CHEMICAL UPDATE WORKSHEET

Chemical Name:	**Isophorone (DD)**
CAS #:	**78-59-1**
Revised By:	RRD Toxicology Unit
Revision Date:	September 24, 2015

(A) Chemical-Physical Properties

	Part 201 Value	Updated Value	Reference Source	Comments
Molecular Weight (g/mol)	138.23	138.21	EPI	EXP
Physical State at ambient temp	Liquid	Liquid	MDEQ	
Melting Point (˚C)	265	-8.10	EPI	EXP
Boiling Point (˚C)	215.2	215.20	EPI	EXP
Solubility (ug/L)	1.20E+7	12000000	EPI	EXP
Vapor Pressure (mmHg at 25˚C)	0.4104	4.38E-01	EPI	EXP
HLC (atm-m^3/mol at 25˚C)	6.20E-6	6.64E-06	SSG	EXP
Log Kow (log P; octanol-water)	1.699	1.70	EPI	EXP
Koc (organic carbon; L/Kg)	46.8	65.15	EPI	EST
Ionizing Koc (L/kg)		NR	NA	NA
Diffusivity in Air (Di; cm^2/s)	0.0623	5.25E-02	W9	EST
Diffusivity in Water (Dw; cm^2/s)	6.76E-6	7.53E-06	W9	EST
Soil Water Partition Coefficient (Kd; inorganics)	NR	NR	NA	NA

	Part 201 Value	Updated Value	Reference Source	Comments
Flash Point (˚C)	184 F	84	CRC	EXP
Lower Explosivity Level (LEL; unitless)	0.008	0.008	CRC	EXP
Critical Temperature (K)		715.00	EPA2001	EXP
Enthalpy of Vaporization (cal/mol)		1.03E+04	EPA2001	EXP
Density (g/mL, g/cm^3)		0.9255	CRC	EXP
EMSOFT Flux Residential 2 m (mg/day/cm^2)	6.83E-06	1.04E-05	EMSOFT	EST
EMSOFT Flux Residential 5 m (mg/day/cm^2)	6.83E-06	1.05E-05	EMSOFT	EST
EMSOFT Flux Nonresidential 2 m (mg/day/cm^2)	8.17E-06	1.33E-05	EMSOFT	EST
EMSOFT Flux Nonresidential 5 m (mg/day/cm^2)	8.17E-06	1.33E-05	EMSOFT	EST

(B) Toxicity Values/Benchmarks

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
Reference Dose (RfD) (mg/kg/day)	1.5E-1	2.0E-1	IRIS, 1991	
RfD details		**Tier 1 Source:** **IRIS:** **Basis:** IRIS is a Tier 1 source and most recent. **IRIS** oral RfD = 2.0E-1 mg/kg-day. **Critical Study**: Nor-Am Agricultural Products, Inc. 1972. MRID No. 00123976. **Method**: Beagle dogs (4/sex/dose) were administered gelatin capsules containing 0, 35, 75, or 150 mg isophorone/kg/day, 7 days/week for 90 days. **Critical effect:** No critical effects were identified. **End point or Point of Departure (POD):** 150 mg/kg-day were identified as the NOEL for lack of critical effects at any test dose. **Uncertainty Factors**: 1,000 (10 for interspecies extrapolation, 10 for intraspecies variability, and 10 for sub chronic-to-chronic extrapolation). **Source and date:** IRIS, 1/1/1991. **Tier 2 Sources**: **MRL (12/1989):** intermediate oral MRL = 3 mg/kg/day. The MDEQ uncertainty factor adjustment would result in a chronic MRL of 3E-1 mg/kg/d. **Critical study**: AME Inc. (Affiliated Medical Enterprises, Inc.). 1972a. 90-Day sub chronic toxicity of isophorone in the rat (final report). Unpublished study performed by AME, Inc. Princeton, NJ, for Rohm and Haas Co. Philadelphia, PA. OTS 8d submission Dot ID. 87812178, Microfiche No. 205975. **Method**: 90-day oral diet feeding study in rats. 311.8 mg/kg/d were the highest dose administered in this study. **Critical effect**: No critical effects were identified. **End point or point of departure (POD)**: A NOAEL of 311.8 mg/kg/d was identified for lack of critical effects at any test dose. **Uncertainty factors**: 100 (10 for interspecies extrapolation and 10 for intraspecies variability). MDEQ would apply an additional uncertainty factor of 10 to account for the use of a sub chronic study, for a total uncertainty factor of 1,000.		Complete

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
		PPRTV: No PPRTV record available at this time. **Tier 3 Source:** **MDEQ:** Per DEQ-CCD, RRD (1989) and WRD (1998), RfD = 0.15 based on the beagle study reported in IRIS. 5/18/1989.		
Oral Cancer Slope Factor (CSF) (mg/kg-day)$^{-1}$)	1.1E-3	9.5E-4	IRIS, 1992	
CSF details	Carcinomas of the preputial gland in male F344/N rats dosed via gavage (vehicle = corn oil), 5 days/week for 103 weeks. Male rats at risk in the 0, 250 and 500 mg/kg dose groups were 49, 46 and 44, respectively (NTP, 1986). Revised species scaling factor of (BWh/BWa) to the 0.25 power used for q* calculation. Unable to duplicate SF presented in IRIS. (IRIS CSF = 9.5E-4.) 1/13/2000	**Tier 1 Source:** **IRIS:** **Basis:** IRIS is a Tier 1 source. **IRIS** oral cancer slope factor = 9.5E-4 per mg/kg-day **Critical Study**: NTP (National Toxicology Program). 1986. Toxicology and carcinogenesis studies of isophorone (CAS No. 78-59-1) in F344/N rats and B6C3F1 mice (gavage studies). NTP TR-291. NIH Pub. No. 86-2547. **Method**: NTP administered isophorone via corn oil gavage to F344/N rats (50/sex/group) at 0, 250, or 500 mg/kg/day, 5 days/week for 103 weeks. **Carcinogen Weight-of-Evidence (WOE) Class**: Classification - C; possible human carcinogen, based on no data in humans; limited evidence of carcinogenicity of one tumor type in one sex of one animal species as shown by an increase of preputial gland carcinomas in male rats. The apparent renal tubular cell tumor in the male rat is associated with alpha-2μ-globulin, considered to be of questionable relevance to humans. **WOE Basis:** Survival of high-dose male rats (28%) was significantly reduced after 96 weeks compared with controls (66%) and low-dose males (66%). The first preputial gland tumor appeared at week 56. The tumor incidences, after adjustment for survival, were 0/49, 0/46 and 5/44 for control, low- and high- dose groups, respectively. The positive trend in tumor incidence was statistically significant by the Life Table Test. The tumor incidence in the high-dose group was statistically significantly elevated when compared with the NTP historical controls (i.e., 12/1094 as of 1986) by the Fisher Exact Test. After survival adjustment, this group differed from the concurrent control as well. The treated male rats showed		Complete

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
	MDEQ/WB	renal cell hyperplasia and a small number of renal tubular cell adenomas and adenocarcinomas after week 99 when the survival rate was down to 32%. Female rats showed a moderate increase in nephropathy, with no neoplastic lesions. **Source and Date:** IRIS, 11/1/1992. **Tier 2 Sources**: **PPRTV:** No PPRTV record available at this time. **MRL:** NA; MRLs are for non-cancer effects only. **Tier 3 Source:** **MDEQ-RRD (01/13/2000):** Per DEQ-CCD, the oral cancer slope factor = 1.1E-3 per mg/kg/day. Carcinomas of the preputial gland in male F344/N rats dosed via gavage (vehicle = corn oil), 5 days/week for 103 weeks. Male rats at risk in the 0, 250 and 500 mg/kg dose groups were 49, 46 and 44, respectively (NTP, 1986). Revised species scaling factor of (BWh/BWa) to the 0.25 power used for q* calculation. Unable to duplicate SF presented in IRIS. Same as WRD.		
Reference Concentration (RfC) or Initial Threshold Screening Level (ITSL) (µg/m³)	2.8E+2	2.0E+3	CalEPA, 12/2001	
RfC/ITSL details	AQD/TLV, 11/23/1992	**Tier 3 Source:** **CALEPA:** **Basis:** CALEPA chronic REL is based on unpublished developmental studies in two different species. MDEQ/AQD ITSL is based on a 1992 TLV. See details below. **Tier 1 and 2 Sources**: **IRIS (03/01/1991):** The health effects data for isophorone were reviewed by the U.S. EPA RfD/RfC Work Group and determined to be inadequate for derivation of an inhalation RfC. **PPRTV:** No PPRTV record available at this time. **MRL:** No inhalation MRL value(s) available at this time.		Complete

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
		Tier 3 Sources: **MDEQ-AQD (11/23/1992):** Per DEQ-CCD, the ITSL = 280 ug/m^3, 1 hr. averaging time. Basis = TLV. Final. **CALEPA/OEHHA** (December, 2001): Chronic Reference Exposure Level (REL) = 2.0E+3 µg/m^3. **Critical studies**: Bio/dynamics. (1984a). Inhalation teratology probe study in rats and mice. Project No. 323771. Unpublished study performed by Bio/dynamics Inc. East Millstone, NJ. OTS Section 4 submission Doc. ID 40-8455042. Microfiche No. OTS0507219, pp. 1-33. Bio/dynamics. (1984b). Inhalation teratology study in rats and mice. Final Report 3223772. Unpublished study performed by Bio/dynamics Inc. East Millstone, NJ for Exxon Biomedical Science, East Millstone NJ. OTS Section 4 submission Doc. ID 40-855049. Microfiche No. OTS 0507224, pp. 1-107. **Methods**: 22 female rats or mice per dose were exposed to 0, 25, 50, or 115 ppm isophorone via whole body exposure for 6 hr./day during gestation days 6-15. **Critical effects**: Developmental effects (reduced crown-rump length of female rat fetuses); teratogenicity (exencephaly in fetal rats and mice) in range finding study at 150 ppm. **Point of departure**: NOAEL = 50 ppm, $NOAEL_{ADJ}$ = 12.5 ppm, $NOAEL_{HEC}$ = 12.5 ppm **Uncertainty factors**: UF = 30 (3 for interspecies extrapolation and 10 for intraspecies variability) **MNPCA (06/2015):** RfC = 2E+3 µg/m^3 based on CALEPA. **NJDEP (08/2011)**: RfC = 2E+3 µg/m^3 based on CALEPA. **Other Tier 3:** No value is available at this time from these Tier 3 sources/databases: HEAST, NTP ROC, health and environmental agencies of Massachusetts, New York, and Texas, WHO (IARC), WHO (IPCS/INCHEM), Canada,		

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
		The Netherlands (RIVM), ECHA (REACH) and OECD HPV.		
Inhalation Unit Risk Factor (IURF) ((µg/m^3)$^{-1}$)	2.7E-7	2.7E-7	MDEQ, 1998	
IURF details	AQD/EPA, 6/3/1998; Based on EPA oral CSF of 9.5E^{-4} per mg/kg/day.	**Tier 3 Source:** **MDEQ:** **Basis:** MDEQ is the only available value. See details below. **Tier 1 and 2 Sources**: **IRIS:** An inhalation cancer evaluation is not available at this time, 11/1/1992. **PPRTV:** No PPRTV record available at this time. **MRL:** NA; MRLs are for non-cancer effects only. **Tier 3 Sources:** **MDEQ-AQD** (6/2/1998): Per DEQ-CCD, the IURF = 2.7E-7 per µg/m^3. The IRSL is based on an EPA oral cancer slope factor of 9.5E-4 (mg/kg/day)$^{-1}$. This was based on increased incidence of preputial gland carcinomas observed in male rats in a National Toxicology Program (1986) bioassay (TR-291). **Other Tier 3:** No value is available at this time from these Tier 3 sources/databases: HEAST, NTP ROC, health and environmental agencies of California, Massachusetts, Minnesota, New Jersey, New York, and Texas, WHO (IARC), WHO (IPCS/INCHEM), Canada, The Netherlands (RIVM), ECHA (REACH) and OECD HPV.		Complete
Mutagenic Mode of Action (MMOA)? (Y/N)	--	No	USEPA, 2015	
MMOA Details	--	Not listed as a carcinogen with mutagenic MOA in the USEPA OSWER List.		
Developmental or Reproductive Effector? (Y/N)	No	Yes-inhalation; the RfC is based on a reproductive-developmental effect. Inhalation Exposure Pathways- Single Exposure No – oral. The RfD is not based on a reproductive-	MDEQ, 2015	

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
		developmental effect.		
Developmental or Reproductive Toxicity Details	NA	**Critical effects**: Developmental effects (reduced crown-rump length of female rat fetuses); teratogenicity (exencephaly in fetal rats and mice) in range finding study at 150 ppm. **Critical studies**: Bio/dynamics. (1984a). Inhalation teratology probe study in rats and mice. Project No. 323771. Unpublished study performed by Bio/dynamics Inc. East Millstone, NJ. OTS Section 4 submission Doc. ID 40-8455042. Microfiche No. OTS0507219, pp. 1-33. Bio/dynamics. (1984b). Inhalation teratology study in rats and mice. Final Report 3223772. Unpublished study performed by Bio/dynamics Inc. East Millstone, NJ for Exxon Biomedical Science, East Millstone NJ. OTS Section 4 submission Doc. ID 40-855049. Microfiche No. OTS 0507224, pp. 1-107. **Methods**: 22 female rats or mice per dose were exposed to 0, 25, 50, or 115 ppm isophorone via whole body exposure for 6 hr./day during gestation days 6-15.		
State Drinking Water Standard (SDWS) (µg/L)	--	NO	SDWA, 1976	
SDWS details	NA	MI Safe Drinking Water Act (SDWA) 1976 PA 399		
Secondary Maximum Contaminant Level (SMCL) (µg/L)	--	NO	SDWA, 1976 and USEPA SMCL List	
SMCL details	NA	MI Safe Drinking Water Act (SDWA) 1976 PA 399 and USEPA SMCL List, 2015		
Is there an Aesthetic Value? (Y/N)	No	Not evaluated.	NA	
Aesthetic value details	NA	NA		
Is there a Phytotoxicity Value? (Y/N)	No	Not evaluated.	NA	

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
Phytotoxicity details	NA	NA		
Others:				

(C) Chemical-specific Absorption Factors

	Part 201 Value	Update	Source/Reference/ Dates	Comments/Notes /Issues
Gastrointestinal absorption efficiency value (ABSgi)	---	1.0	MDEQ, 2015/USEPA RAGS-E, 2004	
ABSgi details		RAGS E (USEPA, 2004) Default Value		
Skin absorption efficiency value (AEd)	---	0.1	MDEQ, 2015	
AEd details				
Ingestion Absorption Efficiency (AEi)		1.0	MDEQ, 2015	
AEi Details				
Relative Source Contribution for Water (RSC_W)		0.2	MDEQ, 2015	
Relative Source Contribution for Soil (RSC_S)		1.0	MDEQ, 2015	
Relative Source Contribution for Air (RSC_A)		1.0	MDEQ, 2015	
Others				

(D) Rule 57 Water Quality Values and GSI Criteria

Current GSI value (µg/L)	1,300 (X)
Updated GSI value (µg/L)	1,300 (X)
Rule 57 Drinking Water Value (µg/L)	310

	Rule 57 Value (µg/L)	Verification Date
Human Non-cancer Values- Drinking water source (HNV-drink)	4,100	11/1998
Human Non-Cancer Values- Non-drinking water sources (HNV-Non-drink)	110,000	11/1998
Wildlife Value (WV)	NA	NA
Human Cancer Values for Drinking Water Source (HCV-drink)	310	11/1998
Human Cancer values for non-drinking water source (HCV-Non-drink)	8,200	11/1998
Final Chronic Value (FCV)	1,300	7/2002
Aquatic maximum value (AMV)	4,600	7/2002
Final Acute Value (FAV)	9,200	7/2002

Sources:

1. MDEQ Surface Water Assessment Section Rule 57 website
2. MDEQ Rule 57 table

(E) Target Detection Limits (TDL)

	Value	Source
Target Detection Limit – Soil (μg/kg)	330	MDEQ, 2015
Target Detection Limit – Water (μg/L)	5	MDEQ, 2015
Target Detection Limit – Air (ppbv)	NA	MDEQ, 2015
Target Detection Limit – Soil Gas (ppbv)	NA	MDEQ, 2015

CHEMICAL UPDATE WORKSHEET ABBREVIATIONS:

CAS # - Chemical Abstract Service Number.

Section (A) Chemical-Physical Properties

Reference Source(s):

CRC	Chemical Rubber Company Handbook of Chemistry and Physics, 95th edition, 2014-2015
EMSOFT	USEPA Exposure Model for Soil-Organic Fate and Transport (EMSOFT) (EPA, 2002)
EPA2001	USEPA (2001) Fact Sheet, Correcting the Henry's Law Constant for Soil Temperature. Office of Solid Waste and Emergency Response, Washington, D.C.
EPA4	USEPA (2004) User's Guide for Evaluating Subsurface Vapor Intrusion into Buildings. February 22, 2004.
EPI	USEPA's Estimation Programs Interface SUITE 4.1, Copyright 2000-2012
HSDB	Hazardous Substances Data Bank
MDEQ	Michigan Department of Environmental Quality
NPG	National Institute for Occupational Safety and Health Pocket Guide to Chemical Hazards
PC	National Center for Biotechnology Information's PubChem database
PP	Syracuse Research Corporation's PhysProp database
SCDM	USEPA's Superfund Chemical Data Matrix
SSG	USEPA's Soil Screening Guidance: Technical Background Document, Second Edition, 1996
USEPA/EPA	United States environmental protection agency's Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment). July, 2004.
W9	USEPA's User Guide for Water9 Software, Version 2.0.0, 2001

Basis/Comments:

EST	estimated
EXP	experimental
EXT	extrapolated
NA	not available or not applicable
NR	not relevant

Section (B) Toxicity Values/Benchmarks

Sources/References:

ATSDR	Agency for Toxic Substances and Disease Registry
CALEPA	California Environmental Protection Agency
CAL DTSC	California Department of Toxic Substances Control
CAL OEHHA	CAEPA Office of Environmental Health Hazard Assessment
CCD	MDEQ Chemical Criteria Database
ECHA	European Chemicals Agency (REACH)
OECD HPV	Organization for Economic Cooperation and Development HPV Database
HEAST	USEPA's Health Effects Assessment Summary Tables
IRIS	USEPA's Integrated Risk Information System
MADEP	Massachusetts Department of Environmental Protection
MDEQ/DEQ	Michigan Department of Environmental Quality
DEQ-CCD/AQD	MDEQ Air Quality Division
DEQ-CCD/RRD	MDEQ Remediation and Redevelopment Division
DEQ-CCD/WRD	MDEQ Water Resources Division
MNDOH	Minnesota Department of Health

NJDEP	New Jersey Department of Environmental Protection
NYDEC	New York State Department of Environmental Conservation
OPP/OPPT	USEPA's Office of Pesticide Programs
PPRTV	USEPA's Provisional Peer Reviewed Toxicity Values
RIVM	The Netherlands National Institute of Public Health and the Environment
TCEQ	Texas Commission on Environmental Quality
USEPA	United States Environmental Protection Agency
USEPA OSWER	USEPA Office of Solid Waste and Emergency Response
USEPA MCL	USEPA Maximum Contaminant Level
WHO	World Health Organization
WHO IPCS	International Programme on Chemical Safety (IPCS/INCHEM)
WHO IARC	International Agency for Research on Cancers
NA	Not Available.
NR	Not Relevant.

Toxicity terms:

BMC	Benchmark concentration
BMCL	Lower bound confidence limit on the BMC
BMD	benchmark dose
BMDL	Lower bound confidence limit on the BMD
CSF	Cancer slope Factor
CNS	Central nervous system
IURF or IUR	Inhalation unit risk factor
LOAEL	Lowest observed adverse effect level
LOEL	Lowest observed effect level
MRL	Minimal risk level (ATSDR)
NOAEL	No observed adverse effect level
NOEL	No observed effect level
RfC	Reference concentration
RfD	Reference dose
p-RfD	Provisional RfD
aRfD	Acute RfD
UF	Uncertainty factor
WOE	Weight of evidence

Section (C) Chemical-specific Absorption Factors

MDEQ	Michigan Department of Environmental Quality
USEPA RAGS-E	United States Environmental Protection Agency's Risk Assessment Guidance for Superfund Volume I: Human Health Evaluation Manual (Part E, Supplemental Guidance for Dermal Risk Assessment). July, 2004.

Section (D) Rule 57 Water Quality Values and GSI Criteria

GSI	Groundwater-surface water interface
NA	A value is not available or not applicable.
ID	Insufficient data to derive value
NLS	No literature search has been conducted