Isobutanol (CAS #78-83-1) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment

Prepared for:

Washington State Department of Ecology

Prepared by:

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GreenScreen® Executive Summary for Isobutanol (CAS #78-83-1)

Isobutanol is a chemical that functions as a solvent in surface coatings, adhesives, paint strippers, lacquers, perfumes, cleaners, and hydraulic fluid, and is used in the production of isobutyl esters and flavoring agents.

Isobutanol was assigned a GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") as it has Very High Group II Human Health Hazard (eye irritation (IrE)). This corresponds to GreenScreen® benchmark classification 2f ("Very High T (Ecotoxicity or Group II Human) or High T (Group II* Human)") in CPA 2011. Data gaps (DG) exist for endocrine activity (E) and respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Conduct a Data Gap Analysis to assign a final Benchmark score), isobutanol meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if isobutanol were assigned a High score for the data gap endocrine activity (E), it would be categorized as a Benchmark 1 Chemical.

GreenScreen® Benchmark Score for Relevant Route of Exposure:
As a standard approach for GreenScreen® evaluations, all exposure routes (oral, dermal, and inhalation) were evaluated together, so the GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") is applicable for all routes of exposure.

GreenScreen® Hazard Ratings for Isobutanol

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*										
L	L	L	L	DG	L	M	L	M	L	*L*	DG	H	vH	L	L	*vL*	vL	*L*	M

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated 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 Isobutanol (CAS #78-83-1)

Method Version: GreenScreen® Version 1.2[1]
Assessment Type[2]: Certified

Chemical Name: Isobutanol

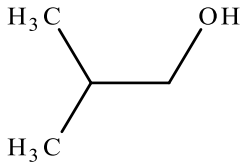
CAS Number: 78-83-1

GreenScreen® Assessment Prepared By:
Name: Zach Guerrette, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: October 14, 2014
Assessor Type: Licensed GreenScreen® Profiler

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: December 1, 2014

Confirm application of the *de minimus* rule[3]: N/A

Chemical Structure(s):



Also called:
Isobutyl alcohol; 1-Hydroxymethylpropane; 1-Propanol, 2-methyl-; 2-Methyl propanol; 2-Methyl-1-propanol; 2-Methylpropyl alcohol; EINECS 201-148-0; Fermentation butyl alcohol; Isobutanol; Isopropylcarbinol; 2-Methylpropan-1-ol; Iso-butyl alcohol; Isobutanol or isobutyl alcohol [UN1212] [Flammable liquid] (ChemIDplus 2014)

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:
No data were identified for the endocrine activity or respiratory sensitization endpoints. ToxServices attempted to identify potential chemical surrogates using the structural similarity search function of ChemIDplus and the U.S. EPA's Analog Identification Methodology (AIM) software but not of the surrogates identified using these strategies possessed data for these endpoints. Therefore, the endocrine activity and respiratory sensitization endpoints were assigned data gaps.

[1] Use GreenScreen® Assessment Procedure (Guidance) V1.2

[2] GreenScreen® reports are either "UNACCREDITED" (by unaccredited person), "AUTHORIZED" (by Authorized GreenScreen® Practitioner), "CERTIFIED" (by Licensed GreenScreen® Profiler or equivalent) or "CERTIFIED WITH VERIFICATION" (Certified or Authorized assessment that has passed GreenScreen® Verification Program)

[3] 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

Identify Applications/Functional Uses (HSDB 2005)**:**
1. Solvent in surface coatings, adhesives, paint strippers, lacquers, perfumes, cleaners, and hydraulic fluid
2. Production of isobutyl esters and flavoring agents

GreenScreen® Summary Rating for Isobutanol[4]: Isobutanol was assigned a GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") as it has Very High Group II Human Health Hazard (eye irritation (IrE)). This corresponds to GreenScreen® benchmark classification 2f ("Very High T (Ecotoxicity or Group II Human) or High T (Group II* Human)") in CPA 2011. Data gaps (DG) exist for endocrine activity (E) and respiratory sensitization (SnR*). As outlined in CPA (2013) Section 12.2 (Conduct a Data Gap Analysis to assign a final Benchmark score), isobutanol meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if isobutanol were assigned a High score for the data gap endocrine activity (E), it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Ratings for Isobutanol

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*										
L	L	L	L	DG	L	M	L	M	L	*L*	DG	H	vH	L	L	*vL*	vL	*L*	M

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**[5]

No transformation products were identified for isobutanol. Hydrolysis is not expected to be a significant environmental fate process due to the lack of hydrolysable functional groups present in isobutanol's chemical structure (HSDB 2005). Based on the lack of feasible transformation products, the Benchmark Score for isobutanol is not adjusted by transformation products.

Introduction
Isobutanol is used as a solvent in surface coatings, adhesives, paint strippers, lacquers, perfumes, cleaners, and hydraulic fluid, and is used in the production of isobutyl esters and flavoring agents (HSDB 2005). It is produced via the fermentation of carbohydrates, reduction of isobutyraldehyde with

[4] 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.
[5] 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.

sodium amalgam or in the presence of a catalyst, or via the fermentation of isobutyraldehyde (HSDB 2005).

ToxServices assessed isobutanol against GreenScreen® Version 1.2 (CPA 2013) following procedures outlined in ToxServices' SOP 1.69 (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. It checks all of the lists in the List Translator with the exception of the U.S. Department of Transportation (U.S. DOT) lists (U.S. DOT 2008a,b) and these should be checked separately in conjunction with running the Pharos query. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. The output for isobutanol can be found in Appendix C and a summary of the results can be found below:

- Very High Hazard
  - Eye Irritation
    - GHS Hazard Phrase H318 – causes serious eye damage
    - EU Risk Phrase R41 – risk of serious damage to eyes
- High Hazard
  - Eye Irritation
    - GHS Japan Category 2A eye irritant
  - Skin Irritation
    - GHS Hazard Phrase H315 – causes skin irritation
    - EU Risk Phrase R37/38 – irritating to respiratory system and skin
- Medium Hazard
  - Eye Irritation
    - GHS New Zealand Category 6.4A (equivalent to GHS Category 2 eye irritant) – irritating to the eye
  - Skin Irritation
    - GHS Japan Category 2 skin irritant
    - GHS New Zealand Category 6.3B (equivalent to GHS Category 3 skin irritant) – mildly irritating to the skin
  - Developmental Toxicity
    - German MAK Pregnancy Risk Group C
  - Systemic Toxicity (single dose)
    - GHS Hazard Phrase H335 – may cause respiratory irritation
    - EU Risk Phrase R37/38 – irritating to the respiratory system and skin
    - GHS Japan Category 3
  - Neurotoxicity
    - Patty's Toxicology – Boyes Neurotoxicants - neurotoxic
    - GHS Hazard Phrase H336 – may cause drowsiness or dizziness
  - Flammability
    - GHS Hazard Phrase H226 – flammable liquid and vapor
    - Quebec CSST – WHMIS classifications – Class B2 – flammable liquid
    - GHS Japan Category 3 flammable liquid

    - GHS New Zealand Category 3.1C (equivalent to GHS Category 3 flammable liquid) – flammable liquids: medium hazard
- Isobutanol is listed on U.S. DOT (2008a) as a Hazard class or division 3 chemical, identification number UN 1212, packaging group III, label code 3 (flammable liquid). It is not listed on U.S. DOT (2008b).

PhysicoChemical Properties of Isobutanol

Isobutanol is a clear, colorless liquid under standard temperature and pressure. It has a vapor pressure of 10.5 mm Hg, indicating that it exists mostly in the vapor phase. It is miscible in water (solubility of 70,000-85,000 mg/L). The log K_{ow} of 1 indicates that it is not likely to bioaccumulate in aquatic biota.

Table 1: Physical and Chemical Properties of Isobutanol (CAS #78-83-1)

Property	Value	Reference
Molecular formula	C4-H10-O	ChemIDplus 2014
SMILES Notation	C(CO)(C)C	ChemIDplus 2014
Molecular weight	74.122 g/mol	ChemIDplus 2014
Physical state	Liquid	ECHA 2014
Appearance	Clear, colorless	ECHA 2014
Melting point	-108°C Less than -90°C (DIN ISO 3016)	ChemIDplus 2014 ECHA 2014
Vapor pressure	10.5 mm Hg at 25°C Less than 16 hPa at 20°C (DIN-EN 13016-2)	ChemIDplus 2014 ECHA 2014
Water solubility	85,000 mg/L at 25°C 70,000 mg/L at 20°C (OECD 105)	ChemIDplus 2014 ECHA 2014
Dissociation constant	Not identified	
Density/specific gravity	0.8017 g/cm^3 at 20°C (DIN 51757)	ECHA 2014
Partition coefficient	Log K_{ow} = 0.76 Log K_{ow} = 1 at 25°C (OECD 117)	ChemIDplus 2014 ECHA 2014

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

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

Isobutanol was assigned a score of Low for carcinogenicity based on modeled data supported by limited experimental data. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when negative data, no structural alerts, and no GHS classification are available (CPA 2012a). The confidence in the score is adjusted as it is based on modeling.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- EC 2000
    - A life-time carcinogenicity study was performed with Wistar rats (19/dose group, sex not specified) administered oral doses of isobutanol (purity not specified) at 0 or 160 mg/kg twice per week via gavage. Survival was reduced from 643 days to 495 days with treatment. The incidence of benign tumor increased from 3 to 9 with treatment, and malignant tumors

of the forestomach, liver, or bone marrow were found in 3/19 rats in the treatment group. No malignancies were observed in the control group.
    - This study has several design deficiencies including the low number of animals used, the use of a single dose, and a lack of reporting on data for historical controls. Therefore, ToxServices discounted the results of this study and based the score for this endpoint on the results of modeling presented below.
- ToxTree 2013
    - Isobutanol does not contain structural alerts for genotoxic or non-genotoxic carcinogenicity (see Appendix D).
- U.S. EPA 2013
    - In general, aliphatic alcohols with molecular weight greater than 20 g/mol (isobutanol has a molecular weight of 74.122 g/mol) have low potential to be carcinogenic. Aliphatic alcohols with a terminal double bond, halogenation, α,β-unsaturation, or mono-substitution with a halogen at the α-carbon are of concern for genotoxic carcinogenicity. As isobutanol does not contain any of these structural groups, it has a low potential for carcinogenicity.

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

Isobutanol was assigned a score of Low for mutagenicity/genotoxicity based on negative results for mutagenicity and clastogenicity in a battery of *in vitro* and *in vivo* tests. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when negative data for mutagenicity and clastogenicity, negative structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2014
    - *In vitro*: Negative results for mutagenicity were obtained in a mammalian cell gene mutation assay. Chinese hamster lung fibroblasts (V79) were exposed to isobutanol (greater than 99% purity) at concentrations up to 107 mM with and without metabolic activation. No increase in the mutation frequency was observed with treatment in the presence or absence of metabolic activation.
    - *In vitro*: Negative results for mutagenicity were obtained in an Ames test conducted according to OECD 471. *Salmonella typhimurium* tester strains TA 98, TA 100, TA 1535, TA 1537, and TA 1538 and *Escherichia coli* tester strain WP2uvrA were exposed to isobutanol (99.7% purity) at 5-5,000 µg/plate with and without metabolic activation. No increase in the mutation frequency was observed with treatment in the presence or absence of metabolic activation.
    - *In vitro*: Negative results for clastogenicity were obtained in a mammalian cell micronucleus test. Chinese hamster lung fibroblasts (V79) were exposed to isobutanol (greater than 99% purity) at 11-53 mM without metabolic activation. No increase in the frequency of micronuclei was observed with treatment in the absence of metabolic activation.
    - *In vitro*: Negative results for mutagenicity were obtained in an Ames test conducted according OECD 471. *S. typhimurium* tester strains TA 97, TA 98, TA 100, TA 1535, and TA 1537 were exposed to isobutanol (greater than 99% purity) at 100-10,000 µg/plate with and without metabolic activation. No increase in the mutation frequency was observed with treatment in the presence or absence of metabolic activation.
    - *In vivo*: Negative results for clastogenicity were obtained in a GLP-compliant micronucleus test conducted according to OECD 474. NMRI mice (5/sex/dose group) were administered single oral doses of isobutanol (99.87% purity) at 0, 500, 1,000 or 2,000 mg/kg via gavage.

After 24 or 48 hours, the animals were sacrificed and bone marrow samples were isolated for quantification of micronuclei. No increase in the frequency of micronuclei was observed with treatment.

- *In vivo*: Negative results for clastogenicity were obtained in a GLP-compliant micronucleus test conducted according to OECD 474. NMRI mice (5 males in low dose, 5 females in high dose) were administered single oral doses of isobutanol (greater than 99% purity) at 0, 500, or 1,500 mg/kg via gavage. After 24 or 48 hours, the animals were sacrificed and bone marrow samples were isolated for quantification of micronuclei. No increase in the frequency of micronuclei was observed with treatment.

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

Isobutanol was assigned a score of Low for reproductive toxicity based on negative results from a rat two-generation reproductive toxicity study. GreenScreen® criteria classify chemicals as a Low hazard for reproductive toxicity when negative data, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2014
  - A GLP-compliant two-generation reproductive toxicity study conducted according to EPA OPPTS 870.3800 was performed with Sprague-Dawley rats (30/sex/dose group) administered whole body inhalation exposures of isobutanol (99.9% purity) vapor at 0, 500, 1,000, or 2,500 ppm (equivalent to 0, 1.5, 3.0, and 7.5 mg/L, respectively). The F_0 parental animals were exposed for at least 10 weeks prior to mating then during mating and gestation. Treatment was suspended on postnatal days 0-4 and then re-initiated on postnatal day 5. The F_1 parental animals were then exposed under the same schedule as the F_0 parental animals. The parental evaluations consisted of clinical signs of toxicity, body weight, food consumption, estrous cyclicity, and sperm parameters. The offspring evaluations included the number and sex of pups, stillbirths, live births, postnatal mortality, presence of gross abnormalities, weight gain, and physical or behavioral abnormalities. No treatment-related effects were observed and the study authors identified a reproductive toxicity NOAEC of 7.5 mg/L.

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

Isobutanol was assigned a score of Low for developmental toxicity based on the lack of developmental toxicity observed in rat and rabbit prenatal developmental toxicity studies. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when negative results, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:*
    - German MAK Pregnancy Risk Group C
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2014
  - *Inhalation*: A GLP-compliant prenatal developmental toxicity test conducted according to OECD 414 was performed with pregnant female Wistar rats (25/dose group) administered whole body inhalation exposures of isobutanol (99.8% purity) vapor at 0, 0.5, 2.5, or 10 mg/L for 6 hours/day on gestational days (GD) 6-15. The animals were sacrificed on GD 20. Maternal evaluations consisted of clinical signs of toxicity, body weight, and ovarian

and uterine content. Fetal examinations consisted of evaluating the incidences of external, visceral, and skeletal malformations. No maternal toxicity, embryotoxicity, or teratogenicity was observed with treatment, and the study authors identified a maternal toxicity and developmental toxicity NOAEC of 10 mg/L.

- *Inhalation*: A GLP-complaint prenatal developmental toxicity test conducted according to OECD 414 was performed with pregnant female Himalayan rabbits (15/dose group) administered whole body exposures of isobutanol (99.8% purity) vapor at 0, 0.5, 2.5, or 10 mg/L for 6 hours/day on GD 7-19. The animals were sacrificed on GD 29. The maternal observations included clinical signs of toxicity, body weight, and ovarian and uterine content. The fetal examinations consisted of evaluating the incidence of external, visceral, and skeletal abnormalities. A slight decrease in maternal body weight gain was observed in the high concentration group. No treatment-related embryotoxicity or teratogenicity was observed. The study authors identified a maternal NOAEC and LOAEC of 2.5 and 10 mg/L, respectively, based on the decreased body weight observed in the high concentration group. A developmental toxicity NOAEC of 10 mg/L was identified based on the lack of teratogenicity and embryotoxicity observed with treatment.

Endocrine Activity (E) Score (H, M, or L): DG
Isobutanol was assigned a score of Data Gap for endocrine disruption based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- 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.
- High Throughput Screening (HTS) Data
  - HTS data were identified for isobutanol using PubChem (http://pubchem.ncbi.nlm.nih.gov/).
  - The data included the following results:
    - Isobutanol was active in 0/4 androgen receptor agonist assays and 0/5 androgen receptor antagonist assays.
    - Isobutanol was active in 0/4 estrogen receptor-alpha agonist assays and 0/7 estrogen receptor-alpha antagonist assays.
    - Isobutanol was active in 0/2 thyroid receptor agonist assays and 0/4 thyroid receptor antagonist assays.
    - Isobutanol was active in 0/2 thyroid stimulating hormone receptor agonist assays. No data were available for thyroid stimulating hormone receptor antagonist assays.
- These data are insufficient to assign a score for endocrine activity.

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

Isobutanol was assigned a score of Low for acute toxicity based on oral LD_{50} values of at least 2,460 mg/kg, dermal LD_{50} values of greater than 2,000 mg/kg, and a 4-hour inhalation vapor LC_{50} value of 24.6 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral and dermal LD_{50} values are greater than 2,000 mg/kg and inhalation vapor LC_{50} values are greater than 20 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ChemIDplus 2014
  - *Oral*: LD_{50} (rat) = 2,460 mg/kg
  - *Dermal*: LD_{50} (rabbit) = 3,400 mg/kg
- ECHA 2014
  - *Oral*: LD_{50} (Sprague-Dawley rat) = greater than 2,830 mg/kg for males and 3,350 mg/kg for females (GLP-compliant, OECD 401)
  - *Inhalation*: 4-hour vapor LC_{50} (Sherman rat) = 24.6 mg/L (non-GLP-compliant)
  - *Inhalation*: 6-hour whole body vapor LC_{50} (Sprague-Dawley rat) = greater than 18.18 mg/L (GLP-compliant, 40 CFR 799 and 40 CFR 798.1150)
  - *Dermal*: LD_{50} (New Zealand White rabbit) = greater than 2,000 mg/kg for males and 2,460 mg/kg for females (GLP-compliant, OECD 402)

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

Isobutanol was assigned a score of Moderate for systemic toxicity (single dose) based on authoritative listings. GreenScreen® criteria classify chemicals as a Moderate hazard for systemic toxicity (single dose) when they are associated with GHS Hazard Phrase H335 and EU Risk Phrase R37 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:*
    - GHS Hazard Phrase H335 – may cause respiratory irritation
    - EU Risk Phrase R37/38 – irritating to the respiratory system and skin
  - *Screening:*
    - GHS Japan Category 3 systemic toxicant (single dose)
- ECHA 2014
  - *Oral*: In the acute oral toxicity study that identified an oral LD_{50} of 3,350 mg/kg and greater than 2,830 mg/kg in female and male Sprague-Dawley rats, respectively, clinical signs of toxicity included piloerection, sluggishness, unsteady gait, lacrimation, slow breathing, prostration, and a trace to large amount of blood in the urine. Slight body weight loss was observed within 7 to 14 days in several females. At necropsy, the animals that died prior to the scheduled sacrifice exhibited discolored and/or mottled lungs that were bright to dark red in color, tan to dark maroon and/or mottled livers, gray and/or yellow discolored stomachs, liquid-filled stomach, dark red and/or gray areas on the intestines, red to brown kidneys, and a large amount of blood in the urine. No gross lesions were observed in animals that survived to the scheduled sacrifice. Kidneys and urinary bladders were evaluated microscopically but no treatment-related lesions were observed.
  - *Inhalation*: No systemic toxicity data were presented for the acute inhalation toxicity study that identified an LC_{50} of 24.6 mg/L.
  - *Inhalation*: In the acute inhalation toxicity study that identified an inhalation LC_{50} of greater than 18.18 mg/L, labored respiration were observed at 9.09 and 18.18 mg/L, while single

males exhibited prostration or lacrimation at 18.18 mg/L. Only hypoactivity was observed at 4.54 mg/L. No treatment-related gross lesions were observed at necropsy.

- *Dermal*: Dermal reactions observed in the acute dermal toxicity test that identified an LD_{50} of greater than 2,000 and 2,460 mg/kg for males and females, respectively, included erythema, edema, necrosis, ecchymoses (subcutaneous extravasation of blood), ulceration, fissuring, desquamation, scabs, and alopecia. Clinical signs of toxicity included prostration, sluggishness, slow and/or labored breathing, reddened eyes, as well as single instances of wetness of the periurogenital fur, unsteady gait, lacrimation, and transient tumors. Weight loss by day 7 was observed in several animals but most recovered by day 14. At necropsy, animals that died prior to the scheduled sacrifice exhibited red patches or areas on the lungs, and discolored and/or mottled livers (tan or darkened), and sporadic cases of dark red lungs, gas-filled intestines, darkened spleens, enlarged adrenals, dark red foci on the spleen, kidneys with a pitted surface, and a trace amount of blood in the urine. Animals that survived to the scheduled sacrifice exhibited sporadic cases of red to dark red patches or areas on the lungs, gas-filled intestines, mottled dark maroon and light tan spleens, tan kidneys, and kidneys with pitted surfaces.

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

Isobutanol was assigned a score of Low for systemic toxicity (repeated dose) based on an oral NOAEL of 1,450 mg/kg/day and inhalation vapor NOAECs of 5.36 to 7.5 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when oral NOAELs are greater than 100 mg/kg/day and inhalation vapor NOAECs are greater than 1 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2014
  - *Oral*: A GLP-compliant oral subchronic toxicity test conducted according to OECD 408 was performed with Wistar rats (10/sex/dose group) provided drinking water containing isobutanol (99.8% purity) at 0, 1,000, 4,000, or 16,000 ppm (equivalent to 0, 80, 340, and 1,450 mg/kg/day, respectively) for 90 days. The animals were evaluated for clinical signs of toxicity, body weight, food and water consumption, hematology, clinical chemistry, gross pathology, and histopathology. No treatment-related effects on these parameters were observed with treatment and the study authors identified a NOAEL of 1,450 mg/kg/day.
  - *Inhalation*: A GLP-compliant inhalation subchronic toxicity test conducted according to Guideline 82-7, Subdivision F (Neurotoxicity Screening Battery) was performed with Sprague-Dawley rats (10-20/sex/concentration group) administered whole body inhalation exposures to isobutanol (purity not specified) vapors at 0, 250, 1,000, or 2,500 ppm (equivalent to 0, 0.75, 2.0, and 7.5 mg/L, respectively) for 6 hours/day, 5 days/week for 102 days. The equivalent concentrations for a 7-day/week exposure frequency were 0, 0.54, 1.43, and 5.36 mg/L, respectively. The animals were evaluated for clinical signs of toxicity, body weight, food consumption, hematology, clinical chemistry, gross pathology, and histopathology. No treatment-related effects were observed with treatment and the study authors identified a NOAEC of 7.5 mg/L (equivalent to 5.36 mg/L for a 7-day/week exposure frequency).
  - *Inhalation*: A GLP-compliant systemic toxicity test conducted according to EPA OPPTS 870.3800 was performed with Sprague-Dawley rats (30/sex/concentration group) administered whole body inhalation exposures isobutanol (purity not specified) vapor at 0, 500, 1,000, or 2,500 ppm (equivalent to 0, 1.5, 3.0, and 7.5 mg/L, respectively) for 17

weeks. The animals were evaluated for clinical signs of toxicity, body weight, food consumption, gross pathology, and histopathology. No treatment-related effects were observed on these parameters and the study authors identified a NOAEC of 7.5 mg/L.

Neurotoxicity (N)

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

Isobutanol was assigned a score of Moderate for neurotoxicity (single dose) based on authoritative lists. GreenScreen® criteria classify chemicals as a Low to Moderate hazard for neurotoxicity (single dose) when they are associated with GHS Hazard Phrase H336 and EU Risk Phrase R67 (CPA 2012a). ToxServices assigned a Moderate score based on the central nervous system depression observed in animal studies following single inhalation exposures.

- Authoritative and Screening Lists
  - *Authoritative:*
    - GHS Hazard Phrase H336 – may cause drowsiness or dizziness
    - EU Risk Phrase R67 – vapors may cause drowsiness and dizziness
  - *Screening:*
    - Patty's Toxicology – Boyes Neurotoxicants - neurotoxic
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- ECHA 2014
  - *Inhalation*: Generalized depression of the central nervous system was observed following single inhalation exposures of 9.09 and 18.18 mg/L in the acute inhalation toxicity study that identified an LC_{50} of greater than 18.18 mg/L.
  - *Inhalation*: A GLP-compliant neurotoxicity screening battery test conducted according to EPA OTS 798.6050 was performed with Sprague-Dawley rats (10/sex/concentration group) administered a single 6-hour inhalation exposure of isobutanol (greater than 99.9% purity) vapor at 0, 1,555, 3,003, or 5,961 ppm (equivalent to 0, 4.71, 9.10, and 18.07 mg/L, respectively[6]). The animals were evaluated in a FOB and motor activity test before the exposure, shortly after the exposure and 1, 7, and 14 days after the exposure. A slight and transient, but statistically significant, decrease in the motor activity was observed in high concentration males and females immediately after exposure. In the FOB, one male rat in the high concentration group exhibited an abnormal gait. No other treatment-related effects were observed.

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

Isobutanol was assigned a score of Low for neurotoxicity (repeated dose) based on the lack of neurotoxicity observed in repeat inhalation exposure studies. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when negative data, no structural alerts, and no GHS classification are available (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:*
    - Patty's Toxicology – Boyes Neurotoxicants - neurotoxic
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- ECHA 2014
  - *Inhalation*: A GLP-compliant inhalation subchronic toxicity test conducted according to Guideline 82-7, Subdivision F (Neurotoxicity Screening Battery) was performed with

[6] The equivalent concentrations in mg/L were determined using the following equation: mg/L = (ppm x molecular weight) / 24,450. The molecular weight of isobutanol is 74.122 g/mol

Sprague-Dawley rats (10-20/sex/concentration group) administered inhalation exposures to isobutanol (99.9% purity) vapors at 0, 250, 1,000, or 2,500 ppm (equivalent to 0, 0.78, 3.16, and 7.72 mg/L, respectively) for 6 hours/day, 5 days/week for 102 days. The equivalent concentrations for a 7-day/week exposure frequency were 0, 0.56, 2.26, and 5.51 mg/L, respectively. The animals were evaluated in a functional observational battery (FOB) and a locomotor activity test, and neuropathological evaluations were performed at necropsy. No treatment-related effects were observed on these parameters and the study authors identified a NOAEC of 7.5 mg/L (equivalent to 5.51 mg/L for a 7-day/week exposure frequency).

- *Inhalation*: A GLP-compliant neurotoxicity test conducted according to Guideline: 85, Subdivision F –Schedule-Controlled Operant Behavior (SCOB) was performed with male Sprague Dawley rats (10/concentration group) administered inhalation exposures of isobutanol (99.9% purity) vapor at 0, 250, 1,000, or 2,500 ppm (equivalent to 0, 0.78, 3.16, and 7.72 mg/L, respectively) for 6 hours/day, 5 days/week for 13 weeks. The equivalent concentrations for a 7-day/week exposure frequency were 0, 0.56, 2.26, and 5.51 mg/L, respectively. The animals were evaluated in the SCOB apparatus after a training period to establish the baseline performance prior to beginning of the exposure period. No treatment-related effect was observed on the SCOB and the study authors identified a neurotoxicity NOAEC of 7.72 mg/L (equivalent to 5.51 mg/L for a 7-day/week exposure frequency).

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

Isobutanol was assigned a score of Low for skin sensitization based on modeled data for skin sensitization. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when negative data, no structural alerts, and no GHS classification are available (CPA 2012a). The confidence in the score is adjusted as it is based on modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- No data were identified for this endpoint. ToxServices used prediction methods to estimate the skin sensitization potential of isobutanol.
  - OECD 2013
    - Isobutanol is predicted to not be a skin sensitizer using the OECD Toolbox model using the read-across methodology (see Appendix F).
  - Payne and Walsh 1994
    - Isobutanol is not predicted to be a skin sensitizer based on the absence of structural alerts identified by Payne and Walsh (1994) (see Appendix G).
  - ToxTree 2013
    - Isobutanol is predicted to not be a skin sensitizer using the ToxTree model using decision tree methodology. This chemical has not been identified as a substrate for any of the 5 electrophilic mechanisms known to produce a skin sensitization reaction (see Appendix H).
  - VEGA 2012
    - Isobutanol is predicted to not be a skin sensitizer using the VEGA model (see Appendix I).
- In summary, all four prediction tools estimate that isobutanol is not a skin sensitizer. Therefore, ToxServices concludes that isobutanol is not likely to be a skin sensitizer.

Respiratory Sensitization (SnR) Group II* Score (H, M, or L): DG
Isobutanol was assigned a score of Data Gap for respiratory sensitization based on the lack of data identified for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- No data were identified for this endpoint.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M, or L): H
Isobutanol was assigned a score of High for skin irritation/corrosivity based on authoritative listings. GreenScreen® criteria classify chemicals as a High hazard for skin irritation/corrosivity when they are associated with GHS Hazard Phrase H315 or EU Risk Phrase R38 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:*
    - GHS Hazard Phrase H315 – causes skin irritation
    - EU Risk Phrase R37/38 – irritating to respiratory system and skin
  - *Screening:*
    - GHS Japan Category 2 skin irritant
    - GHS New Zealand Category 6.3B (equivalent to GHS Category 3 skin irritant) – mildly irritating to the skin
- ECHA 2014
  - A GLP-complaint dermal irritation test conducted according to OECD 404 was performed with New Zealand White rabbits (3 total, sex not specified) administered dermal applications of 0.5 mL undiluted isobutanol (greater than 99.5% purity) to shaved skin under semi-occlusive dressing for an unspecified amount of time. Reactions were scored at 24, 48, and 72 hours after removal of the dressing. An observation period of 48 hours followed the removal of the dressing. The mean erythema score was 0.44/4 (individual scores of 0, 0.67, and 0.67 out of 4) and the mean edema score was 0.11/4 (individual scores of 0, 0, and 0.33 out of 4). Dry and rough skin was observed in all three animals at the 48 and 72 hour readings. The study authors concluded that isobutanol was not irritating to the skin in this study.
  - A GLP-compliant dermal irritation test conducted according to OECD 404 was performed with New Zealand White rabbits (3/sex) administered dermal applications of 0.5 mL undiluted isobutanol (~99.9% purity) to shaved skin under occlusive dressing for 4 hours. Skin reactions were scored at 1, 24, 48, and 72 hours and at 7 and 14 days. The mean erythema score was 1.2/2 and the mean edema score was 1/2. The erythema and edema effects were not fully reversible by the end of the 14 day observation period. The study authors concluded that isobutanol was moderately irritating to the skin.

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M, or L): vH
Isobutanol was assigned a score of Very High for eye irritation/corrosivity based on authoritative listings. GreenScreen® criteria classify chemicals as a Very High hazard for eye irritation/corrosivity when they are associated with GHS Hazard Phrase H318 or EU Risk Phrase R41 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:*
    - GHS Hazard Phrase H318 – causes serious eye damage
    - EU Risk Phrase R41 – risk of serious damage to eyes
  - *Screening:*

  - GHS Japan Category 2A eye irritant
  - GHS New Zealand Category 6.4A (equivalent to GHS Category 2 eye irritant) – irritating to the eye
- ECHA 2014
  - A GLP-compliant eye irritation test conducted according to OECD 405 was performed with New Zealand White rabbits (3 total, sex not specified) administered ocular instillations of 0.1 mL undiluted isobutanol (at least 99.5% purity). After 24 hours, the eyes were washed with physiological saline. The eyes were scored at 24, 48, and 72 hours after instillation and the animals were observed for 14 days. The mean corneal score was 1/4 (individual scores of 0, 1.33, and 1.67 out of 4) with the effects in one animal not being fully reversible, the mean iris score was 0.33/2, the mean conjunctival score was 2.55/3 (individual scores of 3, 2.33, and 2.33 out of 3) with the effects in one animal not being fully reversible, and the mean chemosis score was 1.55/4 (individual scores of 2.33, 1, and 1.33). Based on the irreversible effects to the eye, the study authors classified isobutanol as a GHS Category 1 eye irritant.

Ecotoxicity (Ecotox)

Acute Aquatic Toxicity (AA) Score (vH, H, M, or L): L
Isobutanol was assigned a score of Low for acute aquatic toxicity based on acute aquatic toxicity values of at least 593 mg/L. GreenScreen® criteria classify chemicals as a Low hazard for acute aquatic toxicity when acute aquatic toxicity values are greater than 100 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2014
  - 96-hour LC_{50} (*Pimephales promelas*, fathead minnow) = 1,430 mg/L (non-GLP-compliant)
  - 48-hour mobility EC_{50} (*Daphnia pulex*) = 1,100 mg/L (non-GLP-compliant)
  - 72-hour growth rate EC_{50} (*Pseudokirchnerella subcapitata*, green algae) = 1,799 mg/L (GLP-compliant, OECD 201)
  - 72-hour cell number EC_{50} (*Pseudokirchnerella subcapitata*, green algae) = 593 mg/L (GLP-compliant, OECD 201)
  - 72-hour biomass EC_{50} (*Pseudokirchnerella subcapitata*, green algae) = 632 mg/L (GLP-compliant, OECD 201)

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): L
Isobutanol was assigned a score of Low for chronic aquatic toxicity based on chronic aquatic toxicity values of 20 mg/L and greater. GreenScreen® criteria classify chemicals as a Low hazard for chronic aquatic toxicity when chronic aquatic toxicity values are greater than 10 mg/L (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2014
  - 21-day reproduction NOEC (*Daphnia magna*) = 20 mg/L (non-GLP-compliant)
  - 72-hour cell number NOEC (*Pseudokirchnerella subcapitata*, green algae) = less than 53 mg/L (GLP-compliant, OECD 201)
  - 72-hour biomass NOEC (*Pseudokirchnerella subcapitata*, green algae) = 53 mg/L (GLP-compliant, OECD 201)

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *vL*
Isobutanol was assigned a score of Very Low for persistence based on the prediction that it will meet the 10-day biodegradation window. GreenScreen® criteria classify chemicals as a Very Low hazard for persistence when chemicals meet the 10-day biodegradation window (CPA 2012a). The score is adjusted as the 10-day biodegradation window prediction is based on modeling.

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2014
  - A non-GLP-compliant ready biodegradation test conducted according to OECD 301 D (closed bottle test) was performed with an inoculum seed (coarse-filtered mixture of domestic treatment plant effluents and rich soil microorganisms) exposed to isobutanol (purity not specified) at an unspecified concentration for 28 days. The level of degradation was 14% after 5 days and 74% after 28 days. The authors concluded that isobutanol was readily biodegradable in this test. No details about the 10-day window were provided.
  - A non-GLP-compliant ready biodegradation test conducted according to OECD 301 C (Modified MITI test) was performed with activated sludge exposed to isobutanol (purity not specified) at 100 mg/L. After 14 days, the level of degradation was 90-100%. The study authors concluded that isobutanol was readily biodegradable in this test. No details about the 10-day window were provided.
- U.S. EPA 2012
  - The BIOWIN modeling Ready Biodegradable Predictor indicates that isobutanol is expected to be readily biodegradable (see Appendix J). Fugacity modeling predicts 51.9% will partition to soil with a half-life of 30 days, 44.2% will partition to water with a half-life of 15 days, and 3.86% will partition to air with a half-life of 37.3 hours.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
Isobutanol was assigned a score of Very Low for bioaccumulation based on a measured log K_{ow} of 1. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when log K_{ow} values are no greater than 4 (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:* Not listed on any authoritative lists for this endpoint.
  - *Screening:* Not listed on any screening lists for this endpoint.
- ECHA 2014
  - Isobutanol has a log K_{ow} of 1 as measured in a GLP-compliant OECD 117 test.
- U.S. EPA 2012
  - BCFBAF predicts a BCF of 1.659 based on a measured log K_{ow} of 1.00 (see Appendix J).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Isobutanol was assigned a score of Low for reactivity based on the surrogate triethylene glycol not being classified as reactive under GHS criteria (2013). GreenScreen® criteria classify chemicals as a Low hazard for reactivity when no GHS classification can be assigned (CPA 2012a). The confidence in the classification is adjusted as it is not based on data or an authoritative list.

- Authoritative and Screening Lists
    - *Authoritative:* Not listed on any authoritative lists for this endpoint.
    - *Screening:* Not listed on any screening lists for this endpoint.
- Sigma-Aldrich 2014
    - A material safety data sheet for isobutanol states that it has a reactivity rating of 0 from the NFPA ("Normally stable, even under fire exposure conditions, and is not reactive with water") and HMIS ("Materials that are normally stable, even under fire conditions, and will not react with water, polymerize, decompose, condense, or self-react. Non-explosives").
- Based on the MSDS identified above stating that isobutanol is nonreactive, ToxServices did not classify isobutanol as a reactive chemical based on GHS criteria (UN 2013).

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

Isobutanol was assigned a score of Moderate for flammability based on authoritative lists. GreenScreen® criteria classify chemicals as a Moderate hazard for flammability when they are associated with GHS Hazard Phrase H226 (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:*
        - GHS Hazard Phrase H226 – flammable liquid and vapor
        - EU Risk Phrase R10 – flammable liquid
    - *Screening:*
        - Quebec CSST – WHMIS classifications – Class B2 – flammable liquid
        - GHS Japan Category 3 flammable liquid
        - GHS New Zealand Category 3.1C (equivalent to GHS Category 3 flammable liquid) – flammable liquids: medium hazard
- ECHA 2014
    - Isobutanol has a flash point of 31°C at 1,013 hPa as measured in a non-GLP-compliant ISO 2719:2002 test.
        - Based on the flash point of 31°C, ToxServices classified isobutanol as a GHS Category 3 flammable liquid. GHS Category 3 flammable liquids have flash points of at least 23°C and up to 60°C (UN 2013).

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APPENDIX A: Hazard Benchmark Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(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 Isobutanol (CAS #78-83-1)

TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING

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 / Isobutanol / 78-83-1	*L*	L	L	L	DG	L	M	L	M	L	*L*	DG	H	vH	L	L	*vL*	vL	*L*	M

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Isobutanol	2

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

Table 6

Chemical Name	Final GreenScreen® Benchmark Score
Isobutanol	2

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												
2	Yes	Yes	Yes	Yes	Yes							2
3												
4												

APPENDIX C: Pharos Output for Isobutanol (CAS #78-83-1)

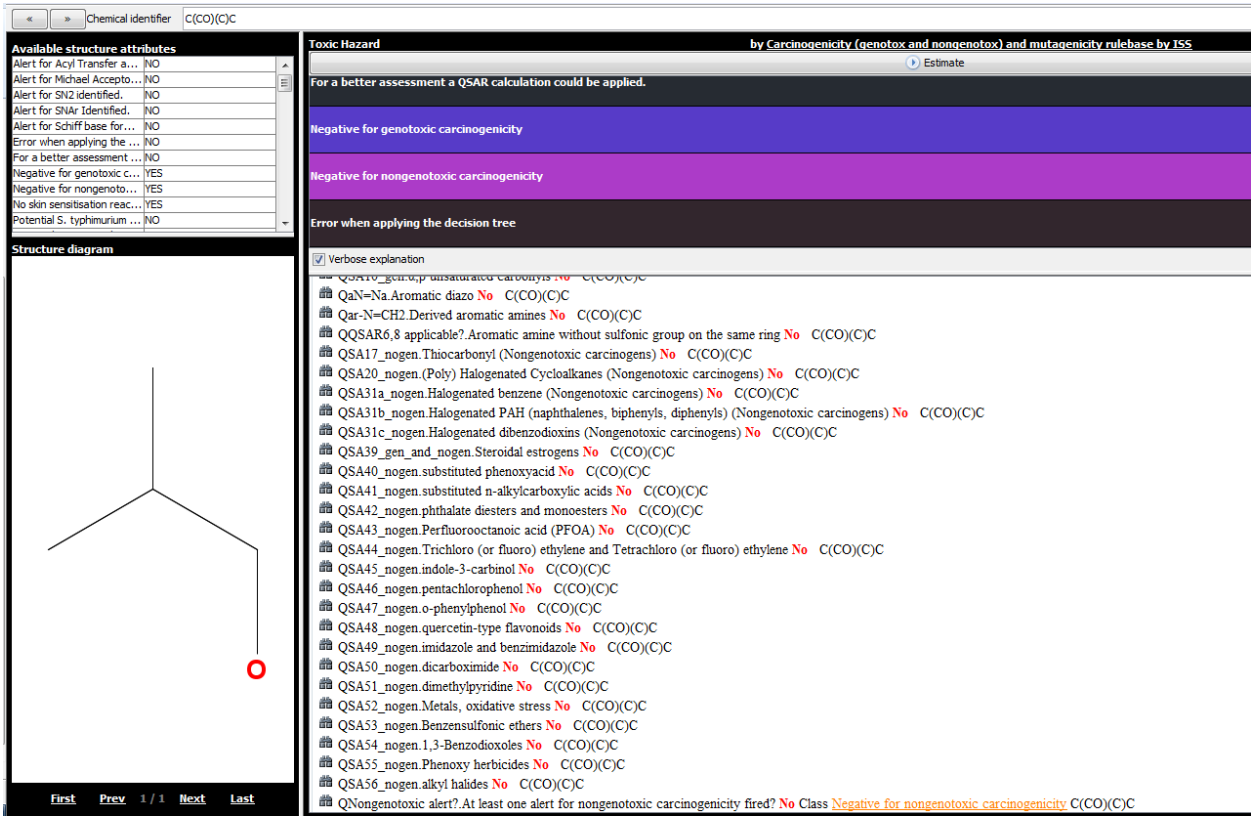
ISOBUTYL ALCOHOL

CAS RN: 78-83-1

Detailed Direct Hazard Listings — Quickscreen

EYE IRRITATION	EC - CLP/GHS Hazard Statements (EU H-Statements) H318 Causes serious eye damage - GreenScreen Benchmark Unspecified (LT-U) - HPD
EYE IRRITATION	EC - Risk Phrases (EU R-Phrases) R41: Risk of serious damage to eyes. - GreenScreen Benchmark Unspecified (LT-U) - HPD
EYE IRRITATION	Japan METI/MOE - GHS Classifications (GHS-Japan) Serious eye damage / eye irritation - Category 2A - GreenScreen Benchmark Unspecified (LT-U)
DEVELOPMENTAL	German MAK - List of Substances (MAK) Pregnancy Risk Group C - GreenScreen Benchmark Unspecified (LT-U)
RESPIRATORY	EC - Risk Phrases (EU R-Phrases) R37: Irritating to respiratory system. - GreenScreen Benchmark Unspecified (LT-U)
NEUROTOXICITY	EC - Risk Phrases (EU R-Phrases) R67: Vapours may cause drowsiness and dizziness - GreenScreen Benchmark Unspecified (LT-U)
NEUROTOXICITY	EC - CLP/GHS Hazard Statements (EU H-Statements) H336 May cause drowsiness or dizziness - GreenScreen Benchmark Unspecified (LT-U)
NEUROTOXICITY	Pattys Toxicology - Boyes Neurotoxicants (Boyes-N) Neurotoxic - 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	Japan METI/MOE - GHS Classifications (GHS-Japan) Acute toxicity (dermal) - Category 5 - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Acute toxicity (oral) - Category 5 - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Acute toxicity (inhalation: vapor) - Category 5 - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Specific target organs/systemic toxicity following single exposure - Category 3 - GreenScreen Benchmark Unspecified (LT-U)
EYE IRRITATION	New Zealand HSNO/GHS (GHS-New Zealand) 6.4A - Irritating to the eye - GreenScreen Benchmark Unspecified (LT-U)
SKIN IRRITATION	EC - Risk Phrases (EU R-Phrases) R38: Irritating to skin. - GreenScreen Benchmark Unspecified (LT-U) - HPD
SKIN IRRITATION	EC - CLP/GHS Hazard Statements (EU H-Statements) H315 Causes skin irritation - GreenScreen Benchmark Unspecified (LT-U) - HPD
SKIN IRRITATION	New Zealand HSNO/GHS (GHS-New Zealand) 6.3B - Mildly 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)
ORGAN TOXICANT	EC - CLP/GHS Hazard Statements (EU H-Statements) H335 May cause respiratory irritation - GreenScreen Benchmark Unspecified (LT-U)
FLAMMABLE	EC - CLP/GHS Hazard Statements (EU H-Statements) H226 Flammable liquid and vapour - GreenScreen Benchmark Unspecified (LT-U) - occupational hazard only
FLAMMABLE	Québec CSST - WHMIS Classifications (WHMIS) Class B2 - Flammable liquids - GreenScreen Benchmark Unspecified (LT-U)
FLAMMABLE	New Zealand HSNO/GHS (GHS-New Zealand) 3.1C - Flammable Liquids: medium hazard - GreenScreen Benchmark Unspecified (LT-U)
FLAMMABLE	Japan METI/MOE - GHS Classifications (GHS-Japan) Flammable liquids - Category 3 - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	New Zealand HSNO/GHS (GHS-New Zealand) 6.1E (dermal) - Acutely toxic - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	New Zealand HSNO/GHS (GHS-New Zealand) 6.1E (oral) - Acutely toxic - GreenScreen Benchmark Unspecified (LT-U)
MAMMALIAN	Japan METI/MOE - GHS Classifications (GHS-Japan) Aspiration hazard - Category 2 - Not included in GreenScreen - occupational hazard only
FLAMMABLE	EC - Risk Phrases (EU R-Phrases) R10: Flammable LIQUID - Not included in GreenScreen
RESTRICTED LIST	German FEA - Substances Hazardous to Waters (VwVwS) Class 1 Low Hazard to Waters - GreenScreen Benchmark Unspecified (LT-U) - occupational hazard only
RESTRICTED LIST	Environment Canada - Domestic Substances List (DSL) Inherently Toxic to Humans: DSL substances that meet human health categorization criteria - GreenScreen Benchmark Unspecified (LT-U)

APPENDIX D: ToxTree Carcinogenicity Results for Isobutanol (CAS #78-83-1)



APPENDIX E: Oncologic Carcinogenicity Results for Isobutanol (CAS #78-83-1)

OncoLogic Justification Report

SUMMARY :

CODE NUMBER : 78831

SUBSTANCE ID :

JUSTIFICATION:

Aliphatic Alcohols*

Aliphatic alcohols (R-OH) may be loosely divided into (a) high M.W. alcohols (C > 20), (b) medium size alcohols (C = 6 to 20), and (c) low M.W. alcohols (C < 6). In general, high M.W. aliphatic alcohols have low potential to be significant carcinogens. A number of medium size alcohols (e.g., CF3(CF2)6CH2OH; 2-ethylhexanol) that can be oxidized to metabolically persistent aliphatic carboxylic acids (e.g., perfluorinated fatty acid like perfluoroooctanoic; ω – 1 branched fatty acids like 2-ethylhexanoic acid) are potential nongenotoxic carcinongens. Most of these are medium sized with the most potent ones peaking around 7 – 9 carbons. Low M.W. alcohols, (especially methanol and ethanol) are of carcinogenic concern because of possible oxidation to reactive aldehydes. The concern for carcinogenic risk is especially higher in individuals who are genetically deficient in aldehyde dehydrogenase which detoxifies aldehydes to carboxylic acids. A number of low M.W. tertiary alcohols (e.g., t-butyl, t-amyl) have been shown to induce kidney tumors in male rats by a mechanism (alpha-2-mu nephropathy) not relevant to humans. In addition, low M.W. alcohols with

(i) terminal double bond or Cl/Br/I,
(ii) α,β-unsaturation,
(iii) monosubstitution with Cl/Br/I at α-carbon are of concern as potential genotoxic carcinogens.

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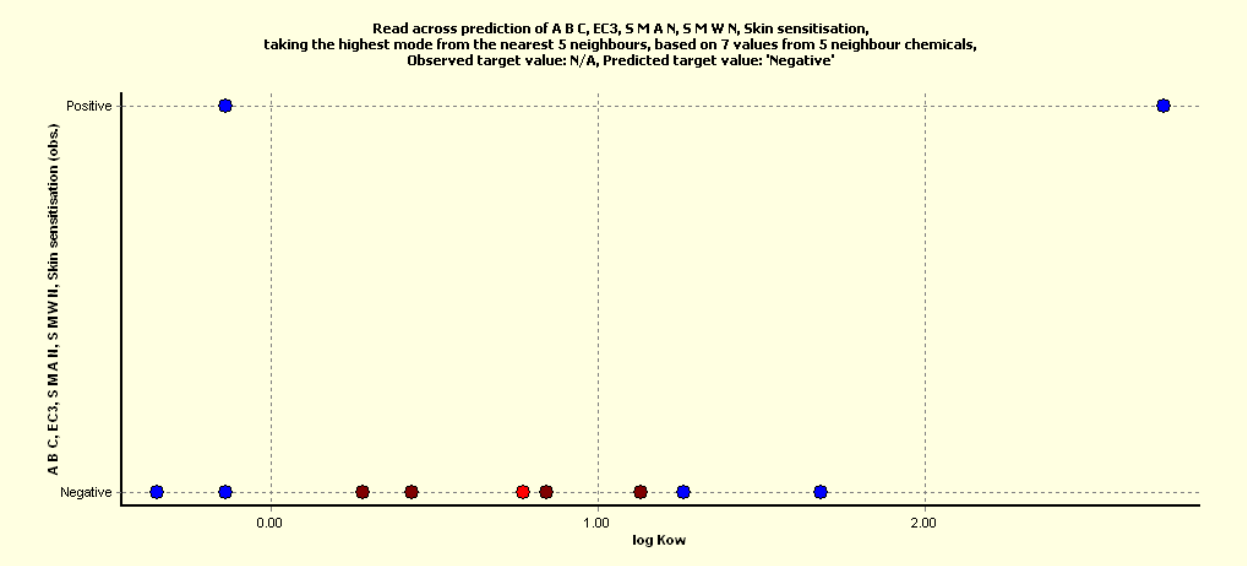
*This is only a brief summary of the structure activity relationships (SAR) knowledge of this class. A more detailed decision logic will be developed in future version of OncoLogic. If the compound of your interest has been tested in any short-term predictive tests, the results of the tests should be entered into OncoLogic's Functional Arm to give an evaluation of carcinogenic potential based on short-term predictive tests.

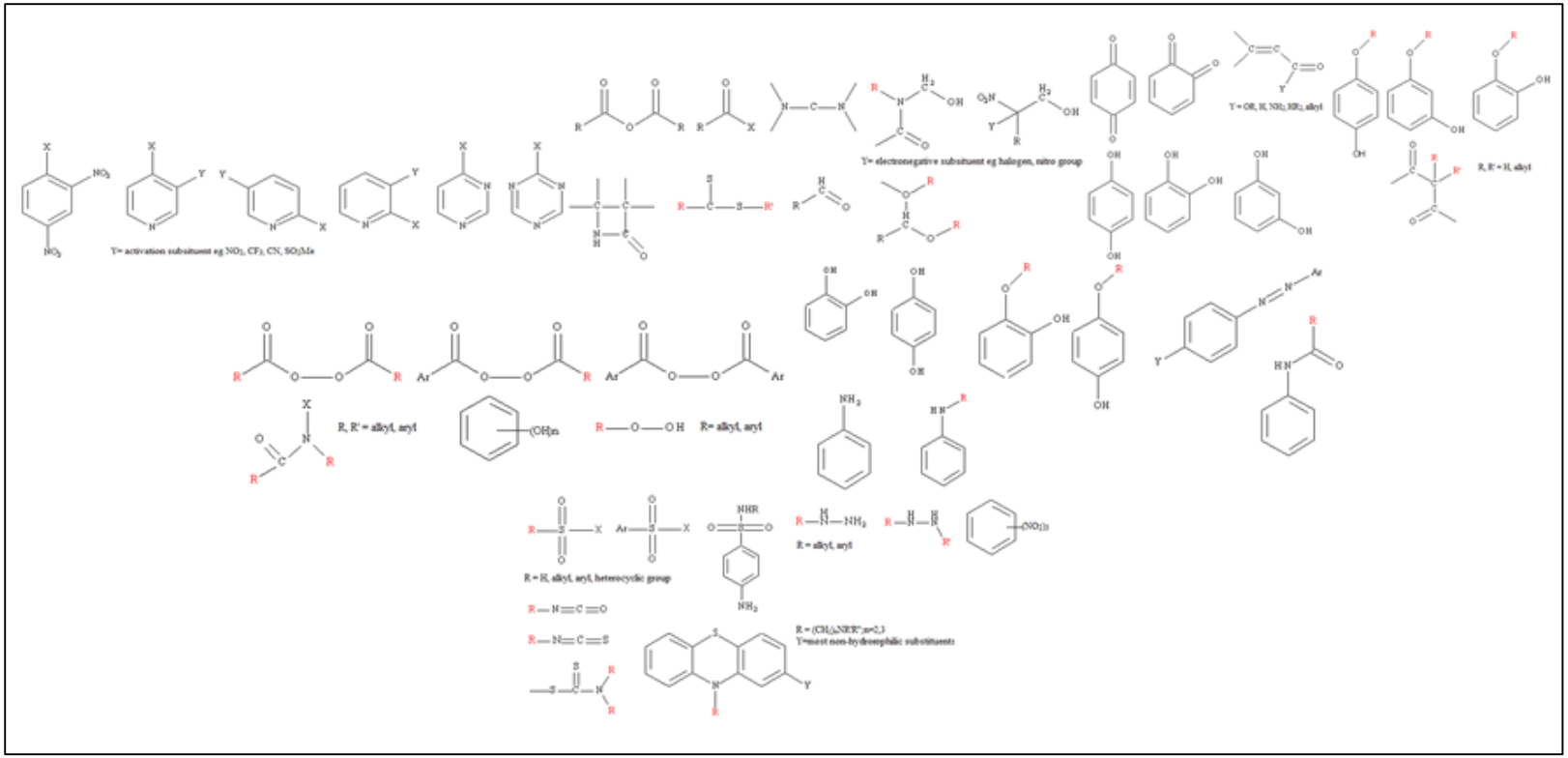
APPENDIX F: OECD Toolbox Skin Sensitization Results for Isobutanol (CAS #78-83-1)

Isobutanol was assessed as a neutral organic chemical under the U.S. EPA New Chemicals Category. Low quality analogs were removed from the read-across using 1.) structural similarity at least 20% and 2.) organic functional groups.

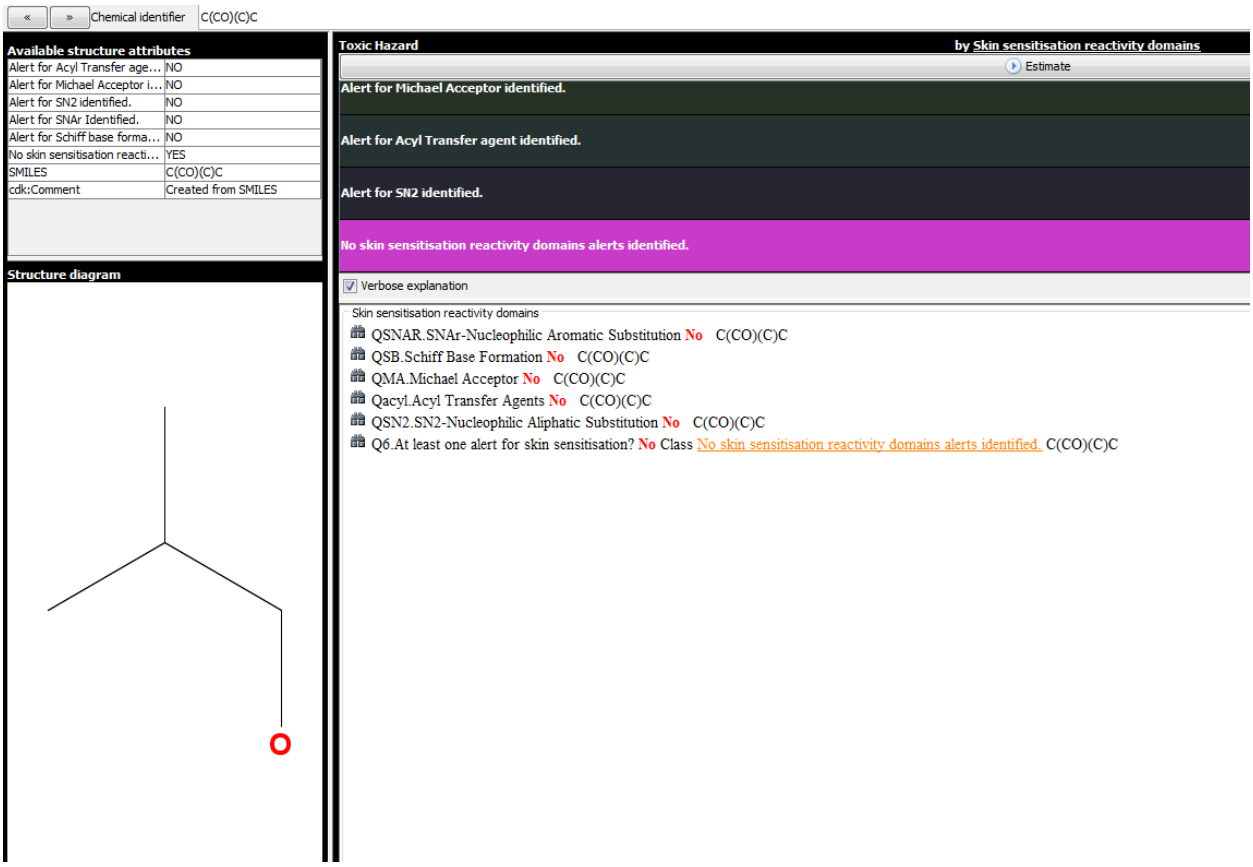


APPENDIX G: Known Structural Alerts for Skin Sensitization

Below are known structural alerts for skin sensitizers (Payne and Walsh 1994). Isobutanol possesses none of the known structural alerts for skin sensitization.



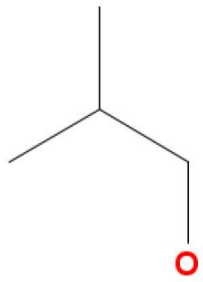
APPENDIX H: ToxTree Skin Sensitization Results for Isobutanol (CAS #78-83-1)



APPENDIX I: VEGA Skin Sensitization Results for Isobutanol (CAS #78-83-1)

1. Prediction Summary

Prediction for compound 1 (Molecule 1)

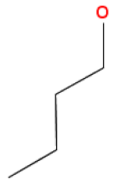


Prediction: Reliability:

Model assessment: Prediction is NON-Sensitizer, the result appears reliable. Anyhow, you should check it through the evaluation of the information given in the following sections.

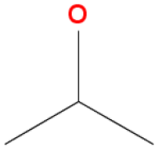
Compound: 1
Compound SMILES: OCC(C)C
Experimental value: -
Prediction: NON-Sensitizer
O(Active): 0.43
O(Inactive): 0.57
Reliability: Compound is in model Applicability Domain
Remarks for the prediction:
none

3.1 Applicability Domain:
Similar Compounds, with Predicted and Experimental Values



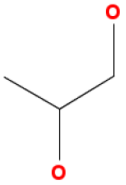
CAS: 71-36-3
Dataset id: 42 (training set)
SMILES: OCCCC
Similarity: 0.933

Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer



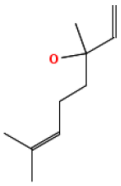
CAS: 67-63-0
Dataset id: 122 (training set)
SMILES: OC(C)C
Similarity: 0.906

Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer



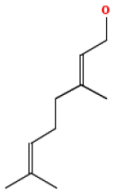
CAS: 57-55-6
Dataset id: 184 (training set)
SMILES: OCC(O)C
Similarity: 0.858

Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer



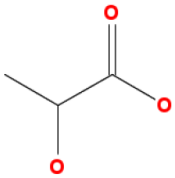
CAS: 78-70-6
Dataset id: 130 (training set)
SMILES: OC(C=C)(C)CCC=C(C)C
Similarity: 0.746

Experimental value: Sensitizer
Predicted value: Sensitizer



CAS: 106-24-1
Dataset id: 100 (training set)
SMILES: OCC=C(C)CCC=C(C)C
Similarity: 0.727

Experimental value: Sensitizer
Predicted value: Sensitizer



CAS: 50-21-5
Dataset id: 127 (training set)
SMILES: O=C(O)C(O)C
Similarity: 0.72

Experimental value: NON-Sensitizer
Predicted value: NON-Sensitizer

APPENDIX J: EPISuite Modeling Results for Isobutanol (CAS #78-83-1)

CAS Number: 78-83-1
SMILES: OCC(C)C
CHEM: 1-Propanol, 2-methyl-
MOL FOR: C4 H10 O1
MOL WT: 74.12
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log K_{ow} (octanol-water): 1.00
Boiling Point (deg C): ------
Melting Point (deg C): -90.00
Vapor Pressure (mm Hg): 10.5
Water Solubility (mg/L): 70000
Henry LC (atm-m^3/mole): ------

Log Octanol-Water Partition Coef (SRC):
Log K_{ow} (K_{ow}WIN v1.68 estimate) = 0.77
Log K_{ow} (Exper. database match) = 0.76
Exper. Ref: HANSCH, C. ET AL. (1995)

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 99.58 (Adapted Stein & Brown method)
Melting Pt (deg C): -74.01 (Mean or Weighted MP)
VP (mm Hg,25 deg C): 13.4 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C): 1.78E+003 (Mean VP of Antoine & Grain methods)
MP (exp database): -108 deg C
BP (exp database): 107.8 deg C
VP (exp database): 1.05E+01 mm Hg (1.40E+003 Pa) at 25 deg C

Water Solubility Estimate from Log K_{ow} (WSK_{ow} v1.42):
Water Solubility at 25 deg C (mg/L): 6.226e+004
log K_{ow} used: 1.00 (user entered)
melt pt used: -90.00 deg C
Water Sol (Exper. database match) = 8.5e+004 mg/L (25 deg C)
Exper. Ref: VALVANI, S.C. ET AL. (1981)

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 1.0288e+005 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method: 9.99E-006 atm-m^3/mole (1.01E+000 Pa-m^3/mole)
Group Method: 1.17E-005 atm-m^3/mole (1.19E+000 Pa-m^3/mole)
Exper Database: 9.78E-06 atm-m^3/mole (9.91E-001 Pa-m^3/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: 1.463E-005 atm-m^3/mole (1.482E+000 Pa-m^3/mole)
VP: 10.5 mm Hg (source: User-Entered)
WS: 7E+004 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [K_{oa}WIN v1.10]:
Log K_{ow} used: 1.00 (user entered)
Log K_{aw} used: -3.398 (exp database)
Log K_{oa} (K_{oa}WIN v1.10 estimate): 4.398
Log K_{oa} (experimental database): 3.930

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model): 0.8710
Biowin2 (Non-Linear Model): 0.9558
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.1953 (weeks)
Biowin4 (Primary Survey Model): 3.8702 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model): 0.6523
Biowin6 (MITI Non-Linear Model): 0.8530
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): 0.6698
Ready Biodegradability Prediction: YES

Hydrocarbon Biodegradation (BioHCwin v1.01):
Structure incompatible with current estimation method!

Sorption to aerosols (25 Dec C)[AEROWIN v1.00]:
Vapor pressure (liquid/subcooled): 1.4E+003 Pa (10.5 mm Hg)
Log K_{oa} (Exp database): 3.930
Kp (particle/gas partition coef. (m^3/µg)):
Mackay model: 2.14E-009
Octanol/air (K_{oa}) model: 2.09E-009
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model: 7.74E-008
Mackay model: 1.71E-007
Octanol/air (K_{oa}) model: 1.67E-007

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 6.8816 E-12 cm^3/molecule-sec
Half-Life = 1.554 Days (12-hr day; 1.5E6 OH/cm^3)
Half-Life = 18.651 Hrs.
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
1.24E-007 (Junge-Pankow, Mackay avg)
1.67E-007 (K_{oa} method)

Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (K_{oc}WIN v2.00):
K_{oc}: 2.919 L/kg (MCI method)
Log K_{oc}: 0.465 (MCI method)
K_{oc}: 11.66 L/kg (K_{ow} method)
Log K_{oc}: 1.067 (K_{ow} method)

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 = 0.500 (BCF = 3.162 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -1.1582 days (HL = 0.06947 days)
Log BCF Arnot-Gobas method (upper trophic) = 0.220 (BCF = 1.659)
Log BAF Arnot-Gobas method (upper trophic) = 0.220 (BAF = 1.659)
log K_{ow} used: 1.00 (user entered)

Volatilization from Water:
Henry LC: 9.78E-006 atm-m^3/mole (Henry experimental database)
Half-Life from Model River: 52.42 hours (2.184 days)
Half-Life from Model Lake: 644 hours (26.83 days)

Removal in Wastewater Treatment:
Total removal: 2.42 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 1.79 percent
Total to Air: 0.55 percent
(using 10000 hr. Bio P,A,S)

Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr.)	Emissions (kg/hr.)
Air	3.86	37.3	1000
Water	44.2	360	1000
Soil	51.9	720	1000
Sediment	0.0863	3.24e+003	0

Persistence Time: 346 hr.

Sources to Check for GreenScreen® Hazard Assessment

Note: For a GreenScreen® Hazard Assessment, data queries should be initially limited to the following references. If data gaps exist after these references have been checked, additional references may be utilized.

U.S. EPA High Production Volume Information System (HPVIS):
http://www.epa.gov/hpvis/index.html

UNEP OECD Screening Information Datasets (SIDS):
http://www.chem.unep.ch/irptc/sids/OECDSIDS/sidspub.html

OECD Existing Chemicals Database: http://webnet.oecd.org/hpv/ui/SponsoredChemicals.aspx

European Chemical Substances Information System IUCLID Chemical Data Sheets:
http://esis.jrc.ec.europa.eu/index.php?PGM=dat

National Toxicology Program: http://ntp.niehs.nih.gov/

International Agency for the Research on Cancer:
http://monographs.iarc.fr/ENG/Classification/index.php

Human and Environmental Risk Assessment (HERA) on ingredients of household cleaning products:
http://www.heraproject.com/RiskAssessment.cfm

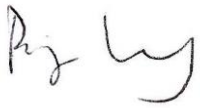
European Chemicals Agency (ECHA) REACH Dossiers: http://echa.europa.eu/

Licensed GreenScreen® Profilers

Isobutanol GreenScreen® Evaluation Prepared by:

Zach Guerrette, Ph.D.
Toxicologist
ToxServices LLC

Isobutanol GreenScreen® Evaluation QC'd by:



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