Benzene (CAS# 71-43-2) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment

Prepared by:

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GreenScreen® Executive Summary for Benzene (CAS #71-43-2)

Benzene is a chemical that functions as a raw material and intermediate for chemical synthesis, a solvent, a gasoline additive, and a natural component of diesel fuel that is used as a solvent in hydraulic fracturing fluids.

Benzene was assigned a GreenScreen® Benchmark Score of 1 ("Avoid-Chemical of High Concern") as it has High Group I Human Toxicity (High carcinogenicity (C), mutagenicity (M), reproductive toxicity (R), and developmental toxicity (D)). This corresponds to GreenScreen® benchmark classification 1e in CPA 2011. There are no data gaps. As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), benzene meets requirements for a GreenScreen® Benchmark Score of 1.

GreenScreen® Benchmark Score for Relevant Route of Exposure:

Data for all routes were combined as a standard GreenScreen® assessment approach. Therefore, the benchmark score applies to all routes of exposure to this compound.

GreenScreen® Hazard Ratings for Benzene

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	repeated*	single	repeated*										
H	H	H	H	*M*	L	vH	H	M	H	L	*L*	H	H	H	H	vL	vL	*L*	H

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

GreenScreen® Assessment for Benzene (CAS #71-43-2)

GreenScreen® Version 1.2 Draft Assessment
Note: Verification Has Not Been Performed on this GreenScreen® Assessment

Chemical Name: Benzene

CAS Number: 71-43-2

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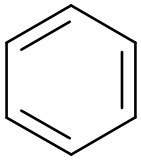
Date: June 25, 2014

Confirm application of the *de minimus* rule[1]: N/A

Chemical Structure(s):



Also called: Benzol, Cyclohexatriene, Phene, Phenyl hydride; Benzole; Carbon oil; Mineral naphtha; Coal naphtha; Motor benzol (ChemIDPlus 2014)

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen™:
No surrogates were sought as there are no data gaps for benzene itself.

Identify Applications/Functional Uses:
1. Starting material and intermediate in chemical synthesis (50% to produce ethylbenzene, 24% to produce cumene, 12% to produce cyclohexane, 5% to produce nitrobenzene)
2. Solvent in the chemical and drug industries (<2%)
3. A gasoline additive thanks to anti-knock property (ATSDR 2007)

GreenScreen® Summary Rating for Benzene[2]: Benzene was assigned a GreenScreen® Benchmark Score of 1 ("Avoid-Chemical of High Concern") as it has High Group I Human Toxicity (High carcinogenicity (C), mutagenicity (M), reproductive toxicity (R), and developmental toxicity (D)). This corresponds to GreenScreen® benchmark classification 1e in CPA 2011. There are no data gaps. As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), benzene meets requirements for a GreenScreen® Benchmark Score of 1.

[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.

Figure 1: GreenScreen® Hazard Ratings for Benzene

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	repeated*	single	repeated*										
H	H	H	H	*M*	L	vH	H	M	H	L	*L*	H	H	H	H	vL	vL	*L*	H

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated (modeled) values, authoritative B lists, screening lists, weak analogues, and lower confidence. Hazard levels in **BOLD** font are used with good quality data, authoritative A lists, or strong analogues. Group II Human Health endpoints differ from Group II* Human Health endpoints in that they have four hazard scores (i.e., vH, H, M, and L) instead of three (i.e., H, M, and L), and are based on single exposures instead of repeated exposures. Please see Appendix A for a glossary of hazard acronyms.

Transformation Products and Ratings:

Identify feasible and relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern**[3]

Benzene is ubiquitous in the air from both natural and anthropogenic sources. Benzene mainly partitions to the air due to its volatility. Chemical degradation mainly via hydroxyl radical reaction results in the atmospheric residence time of benzene from a few hours to a few days. Reaction products of benzene with nitrogen monoxide include nitrobenzene, o- and p-nitrophenol and 2,4- and 2,6-dinitrophenol. However, they are relatively short-lived in the air. Photooxidation of benzene with nitrogen monoxide/nitrogen dioxide in air generates formaldehyde, formic acid, maleic anhydride, phenol, nitrobenzene, and glyoxal. These products appear to be reactive and may be subject to further reactions. In water and soil, benzene is mainly subject to biodegradation (readily biodegradable), but concentrations higher than 2 ppm inhibit aerobic biodegradation (ATSDR 2007). Therefore, no feasible and relevant environmental transformation products are identified for benzene.

Introduction

Benzene is commercially produced from coal and petroleum sources. It is present as a natural part of crude oil, gasoline and cigarette smoke. The production of benzene ranks in the top 20 in the United States. It is widely used in industry, but the specific use as a solvent has decreased due to its adverse health effects (ASTDR 2007). One type of hydraulic fracturing fluids, water-based linear gels, sometimes uses benzene-containing diesel fuel in lieu of water to dissolve the guar powder to form the gel. Although this use has been largely eliminated due to health concerns, there may still be rare instances of use (U.S. EPA 2004).

ToxServices assessed benzene against GreenScreen® Version 1.2 (CPA 2013) following procedures outlined in ToxServices' SOP 1.37 (GreenScreen® Hazard Assessment) (ToxServices 2013).

GreenScreen® List Translator Screening Results

The GreenScreen® List Translator identifies specific authoritative or screening lists that should be searched to identify GreenScreen® benchmark 1 chemicals (CPA 2012b). Pharos (Pharos 2014) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. The output indicates benchmark or possible benchmark scores for each human health and

[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.

environmental endpoint. The output for benzene can be found in Appendix C, and classifications for specific endpoints can be found in the appropriate sections. When a classification from GHS New Zealand was available for any endpoint, it was converted to the harmonized GHS classifications using the "Correlation between GHS and New Zealand HSNO Hazard Classes and Categories" document from the New Zealand Environmental Protection Authority (N.Z. EPA 2009).

PhysicoChemical Properties of Benzene

Benzene is a colorless to yellow liquid at room temperature. However, its high vapor pressure of 75 mm Hg indicates that it is mostly in the vapor (gas) phase. It is soluble in water, and partitions both to the water and organic phase, as suggested by its partition coefficient of 2.13.

Table 1: Physical and Chemical Properties of Benzene (CAS #71-43-2)

Property	Value	Reference
Molecular formula	C_6H_6	ATSDR 2007
SMILES Notation	c1ccccc1	ATSDR 2007
Molecular weight	78.11	ATSDR 2007
Physical state	Liquid	ATSDR 2007
Appearance	Colorless to light yellow liquid	ATSDR 2007
Melting point	5.5ºC	ATSDR 2007
Vapor pressure	75 mmHg at 20ºC	ATSDR 2007
Water solubility	1,790 mg/L at 25ºC	ChemIDplus 2014
Dissociation constant	Does not dissociate	
Density/specific gravity	0.8787 g/cm^3 at 15ºC	ATSDR 2007
Partition coefficient	2.13	ATSDR 2007

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

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

Benzene was assigned a score of High for carcinogenicity based on sufficient evidence in humans and being listed by almost all authoritative bodies. GreenScreen® criteria classify chemicals as a High hazard for carcinogenicity when being listed by the authoritative lists below (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* IARC Group 1: Carcinogenic to humans
  - *Authoritative:* NTP-RoC: Known to be human carcinogen
  - *Authoritative:* EPA-C: Known/likely human carcinogen and Group A human carcinogen
  - *Authoritative:* Prop 65: Cancer
  - *Authoritative:* EU CMR (1): Category 1 – Substances known to be carcinogenic to man
  - *Authoritative:* EU CMR (2): Category 1A
  - *Authoritative:* EU H350: May cause cancer
  - *Authoritative:* EU R45: May cause cancer
  - *Authoritative:* NIOSH-C: Occupational carcinogen
  - *Authoritative:* German MAK: Carcinogen Group 1 – Substances that cause cancer in man
  - *Screening:* GHS-Korea: Category 1
  - *Screening:* GHS-New Zealand: 6.7A – Known or presumed human carcinogens

    - *Screening*: GHS-Japan: Category 1A
- IARC 1987
    - Numerous case reports and cohort studies have linked benzene exposure to various types of leukemia, such as myelogenous leukemia and acute myeloid leukemia, leading to the conclusion that there is sufficient evidence for the carcinogenicity of benzene in humans.
    - The carcinogenicity of benzene in animals has been studied via oral, inhalation, dermal, subcutaneous and intraperitoneal injections. Neoplasms were reported at multiple sites in one or both sexes in rats and mice through oral and inhalation routes of exposure. No evidence of carcinogenicity was found from skin exposure or subcutaneous injections, but most of the experiments were inadequate for evaluation. This led to the conclusion that there is limited evidence for the carcinogenic potential of benzene in animals.

Mutagenicity/Genotoxicity (M) Score (H, M, or L): H
Benzene was assigned a score of High for mutagenicity/genotoxicity based on clear evidence of genotoxicity *in vitro* and *in vivo*, and being listed by authoritative bodies. GreenScreen® criteria classify chemicals as a High hazard for mutagenicity/genotoxicity when they are associated with EU H340, R46, CMR (1) category 2, CMR (2) category 1B, and/or classified to GHS category 1A or 1B (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* EU H340: May cause genetic defects
    - *Authoritative:* EU R46: May cause heritable genetic damage
    - *Authoritative:* EU CMR (1): Mutagen category 2 – Substances which should be regarded as if they are mutagenic to man
    - *Authoritative:* EU CMR (2): Category 1B
    - *Authoritative:* German MAK: Germ cell mutagen 3a
    - *Screening*: GHS-Korea: Germ cell mutagenicity category 1
    - *Screening:* GHS-New Zealand: 6.6A – Known or presumed human mutagens
    - *Screening:* GHS-Japan: Germ cell mutagenicity category 2
- IARC 1987
    - *In vivo*, benzene induced chromosomal aberrations, micronuclei and sister chromatid exchanges in bone marrow cells and sperm-head anomalies in mice. It also induced chromosomal aberrations in bone marrow cells in rat and hamsters. Benzene was weakly positive for somatic mutation and crossing-over in spermatogonia, but did not induce sex-linked recessive lethal mutations or translocations in *Drosophila*.
    - *In vitro*, benzene induced chromosomal aberrations and mutations in human cells, and aneuploidy, mutation, DNA damage and chromosomal aberrations in cultured non-human mammalian cells.
    - Benzene induced aneuploidy, mutation and gene conversion in fungi.
    - Benzene was not mutagenic in bacteria.

Reproductive Toxicity (R) Score (H, M, or L): H
Benzene was assigned a score of High for reproductive toxicity based on data that classify benzene to GHS category 1B and on being listed by an authoritative list. This is supported by the GHS category 1B evaluation result by the screening list GHS-New Zealand. GreenScreen® criteria classify chemicals as a High hazard for reproductive toxicity when they are classified to GHS category 1 and/or are listed by Prop 65 (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Prop 65: Male reproductive toxicity

  - *Screening:* GHS New Zealand: 6.8A – Known or presumed human reproductive or developmental toxicants (based on effects on male fertility) – Equivalent to GHS category 1B
  - *Screening:* GHS-Japan: Toxic to reproduction category 2
- U.S. EPA 2002
  - A few studies in humans were described, but all involved concomitant exposure to other chemicals and therefore could not establish definitive causal effect of benzene exposure and reproductive toxicity in humans.
    - Twelve women who had been occupationally exposed to benzene from 1 to 10 years were examined due to menstrual disorders and/or ovarian hypoplasia. The investigators tentatively attributed the sparseness in menstruation to the ovarian hypoplasia rather than to benzene.
    - A group of females with ovarian hypofunction who were exposed occupationally to benzene had statistically significantly reduced levels of ascorbic acid in the blood.
    - 360 women exposed to gasoline and chlorinated hydrocarbons via inhalation and dermal contact had increased incidences of menstrual disturbances compared to controls, and the number of premature interruptions of pregnancy, the percentage of cases where the placental membrane rupture during parturition was impeded, and the number of cases of intrauterine asphyxia of the fetus were increased with longer exposure duration.
    - 300 workers exposed to benzene, toluene or a mixture of the two were studied. In 174 women, benzene exposure was associated with increased incidence of hypermenorrhea, which was not concentration-related, and was tentatively attributed to pancytopenia.
    - 223 women exposed to benzene and toluene in the leather shoemaking industry had increased incidence of "mense-blood anomaly", dysmenorrhea, spontaneous abortion and gestosis (all statistically significant).
  - *Oral*
    - In the 90-day and 2-year toxicity studies of benzene in mice and rats conducted by NTP, The only reproductive effect reported was ovarian toxicity, which was only found in mice in the 2-year bioassay. Observed effects were ovarian atrophy (2, 79, 65 and 46%) and epithelial hyperplasia (26, 89, 63 and 60%) in mice treated with 0, 50, 100 or 200 mg/kg benzene. Ovarian neoplasia was also observed in these mice.
    - In a non-guideline study, male mice received a single gavage dose of 0, 1, 2, 4, 6 or 7 mL/kg benzene and the cytotoxic effects on the germ cells were measured using flow cytometry 7, 14, 21, 28 and 70 days after the treatment. The ratio of testicular cell types was altered by the treatment. There was a dose-related decrease in the tetraploid cell fraction (mainly primary spermatocytes). In addition, the percentage of round spermatids at the lowest dose was decreased to 80% of control, but no dose-response was found. These effects suggest cytotoxicity to the differentiating spermatogonia. Although a dose-dependent recovery for tetraploid cells was found to begin 21 days after exposure, this process was still not complete by 70 days. Recovery of round spermatids started by day 28 and competed by day 70. A time- and exposure-dependent reduction in the percentage of elongated spermatids was observed at 28 days, which experienced complete recovery by day 70. It was concluded that benzene

induced acute cytotoxicity in mouse germ cells.

- *Inhalation*
  - In subchronic inhalation studies in rats, guinea pigs and rabbits, animals were exposed to difference concentrations of benzene for 7-8 hours/day, 5 days/week for various lengths. Moderately increased testicular weight was reported in rats at 21 mg/L for 13 weeks, but not at 0.281 mg/L for 30 weeks, 7.028 mg/L for 30 weeks, 14.056 mg/L for 5 weeks or 30.030 mg/L for more than 1 – 19 days. A slight increase in testicular weight was found in guinea pigs at 0.281 mg/L for 9.6 months, but not at 0.281 mg/L for 4 weeks. Slight histopathologic changes in the testes (degeneration of the seminiferous tubules) were found in rabbits at 0.281 mg/L for 8.5 months.
  - In a subchronic inhalation study in CD-1 mice and Sprague-Dawley rats, animals were exposed to benzene at 0, 0.0032, 0.032, 0.096 or 0.958 mg/L for 6 hours/day, 5 days/week for 13 weeks. The high dose caused statistically significant decrease in absolute and relative testes weight in mice at the highest concentration. Histological findings in these animals included minimal to moderately severe bilateral atrophy and degeneration, moderate to moderately severe decrease in spermatozoa in the epididymal ducts, and minimal to moderate increase in abnormal sperm forms. Female mice had bilateral ovarian cysts at the highest concentration. Similar lesions were also found at lower concentrations, but were occasional, and with questionable significance. Similar effects were not found in rats.
  - In a study investigating benzene's effect on female fertility, Sprague-Dawley rats and CD rats were exposed to benzene at 0, 0.0032, 0.096 or 0.958 mg/L for 6 hours/day, 5 days/week for a 10-week premating and mating period, then daily from gestation days 0 to 20, and then lactation days 5 – 20. No reproductive toxicity was observed, and a NOAEL of 0.958 mg/L was established for reproductive toxicity in this study.

- Based on the weight of evidence, although studies in humans and animals were not consistent in finding reproductive effects of benzene, most studies report adverse effects on male and female reproduction systems. Therefore, ToxServices classified benzene into category 1B (presumed) for this endpoint.

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

Benzene was assigned a score of High for developmental toxicity based on experimental evidence classifying it to GHS category 1B and being listed by the authoritative list Prop 65. GreenScreen® criteria classify chemicals as a High hazard for developmental toxicity when classified to GHS category 1 and/or being listed by Prop 65 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Prop 65: Developmental toxicity.
  - *Screening:* Not present on any screening lists.
- U.S. EPA 2002
  - Evidence of benzene-related developmental toxicity in humans is weak. No convincing evidence of malformations was found. Benzene is able to cross the human placenta. Case studies and occupational studies were mostly associated with exposure to mixtures of solvents. Only one case study evaluated the fetal effects following inhalation exposure to benzene only: although severe pancytopenia and increased chromosomal aberration was found in one worker exposed to benzene during the entire pregnancy period, no

effects were observed on the fetus. U.S. EPA concluded that data on human were inconclusive on this endpoint, as most of the studies identified had small sample sizes, had insufficient experimental details and involved concomitant exposure to other chemicals.

- A large number of developmental toxicity studies were carried out on benzene. Inhalation of benzene before and during pregnancy led to decreased body and liver weights in weanlings in Sprague-Dawley rats in the absence of maternal toxicity. Skeletal variations and abnormalities were found in fetuses of exposed dams in Sprague-Dawley rats, but the quantitative extent of this effect was marginal at best. In several other studies with similar experimental protocols, reduced fetal growth and delayed ossification were consistently found. Further, fetal body weights were reduced in developmental studies in Sprague-Dawley rats and New Zealand white rabbits. Maternal exposure to benzene also affects the developing the hematopoietic system in mice by increasing granulopoiesis and changing the number of hematopoietic progenitor and precursor cells. These effects are consistent with the hematologic effects associated with benzene exposure in human and adult animals.

- Reprotox 2013
  - Five pregnancy cases were studied in which benzene (and possibly other chemicals) exposure induced aplastic anemia in the mother, leading to 4 maternal deaths and 2 surviving offspring. A case-control study of 669 infants with congenital anomalies did not find any association between concentrations of benzene contaminants in drinking water during first trimester of pregnancies and fetal anomalies. In a retrospective case-control study of 14 women exposed to organic solvents (2 were exposed to benzene) during pregnancy, a significant tendency of children with central nervous system defects was found. But a follow-up study could not duplicate this finding. An association between air concentrations of benzene and neural tube defects was found using the Texas Birth Defects Registry data, even at the lowest concentrations. In a case-control study of 206 female laboratory workers with spontaneous abortion, no association was found between this effect and benzene exposure. In a Chinese petrochemical plant, 485 women were studied who were occupationally exposed to benzene during the first trimester. A significant increase in the frequency of spontaneous abortion was observed. But the unexposed group had a low miscarriage rate, suggesting that the ascertainment was incomplete. A case-control study of mothers of 2096 stillborn infants, increased (not statistically significant) employment during pregnancy in occupations associated with benzene exposure was found. Another study from the Chinese plant found an association of exposure during pregnancy to benzene and self-reported stress with a decrease in birth weight. However, in the final model, there was no significant effect on birth weight of benzene exposure alone. Women with a particular CYp1A1 polymorphism had shorter pregnancy length (by 1.5 weeks) associated with benzene exposure. A French cohort study found a small decrease in birth weight and head circumference and increased exposure to benzene in the air, but could not rule out co-exposure to other air pollutants.
  - In animal studies, typical embryo- or fetal toxicity associated with maternal benzene exposure include reduced pup weights and delayed ossification without structural malformations. One study did show an increase in malformation, but used intraperitoneal injection of benzene at 3 mL/kg. On the other hand, a gavage study did not show increased birth defects despite of high doses (1.5 mL/kg or greater) and maternal toxicity. Inhalation exposure to benzene during pregnancy did not show birth defects at concentrations that produced maternal toxicity (up to 2,200 ppm).

    - Overall, benzene was concluded to pose no increased risk of congenital malformations. Some human studies showed increased risk of miscarriage and stillbirth and decreased birth weight and gestational age, but the reliability of these results were limited due to small sample sizes, lack of exposure characterizations and the reliance on self-reports.
- Based on the weight of evidence, benzene has been shown to induce pup weight reduction and ossification delay in animals, but evidence in humans is weak. Therefore, ToxServices classified benzene to GHS category 1B (presumed) for this endpoint.

Endocrine Activity (E) Score (H, M, or L): *M*
Benzene was assigned a score of Moderate for endocrine disruption based on limited evidence. GreenScreen® criteria classify chemicals as a Moderate hazard for endocrine disruption when they are listed by screening lists such as TEDX, or there is evidence of endocrine activity and related human health effects (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not listed by any authoritative lists.
    - *Screening:* TEDX: Potential endocrine disruptor
- Not listed as a potential endocrine disruptor on the EU Priority List of Suspected Endocrine Disruptors.
- Not listed as a potential endocrine disruptor on the OSPAR List of Chemicals of Possible Concern.
- TEDX 2011
    - *In vitro* culture of postimplantation rat embryos were used to study the effect of benzene on the disruption of embryonic development. Benzene induced a concentration-dependent embryotoxic effect.
    - Pregnant BALB/C mice were exposed to benzene at 100 mg/kg twice daily from gestation day 12.5 through 19.5 by intraperitoneal injections. There were fewer pre-B cells and B cells in the fetal liver in the embryos, and fetal liver cell cultures established from these embryos also produced fewer B cells. On the other hand, pre-B cells were elevated in the livers of 8-day-old neonates exposed *in utero*. LPS was significantly reduced in the spleen cell culture derived from these neonates. It was concluded that high concentrations of benzene alters fetal B lymphopoiesis and may compromise immune responsiveness postnatally.
- U.S. EPA 2002
    - One of the proposed mechanisms of the reproductive and developmental toxicity caused by benzene involves damage to the peripheral noradrenergic fibers in pregnant rats, leading to ovarian and uterine blood flow abnormality and altered steroid production.
- It is not clear how benzene is associated with endocrine activity from the two sources listed by TEDX, without further study details. Based on benzene's effects on reproduction and developmental toxicity endpoints, the adverse effects observed may be mediated through an endocrine mechanism. Overall, the evidence seems to be weak.

<u>Group II and II* Human Health Effects (Group II and II* Human)</u>
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

Benzene was assigned a score of Low for acute toxicity based on oral LD_{50} values greater than 2,000 mg/kg, inhalation LC_{50} values greater than 20 mg/L/4h, and dermal LD_{50} values greater than 2,000 mg/kg in animals. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when they have oral LD_{50} values greater than 2,000 mg/kg, inhalation LC_{50} values greater than 20 mg/L/4h, and dermal LD_{50} values greater than 2,000 mg/kg in animals (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists.
  - *Screening:* GHS-Korea: Acute toxicity (oral) category 4
  - *Screening:* GHS-New Zealand: 6.1B (dermal) – Acutely toxic (GHS category 2)
  - *Screening:* GHS-New Zealand: 6.1D (oral) – Acutely toxic (GHS category 4)
  - *Screening:* GHS-Japan: Acute oral toxicity category 4
- EU 2008
  - *Inhalation:* Concentrations of 61 – 65 mg/L are lethal to humans after 5 – 10 min exposures; 25 mg/L is dangerous for life after 30 min exposure in humans; 4h LC_{50} = 44.5 mg/L in rats in one study
  - *Oral:* A dose of 176 mg/kg caused death in humans (case report); LD_{50} = 810 – 10,000 mg/kg in rats across different studies, but the weight of evidence from experiments using a large number of rats suggest that the oral LD_{50} is > 2,000 mg/kg.
  - *Dermal:* LD_{50} > 8,260 mg/kg in rabbits and guinea pigs
- ChemIDplus 2014
  - *Dermal*: LD_{50} = 48 mg/kg in mice
  - *Dermal*: TDLo = 920 µL/kg/1h in rats = 808 mg/kg/1h[4]
  - *Dermal*: TDLo = 0.08 mL/kg in rats = 70 mg/kg[5]
- The EU Risk Assessment Document (RAD) on benzene concluded that data on animal experiments do not support labelling for acute oral, dermal or inhalation toxicity. For dermal exposure, the LD_{50} of 48 mg/kg identified for mice is not consistent with the LD_{50} values identified for rabbits and guinea pigs, and the TDLos in rats. Further, repeated dose dermal exposure study in mice used benzene concentrations much higher than 48 mg/kg, suggesting that the 48 mg/kg value may not be valid. As details of this study are not available, ToxServices did not use this value for classification of benzene.

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

Benzene was assigned a score of Very High for systemic toxicity (single dose) based GHS classification to category 1 supported by being listed as GHS category 1 by screening lists. GreenScreen® criteria classify chemicals as a Very High hazard for systemic toxicity single dose when they are classified to GHS category 1 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* GHS-Japan: Specific target organs/systemic toxicity following single exposure category 1
  - *Screening:* GHS-New Zealand: 6.9A (inhalation) – Toxic to human target organs or systems (GHS category 1, can be single or repeated dose)
  - *Screening:* GHS-New Zealand: 6.9A (oral) – Toxic to human target organs or systems (GHS category 1, can be single or repeated dose)

[4] 920 µL/kg = 0.92 mL/kg = 0.92 mL/kg x 0.8787 g/mL (density of benzene) = 0.808 g/kg = 808 mg/kg
[5] 0.08 mL/kg = 0.08 mL/kg x 0.8787 g/mL = 0.07 g/kg = 70 mg/kg

- EU 2008
    - *Inhalation:* In an acute inhalation toxicity study, 44.5 mg/L/4h benzene led to death, increased number of vacuoled hepatocytes in the liver in animals died as the result of exposure, increased lung and liver weights and increased number of red blood cells in the lung and liver in surviving animals 2 weeks after exposure in female rats.
    - *Inhalation:* In an acute toxicity study in mice, benzene was administered at different concentrations for 7 hours. Concentrations above 15.9 mg/L led to death (equivalent to 28 mg/L/4h[6]). Immediate deaths suggestive of respiratory failure were the characteristic effect of acute benzene exposure. Necropsy findings showed change in lungs, kidney and spleen.
    - *Oral:* In an acute toxicity study in rats (10 – 20/group), gavage doses of 2,990 to 10,000 mg/kg undiluted benzene led to deaths (no deaths at 2,000 mg/kg). In a second part of this study, doses of 4,250 or higher led to deaths (no deaths at 3,000 mg/kg). No other information was available.
    - *Oral:* In an acute toxicity study, the dose of 1,870 mg/kg led to death within 20 minutes. This study established the LD_{50} of 810 mg/kg in rats.
- NITE 2006
    - Benzene was classified to category 1 for respiratory organs based on human evidence: irritation to the skin, nose, mouth and larynx, tracheitis, laryngitis, bronchitis, massive pulmonary hemorrhage.
- U.S. EPA 2009
    - *Inhalation:* A 45-year old healthy white male died from acute exposure to light oil containing 67.7% benzene, 5.7% xylene, 14.5% toluol, 2.0% forerunnings from a benzene distillate, 4.8% crude solvents, and 5.3% residues when trying to stop the overflow from a storage tank. Autopsy revealed no structural damage.
    - *Inhalation:* An 18-year old white male died from presumable acute benzene exposure, with a plastic bag over his head containing a folded handkerchief and a partly emptied bottle of reagent grade benzene nearby. Autopsy showed acute granular tracheitis, laryngitis and bronchitis, massive hemorrhages of the lungs, congestive gastritis, spleen infarct, acute congestion of kidneys and cerebral edema.
    - *Inhalation:* Three workers died due to acute exposure to benzene fumes on a ship. Autopsy revealed hemorrhagic airless lungs with alveolar hemorrhage and pulmonary edema and microscopic vascular congestion of the brains.
    - *Inhalation:* It was estimated that 20,000 ppm for 5 – 10 min is lethal; 7,500 ppm for 30 – 60 min is dangerous in humans. Death normally results from CNS depression with ultimate paralysis of the respiratory center. Cardiac arrest was suggested as well. Non-lethal effects (relevant to target organ toxicity) of benzene include irritation, cardiac sensitization, and hematological effects.
    - *Oral:* A workman ingested 80 g of commercial benzene (1.14 mg/kg) and developed acute symptoms (details not provided). When treated medically, recovery of symptoms were observed.
- In summary, in humans, acute inhalation/oral exposure to benzene at high concentrations can result in serious health effects and death. These have been suggested to be mainly related to CNS effects, but pulmonary effects were also observed upon pathological examinations. In animal studies, although deaths were not observed at oral dose of greater than 2,000 mg/kg and inhalation concentrations greater than 20 mg/L/4h, available data are insufficient to evaluate

[6] 15.7 mg/L/7h x 7/4 = 28 mg/L/4h

systemic toxicity at lower doses/concentrations that are needed to classify benzene. Based on significant toxicity (other than CNS effects, which are covered in the neurotoxicity endpoint below) in humans, ToxServices classified benzene into category 1 for this endpoint.

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

Benzene was assigned a score of High for systemic toxicity (repeated dose) based on classification to GHS category 1 with human data, and being associated with authoritative lists. GreenScreen® criteria classify chemicals as a High hazard for systemic toxicity (repeated dose) when they are classified to GHS category 1 and/or associated with EU R48/23/24/25 and/or H372 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* EU R48/23/24/25: danger of serious damage to health by prolonged exposure through inhalation, in contact with skin and if swallowed[7]
  - *Authoritative:* EU H372: Causes damage to organs through prolonged or repeated exposure
  - *Screening:* GHS-Korea: Specific target organ toxicity – Repeated exposure – Category 1
  - *Screening:* GHS-Japan: Specific target organs/systemic toxicity following repeated exposure category 1
  - *Screening:* GHS-New Zealand: 6.9A (inhalation) – Toxic to human target organs or systems (GHS category 1, can be single or repeated dose)
  - *Screening:* GHS-New Zealand: 6.9A (oral) – Toxic to human target organs or systems (GHS category 1, can be single or repeated dose)
- NITE 2006
  - Benzene was classified to GHS category 1 for hematopoietic organs based on human evidence: bone marrow hypoplasia/hyperplasia, hypocytosis associated with normablast, blood toxicity, aplastic anemia, transverse myelitis, a decrease in white/red blood cell counts and an increase in mean cell volume. Evidence from animals include decreased lymphocyte/red blood cell counts, abnormal configuration of circulating erythrocytes and leukocytes, decreased splenic nucleated cells, circulating erythrocytes and lymphocytes, decreased white blood cell count, decreased bone marrow cellularity and bone marrow pluripotent cells, decreased red blood cell, white blood cell and lymphocyte counts, decreased hematocrit value, and decreased mean cell volume. Effects in animals were observed at dose levels consistent with GHS classification guideline values.
- EU 2008
  - Numerous human and animal data were identified, and only a summary is included here.
    - In humans, chronic exposure to benzene induced depression of white and red blood cells. This effect is reversible at low exposure concentrations (>0.032 – 0.064 mg/L) even after years of exposures. Exposure to moderately high concentrations of benzene (0.192 mg/L) for approximately a week may cause increased proportion of large granular lymphocytes, but not severe marrow effects or specific cytopenias. Higher concentrations of benzene may cause aplastic anemia leading to death in 13% of the cases. It has been demonstrated through case control studies that the most sensitive endpoint in response to chronic benzene exposure is lymphopenia, with an overall LOAEC suggested to be 0.032 mg/L and a NOAEC of 0.0032 mg/L. Leucopenia is also a relevant endpoint, with the lowest reported LOAEC between 0.04 and 0.064 mg/L.
    - In animals, the most relevant adverse effects after repeated benzene exposure are

[7] According to ESIS (2014) a combination phrase of R48/23/24/25 is listed for benzene, rather than separate R phrases R23, R24 and R25 as listed in Pharos. A combination phrase has different meanings from separate R phrases.

associated with the hematopoietic system (lymphocytopenia, anemia and pancytopenia characterized by a decrease in all peripheral blood cell types and in marrow progenitor cells) regardless of exposure route, leading to subsequent immunotoxicity (leukocytopenia, effects on lymphocyte cellularity, suppressed humoral and cellular immunity, occasional immune stimulatory response after low dose exposure). Effects were also observed in the kidney (weight changes) and liver (hypertrophy and weight increase), but were considered of minor toxicological significance.

- *Inhalation:* LOAEC = 0.032 mg/L, NOAEC not established, in mice (6 – 178 days)
- *Inhalation:* LOAEC = 0.947 mg/L, NOAEC = 0.097 mg/L in rats (subchronic)
- *Oral:* LOAEL = 25 – 25 mg/kg/day in mice and rats (2-year), NOAEL not established.

- Based on the weight of evidence, ToxServices classified benzene into GHS category 1 due to significant toxicity observed in humans

Neurotoxicity (N)
***Group II Score (single dose)* (vH, H, M, or L): M**
Benzene was assigned a score of Moderate for neurotoxicity (single dose) based on classification to GHS category 3. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when they are classified to GHS category 3 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* Grandjean & Landrigan (2006) Neurotoxic Chemicals
  - *Screening:* GHS-New Zealand: 6.9A (inhalation) – Toxic to human target organs or systems (GHS category 1, can be single or repeated dose)
  - *Screening:* GHS-New Zealand: 6.9A (oral) – Toxic to human target organs or systems (GHS category 1, can be single or repeated dose)
  - *Screening:* GHS-Japan: Category 3 (narcotic effects)
- EU 2008
  - In humans, acute exposure to high concentrations of benzene vapor may lead to acceleration of respiratory rate followed by drowsiness, fatigue, dizziness, headache and nausea, leading to loss of consciousness. Convulsions and tremors occur frequently followed by death minutes or hours after high concentration exposure. In severe cases, breathlessness, nervous irritability and unsteadiness in walking may persist for 2 – 3 weeks.
  - Major clinical signs after acute exposure to benzene are sedation and narcosis. Depression of the central nervous system appeared to be related to death.
- U.S. EPA 2009
  - In humans, death from acute exposure to benzene is the result of CNS depression with ultimate paralysis of the respiratory center. In addition, sudden death from cardiac arrest was reported after a short period of euphoria and hyperactivity. Exposure at 50 – 150 ppm for 5 hours lad to headache, lassitude and weariness and 500 ppm for 1 hour leads to symptoms of illness. It was stated that CNS effects could be initially seen at concentrations above 250 ppm.
- Based on the reversible narcotic effects (if not leading to death) common to many organic solvents, ToxServices classified benzene to GHS category 3.

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

Benzene was assigned a score of High for neurotoxicity (repeated dose) based on classification to GHS category 1. GreenScreen® criteria classify chemicals as a High hazard for neurotoxicity (repeated dose) when they are classified to GHS category 1 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* GHS-New Zealand: 6.9A (inhalation) – Toxic to human target organs or systems (GHS category 1, can be single or repeated dose)
  - *Screening:* GHS-New Zealand: 6.9A (oral) – Toxic to human target organs or systems (GHS category 1, can be single or repeated dose)
  - *Screening:* GHS-Japan: Specific target organs/systemic toxicity following repeated exposure category 1 (Central nervous system)
  - *Screening:* Grandjean & Landrigan (2006) Neurotoxic Chemicals
- EU 2008
  - Oral exposure (drinking water) to benzene at 8 mg/kg/day for 4 weeks resulted in increased brain catecholamine concentration, and blood adrenocorticotropin (ACTH) and corticosterone in CD-1 mice. It was proposed that these effects were the indirect action of benzene on the immune system through the hypothalamus-pituitary-adrenal axis. However, behavioral dysfunctions or morphological abnormalities were not examined in this study.
  - In a 4-week drinking water study, CD-1 mice were exposed to benzene in water at 31, 166 or 790 mg/L. Increased norepinephrine was observed in the hypothalamus, medulla oblongata and cerebellum. Dopamine levels also increased significantly in the hypothalamus and corpus striatum. In addition, there was an increase of catecholamine metabolites and indoleamine serotonin in a number of brain regions. It was concluded that benzene included the synthesis and catabolism of these neurotransmitters.
  - Inhalation of 0.042 mg/L benzene vapor led to changes in neurobehavior functions (limb grip strength, rapid response and locomotor activity) and depressed activity of acetylcholinesterase in mice. Decreases in acetylcholine esterase activity were found at concentrations as low as 0.01 mg/L.
- U.S. EPA 2009
  - Long term exposure to benzene in an occupational setting induced changes in electroencephalography patterns, dizziness and headache, fatigue, lightheadedness, and increased sleep requirements.
- NITE 2006
  - Benzene was classified to GHS category 1 for this endpoint based on observations in humans: frequent headache, exhaustion, somnipathy, and dysmnesia.
- Based on the weight of evidence, chronic exposure to benzene led to neurotoxicity in humans and animals. Based on effects in humans, ToxServices classified benzene to GHS category 1.

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

Benzene was assigned a score of Low for skin sensitization based on lack of human evidence and negative findings in animals. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and negative, there are no structural alerts and they are not classified under GHS (CPA 2012a).

- Authoritative and Screening Lists
  - Not present on any authoritative or screening lists.

- EU 2008
    - Dermal sensitization has not been reported in the work place. Based on more than 100 years of human experience with benzene, skin sensitization is not expected.
- ECHA 2014
    - In a non-guideline, non-GLP mouse ear swelling test (MEST) and a reduced guinea pig maximization test, no signs of skin sensitization were found.

Respiratory Sensitization (SnR) Group II* Score (H, M, or L): *L*
Benzene was assigned a score of Low for respiratory sensitization based on lack of human evidence of respiratory sensitization. GreenScreen® criteria classify chemicals as a Low hazard for respiratory sensitization when adequate data are available and negative, there are no structural alerts and they are not classified under GHS (CPA 2012a).

- Authoritative and Screening Lists
    - Not present on any authoritative or screening lists.
- EU 2008
    - Respiratory sensitization has not been reported in the work place. Based on more than 100 years of human experience with benzene, respiratory sensitization is not expected.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M, or L): H
Benzene was assigned a score of High for skin irritation/corrosivity based on animal and human data classifying it to GHS category 2, and association with EU H315 and R38. GreenScreen® criteria classify chemicals as a High hazard for skin irritation/corrosivity when they are classified to GHS category 2 and/or they are associated with EU H315 and/or R38 (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* EU H315: Causes skin irritation
    - *Authoritative:* R36/38: Irritating to eyes and skin
    - *Screening:* GHS-Korea: Category 2
    - *Screening:* GHS-New Zealand: 6.3A – Irritating to the skin (GHS category 2)
    - *Screening:* GHS-Japan: Category 2
- EU 2008
    - Direct contact with liquid benzene may cause erythema and blistering in humans. In addition, benzene removes fat from the tissue, leaving skin with a dry, scaly dermatitis with repeated or prolonged exposure. In a case report, acute dermal exposure to benzene at high concentrations led to second degree chemical burns to face, trunk and limbs.
    - In animals, benzene tested to be a skin irritant and a skin defatting agent in rabbits and rats. There were moderate edema and/or erythema on the skin, with a chapped appearance.
- Based on the weight of evidence, benzene is irritating to the skin, but not corrosive. Therefore, ToxServices classified benzene to GHS category 2.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M, or L): H
Benzene was assigned a score of High for eye irritation/corrosivity based on classification to GHS category 2A, and association with EU H319. GreenScreen® criteria classify chemicals as a High hazard for eye irritation/corrosivity when they are classified to GHS category 2A, and/or associated with EU H319 (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* EU H319: Causes serious eye irritation
    - *Screening:* GHS-Korea: Category 2

  - *Screening:* GHS-Japan: Category 2A
  - *Screening:* GHS-New Zealand: 6.4A – Irritating to the eye (GHS category 2A/2B)
- EU 2008
  - In humans, high concentrations of benzene vapors are irritating to the mucous membranes of the eyes.
  - In animals, benzene may cause serious eye damages: inflammation and slight swelling of the eyelids, and questionable/just perceptible transient superficial necrosis of the cornea involving an area of less than 50% (corneal opacity < 3). The inflammation couldn't be scored and the edema was only slight. The effects were classified to Carpenter and Smyth grade 3 (5 represent severe injury with necrosis visible only after staining covering ¾ of the surface of cornea, or a more severe necrosis covering a smaller area).
- ECHA 2014
  - Instillation of benzene into the eyes of rabbits caused a moderate conjunctival irritation and very slight, transient corneal injury.
- Based on the weight of evidence, ToxServices classified benzene to category 2A (Irritating) for this endpoint.

Ecotoxicity (Ecotox)

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

Benzene was assigned a score of High for acute aquatic toxicity based on the lowest 96h LC_{50} of 5.3 mg/L in fish. GreenScreen® criteria classify chemicals as a High hazard for acute aquatic toxicity when acute aquatic L/EC_{50} values are between 1 and 10 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening:* GHS-Japan: Category 2
  - *Screening:* GHS-New Zealand: 9.1D (algal, crustacean and fish) – Slightly harmful in the aquatic environment or are otherwise designed for biocidal action
- EU 2008
  - 96h LC_{50} = 5.3 – 36.6 mg/L in fresh and salt water fish species
  - 48h E/LC_{50} = 10 – >320 mg/L in multiple aquatic invertebrate species
  - 72h EC_{50} = 28 – 100 mg/L in multiple algae species

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

Benzene was assigned a score of High for chronic aquatic toxicity based on the lowest NOEC of 0.8 mg/L in fish in a 32-day study. GreenScreen® criteria classify chemicals as a High hazard for chronic aquatic toxicity when chronic toxicity values are between 0.1 and 1 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists.
  - *Screening*: Not present on any screening lists.
- EU 2008
  - In a 23-27 day early life reproduction toxicity study in rainbow trout, LC_{50} = 8.25 - 8.64 mg/L. No NOEC or EC_{10} was reported by the authors, and an EU RAR derived EC_{10} = 3.5 µg/L was regarded as the NOEC for 23-27 day exposure to benzene. Results for the control were not reported. This study was considered not reliable by ECHA dossier of benzene.
  - NOEC = 0.8 mg/L and LOEC = 1.6 mg/L for benzene's effect on larvae in an early life stage test lasting 32 days in fathead minnow.

  - 14-day LC_{50} = 63.5 mg/L in guppy.
  - NOEC = 3 mg/L and LOEC = 8.9 mg/L for reproduction in a 7-day study with *Ceriodaphnia dubia*
  - 8-day EC_{50} = 41 mg/L for growth inhibition in green algae *Selenastrum capricornutum*.
- ECHA 2014
  - 32-day NOEC = 3.1 mg/L and LOEC = 5.3 mg/L for growth in juvenile striped bass.
- Fish seem to be the most sensitive species in the toxicity of benzene, as seen in acute studies. The lowest LOEC is 1.6 mg/L (NOEC = 0.8 mg/L) in fish. The study that established the NOEC of 3.5 µg/L does not seem to be reliable when compared to other studies in fish. It was not clear if any effects would be observed at concentrations lower than 1 mg/L. As a conservative approach, ToxServices used the NOEC of 0.8 mg/L rather than LOEC to classify benzene.

Environmental Fate (Fate)

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

Benzene was assigned a score of Very Low for persistence based on ready biodegradability meeting the 10 day window in multiple screening tests. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when they meet the 10-day window in ready biodegradation tests (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* There are no authoritative lists for this endpoint.
  - *Screening:* Environmental Canada DSL: Persistent
- EU 2008
  - Many studies were identified. Some tests reported complete mineralization within 28 days, meeting the 10-day window, while in other tests nearly no degradation was observed. It was stated that when more than 1 screening tests were available, positive results should be considered for assessment purposes, regardless of the negative results, provided all studies are of good quality. Therefore, benzene was classified as readily biodegradable.
- Environmental Canada 1993
  - Benzene has a short atmospheric half-life with overall half-lives of 00.1 – 21 days
  - Biodegradation half-lives range from 1.375 – 16 days in surface waters under aerobic environment, and 28 – 720 days under anaerobic conditions in deeper waters or ground water.
  - Benzene is considered to be moderately to highly mobile in the soil, with volatilization and runoff to surface water as main mechanisms of removal.
- ATSDR 2007
  - In water and soil, benzene is mainly subject to biodegradation (readily biodegradable), but concentrations higher than 2 ppm inhibit aerobic biodegradation.
- U.S. EPA 2012
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that benzene is not expected to be readily biodegradable. Fugacity modeling predicts 41.1% will partition to water with a half-life of 37.5 days, 31.8% will partition to air with a half-life of 8.7 days, and 26.7% will partition to soil with a half-life of 75 days.
- Based on the weight of the evidence, a score of Very Low was assigned. It's not clear why DSL listed benzene as persistent, while Environment Canada did not consider this chemical persistent. Fugacity modeling predicts that benzene will partition primarily to water. Based on the best experimental test results, benzene is considered to be readily biodegradable, meeting the 10-day

window. When the major compartment is water, GreenScreen® criteria specify a score of Very Low if the chemical meets the 10-day window in a ready biodegradation test. It should be noted, however, that higher concentrations of benzene may inhibit its biodegradation.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
Benzene was assigned a score of Very Low for bioaccumulation based on measured BCFs less than 100. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when BCF values are no bigger than 100 (CPA 2012a).

- Authoritative and Screening Lists
  - Not present on any authoritative or screening lists.
- EU 2008
  - Multiple tests were identified measuring BCF of benzene. In all but one test in fish BCFs are less than 100. The study reported a BCF of 8,450 in northern anchovies as measured in the gallbladder. Only ^{14}C-analysis was conducted, the substances measured may include metabolites of benzene as well. Further, bioaccumulation in certain organs of fish is difficult to interpret due to lack of information on BCF in the whole fish. Therefore, the weight of evidence supports the use of BCFs in the whole fish (less than 100 for benzene).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Benzene was assigned a score of Low for reactivity based on lack of explosiveness and other reactive properties based on structural analysis. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when adequate data are available and they are not classified by GHS (CPA 2012a).

- Authoritative and Screening Lists
  - Not present on any authoritative or screening lists.
- EU 2008
  - Benzene is not explosive and does not have oxidizing properties (no tests conducted due to structural reasons).
- NITE 2006
  - Benzene does not contain chemical groups with explosive or self-reactive properties. It does not contain oxygen, fluorine or chlorine for oxidizing properties. It does not contain O-O structures typical of organic peroxides.
  - As a liquid, there are currently no tests available to test benzene for self-heating properties.
  - Benzene is not corrosive to metals.

Flammability (F) Score (vH, H, M, or L): H
Benzene was assigned a score of High for flammability based on being a GHS category 2 flammable liquid, being classified to DOT class 3 PGII, and association with EU H225. GreenScreen® criteria classify chemicals as a High hazard for flammability when they are GHS category 2 flammable liquids, being classified to DOT class 3 PGII, and/or associated with EU H225 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* EU H225: Slightly flammable liquid and vapor
  - *Authoritative:* WHMIS: Class B2 – Flammable liquids
  - *Authoritative:* DOT: Class 3, packing group II
  - *Authoritative:* R11: Highly flammable

  - *Screening:* Not on any screening lists
- EU 2008
  - Benzene is highly flammable. Its flash point is -11ºC and boiling point is 80.1ºC.
- Based on the weight of evidence, benzene is categorized to GHS category 2 as a flammable liquid (flash point less than 23ºC, boiling point greater than 35ºC)

References

Agency for Toxic Substances and Disease Registry (ATSDR). 2007. Toxicological profile for benzene. Available: http://www.atsdr.cdc.gov/toxprofiles/tp.asp?id=40&tid=14

ChemIDplus. 2014. Entry for Benzene (CAS #71-43-2). United States National Library of Medicine. Available: http://chem.sis.nlm.nih.gov/chemidplus/chemidheavy.jsp

Clean Production Action (CPA). 2011. The GreenScreen® for Safer Chemicals Version 1.2 Benchmarks. Available: http://www.greenscreenchemicals.org/method/method-documents

Clean Production Action (CPA). 2012a. The GreenScreen® for Safer Chemicals Version 1.2 Criteria. Dated: November 2012. Available: http://www.greenscreenchemicals.org/method/method-documents

Clean Production Action (CPA). 2012b. List Translator. Dated February 2012. Available: http://www.greenscreenchemicals.org/method/method-documents

Clean Production Action (CPA). 2013. The GreenScreen® for Safer Chemicals Chemical Hazard Assessment Procedure. Version 1.2 Guidance. Dated August 31, 2013. Available: http://www.greenscreenchemicals.org/method/method-documents

Environment Canada. 1993. Canadian Environmental Protection Act Priority Substances List Assessment Report. Benzene. Available: http://www.hc-sc.gc.ca/ewh-semt/alt_formats/hecs-sesc/pdf/pubs/contaminants/psl1-lsp1/benzene/benzene-eng.pdf

European Chemicals Agency (ECHA). 2014. REACH Dossier on benzene. Registered substances. Available: http://apps.echa.europa.eu/registered/data/dossiers/DISS-9d862eda-63cd-4c78-e044-00144f67d249/AGGR-cc0ca73f-30c5-4db3-abe2-c3c2f7b5305a_DISS-9d862eda-63cd-4c78-e044-00144f67d249.html#AGGR-cc0ca73f-30c5-4db3-abe2-c3c2f7b5305a

European Union (EU). 2008. European Union Risk Assessment Report. Benzene. Risk assessment. Final approved version. Available: http://esis.jrc.ec.europa.eu/doc/risk_assessment/REPORT/benzenereport063.pdf

Grandjean, P. and P.J. Landrigan. 2006. Developmental neurotoxicity of industrial chemicals. Lancet 368: 2167-2178.

Grandjean, P. and P.J. Landrigan. 2014. Neurobehavioural effects of developmental toxicity. The Lancet 13: 330-338.

International Agency for Research on Cancer (IARC). 1987. Summaries and evaluations. Benzene. Supplement 7: p.120. Available: http://www.inchem.org/documents/iarc/suppl7/benzene.html

National Institute of Technology and Evaluation (NITE). 2006. GHS classification results for benzene. ID194. Japan. Available: http://www.safe.nite.go.jp/english/ghs/ghs_download.html

New Zealand Environmental Protection Authority (N.Z. EPA). 2009. Correlation between GHS and New Zealand HSNO Hazard Classes and Categories. Available: http://www.epa.govt.nz/Publications/hsnogen-ghs-nz-hazard.pdf

Pharos. 2014. Pharos Chemical and Material Library Entry for Benzene (CAS #71-43-2). Available: http://www.pharosproject.net/material/

Reprotox. 2013. Record for benzene. Available: www.expub.com

ToxServices. 2013. SOP 1.37: GreenScreen® Hazard Assessments. Dated: April 24, 2013.

United States Environmental Protection Agency (U.S. EPA). 2002. Toxicological review of benzene (noncancerous effects). In support of summary information on the integrated risk information system (IRIS). Available: http://www.epa.gov/iris/toxreviews/0276tr.pdf

United States Environmental Protection Agency (U.S. EPA). 2004. Hydraulic fracturing fluids. Chapter 4. EPA 816-R-04-003. Available: http://www.epa.gov/ogwdw/uic/pdfs/cbmstudy_attach_uic_ch04_hyd_frac_fluids.pdf

United States Environmental Protection Agency (U.S. EPA). 2009. Benzene. Interim acute exposure guideline levels (AEGLs) for NAS/COT Subcommittee for AEGLS. Available: http://www.epa.gov/oppt/aegl/pubs/benzene_interim_dec_2008_v1.pdf

United States Environmental Protection Agency (U.S. EPA). 2012. Estimation Programs Interface (EPI) Suite® Web, v4.11, Washington, DC, USA. Available: http://www.epa.gov/opptintr/exposure/pubs/episuitedl.htm.

APPENDIX A: Hazard Benchmark Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(Cr) Corrosion/ Irritation (Skin/ Eye)

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: Results of Automated GreenScreen® Score Calculation for Benzene (CAS #71-43-2)

TOXSERVICES TOXICOLOGY RISK ASSESSMENT CONSULTING

GREEN SCREEN FOR SAFER CHEMICALS

GreenScreen® Score Inspector

Table 1: Hazard Table

	Group I Human					Group II and II* Human									Ecotox		Fate		Physical	
	Carcinogenicity	Mutagenicity/Genotoxicity	Reproductive Toxicity	Developmental Toxicity	Endocrine Activity	Acute Toxicity	Systemic Toxicity		Neurotoxicity		Skin Sensitization*	Respiratory Sensitization*	Skin Irritation	Eye Irritation	Acute Aquatic Toxicity	Chronic Aquatic Toxicity	Persistence	Bioaccumulation	Reactivity	Flammability
Table 2: Chemical Details							S	R *	S	R *	*	*								
Inorganic Chemical? / Chemical Name / CAS#	C	M	R	D	E	AT	STs	STr	Ns	Nr	SNS*	SNR*	IrS	IrE	AA	CA	P	B	Rx	F
No / Benzene / 71-43-2	H	H	H	H	*M*	L	vH	H	M	H	L	*L*	H	H	H	H	vL	vL	*L*	H

Table 3: Hazard Summary Table

Benchmark	a	b	c	d	e	f	g
1	No	No	No	No	Yes		
2	STOP						
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Benzene	1

Note: Chemical has not undergone a data gap assessment. Not a Final GreenScreen™ Score

Table 6

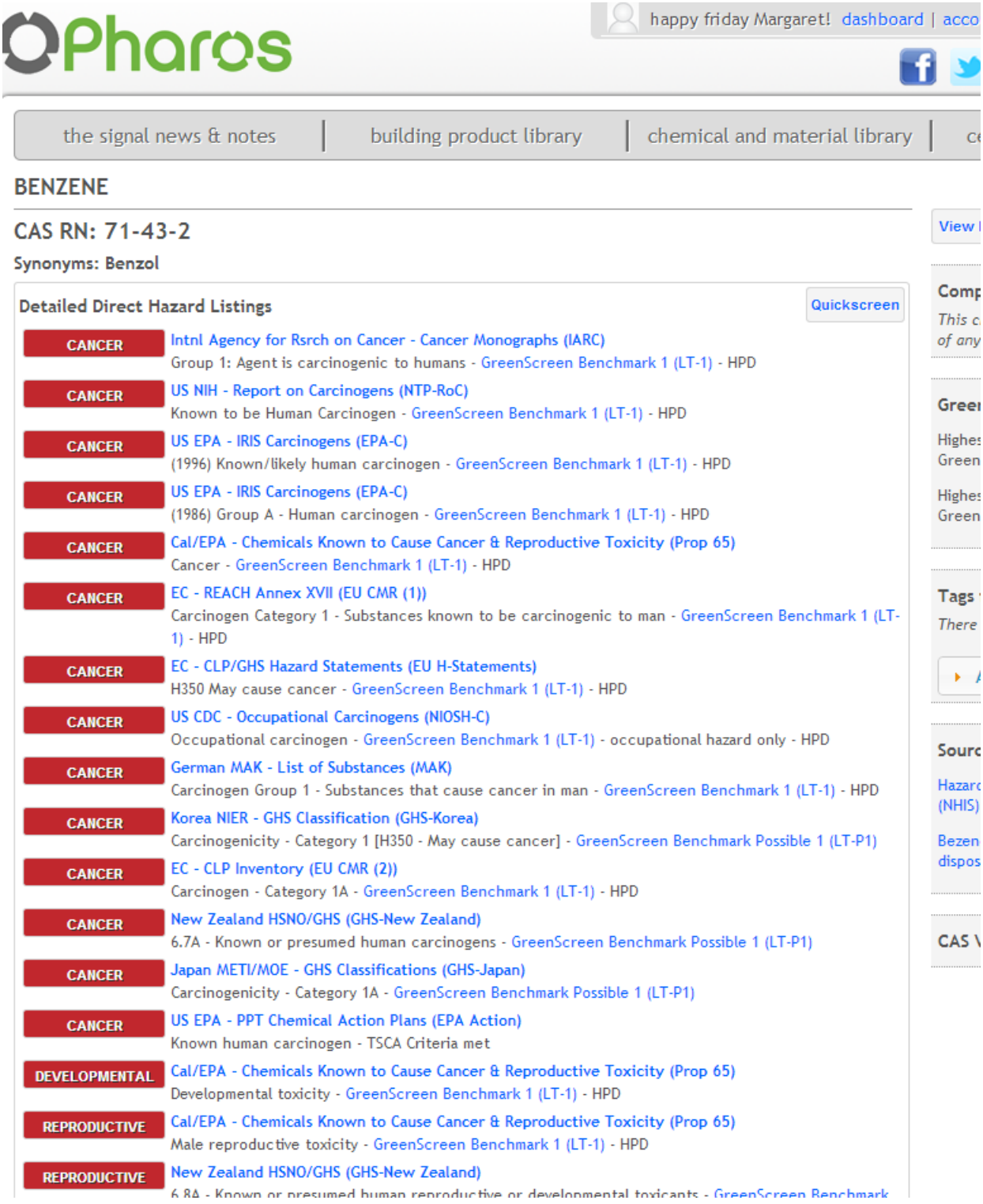
Chemical Name	Final GreenScreen® Benchmark Score
Benzene	1

After Data gap Assessment
Note: No Data gap Assessment Done if Preliminary GS Benchmark Score is 1.

Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												1
2												
3												
4												

APPENDIX C: Pharos Output for Benzene (CAS #71-43-2)



Pharos

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BENZENE

CAS RN: 71-43-2

Synonyms: Benzol

Detailed Direct Hazard Listings

Quickscreen

CANCER	Intnl Agency for Rsrch on Cancer - Cancer Monographs (IARC) Group 1: Agent is carcinogenic to humans - GreenScreen Benchmark 1 (LT-1) - HPD
CANCER	US NIH - Report on Carcinogens (NTP-RoC) Known to be Human Carcinogen - GreenScreen Benchmark 1 (LT-1) - HPD
CANCER	US EPA - IRIS Carcinogens (EPA-C) (1996) Known/likely human carcinogen - GreenScreen Benchmark 1 (LT-1) - HPD
CANCER	US EPA - IRIS Carcinogens (EPA-C) (1986) Group A - Human carcinogen - GreenScreen Benchmark 1 (LT-1) - HPD
CANCER	Cal/EPA - Chemicals Known to Cause Cancer & Reproductive Toxicity (Prop 65) Cancer - GreenScreen Benchmark 1 (LT-1) - HPD
CANCER	EC - REACH Annex XVII (EU CMR (1)) Carcinogen Category 1 - Substances known to be carcinogenic to man - GreenScreen Benchmark 1 (LT-1) - HPD
CANCER	EC - CLP/GHS Hazard Statements (EU H-Statements) H350 May cause cancer - GreenScreen Benchmark 1 (LT-1) - HPD
CANCER	US CDC - Occupational Carcinogens (NIOSH-C) Occupational carcinogen - GreenScreen Benchmark 1 (LT-1) - occupational hazard only - HPD
CANCER	German MAK - List of Substances (MAK) Carcinogen Group 1 - Substances that cause cancer in man - GreenScreen Benchmark 1 (LT-1) - HPD
CANCER	Korea NIER - GHS Classification (GHS-Korea) Carcinogenicity - Category 1 [H350 - May cause cancer] - GreenScreen Benchmark Possible 1 (LT-P1)
CANCER	EC - CLP Inventory (EU CMR (2)) Carcinogen - Category 1A - GreenScreen Benchmark 1 (LT-1) - HPD
CANCER	New Zealand HSNO/GHS (GHS-New Zealand) 6.7A - Known or presumed human carcinogens - GreenScreen Benchmark Possible 1 (LT-P1)
CANCER	Japan METI/MOE - GHS Classifications (GHS-Japan) Carcinogenicity - Category 1A - GreenScreen Benchmark Possible 1 (LT-P1)
CANCER	US EPA - PPT Chemical Action Plans (EPA Action) Known human carcinogen - TSCA Criteria met
DEVELOPMENTAL	Cal/EPA - Chemicals Known to Cause Cancer & Reproductive Toxicity (Prop 65) Developmental toxicity - GreenScreen Benchmark 1 (LT-1) - HPD
REPRODUCTIVE	Cal/EPA - Chemicals Known to Cause Cancer & Reproductive Toxicity (Prop 65) Male reproductive toxicity - GreenScreen Benchmark 1 (LT-1) - HPD
REPRODUCTIVE	New Zealand HSNO/GHS (GHS-New Zealand) 6.8A - Known or presumed human reproductive or developmental toxicants - GreenScreen Benchmark

REPRODUCTIVE	New Zealand HSNO/GHS (GHS-New Zealand) 6.8A - Known or presumed human reproductive or developmental toxicants - GreenScreen Benchmark Possible 1 (LT-P1)
GENE MUTATION	EC - CLP/GHS Hazard Statements (EU H-Statements) H340 May cause genetic defects - GreenScreen Benchmark 1 (LT-1) - HPD
GENE MUTATION	EC - REACH Annex XVII (EU CMR (1)) Mutagen Category 2 - Substances which should be regarded as if they are mutagenic to man - GreenScreen Benchmark 1 (LT-1) - HPD
GENE MUTATION	Korea NIER - GHS Classification (GHS-Korea) Germ cell mutagenicity - Category 1 [H340 - May cause genetic defects] - GreenScreen Benchmark Possible 1 (LT-P1)
GENE MUTATION	EC - CLP Inventory (EU CMR (2)) Mutagen - Category 1B - GreenScreen Benchmark 1 (LT-1) - HPD
GENE MUTATION	New Zealand HSNO/GHS (GHS-New Zealand) 6.6A - Known or presumed human mutagens - GreenScreen Benchmark Possible 1 (LT-P1)
REPRODUCTIVE	Japan METI/MOE - GHS Classifications (GHS-Japan) Toxic to reproduction - Category 2 - GreenScreen Benchmark Unspecified (LT-U)
ENDOCRINE	TEDX - Potential Endocrine Disruptors (TEDX) Potential Endocrine Disruptor - GreenScreen Benchmark Possible 1 (LT-P1) - HPD
GENE MUTATION	Japan METI/MOE - GHS Classifications (GHS-Japan) Germ cell mutagenicity - Category 2 - GreenScreen Benchmark Unspecified (LT-U)
GENE MUTATION	German MAK - List of Substances (MAK) Germ Cell Mutagen 3a - GreenScreen Benchmark Possible 1 (LT-P1)
MAMMALIAN	EC - CLP/GHS Hazard Statements (EU H-Statements) H304: May be fatal if swallowed and enters airways - Not included in GreenScreen - HPD
MAMMALIAN	Korea NIER - GHS Classification (GHS-Korea) Specific target organ toxicity - Repeated exposure - Category 1 [H372 - Causes damage to organs through prolonged or repeated exposure] - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	New Zealand HSNO/GHS (GHS-New Zealand) 6.1B (dermal) - Acutely toxic - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Specific target organs/systemic toxicity following repeated exposure - Category 1 - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Specific target organs/systemic toxicity following single exposure - Category 1 - GreenScreen Benchmark Unspecified (LT-U)
EYE IRRITATION	Korea NIER - GHS Classification (GHS-Korea) Serious eye damage/irritation - Category 2 [H319 - Causes serious eye irritation] - GreenScreen Benchmark Unspecified (LT-U)
EYE IRRITATION	Japan METI/MOE - GHS Classifications (GHS-Japan) Serious eye damage / eye irritation - Category 2A - GreenScreen Benchmark Unspecified (LT-U)
ORGAN TOXICANT	EC - CLP/GHS Hazard Statements (EU H-Statements) H372 Causes damage to organs through prolonged or repeated exposure - GreenScreen Benchmark Unspecified (LT-U) - HPD
ORGAN TOXICANT	New Zealand HSNO/GHS (GHS-New Zealand) 6.9A (inhalation) - Toxic to human target organs or systems - GreenScreen Benchmark Unspecified (LT-U)
ORGAN TOXICANT	New Zealand HSNO/GHS (GHS-New Zealand)

ORGAN TOXICANT	New Zealand HSNO/GHS (GHS-New Zealand) 6.9A (oral) - Toxic to human target organs or systems - GreenScreen Benchmark Unspecified (LT-U)
ACUTE AQUATIC	Japan METI/MOE - GHS Classifications (GHS-Japan) Hazardous to the aquatic environment (acute) - Category 2 - GreenScreen Benchmark Unspecified (LT-U)
CHRON AQUATIC	Japan METI/MOE - GHS Classifications (GHS-Japan) Hazardous to the aquatic environment (chronic) - Category 2 - GreenScreen Benchmark Unspecified (LT-U)
FLAMMABLE	EC - CLP/GHS Hazard Statements (EU H-Statements) H225 Highly flammable liquid and vapour. - GreenScreen Benchmark Unspecified (LT-U) - occupational hazard only - HPD
FLAMMABLE	Korea NIER - GHS Classification (GHS-Korea) Flammable liquids - Category 2 [H225 - Highly flammable liquid and vapour] - GreenScreen Benchmark Unspecified (LT-U)
FLAMMABLE	New Zealand HSNO/GHS (GHS-New Zealand) 3.1B - Flammable Liquids: high hazard - GreenScreen Benchmark Unspecified (LT-U)
FLAMMABLE	Japan METI/MOE - GHS Classifications (GHS-Japan) Flammable liquids - Category 2 - GreenScreen Benchmark Unspecified (LT-U)
RESPIRATORY	CHE - Toxicant Database Asthma - irritant - limited evidence - Not included in GreenScreen
NEUROTOXICITY	Lancet - Grandjean & Landrigan Neurotoxic Chemicals (G&L Neuro) Known to be neurotoxic in man - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	EC - Risk Phrases (EU R-Phrases) R23: Toxic by inhalation. - GreenScreen Benchmark Unspecified (LT-U) - HPD
MAMMALIAN	EC - Risk Phrases (EU R-Phrases) R24: Toxic in contact with skin. - GreenScreen Benchmark Unspecified (LT-U) - HPD
MAMMALIAN	EC - Risk Phrases (EU R-Phrases) R25: Toxic if swallowed. - GreenScreen Benchmark Unspecified (LT-U) - HPD
MAMMALIAN	Korea NIER - GHS Classification (GHS-Korea) Acute toxicity (oral) - Category 4 [H302 - Harmful if swallowed] - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	Québec CSST - WHMIS Classifications (WHMIS) Class D2A - Very toxic material causing other toxic effects - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	Québec CSST - WHMIS Classifications (WHMIS) Class D2B - Toxic material causing other toxic effects - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	New Zealand HSNO/GHS (GHS-New Zealand) 6.1D (oral) - Acutely toxic - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Acute toxicity (oral) - Category 4 - GreenScreen Benchmark Unspecified (LT-U)
EYE IRRITATION	EC - CLP/GHS Hazard Statements (EU H-Statements) H319 Causes serious eye irritation - GreenScreen Benchmark Unspecified (LT-U) - HPD
EYE IRRITATION	New Zealand HSNO/GHS (GHS-New Zealand) 6.4A - Irritating to the eye - GreenScreen Benchmark Unspecified (LT-U)
SKIN IRRITATION	EC - CLP/GHS Hazard Statements (EU H-Statements) H315 Causes skin irritation - GreenScreen Benchmark Unspecified (LT-U) - HPD
SKIN IRRITATION	Korea NIER - GHS Classification (GHS-Korea) Skin corrosion/irritation - Category 2 [H315 - Causes skin irritation] - GreenScreen Benchmark

SKIN IRRITATION	Korea NIER - GHS Classification (GHS-Korea) Skin corrosion/irritation - Category 2 [H315 - Causes skin irritation] - GreenScreen Benchmark Unspecified (LT-U)
SKIN IRRITATION	New Zealand HSNO/GHS (GHS-New Zealand) 6.3A - Irritating to the skin - GreenScreen Benchmark Unspecified (LT-U)
SKIN IRRITATION	Japan METI/MOE - GHS Classifications (GHS-Japan) Skin corrosion / irritation - Category 2 - GreenScreen Benchmark Unspecified (LT-U)
ACUTE AQUATIC	New Zealand HSNO/GHS (GHS-New Zealand) 9.1D (algal) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action - GreenScreen Benchmark Unspecified (LT-U)
ACUTE AQUATIC	New Zealand HSNO/GHS (GHS-New Zealand) 9.1D (crustacean) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action - GreenScreen Benchmark Unspecified (LT-U)
ACUTE AQUATIC	New Zealand HSNO/GHS (GHS-New Zealand) 9.1D (fish) - Slightly harmful in the aquatic environment or are otherwise designed for biocidal action - GreenScreen Benchmark Unspecified (LT-U)
CHRON AQUATIC	Korea NIER - GHS Classification (GHS-Korea) Hazardous to the aquatic environment (chronic) - Category 3 [H412 - Harmful to aquatic life with long lasting effects] - GreenScreen Benchmark Unspecified (LT-U)
TERRESTRIAL	New Zealand HSNO/GHS (GHS-New Zealand) 9.3C - Harmful to terrestrial vertebrates - Not included in GreenScreen
FLAMMABLE	Québec CSST - WHMIS Classifications (WHMIS) Class B2 - Flammable liquids - GreenScreen Benchmark Unspecified (LT-U)
PBT	Environment Canada - Domestic Substances List (DSL) DSL substances that are Persistent - GreenScreen Benchmark Unspecified (LT-U)
CANCER	Silent Spring - Breast Cancer Chemicals (SSI-BC) Chemicals that increased mammary gland tumors in animal studies - Not included in GreenScreen
MAMMALIAN	Korea NIER - GHS Classification (GHS-Korea) Aspiration hazard - Category 1 [H304 - May be fatal if swallowed and enters airways] - Not included in GreenScreen - occupational hazard only
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Aspiration hazard - Category 1 - Not included in GreenScreen - occupational hazard only
RESTRICTED LIST	US EPA - Hazardous Air Pollutants (HAPs) Hazardous Air Pollutant subject to the Clean Air Act - Not included in GreenScreen
RESTRICTED LIST	ChemSec - Substitute List (SIN) Classified CMR (Carcinogen, Mutagen &/or Reproductive Toxicant) - GreenScreen Benchmark Possible 1 (LT-P1) - HPD
RESTRICTED LIST	German FEA - Substances Hazardous to Waters (VwVwS) Class 3 Severe Hazard to Waters - GreenScreen Benchmark Possible 1 (LT-P1) - HPD
RESTRICTED LIST	US OSHA - Carcinogens Cancer causing substances subject to workplace management or avoidance - Not included in GreenScreen - occupational hazard only
RESTRICTED LIST	Hazardous 100 (SCHF) Chemicals of high concern - Not included in GreenScreen
RESTRICTED LIST	Environment Canada - Toxic Substances List - Sched 1 (CEPA) CEPA Toxic - GreenScreen Benchmark Unspecified (LT-U)
RESTRICTED LIST	CA SCP Candidate Chemicals Full Candidate Chemical List - Not included in GreenScreen

RESTRICTED LIST	CA SCP Candidate Chemicals Full Candidate Chemical List - Not included in GreenScreen
RESTRICTED LIST	CA SCP Candidate Chemicals Initial Candidate Chemicals List - Not included in GreenScreen
PBT	US EPA - PPT Chemical Action Plans (EPA Action) Low bioaccumulation potential - TSCA Criteria met
PBT	US EPA - PPT Chemical Action Plans (EPA Action) Low environmental persistence - TSCA Criteria met

Lifecycle Hazard Quickscreen Full Lifecycle Map

Research Status: Preliminary literature review drafted
The Pharos team has undertaken a preliminary literature review of some of the processes involved in the manufacture of this substance and identified the following chemicals. This list of chemicals is not exhaustive of all chemicals that may be involved in the production or life cycle of this substance.

May contain residual manufacturing chemicals that have a hazard of...

Comes from additional manufacturing chemicals that have a hazard of...

PBT	TOLUENE [108-88-3] - Occasional/Rare Feedstock
CANCER	N-HEXANE [110-54-3] - Frequent Feedstock
DEVELOPMENTAL	TOLUENE [108-88-3] - Occasional/Rare Feedstock
REPRODUCTIVE	TOLUENE [108-88-3] - Occasional/Rare Feedstock
ENDOCRINE	N-HEXANE [110-54-3] - Frequent Feedstock
RESPIRATORY	TOLUENE [108-88-3] - Occasional/Rare Feedstock
NEUROTOXICITY	N-HEXANE [110-54-3] - Frequent Feedstock
MAMMALIAN	N-HEXANE [110-54-3] - Frequent Feedstock
EYE IRRITATION	N-HEXANE [110-54-3] - Frequent Feedstock
SKIN IRRITATION	N-HEXANE [110-54-3] - Frequent Feedstock
ORGAN TOXICANT	N-HEXANE [110-54-3] - Frequent Feedstock
ACUTE AQUATIC	N-HEXANE [110-54-3] - Frequent Feedstock
CHRON AQUATIC	N-HEXANE [110-54-3] - Frequent Feedstock
TERRESTRIAL	CYCLOHEXANE [110-82-7] - Frequent Feedstock
FLAMMABLE	N-HEXANE [110-54-3] - Frequent Feedstock
RESTRICTED LIST	N-HEXANE [110-54-3] - Frequent Feedstock

Description:

"Benzene is a colorless liquid with a sweet odor. It evaporates into the air very quickly and dissolves slightly in water. It is highly flammable and is formed from both natural processes and human activities. Benzene is widely used in the United States; it ranks in the top 20 chemicals for production volume. Some industries use benzene to make other chemicals which are used to make plastics, resins, and nylon and synthetic fibers. Benzene is also used to make some types of rubbers, lubricants, dyes, detergents, drugs, and pesticides. Natural sources of benzene include volcanoes and forest fires. Benzene is also a natural part of crude oil, gasoline, and cigarette smoke." (ATSDR)

"Benzene is used as an intermediate in the manufacture of a number of chemicals, including ethylbenzene (used in the

APPENDIX D: EPISuite Modeling Results for Benzene (CAS #71-43-2)

CAS Number: 71-43-2
SMILES : c1ccccc1
CHEM : benzene
MOL FOR: C6 H6
MOL WT : 78.11
---------- EPI SUMMARY (v4.11) ----------

Physical Property Inputs:
Log K_{ow} (octanol-water): 2.13
Boiling Point (deg C) : ------
Melting Point (deg C) : 5.50
Vapor Pressure (mm Hg) : 75
Water Solubility (mg/L): 1790
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log K_{ow} (K_{ow}WIN v1.68 estimate) = 1.99
Log K_{ow} (Exper. database match) = 2.13
Exper. Ref: HANSCH,C ET AL. (1995)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 102.24 (Adapted Stein & Brown method)
Melting Pt (deg C): -77.92 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 87.2 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 1.16E+004 (Mean VP of Antoine & Grain methods)
MP (exp database): 5.5 deg C
BP (exp database): 80.0 deg C
VP (exp database): 9.48E+01 mm Hg (1.26E+004 Pa) at 25 deg C

Water Solubility Estimate from Log K_{ow} (WSK_{ow} v1.42):
Water Solubility at 25 deg C (mg/L): 1975
log K_{ow} used: 2.13 (user entered)
melt pt used: 5.50 deg C
Water Sol (Exper. database match) = 1790 mg/L (25 deg C)
Exper. Ref: MAY,WE ET AL. (1983)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 1339 mg/L

ECOSAR Class Program (ECOSAR v1.11):
Class(es) found:
Neutral Organics

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 5.39E-003 atm-m3/mole (5.46E+002 Pa-m3/mole)
Group Method: 5.35E-003 atm-m3/mole (5.42E+002 Pa-m3/mole)
Exper Database: 5.55E-03 atm-m3/mole (5.62E+002 Pa-m3/mole)

For Henry LC Comparison Purposes:
User-Entered Henry LC: not entered
Henrys LC [via VP/WSol estimate using User-Entered or Estimated values]:
HLC: 4.306E-003 atm-m3/mole (4.363E+002 Pa-m3/mole)
VP: 75 mm Hg (source: User-Entered)
WS: 1.79E+003 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [K_{oa}WIN v1.10]:
Log K_{ow} used: 2.13 (user entered)
Log K_{aw} used: -0.644 (exp database)
Log K_{oa} (K_{oa}WIN v1.10 estimate): 2.774
Log K_{oa} (experimental database): 2.780

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 1.0296
Biowin2 (Non-Linear Model) : 0.9999
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 2.4406 (weeks-months)
Biowin4 (Primary Survey Model) : 3.3922 (days-weeks)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.5291
Biowin6 (MITI Non-Linear Model): 0.7294
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.0000
Ready Biodegradability Prediction: NO

Hydrocarbon Biodegradation (BioHCwin v1.01):
LOG BioHC Half-Life (days) : 0.6577
BioHC Half-Life (days) : 4.5464

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 1E+004 Pa (75 mm Hg)
Log K_{oa} (Exp database): 2.780
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 3E-010
Octanol/air (K_{oa}) model: 1.48E-010
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 1.08E-008
Mackay model : 2.4E-008
Octanol/air (K_{oa}) model: 1.18E-008

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 1.9498 E-12 cm3/molecule-sec
Half-Life = 5.486 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 65.827 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):

1.74E-008 (Junge-Pankow, Mackay avg)
1.18E-008 (K_{oa} method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (K_{oc}WIN v2.00):
K_{oc} : 145.8 L/kg (MCI method)
Log K_{oc}: 2.164 (MCI method)
K_{oc} : 70.51 L/kg (K_{ow} method)
Log K_{oc}: 1.848 (K_{ow} method)
Experimental Log K_{oc}: 1.75 (database)

Aqueous Base/Acid-Catalyzed Hydrolysis (25 deg C) [HYDROWIN v2.00]:
Rate constants can NOT be estimated for this structure!

Bioaccumulation Estimates (BCFBAF v3.01):
Log BCF from regression-based method = 1.072 (BCF = 11.81 L/kg wet-wt)
Log Biotransformation Half-life (HL) = 0.1880 days (HL = 1.542 days)
Log BCF Arnot-Gobas method (upper trophic) = 1.170 (BCF = 14.79)
Log BAF Arnot-Gobas method (upper trophic) = 1.170 (BAF = 14.79)
log K_{ow} used: 2.13 (user entered)

Volatilization from Water:
Henry LC: 0.00555 atm-m3/mole (Henry experimental database)
Half-Life from Model River: 0.9951 hours (59.71 min)
Half-Life from Model Lake : 84.96 hours (3.54 days)

Removal In Wastewater Treatment:
Total removal: 68.94 percent
Total biodegradation: 0.04 percent
Total sludge adsorption: 1.11 percent
Total to Air: 67.78 percent
(using 10000 hr Bio P,A,S)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	31.8	209	1000
Water	41.1	900	1000
Soil	26.7	1.8e+003	1000
Sediment	0.37	8.1e+003	0

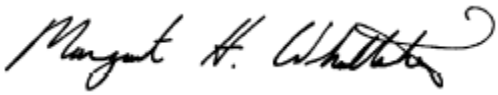
Persistence Time: 197 hr

Authorized Reviewers

Benzene GreenScreen® Evaluation Prepared By:

Bingxuan Wang, Ph.D.
Toxicologist
ToxServices LLC

Benzene GreenScreen® Evaluation QC'd By:



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