CHEMICAL UPDATE WORKSHEET

Chemical Name:	**Phenytoin (DD)**
CAS #:	**57-41-0**
Revised By:	RRD Toxicology Unit
Revision Date:	September 16, 2015

(A) Chemical-Physical Properties

	Part 201 Value	Updated Value	Reference Source	Comments
Molecular Weight (g/mol)	252.2718	252.27	EPI	EXP
Physical State at ambient temp	Solid	Solid	MDEQ	
Melting Point (˚C)	286	295.00	EPI	EXP
Boiling Point (˚C)	511.82	NA	NA	
Solubility (ug/L)	3.2E+4	32000	EPI	EXP
Vapor Pressure (mmHg at 25˚C)	1.2E-10	1.20E-10	PP	EST
HLC (atm-m^3/mol at 25˚C)	1.02E-11	1.02E-11	PP	EST
Log Kow (log P; octanol-water)	2.47	2.47	EPI	EXP
Koc (organic carbon; L/Kg)	1473	1473	EPI	EST
Ionizing Koc (L/kg)		NR	NA	
Diffusivity in Air (Di; cm^2/s)	0.08	4.76E-02	W9	EST
Diffusivity in Water (Dw; cm^2/s)	8.0E-6	5.56E-06	W9	EST
Soil Water Partition Coefficient (Kd; inorganics)	NR	NR	NA	NA

	Part 201 Value	Updated Value	Reference Source	Comments
Flash Point (˚C)	NA	NA	NA	NA
Lower Explosivity Level (LEL; unitless)	NA	NA	NA	NA
Critical Temperature (K)		NA	NA	NA
Enthalpy of Vaporization (cal/mol)		NA	NA	NA
Density (g/mL, g/cm^3)		NA	NA	NA
EMSOFT Flux Residential 2 m (mg/day/cm^2)	NA	5.72E-10	EMSOFT	EST
EMSOFT Flux Residential 5 m (mg/day/cm^2)	NA	5.72E-10	EMSOFT	EST
EMSOFT Flux Nonresidential 2 m (mg/day/cm^2)	NA	5.73E-10	EMSOFT	EST
EMSOFT Flux Nonresidential 5 m (mg/day/cm^2)	NA	5.73E-10	EMSOFT	EST

(B) Toxicity Values/Benchmarks

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
Reference Dose (RfD) (mg/kg/day)	3.0E-2	3.0E-2	MDEQ, 2011	
RfD details	The RfD is based on the lowest reported human therapeutic dose = LOAEL = 3 mg/kg/day. UF = 100 (10 each for intraspecies variability and LOAEL-to-NOAEL extrapolation). CRITICAL EFFECT = neurological and development effects. 3/1/10.	**Tier 3 Source:** **MDEQ:** **Basis:** Canada's PNEC and LTD values are less appropriate for use as toxicity health reference values. MDEQ provides the most recent toxicity assessment. See details below. **Tier 1 and 2 Sources**: **IRIS:** No IRIS file available at this time. **PPRTV:** No PPRTV record available at this time. **MRL:** No MRL record available at this time. **Tier 3 Sources:** **MDEQ RfD =** 3.0E-2 mg/kg/day. **Critical Study and Method**: Per DEQ-RMD, The human studies reported adverse effects using doses within the human therapeutic dose range of 3 to 15 mg phenytoin/kg-day, so the low end of the therapeutic dose range (3 mg/kg-day) (Gilman et al. 1990) was chosen as the LOAEL. A NOAEL could not be identified. Source: Gilman AG, Rall TW, Nies AS, Taylor P (1990). Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th Edition. Pergamon Press). . **Critical effect**: Decreased IQ and language development in offspring in humans (Scolnik et al. 1994), decreased cognition (Akaho, 1996), decreased cognition and mood effects (Meador et al., 1995), and cerebellar atrophy (DeMarco et al. 2003). **End point or Point of Departure (POD):** LOAEL = 3 mg/kg-day **Uncertainty Factors**: UF = 100 (10 each for LOAEL-to-NOAEL and intraspecies extrapolation **Source and date:** MDEQ-RMD, **RMD Toxicological Assessment 3/21/2011.** **MDEQ:** Per CCD/WRD (4/28/2010), RfD = 3.0E-2 mg/kg-day based on the lowest therapeutic dose (3 mg/kg-day) in children (LOAEL). A total UF of 100 is applied to		Complete

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
		account for LOAEL-to-NOAEL and intraspecies extrapolation. **CANADA**: 1) Predicted No Effect Concentration (PNEC) = 0.088 mg/L for water This PNEC value was the iTeco (inherently toxic to non-human organisms) value divided by 100 to account for uncertainty in the data. 2) Lowest therapeutic dose (LTD) = 4.0 mg/kg-day. Source: Screening Assessment Twenty-three Substances on the Domestic Substances List Used Primarily as Pharmaceuticals, 2015. **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, The Netherlands (RIVM), WHO (IARC), WHO (IPCS/INCHEM), ECHA (REACH) and OECD HPV.		
Oral Cancer Slope Factor (CSF) (mg/kg-day)$^{-1}$)	5.1E-2	5.1E-2	MDEQ-RMD, 2011	
CSF details	Oral SF is based on a chronic oral study in mice (NTP, 1993). Male and female B6C3F1 mice were exposed via diet for 2 years. Combined liver tumors were significantly increased over control in female mice.	**Tier 3 Source:** **MDEQ:** **Basis:** MDEQ was the only value returned in the Tier 3 search. See details below. **Carcinogen Weight-of-Evidence (WOE) Class and Basis**: The IARC classification of carcinogenicity: evidence in humans is inadequate and evidence in animals is sufficient, with an overall summary evaluation of carcinogenic risk to humans classified as Group 2B: the agent is possibly carcinogenic to humans. The NTP assessment of carcinogenicity: phenytoin is reasonably anticipated to be a human carcinogen. **Tier 1 and 2 Sources**: **IRIS:** No IRIS file available at this time. **PPRTV:** No PPRTV record available at this time. **MRL:** NA; MRLs are for non-cancer effects only.		Complete

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
		Tier 3 Sources: **MDEQ: MDEQ/WMD (3/2011) CSF** = 5.1E-2 $(mg/kg\text{-}day)^{-1}$) **Critical Study:** NTP (National Toxicology Program) (1993). NTP technical report on the perinatal toxicology and carcinogenesis studies of 5,5-diphenylhydantoin in F344/N rats and B6C3F1 mice. Research Triangle Park, NC, NIH No. 94-2859. **Methods**: The NTP study (NTP 1993) included two-year feed experiments for F344/N rats and B6C3F1 mice. A slope factor of 0.051 $(mg/kg\text{-}day)^{-1}$ was developed based on Benchmark Dose evaluation of the NTP study cancer data for the combined liver tumors in female mice as it provided the best model fit. (See Appendix A of MDEQ/-RMD Toxicological Assessment, 2011). **Source and Date**: DEQ-RMD, 3/ 2011. **MDEQ:** Per DEQ-CCD/WRD (4/28/2010), CSF = 3.0E-2 $(mg/kg\text{-}day)^{-1}$. Basis: NTP (1993) found a statistically significant increase in combined hepatocellular adenomas, hepatocellular carcinomas, and hepatoblastomas in female B6C3F1 mice. Animal weight = 0.03820 kg. **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, Canada, The Netherlands (RIVM), WHO (IARC), WHO (IPCS/INCHEM), ECHA (REACH) and OECD HPV.		
Reference Concentration (RfC) or Initial Threshold Screening Level (ITSL) (µg/m³)	--	NA	MDEQ, 2015	
RfC/ITSL details	Per AQD: health based ITSL for this solid material is greater than PM	**Tier 1 and 2 Sources:** **IRIS:** No IRIS file available at this time. **PPRTV:** No PPRTV record available at this time. **MRL:** No MRL record available at this time.		Complete

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
	NAAQS. Recommended to utilize PM NAAQS instead of setting ITSL. 3/1/10.	**Tier 3 Source:** **MDEQ:** Per DEQ-CCD (10/19/2010), no RfC value at this time.		
Inhalation Unit Risk Factor (IURF) ((µg/m^3)$^{-1}$)	1.4E-5	1.4E-5	MDEQ, 2010	
IURF details	Per AQD: The inhalation SF is based on an oral SF (0.051 (mg/kg)-1 from the NTP 1993 increased incidence of liver tumors in Female mice 5/38, 14/40, 30/45 at doses of 0, 50 and 160 mg/kg. AQD calculation date: 10/19/10.	**Tier 3 Source:** **MDEQ:** **Basis:** MDEQ was the only value returned in the Tier 3 search. See details below. **Carcinogen Weight-of-Evidence (WOE) Class and Basis**: IARC classification of carcinogenicity: evidence in humans is inadequate and evidence in animals is sufficient, with an overall summary evaluation of carcinogenic risk to humans classified as Group 2B: the agent is possibly carcinogenic to humans. NTP assessment of carcinogenicity: reasonably anticipated to be a human carcinogen. **Sources and dates**: IARC. Monograph v.61, 1996, p175; NTP Report on Carcinogens, 13th Ed. (2014) **Tier 1 and 2 Sources:** **IRIS:** No IRIS file available at this time. **PPRTV:** No PPRTV record available at this time. **MRL:** NA; MRLs are for non-cancer effects only. **Tier 3 Sources:** **MDEQ:** AQD (2010) IUR = 1.4E-5 (µg/m^3)$^{-1}$: **Critical Study**: The inhalation SF is based on an oral SF (0.051 (mg/kg)-1 from the NTP 1993 increased incidence of liver tumors in female mice 5/38, 14/40, 30/45 at doses of 0, 50 and 160 mg/kg. Averaging time = annual. **Source and Date**: CCD-AQD; 10/19/2010		Complete

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
		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, Canada, The Netherlands (RIVM), WHO (IARC), WHO (IPCS/INCHEM), ECHA (REACH) and OECD HPV.		
Mutagenic Mode of Action (MMOA)? (Y/N)	--	NO	USEPA, 2015	
MMOA Details	--	NA		
Developmental or Reproductive Effector? (Y/N)	--	Yes-oral, the RfD is based on developmental-reproductive effects in human offspring. Oral Exposure Pathways- Single Exposure	MDEQ, 2015	
Developmental or Reproductive Toxicity Details	--	**Critical Study and Method**: Per DEQ-RMD, The human studies reported adverse effects using doses within the human therapeutic dose range of 3 to 15 mg phenytoin/kg-day, so the low end of the therapeutic dose range (3 mg/kg-day) (Gilman et al. 1990) was chosen as the LOAEL. A NOAEL could not be identified. Source: Gilman AG, Rall TW, Nies AS, Taylor P (1990). Goodman and Gilman's The Pharmacological Basis of Therapeutics, 8th Edition. Pergamon Press). . **Critical effect**: ***Decreased IQ and language development in offspring in humans*** (Scolnik et al. 1994), decreased cognition (Akaho, 1996), decreased cognition and mood effects (Meador et al., 1995), and cerebellar atrophy (DeMarco et al. 2003).		
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	--	MI Safe Drinking Water Act (SDWA) 1976 PA 399 and USEPA SMCL List, 2015		

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
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	
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)	89 (X)
Updated GSI value (µg/L)	89 (X)
Rule 57 Drinking Water Value (µg/L)	15 (M); 6.1

	Rule 57 Value (µg/L)	Verification Date
Human Non-cancer Values- Drinking water source (HNV-drink)	790	4/2010
Human Non-Cancer Values- Non-drinking water sources (HNV-Non-drink)	11,000	4/2010
Wildlife Value (WV)	NA	NA
Human Cancer Values for Drinking Water Source (HCV-drink)	6.1	4/2010
Human Cancer values for non-drinking water source (HCV-Non-drink)	89	4/2010
Final Chronic Value (FCV)	120	6/2006
Aquatic maximum value (AMV)	1,100	6/2006
Final Acute Value (FAV)	2,200	6/2006

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)	250	MDEQ, 2015
Target Detection Limit – Water (μg/L)	15	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