Green Screen Assessment Prepared By:
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Date: 30 June 2012

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Date: 17 April 2013

GreenScreen™ Assessment for Toluene (CAS #108-88-3)

GreenScreen™ Version 1.2 Draft Assessment
Note: Validation Has Not Been Performed on this Green Screen Assessment

Chemical Name: Toluene

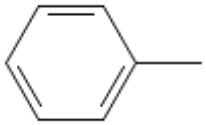
Confirm application of the de minimus rule[1]: (if no, what *de minimus* did you use?) Yes.

Chemical Name (CAS #): Toluene (CAS#108-88-3)

Also Called: "Benzene, methyl-", "Methacide", "Methylbenzene", "Phenylmethane", "TOLU", "Toluene", "Toluol" (US EPA, ACToR database, 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. Toluene is used commercially in the production of benzene and many other chemicals, e.g. benzoic acid, nitrotoluenes, dyes, pharmaceuticals, food additives, plastics, etc.
2. Toluene is also widely used as a solvent in coatings, adhesives, inks, pharmaceuticals and chemical processing.

Reference: European Union 2003, Risk Assessment Report (see references to Substance Background below).

GreenScreen Rating[2]: Toluene was assigned a **Benchmark Score of 1** based on:

- Failure of Benchmark Rule 1e, due to High reproductive and developmental toxicity.

GreenScreen Hazard Ratings: Toluene																			
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*										
DG	L	H	H	M	L	M	H	M	H	L	DG	H	L	H	H	*H*	vL	L	H

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.

[1] 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.

[2] 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[3]

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

A 2003 European Union Risk Assessment Report (see reference below in Substance Background) reviews transformation of toluene in the environment. Toluene is resistant to hydrolysis and photolysis. Photooxidation likely leads to formation of o-, m-and p-cresol, o-, m-and p-nitrotoluene, benzylnitrate, etc. Due to the slow reaction of monocyclic aromatic hydrocarbons with O_3 and NO_3 radicals, there is the potential for rain-out. The report further speculates that the occurrence of the pesticide DNOC (4,6-dinitro-o-cresol) in rain and groundwater after product bans in Denmark may have been due to atmospheric toluene transformation. No additional data was identified.

Substance Background
Toluene is a high-production volume substance with extremely broad use. Toluene is used commercially in the production of benzene and many other chemicals, e.g. benzoic acid, nitrotoluenes, dyes, pharmaceuticals, food additives, plastics, etc. Toluene is also widely used as a solvent in coatings, adhesives, inks, pharmaceuticals and chemical processing. Toluene is also found in consumer products, including aerosols, paints, adhesives, and glues (European Union 2003).

Toluene is produced mainly through the refining of petroleum and the related conversion processes. Catalytic reforming, catalytic cracking, hydrocracking, etc., produce olefinic and aromatic rich streams with benzene, toluene and xylenes in varying concentrations. Commercial toluene is produced by distillation from the mixed aromatic stream. Impurities reflect this process, reported to include benzene and xylene mixed isomers (European Union 2003).

Toluene is highly volatile and exposure to humans occurs from breathing vapors, through drinking contaminated water or dermal contact. Toluene moves readily from the lungs into the bloodstream and from dermal absorption. More than 75% of the toluene taken into the body is removed within 12 hours primarily as urinary metabolites, with most of the remaining exhaled as toluene. Toluene is metabolized by the liver to hippuric acid with minor metabolites including glucoronyl conjugates of benzoic acid and various cresols (US EPA 2005).

As mentioned previously (Transformation Products and Ratings), toluene is reportedly resistant to hydrolysis and photolysis. Photooxidation likely leads to formation of o-, m-and p-cresol, o-, m-and p-nitrotoluene, benzylnitrate, etc. Due to the slow reaction of monocyclic aromatic hydrocarbons with O_3 and NO_3 radicals, there is the potential for rain-out of these compounds. The report further speculates that the occurrence of the pesticide DNOC (4,6-dinitro-o-cresol) in rain and groundwater after product bans in Denmark may have been due to atmospheric toluene transformation.

References
1. European Union 2003, Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012.
2. US EPA 2005, Toxicological Review of Toluene, available at: http://www.epa.gov/iris/toxreviews/0118tr.pdf, accessed May 2012.

[3] 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.
[4] 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.
[5] The way you conduct assessments for transformation products depends on the Benchmark Score of the parent chemical (See Guidance).

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

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

Toluene was assigned a score of Data Gap based on insufficient data to eliminate the potential for carcinogenicity in humans.

- NITE/Japan 2006 assessment. Not classified. Due to the fact that the substance is classified as Group 3 by IARC (1999), Category A4 by ACGIH (2001) and Category D by EPA (2005). Not positively determined to be "negative." Japanese NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.
- US EPA 2005 assessment reports: "Under the Guidelines for Carcinogen Risk Assessment (U.S. EPA, 2005), there is inadequate information to assess the carcinogenic potential of toluene. Studies of humans who were chronically exposed to toluene are inconclusive. Toluene was not carcinogenic in inhalation cancer bioassays of rats and mice exposed for life (CIIT, 1980; NTP, 1990; Huff, 2003). Increased incidences of mammary cancer and leukemia were reported in a lifetime rat oral bioassay at a dose level of 500 mg/kg-day but not at 800 mg/kg-day (Maltoni et al., 1997). Toluene has generally not been found to be genotoxic in short-term testing." [pp. 88-89, references internal to the assessment.] US EPA 2005, Toxicological Review of Toluene, available at: http://www.epa.gov/iris/toxreviews/0118tr.pdf, accessed May 2012.
- EU 2003 assessment reports: "Evaluation: There is inadequate evidence in humans for the carcinogenicity of toluene. There is evidence suggesting lack of carcinogenicity of toluene in experimental animals. Overall evaluation: Toluene is not classified as a carcinogen to humans (Group 3)." [p. 207] EU 2003 Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012.
- IARC 1989 assessment lists as Group 3 - Not classifiable as to its carcinogenicity to humans. Group 3 is used when data is limited or the mechanism is in doubt for humans. IARC is a GreenScreen Authoritative B List. GreenScreen List Translator indicates H, M or L 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.
- Not listed for cancer on authoritative lists, including: NTP, Prop 65, or NIOSH.

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

Toluene was assigned a score of Low for mutagenicity based on GHS-Japan listing as "Not Classified" (GreenScreen Screening A list) and negative results summarized in the US EPA 2005 toxicological review.

- NITE/Japan 2006 reports: "Not classified." The NITE analysis suggests "negative" for mutagenicity based on weight-of-evidence. GHS country classifications are GreenScreen Screening A lists; translates to Low level-of-concern. Japanese National NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.
- US EPA 2005 assessment reports: "Toluene has generally not been found to be genotoxic in short-term testing." [p. 89] Details in the assessment US EPA 2005, Toxicological Review of Toluene, available at: http://www.epa.gov/iris/toxreviews/0118tr.pdf, accessed May 2012.
- EU 2003 assessment reports: "Toluene has been tested for mutagenicity, clastogenicity and other types of DNA interactions in a multitude of in vitro and in vivo experiments. There are extensive data available on the lack of mutagenicity of toluene to the standard Salmonella typhimurium test strains in the plate incorporation assay, and toluene has also been found negative in a well-performed preincubation test, which is more adequate for the test of compounds with volatility comparable to toluene. For this reason, no further testing for bacterial mutagenicity appears to be required. In addition, toluene has not been found to induce DNA repair mediated toxicity to various bacteria, gene conversion in Saccharomyces cerevisiae or genotoxic effects in Drosophila melanogaster. Atnon-cytotoxic doses, toluene has not induced biological significant increases in forward mutations, sister chromatid exhanges, micronuclei or DNA damage in vitro. Significant levels of cytotoxicity have been reached in most studies, indicating the contact between toluene and the biological test objects. In

recent studies, where benzene contamination can be excluded, toluene has not induced biological significant cytogenetic changes in the bone marrow of rodents or DNA damage in peripheral blood cells, bone marrow, and liver of mice. Prolonged exposure to 50 ppm toluene has also not induced increased frequencies of sister chromatid exchange in peripheral blood lymphocytes of human volunteers. In addition, toluene was not considered to be mutagenic to the sperm of mice in a dominant lethal assay. Equivocal results have been obtained in a multitude of studies with biological monitoring of various genotoxic effects in peripheral blood lymphocytes from workers exposed to toluene in the occupational environment, but confounding due to coexposure to ink, other solvents and various genotoxic substances in the environment cannot be excluded, and a clear synergistic effect between toluene exposure and smoking has been demonstrated. On balance, toluene can be considered to be non-genotoxic, and no further testing for genotoxic effects appear to be required." [p. 201] EU 2003 Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012.

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

Toluene was scored as High for reproductive toxicity based on the most conservative assessment from GreenScreen authoritative sources (Prop 65).

- Prop 65 Known to the state to cause female reproductive effects. California Prop 65 List, available at: http://oehha.ca.gov/prop65/prop65_list/Newlist.html, accessed May 2012. Prop 65 is an Authoritative A list.
- EU 2003 Risk Assessment Report (available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012):
  - From "Summary and conclusions for toxicity for reproduction" p. 230: "Toluene does not have clear effects on fertility in rats, however, decreased sperm count was found in a study at 2,000 ppm (90 days, 6 hours/day). The NOAEC for this effect was 600 ppm (Ono et al., 1996). In humans, no study of adequate quality has been found.
  - From "Summary of effects on fertility" p. 211: "Toluene has in two studies not shown adverse effects on fertility in rats, and the NOAECs are 2,000 ppm (7,500 mg/m3). However, significantly decreased sperm count and reduced epididymal weight was found in the Ono et al. (1996) study at an exposure concentration of 2,000 ppm (7,500 mg/m3) during 6 hours/day for 90 days. Although the effects occurred in the presence of other systemic effects (increased kidney and decreased thymus weight), no data support that the effects on sperm count and epididymal weight were secondary to these other effects. The NOAEC was 600 ppm (2,250 mg/m3). The sperm count data actually point to a dose-response relation, i.e. slightly decreased at 600 ppm and significantly decreased at 2,000 ppm."
- US EPA 2005 assessment discusses mode-of-action for reproductive toxicity: "…toluene may also cause molecular damage via free radical oxidation. In female rats exposed to 50 and 500 mg/m3 toluene via inhalation for 4 hours a day, 5 days a week for one month, increased glutathione peroxidase activity and the activation of free radical processes were apparent in both brain and ovarian tissue, while the ovarian tissue also showed an increase in catalase activity and protein peroxidation (Burmistrov et al., 2001). Also, toluene metabolites, methylhydroquinone and methylbenzoquinone, may cause oxidative DNA damage that is reproductively toxic due to the relative inability of spermatogenic cells to repair DNA damage (Murata et al., 1999). Nakai et al. (2003) showed increased formation of 8-hydroxy-2'-deoxyguanosine, a biological marker for oxidative DNA damage, in the testes after subcutaneous injection of toluene at 50 and 500 mg/kg once a day for ten days. These results suggest that the reproductive toxicity of toluene stems from direct oxidative DNA damage to the spermatazoa." [p. 58], US EPA 2005, Toxicological Review of Toluene, available at: http://www.epa.gov/iris/toxreviews/0118tr.pdf, accessed May 2012.
- NITE/Japan 2006 classifies as Category 1A, but largely based on developmental effects; however, endocrine system impacts from toluene exposure are noted: "Based on the results of human epidemiological studies suggesting increased incidence of natural abortion after toluene exposure, abnormal development and malformation of newborns caused by prenatal toluene abuse and decreased plasma concentrations of luteinizing hormone and testosterone after toluene exposure, described in IRIS Toxicological review (2005), EU-RAR No.30 (2003), IARC 71(1999), IARC 47 (1989), EHC 52 (1986) and ATSDR (2000), the following conclusion by Ng et al. (1992) in EU RAR30 (2003): "the study suggests an increased risk of late spontaneous abortions

associated with exposure to toluene at levels around 88 ppm (range 50-150 ppm). The results of this study are used as a basis for the risk characterisation of developmental toxicity in humans," and the evidence of increased incidences of foetal death and delayed ossification, a decrease and unossification of sternebrae, a shift in rib profile, excess ribs, retarded skeletal development, delayed reflex response, learning disability and early vaginal opening and testes descent at dosing levels not toxic to dams from rat and mouse teratogenicity tests. According to Da-Silva et al. (1991), toluene was accumulated in breast milk, although no developmental toxicity via lactation was observed." [References internal to the assessment.] Japanese NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.

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

Toluene was assigned a score of High for developmental toxicity based on the most conservative result from GreenScreen authoritative lists (Prop 65).

- Prop 65: Known to the state to cause developmental effects. California Prop 65 List, available at: http://oehha.ca.gov/prop65/prop65_list/Newlist.html, accessed May 2012. Prop 65 is an Authoritative A list.
- ECHA CLP harmonized classification: Category 2, H361d. Authoritative A list; GreenScreen List Translator scores as Moderate. ECHA C&L Inventory Database, http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=30426&HarmOnly=no?DisclaimerAgr=Agree&Index=108-88-3&ExecuteSearch=true&fc=true&lang=en , accessed May 2012.
- Grandjean & Landrigan (G&L) (2006): Toluene is listed as a developmental human neurotoxicant. G&L is a Screening B list and translates to High or Moderate level-of-concern. Grandjean & Landrigan 2006, Developmental neurotoxicity of industrial chemicals, Lancet, v. 368: 2167–78.
- NITE/Japan 2006 classifies as Category 1A: "Based on the results of human epidemiological studies suggesting increased incidence of natural abortion after toluene exposure, abnormal development and malformation of newborns caused by prenatal toluene abuse and decreased plasma concentrations of luteinizing hormone and testosterone after toluene exposure, described in IRIS Toxiological review (2005), EU-RAR No.30 (2003), IARC 71(1999), IARC 47 (1989), EHC 52 (1986) and ATSDR (2000), the following conclusion by Ng et al. (1992) in EU RAR30 (2003): "the study suggests an increased risk of late spontaneous abortions associated with exposure to toluene at levels around 88 ppm (range 50-150 ppm). The results of this study are used as a basis for the risk characterisation of developmental toxicity in humans, and the evidence of increased incidences of foetal death and delayed ossification, a decrease and unossification of sternebrae, a shift in rib profile, excess ribs, retarded skeletal development, delayed reflex response, learning disability and early vaginal opening and testes descent at dosing levels not toxic to dams from rat and mouse teratogenicity tests. According to Da-Silva et al. (1991), toluene was accumulated in breast milk, although no developmental toxicity via lactation was observed." Japanese NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.
- US EPA 2005 assessment (Toxicological Review of Toluene, available at: http://www.epa.gov/iris/toxreviews/0118tr.pdf, accessed May 2012):
  - p. 88: "In mothers who inhaled very high levels of toluene as an addictive euphoric during pregnancy, the children showed a number of physical (small mid face, deep-set eyes, micrognathia, and blunting of the fingertips) and clinical (microcephaly, CNS dysfunction, attention deficits, and developmental delay/mental deficiency) changes attributed to toluene. Animal studies of toluene inhalation have revealed delayed neurodevelopment and decreased offspring weight at levels that also resulted in maternal toxicity. Gross malformations were not noted at any exposure level."
- EU 2003 Risk Assessment Report (available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012):
  - p. 230: "Case studies on high-level toluene exposure of pregnant women (sniffing) provide evidence of developmental toxicity (physical and neurological abnormalities) in humans."
  - pp. 230-1: "Two studies suggest an increased risk of spontaneous abortions associated with exposure to toluene in the workplace. One of the studies provides no data on exposure levels, while the levels were around 88 ppm (range 50-150 ppm) in the other study (Ng et al., 1992b). The Ng et al. 1992 study cannot

be used to establish definitively a causal relationship between late spontaneous abortions and toluene exposure or the magnitude of the LOAEL To establish a definite relationship, a prospective study including pregnant women exposed to toluene at similar exposure levels (mean 88 ppm, range 50-150 ppm) with individually monitored data on toluene exposure and fetal loss would be needed. However, based on the current evidence suggesting an increased risk for late spontaneous abortions, exposure of pregnant women to such exposure levels would raise serious ethical concerns. Consequently, the results of the Ng study are used as a basis for the risk characterisation of developmental toxicity in humans."

- p. 231: "In conclusion, limited data in humans indicate an increased risk for late spontaneous abortions at dose levels around 88 ppm. Human data as well as studies in rats and limited data in mice provide evidence of similar developmental effects, i.e. lower birth weight, delayed postnatal development and developmental neurotoxicity. Only very high exposure levels were investigated in humans. In animals, the NOAEC for lower birth weight and delayed postnatal development is 600 ppm. A NOAEC for developmental neurotoxicity cannot be determined from the available studies. The LOAEC for this effect is 1,200 ppm."

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

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

- The Endocrine Disruption Exchange (TEDX) lists toluene. TEDX is a Screening B list; translates to High or Moderate (report Moderate for benchmarking). TEDX List of Potential Endocrine Disruptors spreadsheet available at: http://www.endocrinedisruption.com/endocrine.TEDXList.overview.php, 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): L

Toluene was assigned a score of Low for acute mammalian toxicity based on animal test data consistent with GHS Category 5 by all exposure pathways. Translates to Low level-of-concern (GreenScreen List Translator).

- NITE/Japan 2006 classifies as:
  - Acute toxicity (oral) Category 5; Acute toxicity (inhalation, vapor) Category 4; Acute toxicity (dermal) not classified.
  - PPRC: Category 4 for inhalation appears to misread the EU 2003 data for inhalation LC50. The EU RAR reports the rat LC50 as 28.1 mg/L/4hr (see bullet below), while NITE reports this value as 18 mg/L.
  - Japanese NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.
- European Union 2003 reports: "Toluene has low acute toxicity via inhalation and the oral route. In rats, an LC50 of 28.1 mg/l/4h, and an oral LD50 of 5.58 g/kg have been reported. A dermal LD50 of 12.4 g/kg has been determined in the rabbit, however, the method used and quality of the data are unknown. As the acute toxicity via inhalation and the oral route is low, and toluene is absorbed well via these routes, it was considered that a dermal acute toxicity study would not contribute further to the hazard identification. Via the intraperitoneal route LD50s of approximately 2 g/kg for rats and mice have been found." [p. 153], European Union 2003 Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012.

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Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)
Group II Score (single dose: vH, H, M or L): M

Toluene was assigned a score of Moderate for systemic toxicity/organ effects based on human experimental data consistent with Category 3 for respiratory irritation.

- In summarizing human inhalation studies, European Union 2003 reports irritation: "In summary, the above-mentioned exposure chamber studies headache, dizziness, feeling of intoxication, irritation and sleepiness were recorded to occur with significantly increased frequency at exposure levels from 562 mg/m^3 (150 ppm) down to 281 mg/m^3 (75 ppm). At 150 mg/m^3 (40 ppm) and below the effects have not been recorded to occur with increased frequency. For these subjective symptoms a lowest observed adverse effect concentration (LOAEC) of 281 mg/m^3 (75 ppm) and a no observed adverse effect concentration (NOAEC) of 150 mg/m^3 (40 ppm) can be established." [p. 153] European Union 2003 Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012.
  - PPRC: While the EU assessment reports data from experiments with dosing periods beyond 4 hours, irritation was observed in a number of studies with humans at very low concentrations (~100 ppm or 0.38 mg/L). [Dose is not used for GHS Category 3 respiratory irritation classification (GHS rev. 4, Table 3.8.1).]
- NITE/Japan 2006 classifies as Category 3 (respiratory tract irritation); "Based on the human evidence including "toluene is rapidly absorbed mainly through inhalation…Toluene causes…mild respiratory irritation at 50-100 ppm…" (CERI Hazard Data 96-4, 1997) and "irritation to the eyes, nose and pharynx" (EU-RAR No. 30, 2003)…" [References internal to the assessment.] Japanese NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.

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

Toluene was assigned a High level-of-concern based on human nephrotoxicity data (case studies) and supporting animal data reported in the US EPA 2005 assessment and NITE/Japan classification as Category 1.

- European Union harmonized classification as STOT RE Category 2, H373 (GreenScreen Authoritative A List). GreenScreen List Translator guidance indicates Moderate level-of-concern. European Chemicals Agency Classification and Labelling Inventory Database available at: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=30426&HarmOnly=no?fc=true&lang=en, accessed May 2012.
- NITE/Japan 2006 reports STOT RE Category 1, CNS, kidneys and liver, based on the human evidence including: "Toluene induces drug dependency, and inhalant abuse of toluene causes chronic central nervous system damage including restricted vision, headache associated with nystagmus and hearing loss, tremor, ataxia and amnesia. Cerebral atrophy was found in CT tests, and renal dysfunction manifested as proteinuria and hematuria was also observed (CERI Hazard Data 96-4, 1997), "hearing loss, changes in brain-stem auditory evoked potential" (ATSDR, 2000) and "hepatic toxicity associated with an increase in SGOT, fatty degeneration of hepatic cells and lymphocytic infiltration (EU-RAR No. 30, 2003)." NITE/Japan is a Screening A List. GreenScreen List Translator indicates High level-of-concern for GHS-country Cat. 1 classification.
- European Union 2003 reports that: "R48/20 is justified because toluene causes several types of serious toxic effects after inhalation. Toluene-induced chronic impairment of auditory function has been demonstrated in a number of animal studies. This has been substantiated by morphological evidence of cell loss in the rat cochlea. Existing data suggest that humans are sensitive to this effect at exposure levels, which may be encountered in the working environment. Toluene causes irreversible changes, including neuron loss, in the central nervous system of animals. In humans severe central nervous system effects including brain atrophy have been found at very high exposure levels. Neuropsychological effects at working environment exposure levels have been demonstrated…Toluene causes an increase in the occurrence of non-malignant pituitary tumours in mice." European Union 2003 Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012.
- US EPA 2005 assessment reports on several studies indicating nephrotoxicity: "The choice of increased kidney weight as the critical effect is supported by several acute oral and inhalation human toxicity studies, indicating renal tubule toxicity. One case report following lethal oral exposure to 625 mg/kg toluene (Ameno et al., 1989)

and a nonlethal case report of thinner ingestion (Caravati and Bjerk, 1997) noted acute tubular necrosis and acidosis. Inhalation of high doses of toluene has caused distal renal tubular acidosis (Taher et al., 1974; Fischman and Oster, 1979) among drug users, sometimes with tubular proteinuria (Kamijima et al., 1994). A case of focal segmental glomerulosclerosis was noted for a leather worker exposed to toluene for 40 years (Bosch et al., 1988). Toluene sniffing has been associated with the formation of renal stones (Kroeger et al., 1980), proteinuria (Streicher et al., 1981), and hepato-renal damage (O'Brien et al., 1971). In addition, a case of anti-glomerular basement membrane antibody-mediated glomerulonephritis has also been reported in a woman who sniffed glue for several weeks (Bonzel et al., 1987). It should be noted that several studies involving painters (Askergren, 1982; Franchini et al., 1983) or printers (Gericke et al., 2001) with toluene exposure have reported no effect on renal function. Askergren (1982) and Franchini et al. (1983) found no effect on excretion of β-2-microglobulin, and Gericke et al. (2001) found no effect on serum creatinine levels or glomerular filtration rate. The choice of increased kidney weight as a critical effect is based on the above data and the available animal data indicating an increase in kidney weight in the same studies where overt kidney toxicity was observed at higher doses. The available data on postulated modes of action for toluene-induced kidney toxicity are described in Section 4.5.3." [p. 65; references internal to the assessment.] US EPA 2005, Toxicological Review of Toluene, available at: http://www.epa.gov/iris/toxreviews/0118tr.pdf, accessed May 2012.

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

Toluene was assigned a score of Moderate for neurotoxicity-single dose based on ECHA harmonized classification (a GreenScreen Authoritative A list) as Category 3 and H336. While NITE/Japan assessment is Category 1 (GreenScreen Screening A list), the database of acute toxicity available for review does not seem to support this classification, as most CNS effects are transient in nature. Further expert review of this data may be warranted if toluene is chosen for use in spite of its Benchmark1 status.

- ECHA lists harmonized classification as STOT SE 3, H336 – May cause drowsiness or dizziness. ECHA C&L Inventory Database available at: http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=30426&HarmOnly=no?DisclaimerAgr=Agree&Index=108-88-3&ExecuteSearch=true&fc=true&lang=en , accessed June 2012.
- NITE/Japan 2006 reports Category 1 for CNS: "Based on the human evidence including "toluene is rapidly absorbed mainly through inhalation and acts on the central nervous system. Toluene causes fatigue, sleepiness, dizziness and mild respiratory irritation at 50-100 ppm, excitement associated with paresthesia and nausea at 200-400 ppm and central nervous system suppression leading to drunkenness, delirium and abnormal gait at 500-800 ppm" (CERI Hazard Data 96-4, 1997)…and the evidence from animal studies including "anesthesia" (EU-RAR No. 30, 2003)." [References internal to the assessment.] Japanese NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.
- European Union summary of acute toxicity (European Union 2003 Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012):
  - "The acute toxicity of toluene has been tested in a manner conforming with the data requirements of Annex VIIA of Directive 67/548/EEC. Toluene has low acute toxicity via inhalation and the oral route. In rats, an LC_{50} of 28.1 mg/l/4h, and an oral LD_{50} of 5.58 g/kg have been reported. A dermal LD_{50} of 12.4 g/kg has been determined in the rabbit, however, the method used and quality of the data are unknown. As the acute toxicity via inhalation and the oral route is low, and toluene is absorbed well via these routes, it was considered that a dermal acute toxicity study would not contribute further to the hazard identification. Via the intraperitoneal route LD_{50}s of approximately 2 g/kg for rats and mice have been found. No classification for acute toxicity is proposed. Toluene is classified with R67 (Vapours may cause drowsiness and dizziness) since data from experimental exposure of human volunteers show that dizziness and sleepiness are experienced at air levels substantially below the level of 20 mg/l/4h mentioned in the criteria for R67 (for toluene this equals to 5,300 ppm). In rats exposed to 20 mg/l/4h in the BASF (1980) study rocking gait and narcosis were observed."

  - Regarding human experimental data: "A LOAEC of 281 mg/m^3 (75 ppm) (Echeverria et al., 1989) and a NOAEC of 150 mg/m^3 (40 ppm) (Andersen et al., 1983) for the occurrence in humans of headache, dizziness, feeling of intoxication, irritation and sleepiness will be taken forward to the risk characterisation. For function in performance tests a LOAEC of 281 mg/m^3 (75 ppm) will be taken forward to the risk characterisation (Echeverria et al., 1989)."
  - References internal to the assessment.
- Grandjean & Landrigan (G&L) (2006): Toluene 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): H

Toluene was assigned a score of High for neurotoxicity repeat dose based on NITE/Japan classification as Category 1 with supporting animal experimental and human case study data.

- NITE/Japan 2006 reports Category 1 for CNS: "Based on the human evidence including "Toluene induces drug dependency, and inhalant abuse of toluene causes chronic central nervous system damage including restricted vision, headache associated with nystagmus and hearing loss, tremor, ataxia and amnesia. Cerebral atrophy was found in CT tests, and renal dysfunction manifested as proteinuria and hematuria was also observed (CERI Hazard Data 96-4, 1997), "hearing loss, changes in brain-stem auditory evoked potential" (ATSDR, 2000)…" [References internal to the assessment.] Japanese NITE worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.
- Summarizing repeat dose toxicity, a European Union 2003 report concludes (EU 2003 Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012):
  - p. 189: "Toluene has been shown to affect the central nervous system and the inner ear. Long-term high-level exposure to toluene (abuse) has caused serious damage to the brain."
  - p. 191: "Toluene causes irreversible changes, including neuron loss, in the central nervous system of animals. In humans severe central nervous system effects including brain atrophy have been found at very high exposure levels. Neuropsychological effects at working environment exposure levels have been demonstrated including severe neurological abnormalities and brain atrophy."
- Grandjean & Landrigan (G&L) (2006): Toluene 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

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

- REACH dossier reports a 1996, GLP-compliant reliability 1 study, Guinea Pig Maximization Test: "A guinea pig maximisation test in accordance with EU guideline B6 (Skin sensitisation) has been carried out. Twenty guinea pigs were intradermally injected with a 10% concentration and epidermally exposed to the undiluted test substance. Ten control guinea pigs were similarly treated, but with vehicle (corn oil) only. Two weeks later all animals were challenged with 50% (maximum non-irritant concentration) and 25% test solution, and vehicle. A single guinea pig showed a grade 1 reaction (discrete or patchy erythema) in response to the 50% solution. No other skin reactions were observed. It was concluded that toluene was not a skin sensitizer in this study. Toluene does not require classification for sensitisation properties." REACH registration dossier available at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c7b2ab2-20d7-6aaa-e044-00144f67d249/AGGR-e654ccf0-8a26-46f4-a60f-e1c8c9cc0605_DISS-9c7b2ab2-20d7-6aaa-e044-00144f67d249.html#AGGR-e654ccf0-8a26-46f4-a60f-e1c8c9cc0605, accessed May 2012.
- NITE/Japan 2006 reports Not classified: "Skin sensitizer: Based on the results of guinea pig maximization tests (EU-RAR No. 30, 2003) suggesting that toluene causes no skin irritation." Japanese NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.

- European Union 2003 reports: "No human data are available. In a well-conducted guinea pig maximisation study no evidence of skin sensitisation was found, suggesting that toluene is not a skin sensitiser in humans." [p. 158], European Union 2003 Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012.

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

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

- European Union 2003 reports: "No data have been found with regard to respiratory sensitisation. There are no indications that toluene is a respiratory allergen." [p. 158], European Union 2003 Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012.
- No data or studies were identified for this endpoint.

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

Toluene was assigned a score of High for skin irritation/corrosivity based on H315 (EU H-statements are authoritative). H315 translates to GreenScreen High level-of-concern.

- ECHA reports harmonized classification as Category 2, H315. This Authoritative A list translates to High level-of-concern. ECHA C&L Inventory Database, http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=30426&HarmOnly=no?DisclaimerAgr=Agree&Index=108-88-3&ExecuteSearch=true&fc=true&lang=en , accessed May 2012.
- NITE/Japan classifies as Category 2: "Based on the evidence of moderate skin irritation caused by toluene in rabbit primary skin irritation test (4 hour exposure) (EU-RAR No. 30, 2003)." (Screening A list.). Japanese NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.

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

Toluene was assigned a score of Low for eye irritation/corrosivity based on experimental data in animals consistent with no classification. The Category 2B assessment by NITE/Japan appears to be inconsistent with the data referenced from the European Union report.

- NITE/Japan 2006 classifies as Category 2B: "Based on the description that the subjects recovered from the damage within 7 days in rabbit eye irritation test conducted in accordance with the OECD test guideline (EU-RAR No. 30, 2003), which suggests that toluene causes mild eye irritation." Cat. 2B in a Screening A list translates to Moderate level-of-concern. [References internal to the assessment.] Japanese NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.
  - PPRC: The data reported in the EU-RAR reference cited above were either consistent with no classification, or discounted as inadequate for classification by the EU assessors (see next bullet).
- European Union 2003 assessment reports (European Union 2003 Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012):
  - p. 156: "In conclusion, toluene was found to cause slight eye irritation. Ocular lesions (redness, chemosis) occurred within72 hours after exposure and persisted for at least 24 hours. However, the mean score (24 hours 48 hours and 72 hours together) for redness of the conjunctivae and chemosis did not exceed values of 2.5 and 2, respectively, which are the limits for classification with R36 (Irritating to eyes).Therefore, no classification for eye irritation was proposed."
    - PPRC: The redness mean score is reported as 1.47 (Table 4.2.1). GHS rev. 4 describes redness ≥ 2 as a criterion for classification rather than the ≥2.5 value suggested in the European Union report, however, the experimental data are still outside of the range required for Category 2A/B.
  - p. 157: "The results of three animal studies show that toluene has a potential to cause eye irritation. One of the studies (Exxon, 1995) has explicitly been performed according to the OECD guideline 405. The other two studies appear to have been performed using similar methodology, however, the problem of

interpreting the scoring system used in those two studies means that the Exxon study will be used for the risk assessment. Toluene was slightly irritating in the Exxon study, however not enough to warrant classification according to the EU classification criteria. No classification for eye irritation is proposed."

- PPRC: Additional studies assessed in the report suggest irritation, but insufficient information was provided in the studies to evaluate the data according to GHS criteria. Details of the studies can be found in robust summaries in a REACH registration dossier available at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c7b2ab2-20d7-6aaa-e044-00144f67d249/AGGR-2be35047-6a9e-47c9-8a25-eebb85670516_DISS-9c7b2ab2-20d7-6aaa-e044-00144f67d249.html#AGGR-2be35047-6a9e-47c9-8a25-eebb85670516, accessed May 2012.

Ecotoxicity (Ecotox)

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

Toluene was assigned a score of High for acute aquatic toxicity based on measured test data (L/EC_{50} between 1 and 10 mg/L) for fish and aquatic invertebrates.

- European Union 2003 assessment reports on a variety of studies. For risk characterization, report recommends LC_{50} of 5.5 mg/l (low value from group of accepted studies - 96 hr. exposure for variety of fish species); results cluster around LC_{50} of 10-30 mg/l for most fish tests; salmon in seawater generally lower, in the LC_{50} 5-7 mg/l range. Crustacea largely in the EC_{50} 3-30 mg/l range. Report includes additional QSAR estimates. European Union 2003 Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012.
- NITE/Japan classifies as Category 2: "It was classified into Category 2 from 96 hours EC_{50}=3.5mg/L of the crustacea (Brown Shrimp) (EU-RAR (2003) and others.)." Japanese NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.

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

Toluene was assigned a score of High for chronic aquatic toxicity based on measured NOEC/LOECs in reproduction studies for crustaceans in or bordering the 0.1-1.0 mg/L range. Daphnia reproduction data is suitable for chronic aquatic toxicity ranking according to GHS rev. 4, section 4.1.1.4.

- REACH registration dossier reports on a 1998, reliability 1 non-GLP study using test guideline US EPA 600/4-91-003 with Ceriodaphnia dubia. The executive summary reports: "The 7 day NOEC for chronic toxicity to invertebrates is 0.74mg/l. This study is based on a standard guideline with acceptable modifications due to volatility of test compound. Measured confirmation of exposure concentrations and results from controls. This is therefore suitable for use as the key study for this endpoint, and was used as the key study in the EU RAR for toluene (2003)." REACH registration dossier available at: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9c7b2ab2-20d7-6aaa-e044-00144f67d249/AGGR-2ec610b5-5877-4c9c-b940-ad565f7f8bbd_DISS-9c7b2ab2-20d7-6aaa-e044-00144f67d249.html#AGGR-2ec610b5-5877-4c9c-b940-ad565f7f8bbd, accessed June 2012.
- European Union 2003 assessment reports:
  - Fish: NOEC for several fish species are reported in the ~1.4-4.7 mg/L range. "Thus a chronic fish NOEC of 1.4 mg/l is concluded based on the available valid experimental data." [pp. 81-2]
  - Crustaceans: Following a discussion of data sources on toxicity in Daphnia: "…a chronic NOEC for reproduction to crustaceans of 0.74 mg/l is used and because this is the lowest reported valid chronic effect concentration of aquatic species [it is] carried over for derivation of $PNEC_{water}$." [PPRC: same study cited in the REACH dossier above].
  - EU 2003 Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012.
- NITE/Japan 2006 reports: "Not classified: Since there was rapidly degrading (the decomposition by BOD: 123% (Existing Chemical Safety Inspections Data)) and the bio-accumulation was low (log Kow=2.73

(PHYSPROP Database, 2005)), it was classified into Not classified." Japanese NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.

- US EPA's PBT Profiler estimates Fish ChV at 2.6 mg/L. US EPA PBT Profiler available at: http://www.pbtprofiler.net/default.asp, accessed May 2012. See Appendix B).
- ECOSAR estimates for "Neutral Organics":
  - Fish ChV 2.567 mg/L
  - Daphnid ChV 1.656 mg/L
  - Green Algae ChV 3.960 mg/L
  - Fish (SW) ChV 4.722 mg/L
  - Mysid (SW) ChV 1.187 mg/L
  - US EPA's ECOSAR 1.11 results in Appendix A. Model software available at: http://www.epa.gov/oppt/newchems/tools/21ecosar.htm

Environmental Fate (Fate)

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

Toluene is volatile and likely to end up in the atmosphere where it is long lived (modeled half-life in air of 3.1 days); translates to High level-of-concern (GreenScreen List Translator).

- Environment Canada lists Toluene 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
- US EPA's PBT Profiler fate model predicts:

Medium	Halflife (days)	% in medium	GreenScreen Level of Concern by Medium
Water	15 days,	39%	Low persistence.
Soil	30 days,	36%	Moderate persistence.
Sediment	140 days,	0%	- (Not likely to accumulate in sediment.)
Air	3.1 days,	24%	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

Toluene was assigned a score of very Low for bioaccumulation based on the measured log K_{ow} of 2.73 and a BCF estimate of 29. Log $K_{ow} \leq 4$ and BCF ≤ 100 translate to very Low level-of-concern (GreenScreen List Translator).

- European Union 2003 assessment reports: "The log Kow is <3 indicating limited bioconcentration in aquatic organisms. A number of bioaccumulation studies with aquatic organisms are available. The BCF value of 90 observed in the fresh water fish Golden Ide (Leuciscus idus melanotus), was the largest value found in fish studies and is used as a worst case in the risk assessment." [p. 40] EU 2003 Risk Assessment Report available at: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/toluenereport032.pdf, accessed May 2012.
- US EPA's PBT Profiler reports: "Bioaccumulation Estimate: The PBT Profiler estimates that Benzene, methyl- [toluene] is not expected to bioaccumulate in the food chain because it does not exceed the BCF criteria." BCF estimated at 29; log K_{ow} experimental value 2.73. US EPA 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

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Date: 30 June 2012

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Name: Alex Stone, Sc. D.
Title: Safer Chemical Alternative Chemist
Organization: WA Department of Ecology
Date: 17 April 2013

Toluene was assigned a score of Low for reactivity based on GHS not classified by NITE/Japan. Furthermore, the chemical structure is inconsistent with explosive, reactive or oxidizing properties as defined by GreenScreen criteria.

- NITE/Japan classification reports: "Containing no atom groups with explosive properties" and "Containing no atom groups with explosive or self-reactive properties." Japanese NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.
- US DOT lists only as Class 3 (flammable and combustible liquids), Packing Group II (medium danger). US DOT Hazardous Materials Table revised January 2012, available at: http://www.phmsa.dot.gov/staticfiles/PHMSA/DownloadableFiles/Files/Hazmat/Hazmat%20Table.xls, accessed May 2012.
- CAMEO Reactivity Profile reports an NFPA Reactivity score of 0 – Normally stable, even under fire conditions. Toluene can react strongly under certain conditions: "TOLUENE reacts vigorously with allyl chloride or other alkyl halides even at minus 70° C in the presence of ethyl aluminum dichloride or ethyl aluminum sesquichloride. Explosions have been reported [NFPA 491M 1991]. Incompatible with strong oxidizing agents. When added to a tank of sulfur dichloride, the tank over pressurized and ruptured in a reaction thought to be catalyzed by iron or iron(III) chloride [Chem. Eng. News, 1988, 66(32), 2]." CAMEO Chemicals Database, available at: http://cameochemicals.noaa.gov/chemical/4654, accessed May 2012.

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

Toluene was assigned a score of High for flammability based on H225 listing in authoritative sources.

- ECHA lists harmonized classification as Flammable Liquid Category 2, H225. ECHA C&L Inventory Database, http://clp-inventory.echa.europa.eu/SummaryOfClassAndLabelling.aspx?SubstanceID=30426&HarmOnly=no?DisclaimerAgr=Agree&Index=108-88-3&ExecuteSearch=true&fc=true&lang=en, accessed May 2012.
- US DOT lists only as Class 3 (flammable and combustible liquids), Packing Group II (medium danger). US DOT Hazardous Materials Table revised January 2012, available at: http://www.phmsa.dot.gov/staticfiles/PHMSA/DownloadableFiles/Files/Hazmat/Hazmat%20Table.xls, accessed May 2012.
- NITE/Japan 2006 classifies as Category 2: "The flashing point is 4℃ (closed cup flash test) and the boiling point is 111℃ (ICSC, 2004), which is classified into Category 2…" Japanese NITE in worksheet ID45 in the Microsoft Excel workbook found at: http://www.safe.nite.go.jp/english/files/ghs_xls/classification_result_e(ID001-100).xls, accessed May 2012.

References

References are 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 Results for Toluene (CAS # 108-88-3)

ECOSAR Version 1.11 Results Page

SMILES : c(cccc1)(c1)C
CHEM : Benzene, methyl-
CAS Num: 000108-88-3
ChemID1:
MOL FOR: C7 H8
MOL WT : 92.14
Log Kow: 2.540 (EPISuite Kowwin v1.68 Estimate)
Log Kow: (User Entered)
Log Kow: 2.73 (PhysProp DB exp value - for comparison only)
Melt Pt: (User Entered for Wat Sol estimate)
Melt Pt: -94.90 (deg C, PhysProp DB exp value for Wat Sol est)
Wat Sol: 558.9 (mg/L, EPISuite WSKowwin v1.43 Estimate)
Wat Sol: (User Entered)
Wat Sol: 526 (mg/L, PhysProp DB exp value)

Values used to Generate ECOSAR Profile

Log Kow: 2.540 (EPISuite Kowwin v1.68 Estimate)
Wat Sol: 526 (mg/L, PhysProp DB exp value)

Available Measured Data from ECOSAR Training Set

CAS No	Organism	Duration	End Pt	Measured mg/L (ppm)	Ecosar Class	Reference
000108-88-3	Daphnid		ChV	1.4	Neutral organics	CAS-Niederlehner et al., 1998
000108-88-3	Green Algae	96-hr	ChV	1.8	Neutral organics	Herman, 1990
000108-88-3	Daphnid	48-hr	LC50	3.8	Neutral organics	CAS-Niederlehner et al., 1998
000108-88-3	Fish (SW)		ChV	5	Neutral organics	CAS-ETFS
000108-88-3	Fish		ChV	8.6	Neutral organics	DUL
000108-88-3	Green Algae	96-hr	EC50	9.4	Neutral organics	Herman, 1990
000108-88-3	Green Algae	96-hr	EC50	12.5	Neutral organics	Galassi, 1988
000108-88-3	Daphnid	48-hr	LC50	14.9	Neutral organics	Hermens et al., 1984
000108-88-3	Fish	96-hr	LC50	17.5	Neutral organics	CAS - ETFS
000108-88-3	Fish	96-hr	LC50	31.7	Neutral organics	DUL
000108-88-3	Fish	96-hr	LC50	36.2	Neutral organics	DUL
000108-88-3	Fish	96-hr	LC50	38.1	Neutral organics	CAS - ETFS
000108-88-3	Mysid	96-hr	LC50	55.5	Neutral organics	Zaroogian et al., 1985
000108-88-3	Mysid	96-hr	LC50	56.3	Neutral organics	CAS-ETFS
000108-88-3	Daphnid	48-hr	LC50	137	Neutral organics	CAS-ETFS
000108-88-3	Fish (SW)	96-hr	LC50	381	Neutral organics	CAS-ETFS

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Date: 17 April 2013

ECOSAR v1.1 Class-specific Estimations

Neutral Organics

ECOSAR Class		Organism	Duration	Predicted End Pt	mg/L (ppm)
Neutral Organics	:	Fish	96-hr	LC50	24.764
Neutral Organics	:	Daphnid	48-hr	LC50	14.780
Neutral Organics	:	Green Algae	96-hr	EC50	13.532
Neutral Organics	:	Fish		ChV	2.567
Neutral Organics	:	Daphnid		ChV	1.656
Neutral Organics	:	Green Algae		ChV	3.960
Neutral Organics	:	Fish (SW)	96-hr	LC50	31.276
Neutral Organics	:	Mysid	96-hr	LC50	16.120
Neutral Organics	:	Fish (SW)		ChV	4.722
Neutral Organics	:	Mysid (SW)		ChV	1.187
Neutral Organics	:	Earthworm	14-day	LC50	140.808

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.

Class Specific LogKow Cut-Offs

If the log Kow of the chemical is greater than the endpoint specific cut-offs
presented below, then no effects at saturation are expected for those endpoints.

Neutral Organics:

Maximum LogKow: 5.0 (Fish 96-hr LC50; Daphnid LC50, Mysid LC50)
Maximum LogKow: 6.0 (Earthworm LC50)
Maximum LogKow: 6.4 (Green Algae EC50)
Maximum LogKow: 8.0 (ChV)

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Appendix B – PBT Profiler Results

Results

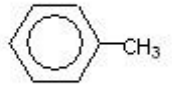
Orange or **red** highlights indicate that the EPA criteria have been exceeded.
Black-and-white version

Persistence	Bioaccumulation	Toxicity

108-88-3 Benzene, methyl-

PBT Profiler Estimate = PBT

Media	Half-Life (days)	Percent in Each Medium	BCF	Fish ChV (mg/l)
Water	**15**	39%	**29**	**2.6**
Soil	**30**	36%		
Sediment	**140**	0%		
Air	**3.1**	24%		



P2 Considerations and more information .

PBT Profiler Physical/Chemical Property Estimates
PBT Profiler Physical/Chemical Property Estimates
Property Value Type Units
Molecular Weight 92.14
Melting Point -94 Experimental degrees C
Vapor Pressure 28 Experimental mm Hg at 25 degrees C
Log Kow 2.73 Experimental at 25 degrees
Water Solubility 530 Experimental mg/L at 25 degrees C
Henry's Law Constant 0.0066 Experimental atm/m3 mole at 25 degrees
Hydroxyl Radical Reaction Rate Constant 0.0000000000052 Estimated cm3/molecule-sec at 25 degrees C
Ozone Reaction Rate Constant Not Estimated
Ultimate Biodegradation Survey 2.943 (Weeks) Estimated