were also exposed throughout gestation until day 20, and then during lactation days 5 to 21.

For parental effects, the NOAEL was 1000 ppm based on transient reduction of bodyweight and food consumption at 2000 ppm. There were no effects on reproductive parameters or sexual maturation of pups at any doses and the reproductive NOAEL was 2000 ppm.

E.3.8.3.2. Genotoxicity

MIBK is considered non-genotoxic by IARC (2013). The following tests were reported to be negative or equivocal: *Salmonella* (various strains) Ames assay, mouse lymphoma thymidine kinase locus $TK^{+/-}$ assay, unscheduled DNA synthesis in rat hepatocytes, micronuclei in mouse bone marrow, cell transformation in mouse embryo cells, and chromosome damage in rat liver cells. MIBK has not been tested for DNA damage (e.g., by the comet assay).

E.3.8.3.3. Chronic Toxicity and Carcinogenicity

The NTP (2007) study was the only chronic and carcinogenicity toxicity study available. In this study, rats (F344/N) and mice ($B6C3F_1$) were exposed to MIBK (0, 450, 900 or 1800 ppm) by inhalation 6 hours per day plus T90 (12 minutes), 5 days per week for 2 years. OEHHA converted the ppm dose to the following units in order to calculate the toxicity criteria for non-cancer and cancer effects, respectively. Explanation of the calculations is provided in Subsection E.3.8.5.3 and Subsection E.3.8.5.4 of this appendix.

- Non-cancer: Air concentration in terms of mg per cubic meter for Chronic TC_{inh}. The estimated HECs are: 0, 329, 659, and 1318 mg per cubic meter.
- Cancer: Lifetime average daily dose (LADD, mg per kg per day) for CSF. The calculated LADD are: 312, 625, and 1250 mg per kg per day for male rats; 380, 760, and 1520 mg per kg per day for male and female mice. No LADD was calculated for female rats because there was no significant increase in tumors for the treated groups when compared to the control group.

MIBK had no effects on the survival of the animals. The LOAEL for non-cancer effects was 450 ppm (329 mg per cubic meter) with kidney effects in rats of both sexes and liver effects in female mice (Table E.3.8.3.3-1). The liver foci were described as consisting of enlarged hepatocytes with “ground-glass appearing cytoplasm.”

Table E.3.8.3.3-1. Incidences of Non-cancer Effects in Rodents Exposed (Human Equivalent Concentrations, HEC, mg per cubic meter) to MIBK by Inhalation for 2 Years (NTP, 2007)

Sex, Species, Effect	0	329	659	1318
Male Rats, Renal tubule hyperplasia[a]	1/50	14/50**	7/50*	21/50**
Male Rats, Chronic nephropathy	42/50	45/50	47/50	50/50**
Male Rats, Renal papilla mineralization	1/50	6/50	22/50**	29/50**
Male Rats Renal pelvis transitional epithelial hyperplasia	1/50	5/50	6/50	19/50**
Female Rats, Chronic nephropathy	19/50	35/50**	38/50**	44/50**
Male Mice, Liver eosinophilic foci	3/50	4/50	5/50	8/50
Female Mice, Liver eosinophilic foci	4/50	11/50*	10/50	14/50**

The incidences shown are for single sections and step sections (combined). Values shown are number of animals with observed effect over (total animals examined). Statistical significance by pair-wise comparison: *p<0.05, ** p<0.01.

Benchmark dose modeling was conducted to determine the POD for endpoints with the lowest LOAEL at 450 ppm (329 mg per cubic meter, Table E.3.8.3.3-1). Using a standard default extrapolation factor of 10-fold, the estimated NOAEL is 33 mg per cubic meter. As shown in Table E.3.8.3.3-2, the lowest POD is the benchmark concentration at 0.95 lower confidence limit of 5 percent response ($BMCL_{05}$) of 28 mg per cubic meter for chronic nephropathy in female rats. This is close to the estimated NOAEL of 33 mg per cubic meter. The data for male rats were not amenable for modeling. OEHHA determined a POD of 28 mg per cubic meter for evaluating the chronic non-cancer effects of inhalation exposure to MIBK.

Table E.3.8.3.3-2. Benchmark Dose Analysis of Non-cancer Effects in Rodents Exposed to MIBK by Inhalation for 2 Years (NTP, 2007)

Sex, Species, Effect	BMD_{05}, mg per m^3	$BMDL_{05}$, mg per m^3	Model fit p-value	Best fit model
Male Rats, Renal tubule hyperplasia	NA	NA	All <0.05	None
Female Rats, Chronic nephropathy	37	28	0.424	Gamma, Weibull, multistage, quantal-linear
Female Mice, Liver eosinophilic foci	245	133	0.432	LogLogistic

BMC_{05}: benchmark dose at 5% response; $BMCL_{05}$: benchmark concentration at 0.95 lower confidence limit of 5% response; NA: not amenable for BMD modeling; NOAEL: no-observed-adverse-effect level.

With respect to carcinogenicity, tumors were found in both rats and mice exposed to MIBK. NTP (2007) concluded the following: (1) Some evidence of carcinogenic activity in male rats based on renal tubule neoplasms, (2) Some evidence of carcinogenic activity in male and female mice based on liver neoplasms, (3) Equivocal evidence of carcinogenic activity in female rats based on renal mesenchymal tumors, and (4) Mononuclear cell leukemia in male rats (1800 ppm) which "may have been related to MIBK exposure."

The LADDs for each sex and species, corresponding to the doses in ppm (450 ppm to 1800 ppm), and number of animals at risk for significant tumor types determined by OEHHA are presented in Table E.3.8.3.3-3 and Table E.3.8.3.3-4. Kidney tumors were found only in the male rats and no tumors for female rats. Mice of both sexes had increased rates of liver tumors. The tumor incidences are for animals at risk, which are animals alive at the time of first tumor detected.

Table E.3.8.3.3-3. Tumor Incidences in Male Rats Exposed to MIBK by Inhalation (Lifetime Average Daily Dose, LADD, mg per kg per day) for 2 Years (NTP, 2007)

Effect	LADD			
	0	312	625	1250
Renal Tubule adenoma or carcinoma	2/41***	4/33	3/36	11/29***

The incidences are animals at risk. Statistical significance at *p<0.05, ** p<0.01, *** p<0.001 for exact trend test (noted at the control group) and for Fisher pairwise comparison with controls (noted at the treated groups).

Table E.3.8.3.3-4. Tumor Incidences in Mice Exposed to MIBK by Inhalation (Lifetime Average Daily Dose, LADD, mg per kg per day) for 2 Years (NTP, 2007)

Sex, Effect	LADD			
	0	380	760	1520
Males, Hepatocellular adenoma or carcinoma	27/50*	34/50	28/48	37/49*
Females, Hepatocellular adenoma or carcinoma	17/47**	17/48	22/47	27/47*

The incidences are animals at risk. Statistical significance at *p<0.05, ** p<0.01, *** p<0.001 for exact trend test (noted at the control group) and for Fisher pairwise comparison with controls (noted at the treated groups).

IARC (2013) determined that while there were no data for humans, there was sufficient evidence from the NTP (2007) study with experimental animals to consider MIBK possibly carcinogenic to humans. For mechanism, IARC concluded the following: (1)

"There is little, if any, evidence that rodent tumors arose through a genotoxic mechanism," (2) For liver tumors in mice, there was no evidence for cytotoxic-regenerative cell proliferation mechanism, and weak evidence for a receptor-mediated mechanism from the induction of enzymes (cytochrome P450 1A1 and cytochrome P450 2B), and (3) weak evidence for kidney tumors in male rats to be caused by an α-2u-nephropathy-associated mechanism. Since the mechanism of carcinogenicity for MIBK is unknown, the default multistage model is assumed. The dose associated with a 5 percent increased risk of developing a tumor at the site of interest was calculated and the lower bound for this dose was estimated using the multistage polynomial model for cancer in the USEPA's Benchmark Dose Software (USEPA, 2023a). The ratio of the 5 percent risk level to that lower bound on dose is known as the animal CSF (Table E.3.8.3.3-5).

OEHHA determined the highest potency was the animal CSF_{inh} of 0.00063 (mg per kg per day)$^{-1}$ for male mouse liver tumors via inhalation exposure. After applying a scaling factor based on bodyweight to the ¾ power, the human CSF_{inh} is 0.0039 (mg per kg per day)$^{-1}$. See Subsection E.3.8.5.4 in this appendix for calculations.

Table E.3.8.3.3-5. Cancer Multistage Model Output and Inhalation Cancer Slope Factors (CSF_{inh}, (mg per kg per day)$^{-1}$) for MIBK Tumor Data from Rodents (NTP, 2007)

Species, Species, Organ	Final Model Choice	Animal CSF_{inh}	Human CSF_{inh}
Male rat kidney	1st degree polynomial	0.00037	0.0013
Male mouse liver	1st degree polynomial	0.00063	0.0039
Female mouse liver	1st degree polynomial	0.00047	0.0029

E.3.8.4. Existing Toxicity Criteria for MIBK

The TCs from OEHHA, USEPA, and published synthetic turf risk assessments are summarized in Table E.3.8.4.1-1.

E.3.8.4.1. Non-cancer Chronic Toxicity Criteria

OEHHA (1999) established a drinking water Action Level (AL) for MIBK at 0.12 mg per Liter. The AL was based on an acceptable daily dose of 0.017 mg per kg per day for kidney and liver effects in rats from a subchronic (13-week) gavage toxicity study, from an unpublished study conducted by Microbiological Associates. The combined UF was 3,000 (10 each for extrapolation from subchronic to chronic duration, animal to human, and human variability in response; and 3 for database deficiency). This acceptable daily dose value was not considered for the Synthetic Turf Study because it was based on an oral and subchronic toxicity study and there were more relevant chronic inhalation studies published by NTP (2007).

USEPA (2003) derived a RfC of 3 mg per cubic meter for MIBK based on results from a developmental toxicity study (Tyl *et al.*, 1987). The RfC was calculated using a

$NOAEL_{HEC}$ of 1026 mg per cubic meter and a 300-fold total UF. USEPA calculated the HEC by adjusting the daily exposure from 6 hours to 24 hours, and performing a subchronic to chronic extrapolation. The rationale was that for developmental effects, the concentration was considered more important than the total exposure period. A UF_D was applied for the lack of developmental neurotoxicity data, and any chronic toxicity data. With the availability of the NTP (2007) study, the RfC could potentially be based on a chronic toxicity endpoint.

Ginsberg *et al.* (2011b) used a reference level of 0.08 mg per cubic meter (80 µg per cubic meter) to calculate the hazard from inhalation exposure to MIBK in outdoor soccer fields. This value was cited from USEPA Health Effects Assessment Summary Tables (HEAST) for liver and kidney toxicity. There was no detail provided on the calculation of the reference level. OEHHA had raised a concern about accuracy of the NOAEL stated in the HEAST document (OEHHA, 1999). Thus, the value used by Ginsberg *et al.* (2011b) was not included in Table E.3.8.4.1-1

In the European synthetic turf study, Schneider *et al.* (2020) used a chronic inhalation benchmark dose lower bound at 10 percent response ($BMDL_{10}$) of 57 mg per cubic meter for nephrotoxic effects from NTP (2007) and ECHA (2012) guidelines to calculate a Derived No-Effect level (DNEL) of 2.3 mg per cubic meter as a reference level. They also cited reference values of 5 mg per kg per day for oral and dermal exposures from a subchronic NOAEL of 1000 mg per kg per day (citing USEPA (2003); USEPA and CDC/ATSDR (2019); ECHA (2012)).

Table E.3.8.4.1-1. Existing Oral and Inhalation Non-Cancer Toxicity Criteria (Chronic TC_{oral} and Chronic TC_{inh}, respectively) for MIBK

Species, Route, Duration	Toxicity Endpoint	Point of Departure	UF	Toxicity Criterion	Cited Study	Source
Rat, Gavage, 13 weeks	Increased relative kidney and liver weights, nephropathy	50 mg per kg per day (NOAEL)	UF_S = 10 UF_A = 10 UF_H = 10 UF_D = 3 Combined UF = 3000	Chronic TC_{oral}: 0.017 mg per kg per day	Un-published	(OEHHA, 1999)
Rat and mouse, Inhalation, Gestation Days 6 to 15	Skeletal variations in mice and rats, and reduced bodyweight and increased death in fetal mice	1026 mg per cubic meter (HEC)	UF_A = 3 UF_H =10 UF_D =10 Combined UF = 300	Chronic TC_{inh}: 3 mg per cubic meter	(Tyl *et al.*, 1987)	(USEPA, 2003)

Species, Route, Duration	Toxicity Endpoint	Point of Departure	UF	Toxicity Criterion	Cited Study	Source
Rat, inhalation, 2 years	Kidney effects	57 mg per cubic meter ($BMDL_{10}$)	Not specified Combined UF = 25	Chronic TC_{inh}: 2.3 mg per cubic meter	(NTP, 2007)	(Schneider *et al.*, 2020)

The toxicity criteria were calculated as the value for point of departures divided by the values for combined uncertainty factors.
HEC: human equivalent concentration; NOAEL: no-observed-adverse-effect level; UF: uncertainty factor; UF_S: subchronic to chronic extrapolation UF; UF_A: animal to human (interspecies) extrapolation UF; UF_H: human variability in response (intraspecies) UF; and UF_D: database deficiency UF.

E.3.8.4.2. Cancer Toxicity Criteria

There was no established CSF from any source.

E.3.8.5. OEHHA Derived Screening Toxicity Criteria for MIBK

E.3.8.5.1. Non-cancer Toxicity Criteria

For chronic inhalation exposure, OEHHA developed a Chronic TC_{inh} using the NTP (2007) lifetime inhalation toxicity study. The POD was 28 mg per cubic meter as the HEC for kidney effects in female rats (Table E.3.8.3.3-2) and a combined UF was 180 to calculate a toxicity criterion of 0.16 mg per cubic meter (Table E.3.8.5.2-1 and Subsection E.3.8.5.3 on calculation). The UF_A was 6 because the POD was expressed as HEC, and the UF_H was 30. This Chronic TC_{inh} is lower than the USEPA RfC of 3 mg per cubic meter.

E.3.8.5.2. Cancer Toxicity Criteria

OEHHA derived a human CSF_{inh} of 0.0039 mg per kg per day^{-1} for liver tumors in male mice (Table E.3.8.3.3-5 and Table E.3.8.5.2-1). The human CSF is applicable for the inhalation and oral routes since the target organ is a systemic effect, and not site of contact.

Table E.3.8.5.2-1. OEHHA Synthetic Turf Study-Specific Chronic Non-Cancer Toxicity Criteria (Chronic TC_{inh}, mg per cubic meter) and Lifetime Cancer Toxicity Criteria (CSF_{inh}, $(mg\ per\ kg\ per\ day)^{-1}$) for Inhalation Exposures to MIBK

Species Route, and Duration	Endpoint	Point of Departure	Uncertainty Factor	Toxicity Criterion	Reference
Rat, Inhalation, 2 Years	Kidney effects	28 mg per cubic meter ($BMDL_{05}$ HEC)	$UF_A = 6$ $UF_H = 30$ Combined UF = 180	Chronic TC_{inh}[a] = 0.16	(NTP, 2007)

Species Route, and Duration	Endpoint	Point of Departure	Uncertainty Factor	Toxicity Criterion	Reference
Mouse, Inhalation, 2 Years	Liver tumors	Not applicable	Not applicable	CSF_{inh}[b] = 0.0039	(NTP, 2007)

[a] The Chronic TC_{inh} was calculated as the value for point of departure divided by the value for combined uncertainty factors.
[b] The CSF_{inh} is the human CSF_{inh}.
$BMCL_{05}$: benchmark concentration at 0.95 lower confidence limit of 5% response; HEC: human equivalent concentration; UF: uncertainty factor; UF_A: animal to human (interspecies) extrapolation UF; UF_H: human variability in response (intraspecies) UF.

E.3.8.5.3. Equations for Non-Cancer Effects

Administered dose in ppm is converted to HEC (mg per cubic meter) for non-cancer effect using Equation E.3.8.5.3-1:

$$HEC(mg/m^3) = C_{air}(ppm) \times \frac{4.1(mg/m^3)}{1\ ppm} \times \frac{hours\ exposed}{24\ hours} \times \frac{days\ exposed}{7\ days} \times RGDR$$

Equation E.3.8.5.3-1

Where MIBK molecular weight=100.16 g per mole and 1 ppm = 4.1 mg per cubic meter. The RGDR is a factor to account for the pharmacokinetic difference between laboratory animal and human. For systemic effects, the default is a value of 1.

For example, in Table E.3.8.3.3-1, the HEC for 450 ppm is 329 mg per cubic meter using Equation E.3.8.5.3-1:

$$HEC = 450ppm \times \frac{4.1\ mg/m^3}{1\ ppm} \times \frac{6\ hours}{24\ hours} \times \frac{5\ days}{7\ days} \times 1 = 329\ mg/m^3$$

For the calculation of Chronic TC_{inh}, the remaining animal to human extrapolation uncertainty is pharmacodynamic difference. This difference is addressed with a $UF_{A\text{-}PD}$ of √10. Additional UFs applied are UF_H, 30 and any remaining uncertainty such as database deficiency, if applicable.

For example, in Table E.3.8.4.1-1, the screening Chronic TC_{inh} is 0.16 mg per cubic meter, calculated from a POD of 28 mg per m^3 ($BMDL_{05}$ HEC) and combined UF of 180, as shown in Equation E.3.8.5.3-2:

$$Chronic\ TC_{inh} = POD \times \frac{1}{UF_{A-PK\ of\ 30} \times UF_{A-PD\ of\ \sqrt{10}}} \times \frac{1}{UF_{H\ of\ 30}}$$

Equation E.3.8.5.3-2

and,

$$Chronic\ TC_{inh} = 28\,mg/m^3 \times \frac{1}{30 \times \sqrt{10}} \times \frac{1}{30} = \mathbf{0.16\ mg/m^3}$$

E.3.8.5.4. Equations for Cancer Effects

Conversion of administered dose in ppm to lifetime average daily dose (LADD, mg per kg per day) is shown in Equation E.3.8.5.4-1:

$$LADD\ (mg/kg-day) = C_{air}(ppm) \times \frac{4.1 mg/m^3}{1\ ppm} \times \frac{Animal\ Inhalation\ Rate\ (m^3/day)}{Bodyweight\ (kg)} \times \frac{hour\ exposed}{24\ hours} \times \frac{days\ exposed}{7\ days} \times \frac{weeks\ on\ study}{104\ weeks}$$

Equation E.3.8.5.4-1

Default inhalation rate equations for rats (OEHHA, 2018) and mice (Anderson, 1983):

Inhalation rate for rats, cubic meter per day = 0.702 cubic meter per day x (rat bodyweight in kg)$^{2/3}$

Inhalation rate for mice, cubic meter per day = 0.0345 cubic meter per day x (mouse bodyweight in kg ÷ 0.025 kg)$^{2/3}$

The slope of the dose-response relationship (daily dose vs. tumor incidences) is the animal CSF (CSF_A) for the laboratory animal studied. For the extrapolation of CSF_A to human CSF (CSF_H), a scaling factor of bodyweight (BW) to the ¾ power is used as shown in Equation E.3.8.5.4-2 to Equation E.3.8.5.4-4. The human default bodyweight is generally 70 kg and animal bodyweight from the study.

$$\frac{Dose_A}{Dose_H} \times \frac{BW_A}{BW_H} = \frac{(BW_A)^{\frac{3}{4}}}{(BW_H)^{\frac{3}{4}}}$$

Equation E.3.8.5.4-2

and,

$$Dose_H = Dose_A \times \frac{BW_A}{(BW_A)^{\frac{3}{4}}} \times \frac{(BW_H)^{\frac{3}{4}}}{BW_H}$$

$$Dose_H = Dose_A \times \frac{(BW_A)^{\frac{1}{4}}}{(BW_H)^{\frac{1}{4}}}$$

and,

$$\frac{1}{Dose_H} = \frac{1}{Dose_A} \times \frac{(BW_H)^{\frac{1}{4}}}{(BW_A)^{\frac{1}{4}}}$$ Equation E.3.8.5.4-3

Equation E.3.8.5.4-3 is converted for the CSF calculation with CSF expressed as 1/dose or (mg per kg per day)$^{-1}$:

$$CSF_H = CSF_A \times \frac{(BW_H)^{\frac{1}{4}}}{(BW_A)^{\frac{1}{4}}}$$ Equation E.3.8.5.4-4

E.3.9. Cyclopenta[c,d]pyrene (CPP, CASRN 27208-37-3)

E.3.9.1. Introduction

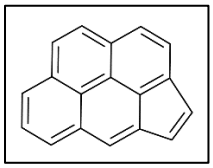
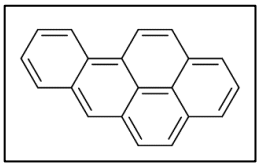

(a)

(b)

Figure E.3.8.5.4-1. Structures of (a) cyclopenta[c,d]pyrene (CPP) and (b) benzo[a]pyrene (BaP, CASRN 50-32-8).

OEHHA evaluated the toxicology database for cyclopenta(c,d)pyrene (CPP, Figure E.3.8.5.4-1) because there were no established toxicity criteria for CPP from OEHHA, USEPA, or ATSDR. OEHHA determined that the database was inadequate to derive chemical-specific TCs for non-cancer effects and CSFs for cancer effects, and BaP would be an appropriate analog chemical.

Since 2011, CPP had been listed as a carcinogen under Proposition 65 by the labor code (OEHHA, 2011b). The listing was based on the IARC (2010) conclusion that (1) there was sufficient evidence in experimental animals for the carcinogenicity of CPP and (2) CPP was classified as “probably carcinogenic to humans” (Group 2A). OEHHA had not developed a human CSF or NSRL for CPP. OEHHA compared available carcinogenicity toxicity studies conducted for CPP, as well as those which included BaP to determine if the established CSF for BaP could be used to develop a relative potency factor for CPP.

E.3.9.2. Toxicity of CPP

E.3.9.2.1. Genotoxicity

CPP was genotoxic in the Ames assay, and mammalian cell *in vitro* assays for mutation (human lymphoblastoid cells and mouse lymphoma cells) and cell transformation (mouse C3H 10T1/2 CL8 cells) (IARC, 1983). These results are similar to some of the effects reported for BaP in both *in vitro* and *in vivo* studies (USEPA, 2017).

E.3.9.2.2. Carcinogenicity

In a 1983 assessment, IARC summarized five studies with CPP applied to the skin of mice of various strains for various durations (IARC, 1983). These studies all showed that CPP caused skin tumors in experimental animals. In three initiation-promotion experiments using 12-*o*-tetradecanolyphorbol-13-acetate as a promoter, CPP was shown to be an initiator.

IARC updated the assessment in 2010 with additional dermal and ip administration studies (IARC, 2010). BaP, CPP, or in a mixture were applied to the skin of female Swiss mice (30 per group) twice a week for 48 weeks (Cavalieri *et al.*, 1983). The doses were 0, 22.2, 66.6 or 200 nmole of each compound. The treatment resulted in dose-related increases in skin tumor incidences with either compound and higher incidences in combination.

In studies conducted by the ip route, CPP caused lung tumors in mice. Newborn Swiss-Webster mice (male and female) were given the CPP by ip three times over a 2-week period to achieve the total doses of 0, 1.55, 3.09, 4.64, 6.19, or 7.73 µmole per animal (0, 350, 700, 1050, 1400, or 1750 µg per animal) (Busby *et al.*, 1988). Bodyweights of the animals were not given in the report. Mice were necropsied at 26 weeks of age for gross observation and histopathological examination of the lungs. There was no information in the report about examination of other tissues. For the lung tumor, an animal was noted as having either adenoma or adenocarcinoma. If both are present, the animal was tabulated as having adenocarcinoma. Thus, the total incidence represented the sum of animals with each tumor type. CPP, at all treatment doses, caused increased incidences of lung adenomas and adenocarcinomas (Table E.3.9.2.2-1 and Table E.3.9.2.2-2).

Table E.3.9.2.2-1. Incidences of Lung Tumors in Male Mice Exposed to CPP by Intraperitoneal Injection (Dose, µmole per animal, Busby *et al.* (1988))

Tumor Incidence	Dose					
	0	1.55	3.09	4.64	6.19	7.73
Adenoma	2/25	4/8	3/9	2/7	2/13	5/9
Adenocarcinoma	0/25	1/8	2/9	4/7	8/13	3/9
Total (percent animals affected)	2/25 (8)	5/8 (62)	5/9 (56)	6/7 (86)	10/13 (77)	8/9 (89)

Incidence is expressed as number of animals affected over total number of animals examined.

Table E.3.9.2.2-2. Incidences of Lung Tumors in Female Mice Exposed to CPP by Intraperitoneal Injection (Dose, µmole per animal, Busby *et al.* (1988))

Tumor Incidence	Dose					
	0	1.55	3.09	4.64	6.19	7.73
Adenoma	2/24	4/10	4/10	9/14	3/7	5/9
Adenocarcinoma	0/24	2/10	3/10	4/14	4/7	4/9
Total (percent animals affected)	2/24 (8)	6/10 (60)	7/10 (70)	13/14 (93)	7/7 (100)	9/9 (100)

Incidence is expressed as number of animals affected over total number of animals examined.

Busby *et al.* (1988) compared the lung tumor results following ip injection for CPP with those for BaP and 6-nitrochrysene (6-NC) from published studies and unpublished data from their laboratory. There were no details on the species and strains of animals used for these BaP and 6-NC studies. For the latter compounds, only summarized data were provided indicated that 6-NC was the most potent compound. The dose required to induce one lung tumor/mouse ($TM_{1.0}$) was lowest for 6-NC (0.01 µmole), and higher for BaP (0.25 µmole) and CPP (1.35 µmole). The rank order of compound potency in terms of dose to cause 50 percent increase in total tumor incidence (ED_{50}) was 6-NC (0.02 µmole), BaP (0.2 µmole), and CPP (1.53 µmole). However, the malignancy index (ratio of ED_{50} for total tumors and ED_{50} for adenocarcinoma) showed CPP was more malignant with the highest ratio (0.25), compared to those for BaP (0.03) and 6-NC (0.18).

Other researchers also compared the potencies of CPP and BaP in causing lung tumors. Male Strain A/J mice (20 per group, except 24 mice for BaP 200 mg per kg group) were given a single ip dose of 0, 10, 50, 100, or 200 mg per kg of CPP (Nesnow *et al.*, 1998a; Nesnow *et al.*, 1998b). This experiment also included BaP given the same doses, with the addition of the 5 mg per kg dose. Eight months after treatment, surface lung adenomas were counted. There was no effect on the survival of the mice in the CPP group (Table E.3.9.2.2-3) or BaP group (Table E.3.9.2.2-4). Tumor incidence was expressed as mean lung adenomas per mouse. CPP and BaP have similar potency at lower does (≤50 mg per kg), but CPP potency was higher than BaP at >100 mg per kg.

Table E.3.9.2.2-3. Incidences of Lung Adenomas in Male Mice Eight Months after a Single Intraperitoneal Injection (Dose, mg per kg) with CPP (Nesnow *et al.*, 1998a)

Tumor Incidence	Dose				
	0	10	50	100	200
Number of animals examined	20	20	20	19	18

Tumor Incidence	Dose				
	0	10	50	100	200
Percent survival	100	100	100	95	90
Mean lung adenomas per mouse (variance)[a]	0.60 (0.358)	0.55 (0.682)	4.75* (4.72)	32.2* (242)	103* (350)
100 Percent tumor incidence[b]	No	No	Yes	Yes	Yes

[a] Statistical significance from the control at p<0.01 indicated by * from the Bonferroni multiple comparison test, provided in the report.
[b] Yes: group with 100 percent tumor incidence. No: group with no tumor incidence given in the report.

Table E.3.9.2.2-4. Incidences of Lung Adenomas in Male Mice Eight Months after a Single Intraperitoneal Injection (Dose, mg per kg) with Benzo[a]pyrene (Nesnow *et al.*, 1998a)

Tumor Incidence	Dose					
	0	5	10	50	100	200
Number of animals examined	20	20	17	19	16	24
Percent survival	100	100	85	95	80	100
Mean lung adenomas per mouse (variance)[a]	0.60 (0.358)	0.45 (0.682)	0.529 (0.64)	4.37* (7.91)	12.7* (19.5)	33.0* (109)
100 Percent tumor incidence[b]	No	No	No	Yes	Yes	Yes

[a] Statistical significance from the control at p<0.01 indicated by * from the Bonferroni multiple comparison test, provided in the report.
[b] Yes: group with 100 percent tumor incidence. No: group with no tumor incidence given in the report.

E.3.9.2.3. Supplemental Information

There were no toxicity values for CPP in the USEPA CompTox Chemicals Dashboard (USEPA, 2023b). None of the compounds with structural similarity to CPP had established TCs.

E.3.9.3. OEHHA Derived Screening Toxicity Criteria for CPP

E.3.9.3.1. Non-cancer Toxicity Criteria

There were no data to derive a TC_{inh} of CPP. OEHHA selected the DART TC_{oral} and DART TC_{inh} for BaP, as structural analog to CPP (Table E.3.9.3.1-1). The DART TC_{oral} is applicable for the dermal exposure route.

Table E.3.9.3.1-1. Non-cancer Toxicity Criteria of Benzo[a]pyrene to be Used for Oral (DART TC_{oral}) or Inhalation (DART TC_{inh}) Exposure to CPP Based on Developmental and/or Reproductive Toxicity (DART)

Toxicity Endpoint	Applicable Exposure route	Toxicity Criterion	Source
Developmental, reproductive, and immunological effects in rats	Oral or dermal	DART TC_{oral}: 0.0003 mg per kg per day	USEPA (2017)
Developmental and reproductive effects in rats	Inhalation	DART TC_{inh}: 2 ng per cubic meter	USEPA (2017)

E.3.9.3.2. Cancer Toxicity Criteria

Of the three studies with carcinogenicity data for CPP reviewed, OEHHA determined that none could be used for the derivation of a screening human CSF. The skin tumors from the dermal toxicity study by Cavalieri *et al.* (1983) with mice were due to repeated application of CPP on the skin.

While results from ip injection studies generally could be used to extrapolate to inhalation exposure, there were limitations in the ip injection studies by Busby *et al.* (1988) and Nesnow *et al.* (1998a); Nesnow *et al.* (1998b) which precluded the use of data to derive a new CSF. The limitations included: single dose, short exposure duration, too few animals per group, and no or inadequate incidence or histological data. The Nesnow et al study (1998a), nevertheless, was supportive for using the established CSFs for BaP as analog values for CPP (Table E.3.9.3.2-1). The potency of CPP to cause lung tumors at low doses was comparable to that for BaP (Table E.3.9.2.2-3 and Table E.3.9.2.2-4). The CSF_{oral} can also be used in the dermal exposure route.

Table E.3.9.3.2-1. OEHHA Synthetic Turf Study-Specific Screening Human Cancer Slope Factor for Oral (CSF_{oral}, (mg per kg per day)$^{-1}$) or Inhalation (CSF_{inh}, (mg per kg per day)$^{-1}$) Lifetime Exposure to CPP Using the Cancer Slope Factors (CSFs) for Benzo[a]pyrene

Toxicity Endpoint	CSF	Applicable Exposure Route	Reference
Gastric tumor in mice	CSF_{oral}: 12	Oral or Dermal	OEHHA (2015)
Respiratory tract tumors in hamsters	CSF_{inh}: 3.9	Inhalation	OEHHA (2015)

E.3.10. 4-tert-Octylphenol (4t-OP, CASRN 140-66-9)

E.3.10.1. Introduction

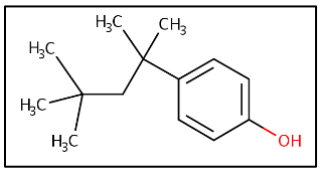


Figure E.3.9.3.2-1. Structure of 4-tert-octylphenol (4t-OP)

OEHHA derived a chemical-specific screening DART TC_{oral} for 4-tert-octylphenol (4t-OP, Figure E.3.9.3.2-1) because there were no established TCs from OEHHA, USEPA, or ATSDR.

E.3.10.2. Pharmacokinetics and Metabolism of 4t-OP

Pharmacokinetic studies showed that 4t-OP is rapidly absorbed and metabolized in rats after oral or intravenous administration (Certa *et al.*, 1996; Hamelin *et al.*, 2010; Upmeier *et al.*, 1999; van den Berg *et al.*, 2003). The metabolism of 4t-OP is in the liver with phase I and II enzymes through glucuronidation, hydroxylation, and sulfonation. After oral exposure, there was a gender difference in the tissue level of 4t-OP with higher levels in females compared to males. This finding was consistent with the faster metabolism of 4t-OP in experiments with male rat liver microsomes. There was also enterohepatic recirculation of 4t-OP. The gender difference for the blood and tissue concentrations of 4t-OP in rats was simulated in a PBPK model (Hamelin *et al.*, 2010). 4t-OP is also cleared rapidly from humans in the urine. Urinary level of 4t-OP is considered an indicator of recent exposure in the Center for Disease Control and Prevention Biomonitoring Program for this chemical.

E.3.10.3. Toxicity of 4t-OP

OEHHA screened the available published toxicity studies to select a critical study to derive a screening TC for 4t-OP. There were no chronic or lifetime bioassays in laboratory animals with 4t-OP. Since 4t-OP is a known endocrine disruptor, acting as an estrogen receptor agonist, there were many published studies on modes of action and associated effects on reproduction and development. Some experiments used injection routes (ip or subcutaneous), ovariectomized animals, and/or high doses. The effects of 4t-OP were reviewed by Van Miller and Staples (2005) and Hines (2014).

OEHHA focused on *in vivo* studies with intact animals of exposure routes (oral or inhalation) relevant to synthetic turf exposure scenarios and low exposure levels (those with doses less than 100 mg per kg per day). Studies which may be used for the selection of a POD are described below. Other animal toxicity studies and epidemiological studies reviewed are summarized in Sections E.3.10.3.5 and E.3.10.3.6E.3.10.3.5, respectively.

E.3.10.3.1. Developmental Toxicity

Harazono and Ema (2001) exposed pregnant Wistar rats (16 per group) to 4t-OP (0, 15.6, 31.3, 62.5, or 125 mg per kg per day) by gavage from gestation day 0 to 8. There was no effect on survival, pregnancy rate, and fetal bodyweight and no external malformations were observed. Maternal food consumption was reduced (85% of control) at ≥15.6 mg per kg per day, and bodyweight gain decreased at ≥ 31.3 mg per kg per day. Post-implantation loss per litter was significantly increased at ≥ 31.3 mg per kg per day, a maternally toxic dose.

E.3.10.3.2. Reproductive Toxicity

Tyl *et al.* (1999) conducted a two-generation reproductive toxicity study with CD rats (30 per sex per group) given 4t-OP at 0, 0.2, 20, 200, or 2000 ppm in diet. The rats were treated during the pre-mating (10 weeks), mating (2 weeks), gestation (3 weeks) and lactation (3 weeks) periods. F1 and F2 rats had *in utero* exposure to 4t-OP. The ranges of doses reported were: 0, 0.034 to 0.011, 3.3 to 1.05, 32.6 to 10.9, and 369 to 111 mg per kg per day. Selected treatment-related results are shown in Table E.3.10.3.2-1 and Table E.3.10.3.2-2 For simplicity, only average values are presented; the report provided average and standard error of the mean values. The authors assigned NOAELs of 200 ppm (10.9 mg per kg per day) for systemic (decreased adult bodyweight and uterine weight reduction, Table E.3.10.3.2-1) and postnatal (postnatal day 14- and 21-day pup reduced bodyweight, Table E.3.10.3.2-2) toxicity. There were no effects on reproductive parameters; testes, prostate, or ovary weights or morphology; sperm (counts, motility, morphology, production); or estrous cycle. For reproductive toxicity, the NOAEL was the highest dose tested, 2000 ppm (111 mg per kg per day).

Table E.3.10.3.2-1. Effects on Mean Terminal Bodyweight and Uterus Weight of Rats Given 4t-OP in the Diet (Dose, mg per kg per day) in a Two-Generation Toxicity Study (Tyl *et al.*, 1999)

Generation, Sex, Effect	Dose				
	0	0.011 to 0.034	1.05 to 3.3	10.9 to 32.6	111 to 369
F0, male, bodyweight, g	574.7	590.0	570.0	564.9	532.7**
F0, female, bodyweight, g	292.0	289.8	286.5	288.3	286.8
F1, male, bodyweight, g	582.6	566.3	554.5	561.5	528.5**
F1, female, bodyweight, g	297.3	313.9	294.6	300.6	288.4
F2, male, bodyweight, g	533.1	540.9	529.9	523.3	493.7*

Generation, Sex, Effect	Dose				
	0	0.011 to 0.034	1.05 to 3.3	10.9 to 32.6	111 to 369
F0, female, absolute uterus weight, g	1.067	1.053	0.969	0.941	0.861**
F0, female, relative uterus weight, percent	0.367	0.364	0.341	0.327	0.302**

Only mean values are shown in the table. The report provided standard error values and statistical significance at *p<0.05, ** p<0.01 versus control group value.
F0: parental generation; F1: first generation; F2: second generation.

Table E.3.10.3.2-2. Effects on Postnatal Mean Bodyweight (g) of Rats Given 4t-OP in the Diet (Dose, mg per kg per day) in a Two-generation Toxicity Study (Tyl *et al.*, 1999)

Generation, Postnatal Day	Dose				
	0	0.011 to 0.034	1.05 to 3.3	10.9 to 32.6	111 to 369
F1, PND14	29.96	31.23	30.42	29.14	26.18**
F1, PND21	47.62	49.75	47.85	46.05	39.79**
F2, PND14	30.38	32.11	30.47	31.08	28.59
F2, PND21	46.53	47.71	44.90	46.09	43.05

Only mean values are shown in the table. The report provided standard error values and statistical significance with *p<0.05, ** p<0.01 versus control group value.
F1: first generation; F2: second generation; and PND: postnatal day.

While Tyl *et al.* (1999) did not observed any effects of 4t-OP on the male reproductive system in the two-generation reproductive toxicity study at the highest dose in the diet (111 to 369 mg per kg per day), several studies have reported effects on the male reproductive system, in particular sperms, at much lower doses (Table E.3.10.3.2-3). One epidemiological study in China indicated a positive association between high urinary 4t-OP and idiopathic male infertility (Chen *et al.*, 2013).

The effect of 4t-OP on sperm may be exposure route-specific; albeit the duration and endpoints are not identical between experiments listed in Table E.3.10.3.2-3. The study by Tyl *et al.* (1999) was conducted with 4t-OP given in the diet. For exposure by gavage, the LOAEL was at 50 mg per kg per day in rats (Bian *et al.*, 2006; Gregory *et al.*, 2009). The LOAEL was apparently much lower for studies with 4t-OP given in the drinking water: 35 ng per kg per day in rats (Blake *et al.*, 2004) and 50 µg per kg per day in mice (Buñay *et al.*, 2018).

Table E.3.10.3.2-3. Summary of Studies on the Effect of 4t-OP on the Male Reproductive System

Study Type, Reference	Species, Dose, Route, Duration	NOAEL, mg per kg per day	Effects at LOAEL
Male reproductive system (Gregory *et al.*, 2009)	Adult male SD rats (5 per group), Gavage dose: 0, 25, 50, or 125 mg per kg per day for 60 Days (1.5 cycles of spermatogenesis)	25	50 mg per kg per day: Effect on sperms but no effect on testicular and epididymal weights and histology, cauda epididymal sperm counts
Male reproductive system (Bian *et al.*, 2006)	Adult male SD rats (12 per group), Gavage dose: 0, 50, 150, or 450 mg per kg per day for 30 Days	<50	50 mg per kg per day: Effects on the size and weight of testis, epididymis, and prostate
Male reproductive system (Blake *et al.*, 2004)	Male Fischer 344 rats (12 per group), Drinking water concentration: 0, $1x10^{-9}$, $1x10^{-7}$, or $1x10^{-5}$ M, for 4 Months	(<$1x10^{-9}$ M)	$1x10^{-9}$ M: Effect on epididymal sperm with abnormal tails at all doses, but no effect on heads
Male testes steroidogenesis (Buñay *et al.*, 2018)	Pregnant female C57BL/6j mice (up to 12 for control, 3 for treated group), Drinking water dose: 0, 0.05 mg per kg per day exposed in utero, lactation, and postnatal days	<0.05	Male mice 0.05 mg per kg per day: Effect on bodyweight, testis and seminiferous tubule

LOAEL: lowest-observed-adverse-effect level; and NOAEL: no-observed-adverse-effect level.

The relevance of these findings with sperms will require further in-depth analysis of the data for potential development of a DART TC based on this endpoint and would be applicable only for the males in the population. In Blake *et al.* (2004), the toxicological significance of the sperm finding is uncertain (Table E.3.10.3.2-4). The concentration in the water was: 0, $1x10^{-9}$, $1x10^{-7}$, or $1x10^{-5}$ M. The beginning dose was: 0, 0.035, 3.5, or 350 µg per kg per day; and the dose at latter part of the experiment was: 0, 0.020, 2.0, or 200 µg per kg per day). The number of samples was low, only 6 per group. While the increase was statistically significant when compared to the control, the change was relatively low (from 10 to 12 percent) over a span of 10000-fold increase in the dose (from 10^{-9} M to 10^{-5} M). The authors noted that the effects may be of "negligible biological importance" given that there were no effects on reproductive parameters and sperm values (i.e., testicular sperm production, male accessory sex organ weights, hormone levels (reproductive organ weight, serum luteinizing hormone, follicle-stimulating hormone, or testosterone levels), and other measures (e.g., food consumption). In addition, the authors noted that the effective dose by drinking water

was 500 to 875 times lower than that (175 mg per kg per day) for the same effect but using subcutaneous injection (3 times weekly for 1 month) in their previous work.

Table E.3.10.3.2-4. Sperm Abnormalities in Male Mice given 4t-OP in the Drinking Water (Dose, mg per kg per day) for Four Months (Blake *et al.*, 2004)

Effect	0	0.00002 to 0.000035	0.002 to 0.0035	0.2 to 0.35
Number of sperm heads per gram tissue (x millions)	780	840	800	680*
Number of sperm heads per epididymis (x millions)	380	400	380	340*
Percent Sperm with head abnormalities	<2	2	<2	<2
Percent Sperm with tail abnormalities	7	10*	11*	12*

Mean value for sperm head counts was estimated from Figure 2 of the report. Mean value for percent of sperm with head or tail abnormalities was estimated from Figure 3 of the report.
Values presented were mean, with statistical significance of p<.01 indicated by *, compared to the control.

In Buñay *et al.* (2018), the objective of the study was to compare the effects of single versus mixture exposures to endocrine disrupting chemicals at low doses and tests mathematical models for various addition predictions with the observed results. The effects examined were mouse testes histology, hormone levels (testosterone and estradiol), and transcription of several genes involved in steroid synthesis. There were up to a total of 12 pregnant mice in the control group, but only three pregnant mice per chemical and only a single dose was tested. The positive testes histology data are presented in Table E.3.10.3.2-5. 4t-OP reduced the intratesticular estradiol, but not testosterone levels or the expression of some genes. While the results of this study supported other studies showing the testes as the target organ, the limitations of this study for TC derivation are low number of animals and only a single dose level. It is unclear if the results, in particular the histological changes, would impact the reproductive function of the testes.

Table E.3.10.3.2-5. Bodyweight and Testis Effects in Male Mice Exposed to 4t-OP (Dose, mg per kg per day) in utero to Adulthood in the Drinking Water (Buñay *et al.*, 2018)

Effect	Dose	
	0	0.05
Bodyweight, g	22.41±1.66	26.18±1.84**
Testis relative weight, percent	0.37±0.03	0.30±0.11*

Effect	Dose	
	0	0.05
Seminiferous tubule diameter, µm	221.8±64.23	136.4±3.30*
Seminiferous tubules with germ cells exfoliated, percent	2.77±1.36	9.00±4.47**
Relative frequency of spermatogenesis states VI and VII, unitless	0.16±0.03	0.08±0.06**
Relative frequency of seminiferous tubules with undetermined stage, unitless	0.03±0.01	0.15±0.09**
Apoptotic index (Active caspase-3 cells/seminiferous tubules), unitless	0.05±0.27	0.40±1.00**

Values are mean ± standard error of the mean from the report. Statistical significance: * for p<.05 and ** for p<0.01, compared to the control.

Additional studies reviewed for this assessment were developmental toxicity studies with rodent exposed to 4t-OP during gestation (Kamei *et al.*, 2008; Kim *et al.*, 2014), and studies on the effect of 4t-OP on the female reproductive system (Laws *et al.*, 2000; Sahambi *et al.*, 2010). These studies provided supplemental information on the DART effects of 4t-OP.

There were also epidemiological studies of 4t-OP; three recent studies were reviewed. The effects included change on carotid artery thickness (Lin *et al.*, 2019), birth outcomes (Lv *et al.*, 2016), and male fertility (Chen *et al.*, 2013). While these studies showed positive association of some effects with urinary levels of 4t-OP, actual exposure levels were not reported.

E.3.10.3.3. Genotoxicity

Ulutaş *et al.* (2011) conducted a comet assay with Wistar male rats (5 per group control, 6 per group treated) exposed to 4t-OP (0, 125, or 250 mg per kg per day) by gavage for 4 weeks. The NOAEL was 125 mg per kg per day, with a LOAEL at 250 mg per kg per day for increased tail length and tail moment, and for hematology assay with increased lymphocytes and reduced granulocytes.

E.3.10.3.4. Carcinogenicity

The carcinogenicity of 4t-OP is unknown due to the lack of a lifetime toxicity study. OEHHA conducted QSAR analysis for carcinogenicity potential of 4t-OP using VEGA. The models are based on structure-activity relationships, which compare the structure of the chemical of concern with a set of carcinogenic structure fragments (training set). Each model may have different sets of data and rules for fragment comparison to determine the applicability and thus reliability of the prediction. Four models predicted 4t-OP to be a non-carcinogen with good reliability and within the applicability domain (Table E.3.10.3.4-1).

Table E.3.10.3.4-1. Carcinogenicity Prediction for 4t-OP Using VEGA QSAR Models

Carcinogenicity Potential	CAESAR 2.1.9	ISS 1.0.2	IRFMN/Antares1.0.0	IRFMN/ISSCAN-CGX 1.0.0
Prediction	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen	Non-Carcinogen
Reliability	Good	Good	Good	Good
AD Index	Into	Into	Into	Into

For carcinogenicity potential, the prediction is either a carcinogen or not a carcinogen. Reliability score: low, moderate, or good reliability (or based on experimental data).
Applicability domain (AD) of the model: Into = into the AD.

E.3.10.3.5. Additional Animal Toxicity Studies on 4t-OP

Table E.3.10.3.5-1 summarizes the additional DART studies of 4t-OP on animals.

Table E.3.10.3.5-1. Summary of Additional Animal Studies on 4t-OP

Study type (Reference)	Species, Route, and Duration	NOAEL, mg per kg-day	Effects at LOAEL
Developmental toxicity (Kamei *et al.*, 2008)	Pregnant ICR mice (3 per group), Drinking water on gestation day10 to end of lactation	<0.2	0.2 mg per kg per day pup (PND31): Effect on bone of females, but not males
Developmental toxicity (Kim *et al.*, 2014)	Pregnant SD rats (5 per group"), Gavage on gestation day 14 to 16	10	100 mg per kg per day: Effect on pregnant rat pituitary gland
Female reproductive system (Sahambi *et al.*, 2010)	Adult female SD rats (7 per group), Gavage for 35 days	<25	25 mg per kg per day: Effect on estrous cycle
Female reproductive system (Laws *et al.*, 2000)	Prepubertal female rats (6 per group), Gavage for 3 days	50	100 mg per kg per day: Effect on uterine weight

E.3.10.3.6. Epidemiological Studies of 4t-OP

The most recent epidemiological studies on 4t-OP are summarized in Table E.3.10.3.6-1. They are conducted mainly because 4t-OP is an endocrine disruptor. While the studies showed positive association of some effects with urinary levels of 4t-OP, actual exposure levels were not available to derive a screening TC.

Table E.3.10.3.6-1. Recent Epidemiological Studies on 4t-OP

Population	Endpoints	Reference
Adolescents and young adults in a urine screening program (1992 and 2008) in Taiwan	Cardiovascular disease risk factors, and the common carotid artery intima-media thickness	Lin *et al.* (2019)
1100 pregnant women in China	Birth outcomes	Lv *et al.* (2016)
Men with fertility problems in China	Male fertility	Chen *et al.* (2013)

E.3.10.4. OEHHA Derived Screening Toxicity Criteria for 4t-OP

OEHHA selected the oral NOAEL of 200 ppm (10.9 mg per kg per day) for systemic and postnatal effects in the F1 and F2 generation rats (Table E.3.10.3.2-1 and Table E.3.10.3.2-2, Tyl *et al.* (1999)) as the POD for a screening DART TC_{oral} (Table E.3.10.3.6-1). The DART TC_{oral} was calculated by applying a combined UF of 3,00 with (UF_A = 10 and UF_H = 30). This Chronic TC_{oral} of 0.004 mg per kg per day is applicable for dermal and inhalation exposures.

The Minnesota Department of Health (2020) also used the study by Tyl *et al.* (1999) for the basis of their calculation of guidance value in drinking water. They also selected 200 ppm as the NOAEL (but used an average dose of 22 mg per kg per day), a dose adjustment factor of 0.23 for animal to human bodyweight scaling, and a combined UF of 30 (UF_A = 3 and UF_H = 10). The calculated reference dose was 0.17 mg per kg per day, a level higher than the OEHHA Chronic TC_{oral}, mainly due to the difference in the magnitude of the combined UFs.

Table E.3.10.3.6-1. OEHHA Synthetic Turf Study-Specific Screening Toxicity Criteria for Oral (DART TC_{oral}) Exposure to 4t-OP Based on Developmental and/or Reproductive Toxicity (DART)

Species, Route, and Duration	Toxicity Endpoint	Point of Departure	Uncertainty Factors	DART TC_{oral}	Reference
Rat, Diet, 2-generation	Bodyweight and uterine weight changes	10.9 mg per kg per day (NOAEL)	UF_A = 10 UF_H = 30 Combined UF = 300	0.04 mg per kg per day	Tyl *et al.* (1999)

The DART TC_{oral} was calculated as the value for point of departure divided by the value for combined uncertainty factors.
NOAEL: no-observed-adverse-effect level; UF: uncertainty factor; UF_A: animal to human (interspecies) extrapolation UF; and UF_H: human variability in response (intraspecies) UF..

E.4. References

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