CHEMICAL UPDATE WORKSHEET

Chemical Name:	**2-Methyl-4,6-dinitrophenol (4,6-Dintro-o-cresol)**
CAS #:	**534-52-1**
Revised By:	RRD Toxicology Unit
Revision Date:	September 21, 2015

(A) Chemical-Physical Properties

	Part 201 Value	Updated Value	Reference Source	Comments
Molecular Weight (g/mol)	198.13	198.14	EPI	EXP
Physical State at ambient temp	Solid	Solid	MDEQ	
Melting Point (˚C)	---	86.60	EPI	EXP
Boiling Point (˚C)	378	378.00	EPI	EXP
Solubility (ug/L)	2.00E+5	198000	EPI	EXP
Vapor Pressure (mmHg at 25˚C)	0.00032	1.20E-04	EPI	EXP
HLC (atm-m^3/mol at 25˚C)	4.30E-7	1.40E-06	EPI	EXP
Log Kow (log P; octanol-water)	2.1	2.13	EPI	EXP
Koc (organic carbon; L/Kg)	116	754.4	EPI	EST
Ionizing Koc (L/kg)		NR	NA	NA
Diffusivity in Air (Di; cm^2/s)	0.08	3.19E-02	W9	EST
Diffusivity in Water (Dw; cm^2/s)	8.0E-6	8.36E-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; unit less)	NA	NA	NA	NA
Critical Temperature (K)		NA	NA	NA
Enthalpy of Vaporization (cal/mol)		NA	NA	NA
Density (g/mL, g/cm^3)		1.58	PC	EXP
EMSOFT Flux Residential 2 m (mg/day/cm^2)	NA	1.22E-06	EMSOFT	EST
EMSOFT Flux Residential 5 m (mg/day/cm^2)	NA	1.22E-06	EMSOFT	EST
EMSOFT Flux Nonresidential 2 m (mg/day/cm^2)	NA	1.55E-06	EMSOFT	EST
EMSOFT Flux Nonresidential 5 m (mg/day/cm^2)	NA	1.55E-06	EMSOFT	EST

(B) Toxicity Values/Benchmarks

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
Reference Dose (RfD) (mg/kg/day)	3.5E-4	4.0E-4	ATSDR, 1998/MDEQ 2015	
RfD details	The RfD is based on human clinical data in obese patients treated with this substance as a metabolic stimulator (Plotz, 1936). Four patients were evaluated in this study following oral exposure at variable doses (0.35 to 1.0 mg/kg/d) and durations (several days to 11 weeks). CRITICAL EFFECT = headache, fatigue, feeling hot, and green sclerae. LOAEL = 0.35 mg/kg/d. UF = 1,000 (10 each for intraspecies variability and sub-chronic to chronic and LOAEL to NOAEL extrapolations). MDEQ / WB – 10/17/1990	**Tier 2 Source:** **ATSDR:** **Basis:** The MRL is a Tier 2 source. PPRTV was not selected as PPRTV chronic screening value is considered a Tier 3 source. **ATSDR oral intermediate MRL** = 0.004 mg/kg/day. MDEQ applied an additional UF = 10 for the use of an intermediate study. Final RfD = 0.0004 mg/kg/day. An oral acute MRL = 0.004 mg/kg/day is also listed. **Critical Study:** Plotz M. 1936. Dinitro-ortho-cresol. A metabolic stimulator and its toxic side-actions. N Y State J Med 41:266-268. **Methods:** male human exposed to 4,6-DNOC via capsule initially received 0.75 mg/kg/day for 3 days, but experienced elevated body temperature, fatigue, and dizziness after 2 days of taking 0.75 mg/kg/day. After a 2-week period of taking no DNOC, treatment was resumed at 0.35 mg/kg/day, and he complained of excessive perspiration, fatigue, and dizziness on the 7th day. **Critical effect:** neurological effects (fatigue, dizziness) **End point or Point of Departure (POD):** LOAEL of 0.35 mg/kg/day **Uncertainty Factors**: ATSDR UF = 100 (10 for use of a LOAEL and 10 for human variability). MDEQ UF = 10. Total UF = 1000. Source and date: ATSDR 8/1998 from April 2015 MRL list **Tier 1 and 2 Sources:** **IRIS:** No IRIS file available at this time. **PPRTV, 04-22-2010;** a subchronic p-RfD is available 8.0E-4mg/kg/day. Only a chronic screening level is available at this time 8.0E-5 mg/kg/day. Because the UF would increase to 10,000 to derive a chronic p-RfD, a chronic p-RfD was not derived. However, a screening value chronic p-RfD was derived in the Appendix: 0.8 mg/kg-day / 10,000 = 8E-5 mg/kg-day and that is the value presented above.		COMPLETE

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
		Critical Study: Ibrahim, H., H. Avad and M.A. Mahdi. 1934. The new treatment of obesity with dinitro-o-cresol or dekrysil. J. Egypt. Med. Assoc. 17:969−990. This study was chosen as the principal study because on the whole, it was the best conducted and utilized an adequate number of human subjects (eight males and seven females). It was also supported by several other human studies (Dodds and Robertson, 1933; Plotz, 1936; Harvey et al., 1951). **Method**: A study of patients taking DNOC to lose weight. 15 patients, 8 males and 7 females, 11 to 38 years old, took initial DNOC doses of 50 mg/day, increasing to 100 mg/day, for an average of 5.5 weeks. Information on body weight, total dose of DNOC received during treatment, and treatment duration were available for 6 males and 6 females. Using these data, the average daily dose was calculated to be 1.05 mg/kg-day for males (range 0.85-1.41 mg/kg-day) and females (range 0.8-1.27 mg/kg-day.) Males and females exhibited an average body weight loss of 4% and 3%, respectively. All of the patients developed signs and symptoms of DNOC toxicity within a few days including excessive sweating, fatigue, decreased appetite, elevated BMR, and greenish-yellow coloration of the conjunctivae. **Critical effect**: Metabolic critical effects including reduced body weight, excessive perspiration and fatigue, and elevated BMR and body temperature, as well as ocular effects (i.e., greenish-yellow coloration of the conjunctivae). **End point or Point of Departure (POD):** A LOAEL of 0.8 mg/kg-day was identified based on the above effects. **Uncertainty Factors**: UF = 10,000 for chronic screening value. A subchronic p-RfD was derived using an UF of 1,000 (10 for variation within the human population; 10 for database deficiencies because the data evaluating developmental and reproductive toxicity are incomplete; 10 for the use of a LOAEL as the POD.		

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
		Tier 3 Source: **MDEQ:** Per DEQ-CCD-RRD, RfD = 3.5E-4 mg/kg-day (10/17/1990) and appears to be the same study as cited in the PPRTV document noted above. See Part 201 value for details.		
Oral Cancer Slope Factor (CSF) (mg/kg-day)$^{-1}$)	--	NA	MDEQ, 2015	
CSF details		**Tier 1 and 2 Sources:** **IRIS:** No IRIS file available at this time. **PPRTV:** Under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), there is "Inadequate Information to Assess [the] Carcinogenic Potential of DNOC.". **MRL:** NA; MRLs are for non-cancer effects only. **Tier 3 Source:** **MDEQ:** Per DEQ-CCD, no value at this time.		Complete
Reference Concentration (RfC) or Initial Threshold Screening Level (ITSL) (µg/m³)	--	2.0E+0	MDEQ, 2011	
RfC/ITSL details		**Tier 3 Source:** **MDEQ:** **Basis:** MDEQ was the only value returned in the Tier 3 search. See details below. **Tier 1 and 2 Sources**: **IRIS:** No IRIS file available at this time. **PPRTV:** Per PPRTV (04-22-2010),due to a lack of suitable human or animal data, a subchronic or chronic p-RfC for DNOC cannot be derived **MRL:** Per ATSDR (08/1995), inhalation-based MRLs are not reported.		Complete

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
		Tier 3 Sources: **MDEQ:** Per DEQ-CCD-AQD (6/23/2011), the ITSL of 2 µg/m^3 is derived from the ACGIH TLV-TWA of 0.2 mg/m^3. 8-hour averaging time. **OTHERS:** 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.		
Inhalation Unit Risk Factor (IURF) ((µg/m^3)$^{-1}$)	--	NA	MDEQ, 2015	
IURF details	--	Per PPRTV (04-22-2010), under the 2005 Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005) there is "inadequate information to assess the carcinogenic potential of DNOC". The WHO (2000) monograph describes an unpublished 2-year feeding study in rats from the United Kingdom (Broadmeadow, 1991). In this study, no increase in the incidence of any tumor was seen in treated groups. However, because the study report is not available, a complete review of the study could not be performed. No other studies examining the carcinogenicity of DNOC in animals have been located, and no relevant human studies have been located. The mutagenicity and genotoxicity data for DNOC, as reviewed by WHO (2000), ATSDR (1995), and EPA (1986), are inconclusive. **Tier 1 Source**: **IRIS:** No IRIS file available at this time. **PPRTV:** No value available. **MRL:** NA; MRLs are for non-cancer effects only. **Tier 3 Source:** **MDEQ:** Per DEQ-CCD-AQD, not value available at this time.		Complete
Mutagenic Mode of Action	--	No	USEPA, 2015	

	Part 201 Value	Updated Value	Source/Reference/ Date	Comments/Notes /Issues
(MMOA)? (Y/N)				
MMOA Details	--	NA Not listed as a carcinogen with mutagenic MOA in the USEPA OSWER List.		
Developmental or Reproductive Effector? (Y/N)	No	No, the RfD is not based on a reproductive-developmental effect.	MDEQ, 2015	
Developmental or Reproductive Toxicity Details	--	NA		
State Drinking Water Standard (SDWS) (ug/L)	No	NO	SDWA, 1976	
SDWS details	NA	NA		
Secondary Maximum Contaminant Level (SMCL) (ug/L)	No	NO	SDWA, 1976 and USEPA SMCL List	
SMCL details	NA	NA		
Is there an aesthetic value for drinking water? (Y/N)	NO	Not evaluated.	NA	
Aesthetic value (ug/L)	Na	NA	NA	
Aesthetic Value details	NA	NA		
Phytotoxicity Value? (Y/N)	NO	Not evaluated.	NA	
Phytotoxicity details	NA	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	
ABSgi details		RAGS E (EPA, 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)	NA
Updated GSI value (µg/L)	NA
Rule 57 Drinking Water Value (µg/L)	NA

	Rule 57 Value (µg/L)	Verification Date
Human Non-cancer Values- Drinking water source (HNV-drink)		
Human Non-Cancer Values- Non-drinking water sources (HNV-Non-drink)		
Wildlife Value (WV)		
Human Cancer Values for Drinking Water Source (HCV-drink)		
Human Cancer values for non-drinking water source (HCV-Non-drink)		
Final Chronic Value (FCV)		
Aquatic maximum value (AMV)		
Final Acute Value (FAV)		

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)	830	MDEQ, 2015
Target Detection Limit – Water (μg/L)	20	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