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 Organization: PNW Pollution Prevention Resource Center  
 Date: 27 June 2012

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 Name: Alex Stone, Sc. D.  
 Title: Safer Chemical Alternative Chemist  
 Organization: WA Department of Ecology  
 Date: 16 May 2013

## **GreenScreen™ Assessment for Dichloromethane (DCM) (CAS #75-09-2)**

**GreenScreen™ Version 1.2 Draft Assessment**

***Note: Validation Has Not Been Performed on this Green Screen Assessment***

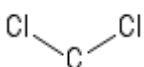
**Chemical Name:** Dichloromethane (DCM)

**Confirm application of the de minimus rule<sup>1</sup>:** (if no, what *de minimus* did you use?) Yes.

**Chemical Name (CAS #):** Dichloromethane (DCM) (CAS#78-93-3)

**Also Called:** "Bichloride, Methylene", "Chloride, Methylene", "Dichloride, Methylene", "Dichloromethane", "Methane, dichloro-", "Methylene chloride", "Methylene dichloride", "1,2-dichloromethane", "Freon 30", "R-30" (US EPA, ACToR database, [actor.epa.gov/](http://actor.epa.gov/))

**Chemical Surrogates, analogs or moieties used in this assessment (CASs #):**

**Chemical Structure(s):** 

**Identify Applications/Functional Uses: (e.g. Cleaning product, TV casing)**

1. Solvent in the pharmaceutical and chemical industry for reactions, and isolation of products.
2. Used as a feedstock for the production of HCFC 32 (R32), as a blowing agent in foam blowing, for plastics processing (e.g., polycarbonate resins), a
3. Used in aerosol products for applying or removing surface finishes or coatings, e.g., paints, varnishes, adhesives.
4. Used for cleaning and degreasing products, e.g., metal cleaning (e.g., cold or vapor degreasing). See Substance Background section below for references.

**GreenScreen Rating<sup>2</sup>:** DCM was assigned a **Benchmark Score of 1** based on:

- Failure of Benchmark Rule 1e, due to High carcinogenicity.

GreenScreen Hazard Ratings: Dichloromethane																			
Group I Human					Group II and II* Human								Ecotox		Fate		Physical		
C	M	R	D	E	AT	ST		N		SnS*	SnR*	IrS	IrE	AA	CA	P	B	Rx	F
						single	repeat*	single	repeat*										
H	NE	DG	DG	M	M	vH	H	vH	vH	L	DG	H	H	M	L	vH	vL	L	L

Note: Hazard levels [Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)] in *italics* reflect estimated values and lower confidence. Hazard levels in **BOLD** font reflect values based on test data (See Guidance). NE indicates no determination was made (conflicting data) and DG indicates insufficient data for assigning hazard level.

<sup>1</sup> Every chemical in a material or formulation should be assessed if it is:

1. intentionally added and/or
2. present at greater than or equal to 100 ppm.

<sup>2</sup> For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.

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**Transformation Products and Ratings:**

Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) and/or moieties of concern<sup>3</sup>

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	On CPA Red List <sup>4</sup> ?	Green Screen Rating <sup>5</sup>
N/A						

No fate or transformation products relevant to toxicity were identified.

**Substance Background**

Dichloromethane (DCM) is a colorless liquid with a sweet, pleasant odor. The major use of DCM is as a solvent in the pharmaceutical and chemical industry for reactions, purification and isolation of intermediates or products. DCM is also used as a feedstock for the production of HCFC 32 (R32), as a blowing agent in foam blowing, for plastics processing (e.g., polycarbonate resins), and in metal cleaning (cold and vapor degreasing). Many aerosol products for applying or removing surface finishes or coatings use DCM, e.g., paints, varnishes, adhesives, and degreasing products. DCM is also used for removal of photoresist coatings in the production of circuit boards (OECD 2011).

DCM is produced together with other chloromethanes by the Stauffer process, in which methanol is reacted with hydrogen chloride to form methyl chloride. Methyl chloride is then chlorinated with chlorine to heavier chloromethanes through thermal, catalytic, or photolytic chlorination. DCM may also be produced via direct chlorination of methane (either thermal or catalytic) (OECD 2011).

The main route of exposure to DCM is by inhalation typically from spray painting or other aerosol use. DCM is rapidly absorbed through the lungs and distributed throughout the body reaching all organs, including the brain. DCM has a high affinity for lipids. Following inhalation or oral exposure of rats, the majority of the dose is exhaled unchanged. DCM metabolites are also excreted via the lungs as carbon monoxide and carbon dioxide. There are two established pathways for the DCM metabolism, one catalysed by a cytochrome P450 and the other by a GST (Glutathione S Transferase). Metabolism via the P450-mediated oxidative pathway generates carbon monoxide and inorganic chloride. The glutathione route produces carbon dioxide after the formation of a postulated glutathione conjugate and formaldehyde (IARC 2000, ATSDR 2000).

DCM is a volatile liquid and will partition to the atmosphere from either water or soil. Within the atmosphere, DCM will break down by reaction with hydroxyl radicals produced photochemically over a period of months. DCM is not strongly adsorbed to soils or sediments. Based on its low soil organic carbon partitioning coefficient, DCM is likely to be highly mobile in soils and may be expected to leach from soils into groundwater (ATSDR 2000).

**References:**

1. OECD 2011, SIDS Dossier available at: <http://webnet.oecd.org/Hpv/UI/handler.axd?id=b8ea971c-0c2c-4976-8706-a9a68033daa0>, accessed May 2012.
2. ATSDR 2000, Toxicological Profile for Methylene Chloride, available at: <http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=234&tid=42>, accessed May 2012.

<sup>3</sup> A moiety is a discrete chemical entity that is a constituent part or component of a substance. A moiety of concern is often the parent substance itself for organic compounds. For inorganic compounds, the moiety of concern is typically a dissociated component of the substance or a transformation product.

<sup>4</sup> The CPA "Red List" refers to chemicals 1. flagged as Benchmark 1 using the GreenScreen™ List Translator or 2. flagged as Benchmark 1 or 2 using the GreenScreen™ List Translator and further assessed and assigned as Benchmark 1. The most recent version of the GreenScreen™ List Translator should be used.

<sup>5</sup> The way you conduct assessments for transformation products depends on the Benchmark Score of the parent chemical (See Guidance).

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3. IARC 1999, Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 71 (1999), Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide, available at: <http://monographs.iarc.fr/ENG/Classification/index.php>, accessed May 2012.

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**Hazard Classification Summary Section:**  
**Group I Human Health Effects (Group I Human)**

**Carcinogenicity (C) Score (H, M or L): **H****

DCM was assigned a score of High based on the most recent evaluation of carcinogenicity by US EPA 2011 (a GreenScreen Authoritative A list).

- US EPA 2011: "Following U.S. EPA (2005a) Guidelines for Carcinogen Risk Assessment, dichloromethane is "likely to be carcinogenic in humans," based predominantly on evidence of carcinogenicity at two sites in 2-year bioassays in male and female B6C3F1 mice (liver and lung tumors) with inhalation exposure (NTP, 1986) and at one site in male B6C3F1 mice (liver tumors) with drinking water exposure (Serota et al., 1986b Hazleton Laboratories, 1983)." [References internal to the assessment.] The IRIS database is denoted as the EPA-C list in the GreenScreen List Translator; "likely" designation translates to High level-of-concern. US EPA 2011, Toxicological Review of Dichloromethane (Methylene Chloride), available at: [http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showQuickView&substance\\_nmbr=0070](http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showQuickView&substance_nmbr=0070), accessed May 2012.
- NTP RoC lists as "Reasonably anticipated to be a human carcinogen." Translates to High level-of-concern. National Toxicology Program, 12th Report on Carcinogens, available at: <http://ntp.niehs.nih.gov/ntp/roc/twelfth/roc12.pdf>, accessed May 2012. Prop 65 lists as a carcinogen (by inhalation). Presence on Prop 65 is sufficient for GreenScreen High level-of-concern. California Proposition 65 list of chemicals known to cause cancer or reproductive toxicity, available at: [http://oehha.ca.gov/prop65/prop65\\_list/files/P65single041511.pdf](http://oehha.ca.gov/prop65/prop65_list/files/P65single041511.pdf), accessed May 2012.
- IARC lists as 2B. "Evaluation: There is inadequate evidence in humans for the carcinogenicity of dichloromethane. There is sufficient evidence in experimental animals for the carcinogenicity of dichloromethane. Overall evaluation: Dichloromethane is possibly carcinogenic to humans (Group 2B)." Translates to Moderate level-of-concern. IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 71 (1999), Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide, available at: <http://monographs.iarc.fr/ENG/Classification/index.php>, accessed May 2012.
- ECHA CLP harmonized classification as Carcinogenic Category 2, H351 "Suspected of causing cancer." Translates to Moderate level-of-concern. ECHA C&L Inventory Database, <http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=7285&HarmOnly=no?DisclaimerAgr=Agree&Index=75-09-2&ExecuteSearch=true&fc=true&lang=en>, accessed May 2012.

**Mutagenicity/Genotoxicity (M) Score (H, M or L): NE**

DCM was not evaluated for mutagenicity due to the conflicting data from authoritative sources. Given DCM's carcinogenicity, the mutagenicity/genotoxicity ranking will not affect its Benchmark 1 status.

- US EPA 2011 assessment reports: "In summary, the available data provide evidence for the mutagenic potential of dichloromethane. Most of the in vitro bacterial assays showed positive results when there was GST activity; nonpositive results were reported only in bacterial assays with low GST activity. Evaluation of the in vitro mammalian studies also demonstrates the influence of GST activity on the observation of genotoxic effects. In rat and hamster cell lines in which GST activity is significantly less than in mouse cells, primarily negative results were reported following dichloromethane exposure. However, when mouse liver cytosol or transfected mouse GST were included in these same cell lines, genotoxic effects were reported. In mouse cell lines, positive results were obtained in Clara cells. In vitro studies using human cells reported effects of dichloromethane on frequency of micronuclei, DNA damage (comet assay), and sister chromatid exchanges, but no effects on unscheduled DNA synthesis, DNA SSBs, or DNA-protein cross-links. The results of in vivo genotoxicity in mice also support the site-specificity of the observed tumors. With the exception of one study of unscheduled DNA synthesis in hepatocytes, numerous studies in either the liver or lung were also positive at various doses. These liver and lung studies included chromosomal aberrations, indicating mutagenic potential, as well as SSBs, sister chromatid exchanges, and DNA-protein cross-links that provide further evidence of the

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genotoxicity of dichloromethane and correspond to genotoxic and mutagenic effects associated with metabolites from the GST pathway.” [p. 119] US EPA 2011, Toxicological Review of Dichloromethane (Methylene Chloride), available at:

[http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showQuickView&substance\\_nmbr=0070](http://cfpub.epa.gov/ncea/iris/index.cfm?fuseaction=iris.showQuickView&substance_nmbr=0070), accessed May 2012.

- OECD 2011 SIDS dossier reports: “Dichloromethane was found to be mutagenic in bacteria (OECD TG 471), and not mutagenic in mammalian cells in vitro (no guideline followed). It was found to be clastogenic in vitro (OECD TG 473). In general, dichloromethane tested negative for genotoxicity in standard in vivo studies in rats and mice. The increase in chromosomal damage (aberrations and micronuclei) seen in B6C3F1 mice is thought to be related to this strain’s high rate of metabolism of dichloromethane by the glutathione transferase. Overall, the data indicate that dichloromethane is not genotoxic in vivo.” [pp. 1-2] OECD SIDS Dossier available at: <http://webnet.oecd.org/Hpv/UI/handler.axd?id=b8ea971c-0c2c-4976-8706-a9a68033daa0>, accessed May 2012.
- NITE/Japan 2006 classification assessment reports: “Not classified: Based on negative data on heritable mutagenicity tests (dominant lethal tests) and somatic cell mutagenicity tests in vivo (micronucleus/ chromosome aberration tests) and the absence of germ cell mutagenicity tests in vivo, described in CERI-NITE Hazard Assessment No.15 (2004), IARC 71 (1999) and EHC 164 (1996). One testing agency reported that the substance was weakly positive for inhalation toxicity in micronucleus, chromosome aberration and SCE tests in mice, but the responses were weak and considered ambiguous and indecisive in EHC 164 (1996) and thus was not considered "positive".” Japanese National Institute of Technology and Evaluation (NITE), worksheet ID141 in the Microsoft Excel workbook found at: [http://www.safe.nite.go.jp/english/files/ghs\\_xls/classification\\_result\\_e\(479chems\).xls](http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(479chems).xls), accessed May 2012.
- IARC 1999 monograph reports: “Dichloromethane is consistently mutagenic in microorganisms. Weaker and less consistent responses are seen in mammalian systems, predominantly in mice, both in vitro and in vivo. It induced sister chromatid exchanges, chromosome breakage and chromosome loss in vitro in human cells. In-vitro results in rodent cells were inconclusive or negative. Dichloromethane induced DNA single-strand breaks in mammalian cell cultures, but inconclusive or negative effects were reported for induction of gene mutations. It did not induce unscheduled DNA synthesis either in vivo in rodents or in human fibroblast cultures. It was genotoxic in fungi but not in *Drosophila* in the sex-linked recessive lethal assay. Mechanistic studies have established a link between glutathione S-transferase-mediated metabolism of dichloromethane and its genotoxicity and carcinogenicity in mice. The glutathione S-transferase responsible for the metabolism of dichloromethane is expressed to significantly greater extents in mouse tissues than in rat, hamster or human tissues. The available data suggest a plausible mechanism for the development of liver and lung tumors which occur in mice but not in rats exposed to dichloromethane.” [pp. 298-9] IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, Volume 71 (1999), Re-evaluation of Some Organic Chemicals, Hydrazine and Hydrogen Peroxide, available at: <http://monographs.iarc.fr/ENG/Classification/index.php>, accessed May 2012.

**Reproductive Toxicity (R) Score (H, M, or L): DG**

DCM data for reproductive toxicity were not assessed due to deficiencies in the available studies.

- US EPA 2011 assessment reports:
  - p. 126: “Results from the available studies do not provide evidence for effects on reproductive or developmental endpoints (Table 4-26).”
  - p. 258: “In the reproductive oral administration studies, no significant effect on reproductive function or parameters was observed in rats up to 225 mg/kg-day (General Electric Company, 1976) or in mice up to 500 mg/kg-day (Raje et al., 1988). A two-generation oral exposure study is not available.”
  - pp. 258-9: “A two-generation inhalation exposure to dichloromethane revealed no significant effects on reproductive performance in rats (up to 1,500 ppm) (Nitschke et al., 1988b). This study is limited in its ability to fully evaluate reproductive and developmental toxicity, however, since exposure was not continued through the gestation and nursing periods. Some evidence of a decrease in fertility index was seen in male mice exposed to 150 and 200 ppm (Raje et al., 1988).”

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- The OECD 2011 reports: “In a two-generation reproduction toxicity study (OECD TG 416, 1983), male and female rats were exposed whole-body to 0, 350, 1,770 or 5,300 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 14 weeks up to mating and for 7 days/week during mating, gestation and lactation. Determinations on estrous cycle, sperm parameters, sexual maturation, organ weights and histopathology of reproductive organs as required by OECD TG 416 (2001) were not performed. F1 and F2 offspring showed no effects on viability, clinical signs or body weight, gross pathology or histopathology. The NOAEC for parental toxicity, reproduction toxicity and developmental toxicity was established to be  $\geq 5,300$  mg/m<sup>3</sup>... Overall, the available data do not indicate that dichloromethane causes effects on fertility or induces developmental toxicity.” [p. 3] OECD SIDS Dossier available at: <http://webnet.oecd.org/Hpv/UI/handler.axd?id=b8ea971c-0c2c-4976-8706-a9a68033daa0>, accessed May 2012.
- ATSDR 2000 assessment reports:
  - p. 40: “No adverse effects on reproduction were observed in rats exposed to concentrations up to 1,500 ppm of methylene chloride for two generations (Nitschke et al. 1988b). In dominant lethal tests involving male mice exposed to 200 ppm methylene chloride for up to 6 weeks, no microscopic lesions were found in the testes (Raje et al. 1988). Uterine, ovarian, and testicular atrophy was observed in rats and mice exposed to vapors of methylene chloride (4,000 ppm) for 2 years (NTP 1986), but the authors considered this effect to be secondary to malignant hepatic and alveolar neoplasms, as described in Section 2.2.1.8 Cancer. Existing data suggest reproductive toxicity may occur following chronic exposure to relatively high concentrations of methylene chloride.”
  - p. 154: “There are no data on reproductive effects in animals following oral or dermal exposure. Intermediate-duration oral and dermal studies that incorporate histopathological analysis of the reproductive organs are needed to address this data need. Part of the analysis should include a determination of whether the reproductive organs express GSTT1 and/or CYP2E1, as a first step in evaluating their possible role in the reproductive toxicity of methylene chloride.”
  - ATSDR 2000 Toxicological Profile for Methylene Chloride, available at: <http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=234&tid=42>, accessed May 2012. [References internal to the assessment.]
- NTP 1986 study reports: “Increased incidences of testicular atrophy in males and ovarian and uterine atrophy in females were detected in dichloromethane exposed mice. These changes may be secondary to the extensive lung and liver neoplasia produced by the inhalation exposures.” p. 63, Toxicology and Carcinogenesis Studies of Dichloromethane (Methylene Chloride) (CAS No. 75-09-2) in F344/N Rats And 6C3Fi Mice (Inhalation Studies), available at: [http://ntp.niehs.nih.gov/ntp/htdocs/LT\\_rpts/tr306.pdf](http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr306.pdf), accessed May 2012.

**Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M or L): DG**

DCM data for developmental toxicity were not assessed due to deficiencies in the available studies.

- US EPA 2011 assessment reports:
  - p. 126: “Results from the available studies do not provide evidence for effects on reproductive or developmental endpoints (Table 4-26).”
  - p. 137: “The reproductive and developmental studies are limited in terms of the exposure regimen used. Nitschke et al. (1988b) used a noncontinuous exposure period (i.e., exposure of dams before mating and on GDs 0–21, and beginning again on PND 4), and two of the developmental studies using only a single, relatively high daily exposure over the gestational period [1,250 ppm, GDs 6–15 in Schwetz et al. (1975) and 4,500 ppm, GDs 1–17 in Bornschein et al. (1980) and Hardin and Manson (1980)]...No adverse effects on fetal development were found following exposure of pregnant Swiss-Webster mice or Sprague-Dawley rats to 1,250 ppm for 6 hours/day on GDs 6–15 (Schwetz et al., 1975). Following exposure of female Long-Evans rats to 4,500 ppm (6 hours/day) for 14 days before breeding, plus during gestation or during gestation alone, a 10% decrease in fetal BW and changed behavioral habituation of the offspring to novel environments were seen (Bornschein et al., 1980; Hardin and Manson, 1980). No exposure-related changes in gross, skeletal, or soft-tissue anomalies were found.”



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- p. 92: "The potential for gestational exposure to CO and to dichloromethane (through its transfer across the placenta) resulting from maternal dichloromethane exposure via oral and inhalation routes raises concerns regarding neurodevelopmental effects. Although few developmental effects were observed at high exposures to dichloromethane (Bornschein et al., 1980; Schwetz et al., 1975), there are no studies that have adequately evaluated neurobehavioral and neurochemical changes resulting from gestational dichloromethane exposure. The available data identify changes in behavior habituation at 4,500 ppm (Bornschein et al., 1980) and increases in COHb at 1,250 ppm (Schwetz et al., 1975). The behavioral changes observed at 4,500 ppm indicate developmental neurotoxic effects; this is the only dose group used in the Bornschein et al. (1980) study. No other neurological endpoints have been evaluated in the available developmental studies of dichloromethane. The potential for developmental neurotoxicity occurring at lower exposures to dichloromethane represents a data gap."
  - p. 262: "The oral database lacks a two-generation reproductive study and a developmental neurotoxicity study;"
  - US EPA 2011, Toxicological Review of Dichloromethane (Methylene Chloride), available at: <http://www.epa.gov/iris/toxreviews/0070tr.pdf>, accessed May 2012. [References internal to assessment.]
- OECD 2011 reports: "In a two-generation reproduction toxicity study (OECD TG 416, 1983), male and female rats were exposed whole-body to 0, 350, 1,770 or 5,300 mg/m<sup>3</sup> for 6 hours/day, 5 days/week for 14 weeks up to mating and for 7 days/week during mating, gestation and lactation. Determinations on estrous cycle, sperm parameters, sexual maturation, organ weights and histopathology of reproductive organs as required by OECD TG 416 (2001) were not performed. F1 and F2 offspring showed no effects on viability, clinical signs or body weight, gross pathology or histopathology. The NOAEC for parental toxicity, reproduction toxicity and developmental toxicity was established to be  $\geq 5,300$  mg/m<sup>3</sup>. In a developmental study, female rats and mice were exposed to 4,300 mg/m<sup>3</sup> for 7 hours/day on gestation days 6-15. This level was shown to be a LOAEC for maternal toxicity based on increased carboxyhaemoglobin levels and increased absolute liver weights. Only minor visceral and skeletal variations were observed in the fetuses. These variations have not been confirmed in other oral or inhalation studies in rats performed at higher dose or concentration levels. Overall, the available data do not indicate that dichloromethane causes effects on fertility or induces developmental toxicity." [p. 3] OECD SIDS Dossier available at: <http://webnet.oecd.org/Hpv/UI/handler.axd?id=b8ea971c-0c2c-4976-8706-a9a68033daa0>, accessed May 2012.
- ATSDR 2000 assessment reports:
  - p. 40: "Several inhalation studies in animals indicate that methylene chloride can cross the placenta (Anders and Sunram 1982). Some of these studies showed statistically nonsignificant malformations in rats and mice or decreased fetal weight at maternally toxic concentrations (Bornschein et al. 1980; Hardin and Manson 1980; Schwetz et al. 1975). However, there was a statistically significant increase in the incidence of delayed ossification of sternebrae (Schwetz et al. 1975). The use of only one concentration in these studies precludes any evaluation of concentration-response relationships.
  - p. 154-5: "...Reitz et al. (1997) developed an inhalation route-to-oral route extrapolation and rodent-to-human species extrapolation using PBPK modeling of the developmental toxicity data in Schwetz et al. (1975). The resulting LOAEL was an intermediate oral dose of 142 mg/kg/day. Additional studies for inhalation and dermal exposures in two species would be useful in clarifying the developmental toxicity potential of this chemical. Conducting studies on animals with known genotypes with respect to metabolizing enzymes GSTT1 and CYP2E1 are needed to evaluate the risk of exposure to methylene chloride."
  - p. 160: "Although developmental studies in animals indicate that methylene chloride is not a teratogen (Bornschein et al. 1980; Hardin and Manson 1980), there is a need to evaluate neurological/neuro-behavioral effects in animals exposed in utero. Subtle neurological effects could result from hypoxia (CO-mediated) or from reactive intermediates of metabolism that would only be revealed by appropriate behavioral testing of the offspring. It is not clear that the "wheel running activity" and "avoidance learning" tests that Bornschein et al. (1980) employed in rats exposed in utero were adequate to reveal neurological deficits. Acute effects observed in an adult human study involved degraded performance on visual and auditory discrimination tasks (Putz et al. 1979). If neurological effects were detected in mice, it would be

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useful to conduct additional developmental studies using mice in which functional genes for GSTT1 and/or CYP2E1 have been knocked-out, to discover which metabolic pathway is implicated in developmental neurological effects.”

- ATSDR 2000 Toxicological Profile for Methylene Chloride, available at: <http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=234&tid=42>, accessed May 2012. [References internal to the assessment.]

**Endocrine Activity (E) Score (H, M or L): **M****

DCM was assigned a score of Moderate for endocrine activity based on presence on the TEDX list.

- The Endocrine Disruption Exchange (TEDX) lists DCM in the List of Potential Endocrine Disruptors. The TEDX list is a Screening B list. Presence on the list translates to Moderate level-of-concern for benchmarking purposes (GreenScreen List Translator). The TEDX spreadsheet List of Potential Endocrine Disruptors available at: <http://www.endocrinedisruption.com/endocrine.TEDXList.overview.php>, accessed May 2012.
- DCM was not listed as an endocrine disruptor in the following lists:
  - European Union Priority List of suspected endocrine disruptors. Database of chemicals found at: [http://ec.europa.eu/environment/endocrine/strategy/substances\\_en.htm#priority\\_list](http://ec.europa.eu/environment/endocrine/strategy/substances_en.htm#priority_list), accessed May 2012.
  - OSPAR Convention for The Protection of the Marine Environment of the North-East Atlantic, List of Chemicals for Priority Action and List of Substances of Possible Concern, 2008 Excel spreadsheet found at: [http://www.ospar.org/v\\_substances/browse.asp?menu=00950304450072\\_000000\\_000000](http://www.ospar.org/v_substances/browse.asp?menu=00950304450072_000000_000000), accessed May 2012.
  - International Chemical Secretariat (ChemSec) Substitute it Now (SIN) List 2.0, found at [http://www.chemsec.org/images/stories/2011/chemsec/SIN\\_List\\_2.0\\_all\\_378.pdf](http://www.chemsec.org/images/stories/2011/chemsec/SIN_List_2.0_all_378.pdf), accessed May 2012.

**Group II and II\* Human Health Effects (Group II and II\* Human)**

*Note: Group II and Group II\* endpoints are distinguished in the v 1.2 Benchmark system. For Systemic Toxicity and Neurotoxicity, Group II and II\* are considered sub-endpoints and test data for single or repeated exposures may be used. If data exist for single OR repeated exposures, then the endpoint is not considered a data gap. If data are available for both single and repeated exposures, then the more conservative value is used.*

**Acute Mammalian Toxicity (AT) Group II Score (vH, H, M or L): **M****

DCM was assigned a score of Moderate for acute mammalian toxicity based on NITE GHS classification (GHS country classifications are Screening A lists) as GHS Category 4 and additional reports of animal data on oral toxicity consistent with Category 4.

- NITE/Japan 2006 reports: “Acute toxicity, oral, Category 4; inhalation: not classified.”
  - Oral exposure: “Based on the rat LD<sub>50</sub> (oral route) value of 1,600 mg/kg representing the lower of the two testing data, 2,100 mg/kg (CERI Hazard Data 96-2, 1997) and 1,600 mg/kg (MOE Risk Assessment Vol.2, 2003).”
  - Dermal exposure: “No data available”
  - Inhalation exposure: “Based on the LC<sub>50</sub> value (4 hours) of 64 mg/L (18,000 ppm), calculated from the testing data of rat LC<sub>50</sub> (6 hour inhalation exposure) of 53mg/L (CERI-NITE Hazard Assessment No.15, 2004), was lower than 90% of the saturated vapor concentration (570,000 ppm) under a saturated vapour pressure of 58 kPa (25°C), the substance was considered as “vapour containing substantially no mist” and was classified based on standard values expressed in ppm.”
  - Japanese National Institute of Technology and Evaluation (NITE), worksheet ID141 in the Microsoft Excel workbook found at: [http://www.safe.nite.go.jp/english/files/ghs\\_xls/classification\\_result\\_e\(479chems\).xls](http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(479chems).xls), accessed May 2012.
- IPCS 1996 reports: “The acute toxicity of methylene chloride by inhalation and oral administration is low. The inhalation 6-h LC<sub>50</sub> values for all species are between 40 200 and 55 870 mg/m<sup>3</sup>. Oral LD<sub>50</sub> values of 1410-



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3000 mg/kg were recorded.” See Table 17. Acute toxicity of methylene chloride, International Program on Chemical Safety, Environmental Health Criteria 164, Methylene Chloride (second edition) available at: <http://www.inchem.org/documents/ehc/ehc/ehc164.htm>, accessed May 2012.

- REACH registration dossier reports:
  - Oral exposure: 1988, reliability 1, GLP-compliant oral toxicity study with Wistar rats, according to OECD TG 401: LD<sub>50</sub> > 2000 mg/kg-bw.
  - Dermal exposure: 1988, reliability 1, GLP-compliant dermal toxicity study with Wistar rats, according to OECD TG 402: LD<sub>50</sub> > 2000 mg/kg-bw.
  - Inhalation exposure: 1947 reliability 2 vapor-inhalation study (whole body exposure; guideline not reported) with Swiss Webster mice: “Because the 4-h LC<sub>50</sub> value (calculated from a 7-h value) was 86 mg/L, and no delayed mortality was expected, no classification is needed for acute inhalation toxicity.”
  - European Chemicals Agency, registration dossier found at: [http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-9899d34b-dc1e-49d8-8cf3-71d57868f56c\\_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#AGGR-9899d34b-dc1e-49d8-8cf3-71d57868f56c](http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-9899d34b-dc1e-49d8-8cf3-71d57868f56c_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#AGGR-9899d34b-dc1e-49d8-8cf3-71d57868f56c), accessed May 2012.

**Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)**

**Group II Score (single dose: vH, H, M or L):** **vH**

DCM was assigned a score of very High based on NITE classification as Category 1.

- PPRC: While NITE/Japan reports Category 1 (respiratory organs), no data were available to corroborate effects in human single exposures beyond irritation and reversible respiratory symptoms. Animal respiratory effects were also reported to be reversible. The NITE assessment references CERI-NITE Hazard Assessment No. 15, which could not be located and may be available only in Japanese.
- NITE/Japan reports classification as Category 1 (respiratory organs): “Based on the human evidence including “cyanosis,...edema associated with pulmonary hemorrhage, pneumonia associated with skin inflammation/induration, cerebral edema associated with tonsillar herniation” (CERI-NITE Hazard Assessment No.15, 2004) and the evidence from animal studies including “necrosis of bronchial/bronchiolar epithelial cells, swelling/vacuolation of clara cells, slight increase in cell division rates...” (CERI-NITE Hazard Assessment No.15, 2004). The effects on experimental animals were observed at dosing levels within the guidance value ranges for Category 2.” Japanese National Institute of Technology and Evaluation (NITE), worksheet ID141 in the Microsoft Excel workbook found at: [http://www.safe.nite.go.jp/english/files/ghs\\_xls/classification\\_result\\_e\(479chems\).xls](http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(479chems).xls), accessed May 2012.
- The US EPA 2011 assessment reports: “Single 6-hour inhalation exposures to concentrations ≥2,000 ppm dichloromethane produced a transient vacuolation of Clara cells in the bronchiolar epithelium of B6C3F1 mice. Vacuolization of the Clara cells disappeared or was diminished with repeated exposure and was correlated with subsequent transient diminishment of CYP metabolic activity. CYP inhibition with piperonyl butoxide counteracted the vacuolation observed in the Clara cells (Foster et al., 1994; Foster et al., 1992). With repeated exposure to 4,000 ppm (up to 13 weeks), the Clara cell vacuolation did not appear to progress to necrosis, and no hyperplasia of the bronchiolar epithelium was found. Foster et al. (1994; 1992) proposed that the diminished severity or disappearance of Clara cell vacuolation with repeated exposure was due to the development of tolerance to dichloromethane, linked with a transient decrease of CYP metabolism of dichloromethane. The available data suggests that CYP metabolism of dichloromethane may be involved in the mode of action for the acute effects of dichloromethane on the bronchiolar epithelium of mice.” [pp. 138, references internal to the assessment.] US EPA 2011, Toxicological Review of Dichloromethane (Methylene Chloride), available at: <http://www.epa.gov/iris/toxreviews/0070tr.pdf>, accessed May 2012.
- OECD 2011 SIDS assessment reports: “Clinical signs included laboured respiration, twitches and/or convulsions and uncoordinated movements, narcosis and paralysis after oral and inhalation exposure... Inhalation exposure of humans showed increased carboxyhaemoglobin levels...at 200 ppm (= 695 mg/m3) for 4 hours.” OECD SIDS Dossier available at: <http://webnet.oecd.org/Hpv/UI/handler.axd?id=b8ea971c-0c2c-4976-8706-a9a68033daa0>, accessed May 2012.

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- ATSDR profile reports: "Irritative symptoms of the respiratory tract were more prevalent among 12 Swedish male graffiti removers, employed to clean underground stations by using methylene chloride-based solvent, than those of the general population (Anundi et al. 1993). The 8-hour time-weighted average (TWA) to which these workers were exposed ranged from 18–1,200 mg/m<sup>3</sup>." Additional occupational exposures document cough and other reversible respiratory symptoms. [p. 29] ATSDR 2000 Toxicological Profile for Methylene Chloride, available at: <http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=234&tid=42>, accessed May 2012.

**Group II\* Score (repeated dose: H, M, L): H**

DCM was assigned a High level-of-concern based on animal data consistent with GHS Category 1.

- NITE/Japan Category 1 (liver). "Based on...the evidence from animal studies including "hepatocytes positively stained for fat, mild vacuolation of hepatocytes" and "mutant hepatocytes" (CERI-NITE Hazard Assessment No.15, 2004). The effects on experimental animals were observed at dosing levels within the guidance value ranges for Category 1." NITE worksheet ID141 in the Microsoft Excel workbook found at: [http://www.safe.nite.go.jp/english/files/ghs\\_xls/classification\\_result\\_e\(479chems\).xls](http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(479chems).xls), accessed May 2012.
- US EPA 2011 assessment reports: "In the case of dichloromethane, hepatocellular vacuolation was characterized by study authors as correlating with fatty change (Burek et al., 1984) or as a vacuolation of lipids in the hepatocyte (Nitschke et al., 1988a). Dose-related increases in the incidence of hepatocellular vacuolation have been observed in rats and mice following both inhalation (Mennear et al., 1988; Nitschke et al., 1988a; NTP, 1986; Burek et al., 1984; Haun et al., 1972) and oral exposure (Kirschman et al., 1986); these study investigators consistently identified vacuole content as lipid. Accumulation of lipids in the hepatocyte may lead to the more serious liver effects observed following dichloromethane exposure, such as hepatic steatosis (fatty liver) reported in dogs (Haun et al., 1971) and rats (Serota et al., 1986a). Given the liver findings for dichloromethane in the database as a whole, the evidence is consistent with hepatic vacuolation as a precursor of toxicity. Accordingly, hepatic vacuolation is considered a toxicologically relevant and adverse effect." [pp. 188-9, references internal to the assessment.] US EPA 2011, Toxicological Review of Dichloromethane (Methylene Chloride), available at: <http://www.epa.gov/iris/toxreviews/0070tr.pdf>, accessed May 2012.
- ATSDR assessment reports:
  - pp. 32-3: "In animals, the effects of methylene chloride have been studied more extensively. For the most part, exposure to methylene chloride has resulted in fatty changes in the liver and elevated plasma enzymes. These effects were reversible when exposure ceased. No histopathological changes were observed in guinea pigs following acute exposure to 5,200 ppm; however, there was a 2.5-fold increase in hepatic triglycerides (Morris et al. 1979). When male guinea pigs were exposed to 5,000 ppm of methylene chloride for up to 6 months, 3/8 died and exhibited moderate centrilobular fatty degeneration of the liver (Heppel et al. 1944); no deaths, but similar liver histopathology was observed after exposure to 10,000 ppm for 8 weeks (guinea pigs) or 1 week (dogs). Fatty changes in the liver were noted in monkeys, mice, and dogs continuously exposed to 5,000 ppm for 4 weeks (MacEwen et al. 1972). In addition, mice exposed to 1,000 ppm exhibited iron pigmentation, nuclear degeneration, and pyknotic cells (MacEwen et al. 1972). Hepatic microsomal enzymes were elevated at 500 ppm (p<0.01) following 10 days of exposure, but were not increased significantly over control levels in rats exposed to methylene chloride at 250 ppm for 28 days (Norpoth et al. 1974). Continuous exposure of mice and rats for 100 days to 25 or 100 ppm caused fatty changes in the liver (Haun et al. 1972; Kjellstrand et al. 1986; Weinstein and Diamond 1972). No effects were seen in mice continuously exposed at 25 ppm, but cytoplasmic vacuolization was reported in rats at this exposure level (Haun et al. 1972). No adverse liver effects were reported in dogs or monkeys exposed to up to 100 ppm methylene chloride in the Haun et al. (1972) study. Using results from the Haun et al. (1972) study, an intermediate inhalation MRL of 0.3 ppm was derived based on the LOAEL of 25 ppm for liver effects in rats."
  - p. 33: "Repeated exposure of rats to 200–500 ppm or greater for 2 years resulted in increased incidences of hepatocellular vacuolization and multinucleate hepatocytes (Burek et al. 1984; Nitschke et al. 1988a; NTP 1986), but not at 50 ppm (Nitschke et al. 1988a). In the 2-year NTP (1986) study, other liver effects in rats included hemosiderosis, focal necrosis of hepatocytes, basophilic change (females only),

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hepatocytomegaly, bile duct fibrosis in males, and granulomatous inflammation in females. The NOAEL of 50 ppm identified in the Nitschke et al. (1988a) study was used as the basis for derivation of a chronic inhalation MRL of 0.3 ppm." [2-yr. study exposure.]

- ATSDR 2000 Toxicological Profile for Methylene Chloride, available at: <http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=234&tid=42>, accessed May 2012.

**Neurotoxicity (N)**

**Group II Score (single dose: vH, H, M or L): vH**

DCM was assigned a score of very High for neurotoxicity-single dose based on NITE classification as Category 1.

- NITE 2006 assessment classifies as: Category 1 (central nervous system), Category 3 (narcotic effects), based on: "the human evidence including "cyanosis", "headache, chest pain, disorientation, progressive loss of alertness, increased feeling of fatigue and psychological inertia, amnesia, loss of time sense", "a decrease in critical flicker frequency among indices in visual function tests)", "neurobehavioral effects..." (CERI-NITE Hazard Assessment No.15, 2004)." Japanese National Institute of Technology and Evaluation (NITE), worksheet ID141 in the Microsoft Excel workbook found at: [http://www.safe.nite.go.jp/english/files/ghs\\_xls/classification\\_result\\_e\(479chems\).xls](http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(479chems).xls), accessed May 2012.
- OECD SIDS assessment reports: "The oral and 24-hour dermal LD<sub>50</sub> values were >2,000 mg/kg bw in rats and the inhalatory 7-h LC<sub>50</sub> value was 49,000 mg/m<sup>3</sup> in mice. Clinical signs included laboured respiration, twitches and/or convulsions and uncoordinated movements, narcosis and paralysis after oral and inhalation exposure. CNS effects were seen in guinea pigs, dogs and rodents at ≥ 14,400 mg/m<sup>3</sup>. Inhalation exposure of humans showed increased carboxyhaemoglobin levels and decreased tracking performance and a decline in response time in the visual-peripheral component of dual-tasking at 200 ppm (= 695 mg/m<sup>3</sup>) for 4 hours." OECD SIDS Dossier available at: <http://webnet.oecd.org/Hpv/UI/handler.axd?id=b8ea971c-0c2c-4976-8706-a9a68033daa0>, accessed May 2012.
- ATSDR profile reports:
  - p. 35: "In volunteers, a single 4-hour exposure to 200 ppm methylene chloride significantly decreased visual and psychomotor performance and auditory function (Putz et al. 1979). Auditory monitoring, eye-hand coordination, and high-difficulty peripheral brightness test performances were not degraded until the final hour of exposure, by which time, the level of carbon monoxide in exhaled breath had risen to 50 ppm and the level of COHb in blood had risen to 5%. A single 3- to 4-hour exposure to methylene chloride at 300 ppm caused decreased visual and auditory functions in volunteers, but the adverse effects were reversible once exposure ceased (Fodor and Winneke 1971; Winneke 1974). Winneke (1974) attributed these effects to methylene chloride rather than its metabolite COHb, since exposure to carbon monoxide at concentrations up to 100 ppm did not cause similar effects. At the lowest exposure level (300 ppm of methylene chloride), critical flicker fusion frequency (visual) and auditory vigilance tasks were impaired. These higher-order functions involved complex visual and central nervous system processes that are assumed to be influenced by the degree of "cortical alertness" mediated by subcortical structures, especially the reticular formation (Fodor and Winneke 1971). Similarly, psychomotor performance (reaction time, hand precision, steadiness) was impaired, but this occurred at higher exposure levels (800 ppm for 4 hours) (Winneke 1974). Since these parameters are sensitive indicators of overt central nervous system-related depression, drowsiness, or narcosis, the Winneke (1974) study was selected as an appropriate basis for deriving an MRL for acute inhalation effects of methylene chloride."
  - p. 35: "Alterations in visual evoked response were observed in humans exposed to methylene chloride at 515–986 ppm for 1–2 hours (Stewart et al. 1972)."
  - p. 38: "Acute studies in animals are consistent with findings in humans that methylene chloride affects the central nervous system. Narcotic effects of methylene chloride (incoordination, reduced activity, somnolence) were observed in monkeys, rabbits, rats, and guinea pigs exposed to 10,000 ppm for up to 4 hours (Heppel et al. 1944); reduced activity was measured in rats exposed to 5,000 ppm (Heppel and Neal 1944). Dogs exposed to 10,000 ppm for 4 hours, first became uncoordinated, then excited and hyperactive to the extent of bruising themselves, but rapidly recovered afterwards (Heppel et al. 1944). Somatosensory-

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- evoked potentials were altered in rats after 1 hour of exposure to methylene chloride at concentration levels of 5,000 ppm or greater (Rebert et al. 1989).” [5000 ppm = 17.4 mg/L]
- ATSDR 2000 Toxicological Profile for Methylene Chloride, available at: <http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=234&tid=42>, accessed May 2012.
  - US EPA 2011 assessment reports:
    - Oral/IP exposure, p. 124-5: “Acute oral or intraperitoneal administration of dichloromethane in animals has resulted in several significant effects. General activity and function were affected as evidenced by decreased neuromuscular activity (Moser et al., 1995). Additionally, decreased sensorimotor function was detected through measurement of evoked potentials (Herr and Boyes, 1997) and by using the FOB (Moser et al., 1995). Neurochemical changes (e.g., acetylcholine, dopamine, norepinephrine, serotonin) were detected 2 hours after oral dosage of dichloromethane within specific parts of the brain. It should be noted that the acute effects observed after oral or intraperitoneal administration occurred within 5 hours after dosage.”
    - p. 126: “The NOAEL and LOAEL, 101 and 337 mg/kg-day, respectively, for altered neurological functions in female F344 rats [as reported by Moser et al. (1995)] were identical to those reported by Berman et al. (1995) for hepatocyte necrosis in female F344 rats. In the 90-day (Kirschman et al., 1986) and 104-week (Serota et al., 1986a, b) drinking water studies, no obvious clinical signs of neurological impairment were observed in rats or mice at exposure levels that induced liver effects (see Table 4-26), but these studies did not include standardized neurological testing batteries.”
    - p. 129: “As discussed in Section 4.1.2, acute inhalation exposure of humans to dichloromethane has been associated with decreased oxygen availability from COHb formation and neurological impairment from interaction of dichloromethane with nervous system membranes. Results from studies of acutely exposed human subjects indicate that acute neurobehavioral deficits measured, for example, by psychomotor tasks, tests of hand-eye coordination, visual evoked response changes, and auditory vigilance, may occur at concentrations >200 ppm with 4–8 hours of exposure (Bos et al., 2006; ACGIH, 2001; ATSDR, 2000; Cherry et al., 1983; Putz et al., 1979; Gamberale et al., 1975; Winneke, 1974).”
    - p. 258: “Acute inhalation exposure of humans to dichloromethane has been associated with decreased oxygen availability from COHb formation and neurological impairment from interaction of dichloromethane with nervous system membranes (Bos et al., 2006; ACGIH, 2001; ATSDR, 2000; Cherry et al., 1983; Putz et al., 1979; Gamberale et al., 1975; Winneke, 1974)... These studies are limited by the relatively small sample sizes and low power for detecting statistically significant results for these endpoints.”
    - p. 130: “Acute and short-term (up to 7 days) inhalational exposure to dichloromethane in animals has resulted in neurological and hepatocellular changes. Several neurological-mediated parameters were reported, including decreased activity (Kjellstrand et al., 1985; Weinstein et al., 1972; Heppel et al., 1944; Heppel and Neal, 1944), impairment of learning and memory (Alexeeff and Kilgore, 1983), and changes in responses to sensory stimuli (Rebert et al., 1989). Although learning and memory properties were impaired in one acute exposure (47,000 ppm until loss of righting reflex), it should be noted that this effect has not been characterized by using other learning and memory tasks nor any other exposure paradigms. In a 3-day exposure to dichloromethane (70, 300, or 1,000 ppm, 6 hours/day), there were changes in catecholamine (dopamine, serotonin, norepinephrine) in the rat hypothalamus and caudate nucleus (Fuxe et al., 1984). The catecholamine level changes did not affect hormonal release, which is a primary function of the hypothalamus.”
    - US EPA 2011, Toxicological Review of Dichloromethane (Methylene Chloride), available at: <http://www.epa.gov/iris/toxreviews/0070tr.pdf>, accessed May 2012.
  - Grandjean & Landrigan (G&L) (2006): Methylene chloride listed as a human neurotoxicant. G&L is a Screening B list and translates to a very High, High or Moderate level-of-concern. Grandjean & Landrigan 2006, Developmental neurotoxicity of industrial chemicals, Lancet, v. 368: 2167–78.

**Group II\* Score (repeated dose: H, M, L): vH**



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DCM was assigned a score of very High based on NITE classification as Category 1.

- NITE 2006 assessment reports: Category 1 (central nervous system). "Based on the human evidence including "intermittent headache, nausea, flickering vision, breathlessness, temporary memory disorder and right brain damage found in electroencephalography" (CERI-NITE Hazard Assessment No.15, 2004) and "cerebroathy associated with auditory/visionary hallucinations after exposure", "memory disorder associated with intellectual impairment, loss of balance, temporary bilateral degeneration of temporal lobe" (HSDB, 2000)..." Japanese NITE worksheet ID141 in the Microsoft Excel workbook found at: [http://www.safe.nite.go.jp/english/files/ghs\\_xls/classification\\_result\\_e\(479chems\).xls](http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(479chems).xls), accessed May 2012.
- US EPA 2011 assessment reports:
  - Occupational exposure: p. 53-4, "Rather, these analyses provide evidence of an increased prevalence of neurological symptoms among workers with average exposures of 75–100 ppm (Cherry et al., 1981) and long-term effects on specific neurological measures (i.e., attention and reaction time) in workers whose past exposures, at least for part of their work history, were in the 100–200 ppm range (Lash et al., 1991). The increased risk of suicide (approximately a twofold increased risk) seen in two of the worker cohort studies (Hearne and Pifer, 1999; Gibbs, 1992) is an additional indication of potential neurological consequences of dichloromethane exposure. Adequate studies addressing these specific issues are not available. Thus, given the suggestions from the currently available studies, the statement that there are no long-term neurological effects of chronic exposures to dichloromethane cannot be made with confidence."
  - p. 258: "Relatively little is known about the long-term neurological effects of chronic exposures, although there are studies that provide some evidence of an increased prevalence of neurological symptoms among workers with average exposures of 75–100 ppm (Cherry et al., 1981) and long-term effects on some neurological measures (i.e., possible detriments in attention and reaction time in complex tasks) in retired workers whose past exposures were in the 100–200 ppm range (Lash et al., 1991). These studies are limited by the relatively small sample sizes and low power for detecting statistically significant results for these endpoints."
  - p. 67: "None of the chronic oral exposure studies included a systematic measurement of potential neurological effects. One 14-day study focusing on neurobehavioral changes is available, however. Changes in autonomic, neuromuscular, and sensorimotor functions were observed in F344 rats exposed for 14 days to gavage doses  $\geq 337$  mg/kg-day (Moser et al., 1995) (see Section 4.4.2 for more details)."
  - p. 75: "No obvious clinical signs of neurological impairment were observed in the 2-year bioassays involving exposure concentrations up to 2,000 ppm in F344 rats (Mennear et al., 1988; NTP, 1986) or 3,500 ppm in Sprague-Dawley rats (Nitschke et al., 1988a; Burek et al., 1984). In B6C3F1 mice exposed to 4,000 ppm, there was some evidence of hyperactivity during the first year of the study and lethargy during the second year, with female mice appearing to be more sensitive (Mennear et al., 1988; NTP, 1986). Evaluation of batteries of neurobehavioral endpoints following subchronic or chronic inhalation exposure is limited to one study in F344 rats exposed to concentrations up to 2,000 ppm for 13 weeks (Mattsson et al., 1990). No effects were observed >64 hours postexposure in an observational battery, a test of hind-limb grip strength, a battery of evoked potentials, or histologic examinations of brain, spinal cord, or peripheral nerves (see Section 4.4.2)."
  - p. 126: "The NOAEL and LOAEL, 101 and 337 mg/kg-day, respectively, for altered neurological functions in female F344 rats [as reported by Moser et al. (1995)] were identical to those reported by Berman et al. (1995) for hepatocyte necrosis in female F344 rats. In the 90-day (Kirschman et al., 1986) and 104-week (Serota et al., 1986a, b) drinking water studies, no obvious clinical signs of neurological impairment were observed in rats or mice at exposure levels that induced liver effects (see Table 4-26), but these studies did not include standardized neurological testing batteries."
  - p. 130: "Acute and short-term (up to 7 days) inhalational exposure to dichloromethane in animals has resulted in neurological and hepatocellular changes. Several neurological-mediated parameters were reported, including decreased activity (Kjellstrand et al., 1985; Weinstein et al., 1972; Heppel et al., 1944; Heppel and Neal, 1944), impairment of learning and memory (Alexeeff and Kilgore, 1983), and changes in responses to sensory stimuli (Rebert et al., 1989). Although learning and memory properties were impaired in one acute exposure (47,000 ppm until loss of righting reflex), it should be noted that this effect has not



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been characterized by using other learning and memory tasks nor any other exposure paradigms. In a 3-day exposure to dichloromethane (70, 300, or 1,000 ppm, 6 hours/day), there were changes in catecholamine (dopamine, serotonin, norepinephrine) in the rat hypothalamus and caudate nucleus (Fuxe et al., 1984). The catecholamine level changes did not affect hormonal release, which is a primary function of the hypothalamus.”

- p. 136: “Gross neurological impairments were observed in several laboratory species with repeated exposure to 1,000 or 5,000 ppm, 24 hours/day for 14 weeks (Haun et al., 1972; Haun et al., 1971). Dogs exposed to 5,000 ppm, 6 hours/day for 90 days showed slight sedation during exposures, but Sprague-Dawley rats exposed to 10,000 ppm for 90 days did not (Leuschner et al., 1984). In F344 rats exposed to concentrations up to 2,000 ppm, 6 hours/day for 13 weeks, no effects were observed on an observational battery, hind-limb grip strength, a battery of evoked potentials, or histology of the brain, spinal cord, or peripheral nerves; these tests were conducted beginning  $\geq 65$  hours after the last exposure (Mattsson et al., 1990).”
- US EPA 2011, Toxicological Review of Dichloromethane (Methylene Chloride), available at: <http://www.epa.gov/iris/toxreviews/0070tr.pdf>, accessed May 2012. [References internal to the assessment.]
- Grandjean & Landrigan (G&L) (2006): Methylene chloride listed as a human neurotoxicant. G&L is a Screening B list and translates to a very High, High or Moderate level-of-concern. Grandjean & Landrigan 2006, Developmental neurotoxicity of industrial chemicals, Lancet, v. 368: 2167–78.

**Skin Sensitization (SnS) Group II\* Score (H, M or L): L**

DCM was assigned a score Low for skin sensitization based on negative studies with animals.

- REACH registration dossier reports on a 2010 GLP-compliant, reliability 1 study according to OECD Guideline 429 (Skin Sensitisation: Local Lymph Node Assay): “The SI values calculated for the substance concentrations 5, 25 and 100% were 1.3, 1.5 and 1.7 respectively. Since there was no indication that the test substance elicits an SI  $\geq 3$  when tested up to 100%, DICHLOROMETHANE was considered not to be a skin sensitizer.” European Chemicals Agency, registration dossier found at: [http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-8669fc3b-6fb4-4262-8bdf-08e89f9548bf\\_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#GEN\\_RESULTS\\_HD](http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-8669fc3b-6fb4-4262-8bdf-08e89f9548bf_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#GEN_RESULTS_HD), accessed May 2012.
- OECD SIDS dossier reports: “There is no direct indication that dichloromethane is a sensitizer of any practical significance in humans. The neat liquid gave no evidence of sensitizing potential in a Local Lymph Node (OECD TG 429) assay in mice.” OECD SIDS Dossier available at: <http://webnet.oecd.org/Hpv/UI/handler.axd?id=b8ea971c-0c2c-4976-8706-a9a68033daa0>, accessed May 2012.

**Respiratory Sensitization (SnR) Group II\* Score (H, M or L): DG**

DCM was assigned a score of Data Gap for respiratory sensitization based on lack of data.

- No data or studies identified.

**Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M or L): H**

DCM was assigned a score of High for skin irritation/corrosivity based on NITE/Japan classification as GHS Category 2 (GHS country classifications are GreenScreen Screening A sources) and animal data consistent with GHS Category 2 (translates to GreenScreen High level-of-concern).

- NITE/Japan Category 2; “Based on the evidence of “moderate irritation but no skin corrosion observed” from rabbit skin irritation tests (CERI-NITE Hazard Assessment No.15, 2004).” Japanese NITE worksheet ID141 in the Microsoft Excel workbook found at: [http://www.safe.nite.go.jp/english/files/ghs\\_xls/classification\\_result\\_e\(479chems\).xls](http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(479chems).xls), accessed May 2012.

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- REACH registration dossier describes a 1990 reliability 1 study with New Zealand white rabbits according to OECD Guideline 404 (Acute Dermal Irritation / Corrosion): "According to the EEC-standards (as published in the Official Journal of the European Communities, L257, Volume 26, 16 September 1983) dichloromethane is irritating to skin but not corrosive." Data described is consistent with GHS Category 2. European Chemicals Agency, registration dossier found at: [http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-3a6130c1-ef39-494e-907d-6074a755fbe9\\_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#AGGR-3a6130c1-ef39-494e-907d-6074a755fbe9](http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-3a6130c1-ef39-494e-907d-6074a755fbe9_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#AGGR-3a6130c1-ef39-494e-907d-6074a755fbe9), accessed May 2012.
- OECD SIDS Based on the available information from animal studies (OECD TG 404), dichloromethane is a skin and eye irritant. OECD SIDS Dossier available at: <http://webnet.oecd.org/Hpv/UI/handler.axd?id=b8ea971c-0c2c-4976-8706-a9a68033daa0>, accessed May 2012.

**Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M or L): **H****

DCM was assigned a score of High for eye irritation/corrosivity based on classification as Category 2A by NITE/Japan (GHS country classifications are GreenScreen Screening A sources) and animal data from the REACH dossier consistent with GHS Category 2A (translates to GreenScreen High level-of-concern).

- NITE/Japan Category 2A; "Based on the evidence of "moderate or severe eyelid irritation" from rabbit eye irritation tests (CERI-NITE Hazard Assessment No.15, 2004)." Japanese NITE worksheet ID141 in the Microsoft Excel workbook found at: [http://www.safe.nite.go.jp/english/files/ghs\\_xls/classification\\_result\\_e\(479chems\).xls](http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(479chems).xls), accessed May 2012.
- REACH registration dossier reports a 1976 reliability 2 study with New Zealand white rabbits; test guideline not reported, but includes method details similar to OECD 405 with additional test conditions investigated. No data on corneal opacity. Irritation/inflammation effects were reversible within 8 days. Data consistent with Category 2A (not reversible within 7 days - required for 2B). European Chemicals Agency, registration dossier found at: [http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-bf9e8617-76ac-4cc6-bcf7-f27b58e0e4ed\\_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#AGGR-bf9e8617-76ac-4cc6-bcf7-f27b58e0e4ed](http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-bf9e8617-76ac-4cc6-bcf7-f27b58e0e4ed_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#AGGR-bf9e8617-76ac-4cc6-bcf7-f27b58e0e4ed), accessed May 2012.
- OECD reports that based on the available information from animal studies (OECD TG 404), dichloromethane is a skin and eye irritant. OECD SIDS Dossier available at: <http://webnet.oecd.org/Hpv/UI/handler.axd?id=b8ea971c-0c2c-4976-8706-a9a68033daa0>, accessed May 2012.

**Ecotoxicity (Ecotox)**

**Acute Aquatic Toxicity (AA) Score (vH, H, M or L): **M****

DCM was assigned a score of Moderate for acute aquatic toxicity based on measured test data (LC<sub>50</sub> near or below 100 mg/L) for aquatic invertebrates (the most sensitive taxon).

- OECD SIDS 2011 dossier reports several acute aquatic toxicity studies.
  - Taxon, Test Species, Endpoint, Value, Method Comments
  - Fish, freshwater, Pimephales promelas, 96h-LC<sub>50</sub>, 193 mg/L (m), Flow-through Method;
  - Fish, freshwater, Pimephales promelas, 96h-LC<sub>50</sub>, 502 mg/L (m), ASTM E729-80;
  - Fish, freshwater, Pimephales promelas, 96h-LC<sub>50</sub>, 330 mg/L (m), -;
  - Fish, marine, Fundulus heteroclitus, 48h-LC<sub>50</sub>, 97 mg/L (m), -;
  - Invertebrates, freshwater, Daphnia magna, 48h-LC<sub>50</sub>, 27 mg/L (n), Static;
  - Invertebrates, marine, Palaemonetes pugio, 48h-LC<sub>50</sub>, 109 mg/L (m), Static, closed system;
  - Aquatic plants, Chlamydomonas sp., 3h-EC<sub>50</sub>, 1478-2292 mg/L (n), Flasks closed with cotton wool;
  - (m) indicates measured concentration; (n) indicates nominal concentration.
  - OECD SIDS Dossier available at: <http://webnet.oecd.org/Hpv/UI/handler.axd?id=b8ea971c-0c2c-4976-8706-a9a68033daa0>, accessed May 2012.

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- REACH registration dossier: Details are presented for the invertebrate results discussed above. Marine and freshwater invertebrate studies were reliability 2; results were below or near threshold for Moderate level-of-concern. European Chemicals Agency, registration dossier found at:  
[http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-8d1207b7-279b-4eb1-9003-1ac61e45ab85\\_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#AGGR-8d1207b7-279b-4eb1-9003-1ac61e45ab85](http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-8d1207b7-279b-4eb1-9003-1ac61e45ab85_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#AGGR-8d1207b7-279b-4eb1-9003-1ac61e45ab85), accessed May 2012.

**Chronic Aquatic Toxicity (CA) Score (vH, H, M or L): L**

DCM was assigned a score of Low for chronic aquatic toxicity based on ECOSAR v.1.11 results for Daphnid ChV > 10 mg/L.

- PPRC: Invertebrates were the most sensitive taxon in acute toxicity measurements. Similarly, QSAR predictions for Daphnia gave the lowest ChV/NOEC values. The GreenScreen score should be assigned based on the most vulnerable taxon, but the estimated toxicity results for invertebrates vary by algorithm. The OECD SIDS results have a broader range of values, including a single value < 10. The latest ECOSAR model predicts NOEC for Daphnia ChV at 12 mg/L, well above the threshold for Low level-of-concern.
- REACH registration dossier reports on a non-GLP-compliant, reliability 2 study with juvenile and embryo-larval Pimephales promelas: 28 day NOEC = 83 mg/L for larval growth, 28-day survival NOEC = 142 mg/L. European Chemicals Agency, registration dossier found at:  
[http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-94b56b12-a03f-4991-85a0-6e64df8b5d84\\_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#AGGR-94b56b12-a03f-4991-85a0-6e64df8b5d84](http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-94b56b12-a03f-4991-85a0-6e64df8b5d84_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#AGGR-94b56b12-a03f-4991-85a0-6e64df8b5d84), accessed May 2012.
- US EPA's PBT Profiler estimates Fish ChV at 25 mg/L. US EPA's PBT Profiler available at:  
<http://www.pbtprofiler.net/default.asp>, accessed May 2012. See Appendix B.
- OECD SIDS 2011 dossier reports:
  - Test data:
    - Taxon, Test Species, Endpoint, Value, Method Comments
    - freshwater, Pimephales promelas, 28d-NOEC, 142 mg/L (m<sup>6</sup>, mortality, larval survival)
    - freshwater, Pimephales promelas, 28d-NOEC, 83 mg/L (m, body weight)
  - Modeling results:
    - "The lowest acute E(L)C50 value has been observed with Daphnia magna. However, no chronic toxicity data are available for daphnia. To reduce the uncertainty of the hazard assessment for the environment, the missing long-term NOEC for Daphnia magna was predicted by using three independent QSARs (QSAR Toolbox v.2.2.1.1120 based on mode of action and structural analogs, and ECOSAR 1.0). A 21d-NOEC for daphnids between 6.2 mg/L and 13.3 mg/L was estimated."
  - OECD SIDS Dossier available at: <http://webnet.oecd.org/Hpv/UI/handler.axd?id=b8ea971c-0c2c-4976-8706-a9a68033daa0>, accessed May 2012
    - ECOSAR estimates for "Neutral Organics":
      - Fish ChV 24.824 mg/L
      - Daphnid ChV 12.001 mg/L
      - Green Algae ChV 19.306 mg/L
      - US EPA ECOSAR 1.11 results in Appendix A. Model software available at:  
<http://www.epa.gov/oppt/newchems/tools/21ecosar.htm>, accessed May 2012.

**Environmental Fate (Fate)**

**Persistence (P) Score (vH, H, M, L, or vL): vH**

<sup>6</sup> "m" indicates measured concentration

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DCM is volatile and likely to end up in the atmosphere where it is long lived (half-life in air of 120 days); translates to GreenScreen very High level-of-concern. Ignoring the air results would lead to a Moderate to High level-of-concern based on the estimated 38 day half-life in water and 75 day half-life in soil.

- Environment Canada lists DCM as "Yes" for Persistence. The GreenScreen List Translator indicates Very High or High level-of-concern for this Screening B list. Environment Canada Categorization Decisions for Substances on the Domestic Substance List (DSL), <http://www.ec.gc.ca/lcpe-cepa/default.asp?lang=En&n=5F213FA8-1&wsdoc=D031CB30-B31B-D54C-0E46-37E32D526A1F>
- REACH dossier reports a 1992, reliability 1, GLP-compliant study equivalent to OECD 301D: MEK is "readily biodegradable." European Chemicals Agency, registration dossier found at: [http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d91195a-65f3-618d-e044-00144f67d249/AGGR-8c260306-392b-4cd7-b6c7-3f516d9fcb76\\_DISS-9d91195a-65f3-618d-e044-00144f67d249.html#AGGR-8c260306-392b-4cd7-b6c7-3f516d9fcb76](http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d91195a-65f3-618d-e044-00144f67d249/AGGR-8c260306-392b-4cd7-b6c7-3f516d9fcb76_DISS-9d91195a-65f3-618d-e044-00144f67d249.html#AGGR-8c260306-392b-4cd7-b6c7-3f516d9fcb76), accessed May 2012.
- US EPA's PBT Profiler fate model predicts:

	Medium	Halflife (days)	% in medium	GreenScreen Rank
Water		38 days,	47%	Moderate persistence.
Soil		75 days,	7%	High persistence.
Sediment		340 days,	0%	- (Not likely to accumulate in sediment.)
Air		120 days,	46%	very High persistence.

  - US EPA's PBT Profiler available at: <http://www.pbtprofiler.net/default.asp> (Appendix B).

**Bioaccumulation (B) Score (vH, H, M, L, or vL): vL**

DCM was assigned a score of very Low for bioaccumulation based on the measured log  $K_{ow}$  of 1.25 and BCF estimates. Log  $K_{ow} \leq 4$  and BCF  $\leq 100$  consistent with GreenScreen v1.2 Criteria very Low level-of-concern.

- REACH registration dossier reports on a reliability 2 study (shake flask method): log  $P_{ow} = 1.25$ ; "The temperature and pH at which the measurement has been performed were not specified in the peer-reviewed handbook, but assumed to correspond to standard conditions of 20 °C and pH 7. As the substance cannot dissociate, it is expected that pH shall not influence the partition coefficient." European Chemicals Agency, registration dossier found at [http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-cde493e1-c7ed-4dba-9f27-59c1d9e4ecea\\_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#AGGR-cde493e1-c7ed-4dba-9f27-59c1d9e4ecea](http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-cde493e1-c7ed-4dba-9f27-59c1d9e4ecea_DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#AGGR-cde493e1-c7ed-4dba-9f27-59c1d9e4ecea), accessed May 2012.
- OECD SIDS 2011 dossier reports: "The bioaccumulation potential seems to be low based on the low log  $K_{ow}$  value of 1.25 and BCF values ranging from 0.91 to 40 L/kg." OECD SIDS dossier available at: <http://webnet.oecd.org/Hpv/UI/handler.axd?id=b8ea971c-0c2c-4976-8706-a9a68033daa0>, accessed May 2012.
- The US EPA's PBT Profiler estimates BCF at 3.1; log  $K_{ow}$  experimental value 1.25. US EPA's PBT Profiler found at: <http://www.pbtprofiler.net/default.asp>, accessed May 2012. (Appendix B)

**Physical Hazards (Physical)**

**Reactivity (Rx) Score (vH, H, M or L): L**

DCM was assigned a score of Low for reactivity based on experimental data and a chemical structure inconsistent with explosive, reactive or oxidizing properties.

- CAMEO reports: "DICHLOROMETHANE is normally stable. It reacts vigorously with active metals such as lithium, sodium and potassium, and with strong bases such as potassium tert-butoxide. It is incompatible with strong oxidizers, strong caustics and chemically active metals such as aluminum or magnesium powders. The liquid will attack some forms of plastic, rubber and coatings. This compound reacts with sodium-potassium alloy, (potassium hydrogen + N-methyl-N-nitrosurea), nitrogen tetroxide and liquid oxygen. It also reacts with titanium. On contact with water it corrodes iron, some stainless steels, copper and nickel. It is incompatible with alkali metals. It is incompatible with amines, zinc and alloys of aluminum, magnesium and zinc. This compound is liable to explode when mixed with dinitrogen pentoxide or nitric acid. Mixtures of this compound

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in air with methanol vapor are flammable. (NTP, 1992).” CAMEO Database of Hazardous Materials, available at: <http://cameochemicals.noaa.gov/chemical/3154>, accessed May 2012.

- HSDB reports: “...will not form explosive mixtures with air at ordinary temperatures.” HSDB available at: <http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+75-09-2>, accessed May 2012.
- NITE/Japan 2006 reports: “Containing no atom groups with explosive or self-reactive properties.” Japanese NITE worksheet ID141 in the Microsoft Excel workbook found at: [http://www.safe.nite.go.jp/english/files/ghs\\_xls/classification\\_result\\_e\(479chems\).xls](http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(479chems).xls), accessed May 2012.
- ATSDR reports: Not explosive (Sax and Lewis 1987). ATSDR Toxicological Profile for Methylene Chloride, available at: <http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=234&tid=42>, accessed May 2012.

**Flammability (F) Score (vH, H, M or L): **L****

DCM was assigned a score of Low for flammability based on experimental data suggesting no flammability.

- ATSDR 2000 reports: Flashpoint - Nonflammable (Sax and Lewis 1987); Flammability limits – Nonflammable (Sax and Lewis 1987). ATSDR Toxicological Profile for Methylene Chloride, available at: <http://www.atsdr.cdc.gov/ToxProfiles/tp.asp?id=234&tid=42>, accessed May 2012.
- REACH registration dossier describes a reliability 2 supporting study (method not specified): “Relevant literature sources and studies indicate that this substance has no flashpoint. However, under certain conditions the substance can form flammable vapour/air mixtures (13-22 % Vol at 20 °C) which under normal circumstances are difficult to ignite (under optimum conditions of 18 % Vol in air at 20 °C the minimum energy needed for ignition is 9300 mJ, which is many 10000 fold higher than for vapours of other common flammable solvents). Classification as flammable is thus not required.” European Chemicals Agency, registration dossier found at: <http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249/AGGR-b6e1ed91-1230-4b24-8a23-e56d06e7752b> DISS-9d8c3b63-3ba5-31d6-e044-00144f67d249.html#AGGR-b6e1ed91-1230-4b24-8a23-e56d06e7752b, accessed May 2012.

**References**

References provided within individual endpoint results.



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**Abbreviations / Acronyms / Initialisms**

ACGIH	American Conference of Industrial Hygienists
ASTDR	Agency for Toxic Substances and Disease Registry
CAMEO	CAMEO Chemicals Database of Hazardous Materials
CEPA-DSL	Canadian EPA Domestic Substances List
ChemSec	International Chemical Secretariat [prepares the Substitute it Now (SIN) List]
CPA	Clean Production Action
ECCSP	Environment Canada Chemical Substances Portal
EC-EDD	European Commission endocrine disrupting substance database
ECHA C&L	ECHA Classification and Labeling Inventory Database
ECHA	European Chemicals Agency
EPA HPV	US EPA High Production Volume Information System
EPA SRS	US EPA Substance Registry System
ESIS	European chemical Substances Information System
EU	European Union
GHS	Globally Harmonized System (of classification and labeling)
HSDB	Hazardous Substances Data Bank
IARC	International Agency for Research on Cancer
IPCS	International Program on Chemical Safety
IRIS	Integrated Risk Information System (US EPA)
ISSCAN	Chemical carcinogens database (Italy)
J-Check	Japan Chemicals Cooperative Knowledge database
KEMI	Swedish Chemicals Agency
MSDS	Material Safety Data Sheet
NFPA	National Fire Protection Association
NIOSH	National Institute of Occupational Safety and Health
NITE	National Institute of Technology and Evaluation (Japan)
NTP	National Toxicology Program
OECD	Organization for Economic Co-operation and Development
OSPAR	Oslo Paris Commission and convention for protection of the marine environment
PBT Profiler	US EPA's PBT Profiler
Prop 65	California Proposition 65 regulation and list of chemicals of concern
REACH	European Commission chemicals regulation
RoC	Report on Carcinogens (National Toxicology Program)
RTECS	Registry of Toxic Effects of Chemical Substances
SIDS	Screening Information Data Sets
TEDX	The Endocrine Disruptor Exchange
UNEP	United Nations Environment Program
US DOT	US Department of Transportation Hazardous Materials Regulations
US EPA	United States Environmental Protection Agency

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**Appendix A - ECOSAR Version 1.11 Results**

SMILES : CLCCL	
CHEM : Methane, dichloro-	Melt Pt: (User Entered for Wat Sol estimate)
CAS Num: 000075-09-2	Melt Pt: -95.10 (deg C, PhysProp DB exp value for Wat Sol est)
ChemID1:	Wat Sol: 1.43E+004 (mg/L, EPISuite WSKowwin v1.43 Estimate)
MOL FOR: C1 H2 CL2	Wat Sol: (User Entered)
MOL WT : 84.93	Wat Sol: 1.3E+004 (mg/L, PhysProp DB exp value)
Log Kow: 1.340 (EPISuite Kowwin v1.68 Estimate)	
Log Kow: 1.25 (PhysProp DB exp value - for comparison only)	

**Values used to Generate ECOSAR Profile**

Log Kow: 1.340 (EPISuite Kowwin v1.68 Estimate); Wat Sol: 1.3E+004 (mg/L, PhysProp DB exp value)

**Available Measured Data from ECOSAR Training Set**

CAS No	Organism	Duration	Measured End Pt mg/L (ppm)	Ecosar Class	Reference
=====	=====	=====	=====	=====	=====
000075-09-2	Fish (SW)	96-hr	LC50 322.9	Neutral organics	Zaroogian et al., 1985
000075-09-2	Fish	96-hr	LC50 330	Neutral organics	DUL
000075-09-2	Daphnid	48-hr	LC50 1682	Neutral organics	Kuhn, 1989

**ECOSAR v1.1 Class-specific Estimations - Neutral Organics**

ECOSAR Class	Organism	Predicted Duration	End Pt	mg/L (ppm)
=====	=====	=====	=====	=====
Neutral Organics	: Fish	96-hr	LC50	272.881
Neutral Organics	: Daphnid	48-hr	LC50	145.790
Neutral Organics	: Green Algae	96-hr	EC50	84.427
Neutral Organics	: Fish		ChV	24.824
Neutral Organics	: Daphnid		ChV	12.001
Neutral Organics	: Green Algae		ChV	19.306
Neutral Organics	: Fish (SW)	96-hr	LC50	342.184
Neutral Organics	: Mysid	96-hr	LC50	397.543
Neutral Organics	: Fish (SW)		ChV	24.829
Neutral Organics	: Mysid (SW)		ChV	41.779
Neutral Organics	: Earthworm	14-day	LC50	172.849

Note: \* = asterisk designates: Chemical may not be soluble enough to measure this predicted effect. If the effect level exceeds the water solubility by 10X, typically no effects at saturation (NES) are reported.

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**Appendix B – US EPA’s PBT Profiler Modeling Results**

**Results**

Orange or red highlights indicate that the EPA [criteria](#) have been exceeded.

[Black-and-white version](#)

**Persistence**

**Bioaccumulation Toxicity**

**75-09-2 Methane, dichloro-**

**PBT Profiler Estimate = PBT**

<u>Media</u>	<u>Half-Life</u> (days)	<u>Percent in</u> <u>Each Medium</u>	<u>BCF</u>	<u>Fish</u> <u>ChV</u> (mg/l)
Water	38	47%	3.1	25
Soil	75	7%		
Sediment	340	0%		
Air	120	46%		

