Dibutoxymethane (CAS #2568-90-3) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment

Prepared for:

Washington Department of Ecology

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TOXSERVICES
TOXICOLOGY RISK ASSESSMENT CONSULTING
1367 Connecticut Ave., N.W., Suite 300
Washington, D.C. 20036

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GreenScreen® Executive Summary for Dibutoxymethane (CAS #2568-90-3)

Dibutoxymethane is an acetal solvent that has applications in adhesives, cleaning formulations, cosmetics, pharmaceuticals, organic synthesis, and agrochemicals. Dibutoxymethane is sold under the trade name Solvon K4, and is increasingly used as a non-chlorinated alternative to perchloroethylene in garment dry cleaning. Dibutoxymethane was assigned a **GreenScreen Benchmark™ Score of U** ("Unspecified due to Data Gaps"). Prior to the data gap analysis, it was assigned a preliminary Benchmark score of 2 ("Use but Search for Safer Substitutes"). This preliminary score is based on the following hazard score combination:

- Benchmark 2e
    - Moderate Group I Human Toxicity (mutagenicity-M)

Data gaps (DG) exist for carcinogenicity-C, reproductive toxicity-R, endocrine activity-E, neurotoxicity-Nr*, and respiratory sensitization –SnR*. As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), dibutoxymethane does not meet requirements for a GreenScreen® Benchmark Score of 2 due to the hazard data gaps. Therefore, it was assigned a Benchmark score of U. In a worst-case scenario, if dibutoxymethane were assigned a High score for the data gaps C, R, or 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 U ("Unspecified Due to Data Gaps") is applicable for all routes of exposure.

GreenScreen® Hazard Ratings for Dibutoxymethane

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*										
DG	*M*	DG	*L*	DG	**L**	*L*	*L*	**M**	DG	**L**	DG	**L**	**L**	*M*	*M*	*M*	**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.

GreenScreen® Assessment for Dibutoxymethane (CAS #2568-90-3)

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

Chemical Name: Dibutoxymethane

CAS Number: 2568-90-3

GreenScreen® Assessment Prepared By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: December 31, 2015
Assessor Type: Licensed GreenScreen® Profiler

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D., D.A.B.T.
Title: Toxicologist
Organization: ToxServices LLC
Date: January 14, 2016

Confirm application of the *de minimus* rule[3]: N/A: This GreenScreen® was performed for the theoretically pure compound dibutoxymethane. Commercial preparations such as Solvon K4 may contain impurities including 1-butanol and formaldehyde at <0.5% and <0.05%, respectively (Whittaker 2013).

Chemical Structure(s):

Also called: Butylal; Di-n-butoxymethane; Di-n-butyl formal; Dibutyl formal; Formaldehyde dibutyl acetal; 1,1'-(Methylenebis(oxy))dibutane; Butane, 1,1'-(methylenebis(oxy))bis-; Methane, dibutoxy- (ChemID plus 2015)

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:
The structurally similar acetal dimethoxymethane was identified as a potential surrogate using the U.S. EPA's Analog Identification Methodology (AIM). In addition, it was identified as a read-across chemical in the REACH dossier for dibutoxymethane. Like dibutoxymethane, it is a diether acetal that differs by the presence of two shorter methoxy rather than two butoxy groups. In addition, ToxServices also identified diethoxymethane as a surrogate as it contains two ethoxy rather than two butoxy groups. All three chemicals are highly volatile, but as dimethoxymethane and diethoxymethane are much more water soluble than dibutoxymethane and therefore may differ in bioavailability, they are considered to be weak surrogates and scores based on solely on surrogate data are reported with reduced confidence. Dipropoxymethane was also considered as a potential surrogate, but no data were identified for this compound. Despite the use of surrogates, insufficient

[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

data were identified to fill data gaps for carcinogenicity, reproductive toxicity, endocrine activity, neurotoxicity, and respiratory sensitization.

Dimethoxymethane (CAS #109-87-5)

Diethoxymethane (CAS #462-95-3)

Identify Applications/Functional Uses:
1. Solvent (Lamboitte 2014)

GreenScreen® Summary Rating for Dibutoxymethane[4]: Dibutoxymethane was assigned a **GreenScreen Benchmark™ Score of U** ("Unspecified due to Data Gaps"). Prior to the data gap analysis, it was assigned a preliminary Benchmark score of 2 ("Use but Search for Safer Substitutes") (CPA 2014). This preliminary score is based on the following hazard score combination:

- Benchmark 2e
    - Moderate Group I Human Toxicity (mutagenicity-M)

Data gaps (DG) exist for carcinogenicity-C, reproductive toxicity-R, endocrine activity-E, neurotoxicity-Nr*, and respiratory sensitization –SnR*. As outlined in CPA (2013) Section 12.2 (Step 8 – Conduct a Data Gap Analysis to assign a final Benchmark score), dibutoxymethane does not meet requirements for a GreenScreen® Benchmark Score of 2 due to the hazard data gaps. Therefore, it was assigned a Benchmark score of U. In a worst-case scenario, if dibutoxymethane were assigned a High score for the data gaps C, R, or E, it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Ratings for Dibutoxymethane

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*										
DG	*M*	DG	*L*	DG	**L**	*L*	*L*	**M**	DG	**L**	DG	**L**	**L**	*M*	*M*	*M*	**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.

[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.

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. Dibutoxymethane is not expected to undergo hydrolysis based on data for structurally similar chemicals. Experimental biodegradation data indicate that it undergoes biodegradation at a moderate rate. Biodegradation products were not measured in the only available biodegradation study. OECD Toolbox (OECD 2015) predicts 24 potential biodegradation products, but the relative likelihood of the production of each was not reported. In addition, the EAWAG-BBD Pathway Prediction System (EAWAG 2014) predicted numerous potential products and pathways, but none were predicted as likely or very likely. Therefore, based on available data and prediction tools it is not possible to make an informed prediction of likely transformation products.

Introduction

Dibutoxymethane is an acetal solvent that has applications in adhesives, cleaning formulations, cosmetics, pharmaceuticals, organic synthesis, and agrochemicals (Lamboitte 2014). Sold under the trade name Solvon K4, it is increasingly used as a non-chlorinated alternative to perchloroethylene in garment dry cleaning (Whittaker 2013, Subsport 2013).

ToxServices assessed dibutoxymethane 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 2016) 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 dibutoxymethane can be found in Appendix C and a summary of the results can be found below:

German FEA - Substances Hazardous to Waters - Class 1 - Low Hazard to Waters

Physicochemical Properties of Dibutoxymethane

Dibutoxymethane is a liquid at room temperature. It has a high vapor pressure of 0.59 mmHg, indicating that it is likely to volatilize. It is moderately soluble in water (222.5 mg/L) and its log K_{ow} of 2.77 indicates that it is not likely to bioaccumulate.

Table 1: Physical and Chemical Properties of Dibutoxymethane (CAS #2568-90-3)

Property	Value	Reference
Molecular formula	C9-H20-O2	ChemIDplus 2015
SMILES Notation	C(OCCCC)OCCCC	ChemIDplus 2015

[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.

Table 1: Physical and Chemical Properties of Dibutoxymethane (CAS #2568-90-3)		
Property	**Value**	**Reference**
Molecular weight	160.255	ChemIDplus 2015
Physical state	Liquid	ECHA 2016a
Appearance	Colorless	ECHA 2016a
Melting point	-59.4°C; -58.1°C	ECHA 2016a; ChemIDplus 2015
Vapor pressure	0.079 kPa (0.59 mmHg)at 20°C; < 0.25 kPa (< 1.9 mmHg) at 20°C; < 0.138 kPa (< 1.0 mmHg) at 20°C	ECHA 2016a
Water solubility	222.5 mg/L (EU A.6, GLP)	ECHA 2016a
Dissociation constant	Not identified	
Density/specific gravity	835.45 kg/m^3 at 20°C	ECHA 2016a
Partition coefficient	log K_{ow} = 2.77 (EU A.8, GLP); log K_{ow} = 2.75 (est.)	ECHA 2016a

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): DG
Dibutoxymethane was assigned a score of Data Gap for carcinogenicity based on a lack of adequate data for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- Toxtree 2015
  - Toxtree did not identify any alerts for genotoxic or nongenotoxic carcinogenicity (Appendix D).
- Based on the weight of evidence, a Data Gap was assigned. Toxtree did not identify any alerts for genotoxic or nongenotoxic carcinogenicity. Modeling was attempted with VEGA (2015), but the compound was out of the applicability domain of the carcinogenicity models. In addition, the chemical does not fall into any of the chemical classes included in OncoLogic (U.S. EPA 2013). Because a lack of alerts is not sufficient to assign a Low, a Data Gap was assigned in the absence of experimental data on dibutoxymethane or the surrogates.

Mutagenicity/Genotoxicity (M) Score (H, M, or L): *M*
Dibutoxymethane was assigned a score of Moderate for mutagenicity/genotoxicity based on positive results in a mammalian cell mutagenicity assay of the surrogate diethoxymethane. GreenScreen® criteria classify chemicals as a Moderate hazard for mutagenicity/genotoxicity when there is limited or marginal evidence of mutagenicity (CPA 2012a). Confidence in the score is reduced because it is based on experimental data for a weak surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2016a
  - Dibutoxymethane (> 99.99% purity) was negative in a GLP-compliant bacterial mutagenicity assay that was conducted according to OECD Guideline 471 in *S.*

typhimurium strains TA102, TA 1535, TA 1537, TA 98 and TA 100 and *E. coli* WP2 uvrA. Cells were tested without metabolic activation at concentrations of 62.5, 125, 250, 500 and 1,000 µg/plate for TA 1535 in both experiments and for TA 1537 in the second experiment, and at 31.25, 62.5, 125, 250 and 500 µg/plate for remaining strains in the first and second experiments. Cells were tested with metabolic activation at concentrations of 31.25, 62.5, 125, 250 and 500 µg/plate for TA 102 in the first experiment and TA 1535, TA 1537, and TA 98 in the second experiment, at 62.5, 125, 250, 500 and 1,000 µg/plate for TA 100 in both experiments, TA 1535 in the first experiment, and TA 102 in the second experiment, and 312.5, 625, 1,250, 2,500 and 5,000 µg/plate for TA 1537 and TA 98 in the first experiment and WP2 uvrA in both experiments. Doses were selected according to the guidelines based on toxicity in the preliminary experiment. There were no increases in revertants at any dose in any strain, and positive and vehicle controls were valid.

Surrogate: Dimethoxymethane (CAS# 109-87-5)

- ECHA 2016b, NIH Undated
    - Dimethoxymethane (97.5% purity) was negative in a GLP-compliant *in vitro* mammalian cell mutagenicity test that was conducted in Chinese Hamster Ovary (CHO) cells (Note: the REACH dossier indicates that the study was conducted according to OECD Guideline 473, but methods and results are consistent with OECD Guideline 476). Cells were tested with and without metabolic activation at concentrations of 0.5, 1.0, 2.0, 3.0, 4.0, 5.0 mg/mL (doses selected based on results of a preliminary range-finding cytotoxicity test). There were no increases in mutants and positive and vehicle controls were valid.
    - Dimethoxymethane (97.5% purity) was negative in a GLP-compliant *in vivo* mammalian micronucleus assay that was conducted according to OECD Guideline 474 in male and female ICR mice. Animals (5/sex/dose) were administered a single dose of 400, 1,333, or 4,000 mg/kg dimethoxymethane via i.p. injection and were sacrificed after 24, 48, or 72 hours. There were no significant increases in micronucleated polychromatic erythrocytes in the bone marrow, and positive and vehicle controls were valid.

Surrogate: Diethoxymethane (CAS# 462-95-3)

- ECHA 2016c
    - Diethoxymethane (purity not reported) was positive in a bacterial mutagenicity assay that was conducted according to OECD Guideline 476 (GLP status not reported) in mouse lymphoma L5178Y cells. Cells were exposed to concentrations of 250, 500, 750, 1,000, and 1,500 µg/mL with metabolic activation and 3,000, 3,500, 4,000, 4,500, and 5,000 µg/mL without metabolic activation. There was an increase in mutant colonies with but not without metabolic activation when compared to solvent controls (statistical significance not specified; 1.9 to 3.2-fold increase; no apparent dose response). Authors concluded that the assay was positive with metabolic activation and negative without metabolic activation.
- Based on the weight of evidence, a conservative score of Moderate was assigned. Dibutoxymethane was negative in a bacterial mutagenicity assay, but there are no data for mammalian cell mutagenicity or clastogenicity. The surrogate dimethoxymethane was negative for clastogenicity in mice *in vivo* and for mammalian cell mutagenicity in CHO cells. However, the surrogate diethoxymethane was positive for mammalian cell mutagenicity in mouse lymphoma L5178Y cells. As both studies appear to be well conducted and diethoxymethane is most similar to dibutoxymethane in size and solubility, ToxServices placed more weight on this study and assigned a conservative score of Moderate for limited or marginal evidence of mutagenicity.

Reproductive Toxicity (R) Score (H, M, or L): DG
Dibutoxymethane was assigned a score of Data Gap for reproductive toxicity based on a lack of data for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- No data were identified.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): *L*
Dibutoxymethane was assigned a score of Low for developmental toxicity based on a lack of embryotoxicity and teratogenicity in an inhalation prenatal developmental toxicity study of a surrogate in rats. GreenScreen® criteria classify chemicals as a Low hazard for developmental toxicity when adequate data are available and indicate that the chemical does not warrant GHS classification for developmental toxicity and the chemical is not present on authoritative or screening lists (CPA 2012a). Confidence in the score is high because it is based on experimental data from a study of a weak surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

Surrogate: Dimethoxymethane (CAS# 109-87-5)

- ECHA 2016b
  - *Inhalation*: In a GLP-compliant prenatal developmental toxicity study that was conducted according to OECD Guideline 414 in Crl:CDRBRVAF/plus rats, animals (25/dose) were exposed to dimethoxymethane (99.5% purity) via whole body inhalation to concentrations of 386, 1,954, or 10,068 ppm (1,290, 6.547, or 33.73 mg/L[6]) for 6 hours/day on gestation days 6-15 and were sacrificed on gestation day 20. Maternal toxicity at the high dose included reduced body weight gain, food consumption, and water intake. There were no effects on embryotoxicity, litter or fetal weight, sex ratio, malformations, or skeletal anomalies. There were slight increases in the incidence of skeletal anomalies (bipartite and incomplete ossification of thoracic vertebral centra) and dilated ureter (statistical significance not reported). Authors did not consider these effects to be treatment-related, although no details were provided. Authors reported a NOAEL of 10,068 ppm (33.73 mg/L).
  - *Inhalation*: In a GLP-compliant prenatal developmental toxicity range-finding study that was conducted according to OECD Guideline 414 in Crl:CD®BR VAF/plus rats, dams (10/dose) were exposed to dimethoxymethane (99.695% purity) via whole body inhalation to concentrations of 400, 2,000 or 10,000 ppm (1.34, 6.7, or 33.5 mg/L[7]) for 6 hour/day on gestation days 6-15 and were sacrificed on gestation day 20. Reduced body weight and food consumption were observed in dams at the high dose. There were no effects on embryo viability or gross pathology.
- Based on the weight of evidence, a score of Low was assigned. In a study of the surrogate, increases in skeletal and visceral anomalies were reported at the high dose, and although the magnitude and statistical significance were not stated the changes were described as "slight". Authors did not provide rationale, but stated that effects were not considered treatment related. Because the increases were described as "slight" and were observed only at an extremely high dose (33.73 mg/L) in the presence of maternal toxicity, ToxServices did not consider these

[6] Concentrations determined using converter at http://www.lenntech.com/calculators/ppm/converter-parts-per-million.htm.
[7] Concentrations determined using converter at http://www.lenntech.com/calculators/ppm/converter-parts-per-million.htm.

effects to be sufficient to classify the surrogate for developmental toxicity. Therefore, a score of Low was assigned, as there was no evidence of embryotoxicity or teratogenicity at any of the doses.

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

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- 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.
- No data were identified.

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
Dibutoxymethane was assigned a score of Low for acute toxicity based on oral and dermal LD_{50} values of 6,873 mg/kg and greater than 2,000 mg/kg, respectively, in rats for dibutoxymethane and inhalation LC_{50} values of 57 and 47.4 mg/L in rats for the surrogate dimethoxymethane and 30.5 mg/L for the surrogate diethoxymethane. 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 LC_{50} values are greater than 20 mg/L/4h for a vapor (CPA 2012a). Confidence in the score is high because it is based on experimental data from well conducted studies of the target compound with support from data for surrogates.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2016a
  - *Oral*: LD_{50} (male and female Sprague-Dawley rat) = 6,873 mg/kg (OECD 401, GLP)
  - *Dermal*: LD_{50} (male and female Sprague-Dawley rat) > 2,000 mg/kg (OECD 402, GLP)

Surrogate: Dimethoxymethane (CAS# 109-87-5)

- ECHA 2016b
  - *Inhalation*: LC_{50} (male Swiss mice) = ~ 57 mg/L/7h
- HCN 2000
  - *Inhalation*: LC_{50} (rat, sex and strain not specified) = 47.4 mg/L (duration not specified)

Surrogate: Diethoxymethane (CAS# 462-95-3)

- ECHA 2016c
  - *Inhalation*: LC_{50} (male and female CRL:CD(SD)BR rat) (OECD 403, GLP) = 6,643

ppm/6h (30.5 mg/L/6h)[8]

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)
***Group II Score (single dose)* (vH, H, M, or L):** *L*
Dibutoxymethane was assigned a score of Low for systemic toxicity (single dose) based on a lack of systemic effects in acute oral and dermal toxicity studies in rats. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (single dose) when no systemic toxicity is observed below the guidance value of 2,000 mg/kg in acute oral and dermal studies (CPA 2012a). Confidence in the score is reduced because it is not possible to assess systemic toxicity via inhalation based on available surrogate data.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2016a
  - *Oral*: In the GLP-compliant acute oral toxicity study that was conducted according to ECD Guideline 401 in male and female Sprague-Dawley rats, animals (5/sex/dose) were administered a single dose of 2,000, 5,000 (females only), 7,000, or 10,000 (females only) mg/kg dibutoxymethane (>99.99% purity) via gavage and were observed for 14 days. Deaths were observed at 7,000 mg/kg and above. Body weight gain was reduced at 5,000 mg/kg/day and above. There were no effects on gross pathology. Clinical signs included hypoactivity, piloerection, and unsteady gait (all doses), and sedation, lateral recumbency, tremors, and coma (5,000 mg/kg/day and above). All surviving animals recovered by the end of the observation period.
  - *Dermal*: In a GLP-compliant acute dermal toxicity study that was conducted according to OECD Guideline 402 in male and female Sprague-Dawley rats (5/sex), animals were administered a single dose of dibutoxymethane (> 99.99% purity) under semiocclusion for 24 hours. There were no deaths or clinical signs of toxicity. Body weight gain in females was slightly reduced (magnitude statistical significance not specified) when compared to historical controls (concurrent controls were not included). There were no gross pathological changes.

<u>Surrogate: Dimethoxymethane (CAS# 109-87-5)</u>

- ECHA 2016b
  - In the acute inhalation study that was conducted in male Swiss mice, animals (10/sex/dose) were exposed to dimethoxymethane (purity not reported) vapors at concentrations of 46, 53, 56, 57, 65, and 67 mg/L for 7 hours. Doses at which deaths occurred were not reported. Clinical signs included excitation and progressive ataxia within 1 hour, unsteadiness in the second hour, and anesthesia from hour 3 onward. Surviving animals regained consciousness and coordination within 2 hours of breathing fresh air.

<u>Surrogate: Diethoxymethane (CAS# 462-95-3)</u>

- ECHA 2016c
  - *Inhalation*: In the GLP-compliant study that was conducted according to OECD Guideline 403 in male and female CRL:CD(SD)BR rats, animals (5/sex/dose) were exposed to diethoxymethane (99.9% purity) at concentrations of 0, 5,000, 10,000, or 20,000 ppm (22.9, 45.8, or 91.7 mg/L[9]) for 6 hours and were observed for 14 days. Deaths were observed at all doses. The only clinical signs observed were narcotic effects

[8] Concentrations determined using converter at http://www.lenntech.com/calculators/ppm/converter-parts-per-million.htm.
[9] Concentrations determined using converter at http://www.lenntech.com/calculators/ppm/converter-parts-per-million.htm

including wobbly gait, lethargy and narcosis at all doses. There were on effects on body weight. Surviving females at the low dose showed incomplete collapse of the lungs and enlarged livers, and authors concluded that the lungs and livers are sites of toxicity at high concentrations.

- Based on the weight of evidence, a score of Low was assigned. Acute oral and dermal toxicity studies showed little evidence of systemic effects other than reversible narcotic effects, which are discussed under neurotoxicity, below. Effects on body weight in the inhalation study were observed only at 5,000 mg/kg, and above in the acute oral study. The magnitude and statistical significance of effects on female body weight in the acute dermal study were not specified, but effects are described only as "slight" and are therefore not sufficient to classify for systemic toxicity. Inhalation data on dimethoxymethane are insufficient, as available studies did not evaluate systemic endpoints such as body weight or gross pathology. In addition, the inhalation study on diethoxymethane is insufficient as the lowest dose tested was higher than the guidance value of 20 mg/L and because exposures were conducted for 6 rather than 4 hours. Neurological effects are discussed below.

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

Dibutoxymethane was assigned a score of Low for systemic toxicity (repeated dose) based on a NOEL of 4.8 mg/L in a subchronic inhalation study of the surrogate in rats. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when there is no evidence of systemic toxicity below the guidance value of 1.0 mg/L (vapor) in a 90-day inhalation study (CPA 2012a). Confidence in the score is reduced because it is based on experimental data from a well conducted study of a weak surrogate.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists

<u>Surrogate: Dimethoxymethane (CAS# 109-87-5)</u>

- ECHA 2016b
  - *Inhalation*: In a GLP-compliant subchronic inhalation toxicity study that was conducted according to OECD Guideline 413 in Wistar Hoe rats, animals (10/sex/dose) were exposed to dimethoxymethane (99.9% purity) via nose only inhalation to concentrations of 400, 2,000, or 10,000 ppm (1.34, 6.7, or 33.5 mg/L[10]) for 6 hours/day, 5 days/week, for 13 weeks (65 exposures). There were no deaths or clinical signs of toxicity. There were no adverse treatment-related effects on body weight or food consumption. Water intake was slightly increased at the high dose (no additional details provided). There were no effects on the ophthalmoscopic examination. Erythrocyte counts and hematocrit values were significantly decreased at the high dose. Authors noted that values remained "well within" the physiological range of rats and there were no additional signs of anemia. Coagulation times were slightly but significantly decreased in females at the mid and high doses; changes were not concentration-dependent. Slight but statistically significant decreases in inorganic phosphate levels were seen in males at the high dose. Urea and GPT values were slightly increased in females at the high dose. Authors did not consider these effects to be toxicologically relevant in the absence of histopathological changes. Other statistically significant changes that were observed (decreases in potassium and bilirubin values in male, increases in total lipid levels in males, decreases in phosphate values in females, decreases in calcium levels in females) were observed but did not show a concentration dependence. Specific gravity of the

[10] Concentrations determined using converter at http://www.lenntech.com/calculators/ppm/converter-parts-per-million.htm.

urine was slightly but significantly decreased in females at the high concentration and males at the mid concentration. Urine volumes were also increased in females at the high dose, and authors speculated that this effect may have resulted from increased water consumption. Absolute and relative liver weights were significantly increased in females at the high dose and relative liver weights were increased in males at the high dose. Absolute and relative spleen weights were significantly decreased in females at the high dose, and relative kidney weights were increased in males at the high dose. There were no gross or histopathological changes in any tissue. Authors reported a NOEL of 2,000 ppm (6.7 mg/L) based on slight changes in clinical chemistry, hematology, and organ weights at the LOEL of 10,000 ppm (33.5 mg/L). These values are equivalent to 4.8 and 23.9 mg/L after adjusting for intermittent exposure[11].

- *Inhalation*: In a non-guideline subacute toxicity study in male and female rats (strain not specified), animals (10/sex/dose) were exposed to dimethoxymethane (purity not reported) at concentrations of 0.164, 1.04, and 3.1 mg/L for 7 hours/day, 5 days/week, for 22 days. There were no treatment-related effects on clinical signs, body weight, hematology, gross pathology, or histopathology. ToxServices identified a NOAEL of 3.1 mg/L, which is equivalent to 2.2 mg/L after adjusting for intermittent exposure[12], based on a lack of effects at the highest dose tested.

Neurotoxicity (N)
***Group II Score (single dose)* (vH, H, M, or L): M**
Dibutoxymethane was assigned a score of Moderate for neurotoxicity (single dose) based on reversible hypoactivity, sedation/anesthesia, and unsteady gait in an acute oral study of dibutoxymethane and an acute inhalation study of the surrogates dimethoxymethane and diethoxymethane. GreenScreen® criteria classify chemicals as a Moderate hazard for neurotoxicity (single dose) when available data indicate that GHS Category 3 classification for transient narcotic effects is warranted (CPA 2012a). Confidence in the score is high because it is based on experimental data from well conducted studies of the target chemical with support from data for surrogates.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- ECHA 2016a
  - *Oral*: In the GLP-compliant acute oral toxicity study that was conducted according to ECD Guideline 401 in male and female Sprague-Dawley rats, animals (5/sex/dose) were administered a single dose of 2,000, 5,000 (females only), 7,000, or 10,000 (females only) mg/kg dibutoxymethane via gavage and were observed for 14 days. Clinical signs included hypoactivity, piloerection, and unsteady gait (all doses), and sedation, lateral recumbency, tremors, and coma (5,000 mg/kg/day and above). All surviving animals recovered by the end of the observation period.

<u>Surrogate: Dimethoxymethane (CAS# 109-87-5)</u>

- ECHA 2016b
  - *Inhalation*: In the acute inhalation study that was conducted in male Swiss mice, animals (10/sex/dose) were exposed to dimethoxymethane (purity not reported) vapors at concentrations of 46, 53, 56, 57, 65, and 67 mg/L for 7 hours. Clinical signs included

[11] 33.5 mg/L x 5 days/7 days = 23.9 mg/L
[12] 3.1 mg/L x 5 days/7 days = 2.2 mg/L

excitation and progressive ataxia within 1 hour, unsteadiness in the second hour, and anesthesia from hour 3 onward. Surviving animals regained consciousness and coordination within 2 hours of breathing fresh air.

- HCN 2000
  - HCN reports that anesthesia was produced by i.v. injection in dogs and inhalation in mice.
- ECHA 2016c
  - *Inhalation*: In the GLP-compliant study that was conducted according to OECD Guideline 403 in male and female CR:CD(SD)BR rats, animals (5/sex/dose) were exposed to diethoxymethane (99.9% purity) at concentrations of 0, 5,000, 10,000, or 20,000 ppm (22.9, 45.8, or 91.7 mg/L[13]) for 6 hours and were observed for 14 days. Deaths were observed at all doses. The only clinical signs observed were narcotic effects including wobbly gait, lethargy and narcosis at all doses.
- Based on the weight of evidence, a score of Moderate was assigned. An acute oral study of dibutoxymethane and acute inhalation studies of dimethoxymethane and diethoxymethane reported narcotic effects (hypoactivity, sedation/anesthesia, unsteady gait), which resolved in surviving animals before the end of the observation period. This is indicative of transient narcotic effects, which corresponds to GHS Category 3 (UN 2015) and a score of Moderate.

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

Dibutoxymethane was assigned a score of Data Gap for neurotoxicity (repeated dose) based on a lack of data for this endpoint.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006, 2014).
- No data were identified.

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

Dibutoxymethane was assigned a score of Low for skin sensitization based on negative results in a guinea pig maximization test. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when available data indicate that the chemical does not warrant GHS classification for skin sensitization and the chemical is not present on authoritative or screening lists (CPA 2012a). Confidence in the score is high because it is based on experimental data from a well conducted study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2016a
  - Dibutoxymethane (> 99.99% purity) was negative in a GLP-compliant guinea pig maximization test that was conducted according to OECD Guideline 406 in male and female Dunkin-Hartley guinea pigs. Animals (10/sex/dose) were induced intradermally with a 10% solution and topically with a 100% solution, and were challenged with a 100% solution. After challenge, positive results were seen in 0/20, 3/20, and 3/20 animals at the 24, 48, and 72 hour observations, respectively.
- Based on the weight of evidence, a score of Low was assigned. Positive responses were seen in 3/20 (15%) or animals in the guinea pig maximization test. Because GHS criteria require positive responses in at least 30% of animals in a guinea pig maximization test in order to

[13] Concentrations determined using converter at http://www.lenntech.com/calculators/ppm/converter-parts-per-million.htm

classify as a skin sensitizer, dibutoxymethane does not warrant GHS classification based on the results of this assay.

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

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- No relevant data were identified.

Skin Irritation/Corrosivity (IrS) Group II Score (vH, H, M, or L): L
Dibutoxymethane was assigned a score of Low for skin irritation/corrosivity based on a dermal irritation study in rabbits demonstrating slight irritation that did not meet classification criteria. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when available data indicate that the chemical does not warrant GHS classification for skin irritation and the chemical is not present on authoritative or screening lists (CPA 2012a). Confidence in the score is high because it is based on experimental data from a well conducted study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2016a
  - Dibutoxymethane (>99.99% purity) was slightly irritating in a GLP-compliant dermal irritation test that was conducted according to OECD Guideline 404 in three male New Zealand White rabbits. The mean 24/48/72 hour scores for erythema were 1.3, 1.0, and 1.7 for the three animals. The mean 24/48/72 hour scores for edema were 0, 0, and 0 for the three animals. Effects resolved within 5 days with the exception of dry skin in one animal on days 6-15.
- Based on the weight of evidence, a score of Low was assigned as the scores for erythema and edema do not meet criteria for classification according to GHS criteria, which specify scores of > 1.5 in at least 2/3 animals (UN 2015).

Eye Irritation/Corrosivity (IrE) Group II Score (vH, H, M, or L): L
Dibutoxymethane was assigned a score of Low for eye irritation/corrosivity based on negative results in an ocular irritation study in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when available data indicate that the chemical does not warrant GHS classification for eye irritation and the chemical is not present on authoritative or screening lists (CPA 2012a). Confidence in the score is high because it is based on experimental data from a well conducted study.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- ECHA 2016a
  - Dibutoxymethane (>99.99% purity) was not irritating in a GLP-compliant dermal irritation test that was conducted according to OECD Guideline 404 in three male New Zealand White rabbits. The mean 24/28/72 hour scores for chemosis were 0.3, 0,3 and 0 in the three animals. The mean 24/48/72 hour scores for conjunctival redness and discharge were 0.3 and 0, respectively for all animals. The mean 24/48/72 hour scores

for the iris and cornea were 0 for all animals.

- Based on the weight of evidence, a score of Low was assigned, as the maximum irritation scores of 0.3 for chemosis in 2 animals do not meet GHS classification criteria of scores of >2 in 2/3 animals.

Ecotoxicity (Ecotox)

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

Dibutoxymethane was assigned a score of Moderate for acute aquatic toxicity based on an LC_{50} of 45.7 mg/L in fish and modeled EC_{50} values of 16.3 mg/L in both daphnia and algae. GreenScreen® criteria classify chemicals as a Moderate hazard for acute aquatic toxicity when L/EC_{50} values are between 10 and 100 mg/L (CPA 2012a). Confidence in the score is reduced due to difficulties maintain test concentrations and reliance on modeling for support.

- Authoritative and Screening Lists
  - *Authoritative:* Not present on any authoritative lists
  - *Screening:* Not present on any screening lists
- Whittaker 2013
  - 96-hour LC_{50} (*Oncorhynchus mykiss*, rainbow trout) = 45.7 mg/L (tested as trade name Solvon K4, containing dibutoxymethane with < 0.5% 1-butanol and < 0.05% formaldehyde) (Authors noted that test substance concentrations declined over 48 hours and were renewed at this time to restore the measured concentrations)
- ECHA 2016a
  - 96-hour LC_{50} (*Daphnia magna*, water flea) > 100 mg/L nominal, > 28.7 mg/L measured (OECD 202, GLP; authors note that the substance was not stable in water and that concentrations were not satisfactorily maintained within 20% of nominal concentrations)
  - 72-hour EC_{50} (*Daphnia magna*, water flea) > 100 mg/L nominal, > 1.3 mg/L measured for growth and biomass (OECD 201, GLP; authors note that the substance was not stable in water and that concentrations were not satisfactorily maintained within 20% of nominal concentrations)
- U.S. EPA 2012a
  - Dibutoxymethane is designated to the Neutral Organics ECOSAR chemical classes (see Appendix E). The most conservative predicted L/EC_{50} values are 26.8 mg/L in fish (96-hr), 16.3 mg/L in daphnia (48-hr), and 16.3 mg/L in green algae (96-hr).
- Based on the weight of evidence, a score of Moderate was assigned. An acute toxicity study in fish indicates a moderate order of toxicity based on the LC_{50} of 45.7 mg/L. Authors noted that test substance concentrations declined, most likely due to the volatility of the substance, and had to be restored to the original concentration after 48 hours (concentrations declined similarly by 96 hours). Studies in daphnia and algae indicate a low order of toxicity, but both studies also showed difficulty maintaining the test substance concentration in the solution. Therefore, modeling was performed to support the hazard classification, and the modeled L/EC_{50} values for all three trophic levels also correspond to a Moderate.

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

Dibutoxymethane was assigned a score of Moderate for chronic aquatic toxicity based predicted ChV values are 2.8 mg/L in fish, 1.9 mg/L in daphnia, and 5.0 mg/L in green algae. GreenScreen® criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when chronic aquatic toxicity values are between 1 and 10 mg/L (CPA 2012a). Confidence in the score is reduced due to the reliance on modeled data.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists
- U.S. EPA 2012a
    - Dibutoxymethane is designated to the Neutral Organics ECOSAR chemical classes (see Appendix E). The most conservative predicted ChV values are 2.8 mg/L in fish, 1.9 mg/L in daphnia, and 5.0 mg/L in green algae.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *M*
Dibutoxymethane was assigned a score of Moderate for persistence based on an estimated half-life of 17 days in soil, which is predicted to be its dominant compartment. GreenScreen® criteria classify chemicals as a Moderate hazard for persistence when the half-life in soil is between 16 and 60 days (CPA 2012a). Confidence in the score is reduced due to the reliance on a modeled half-life.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists
- ECHA 2016a
    - Acetals are hydrolytically stable under acid, neutral, and basic conditions, with estimated hydrolysis half-lives of > 1 year. Based on data for other acetals, dibutoxymethane is expected to have a hydrolysis half-life of > 1 year.
    - Dibutoxymethane (99.78% purity) was not readily biodegradable in a test conducted according to OECD Guideline 301 F (Ready Biodegradability: Manometric Respirometry Test) using domestic non-adapted activated sludge inoculum. When tested at a starting concentration of 100 mg/L, the substance reached 30-40% biodegradation in 28 days and 40-50% biodegradation in 34 days following an adaptation phase of 13 days. Authors concluded that the substance is partly or moderately biodegradable but not readily biodegradable.
- U.S. EPA 2012b
    - The BIOWIN modeling Ready Biodegradable Predictor indicates that dibutoxymethane is expected to be readily biodegradable (see Appendix F). Fugacity modeling predicts 60.3% will partition to soil with a half-life of 17 days, 36% will partition to water with a half-life of 9 days, and 3.61% will partition to air with a half-life of 7.6 hours.
- Based on the weight of evidence, a score of Moderate was assigned. Dibutoxymethane is not expected to undergo hydrolysis but does undergo biodegradation at a moderate rate based on results of a readily biodegradability test. Modeling was performed to obtain a predicted half-life in the environment, and EPIsuite predicts that dibutoxymethane will partition primarily to soil with an estimated half-life of 17 days which corresponds to a score of Moderate.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
Dibutoxymethane was assigned a score of Very Low for bioaccumulation based on an experimental log K_{ow} of 2.77 with support from a modeled BCF of 44.33. GreenScreen® criteria classify chemicals as a Very Low hazard for bioaccumulation when the log K_{ow} is less than 4 and the BCF is less than 100 (CPA 2012a). Confidence in the score is high because it is based on an experimental log K_{ow}.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists

    - *Screening:* Not present on any screening lists
- ECHA 2016a
    - An experimental log K_{ow} of 2.77 was determined in a GLP-compliant test that was conducted according to EU Method A.8.
- U.S. EPA 2012b
    - BCFBAF predicts a BCF of 44.33 based on a log K_{ow} of 2.77, indicating this chemical is not likely to bioaccumulate because the BCF is less than 100 based on a log K_{ow} less than 5 (Appendix F).

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M, or L): *L*
Dibutoxymethane was assigned a score of Low for reactivity based on a an HMIS rating of 0 for physical hazards and a structure indicating that it is not an organic peroxide, does not contain reactive groups associated with self-reactive substances, is not an organometallic substance that may produce flammable gases on contact with water, and does not contain alerts for explosivity. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when available data indicate that the chemical does not warrant GHS classification for any of the reactivity sub-endpoints and the chemical is not present on authoritative or screening lists (CPA 2012a). Confidence in the score is reduced due to the lack of experimental data.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists
- UN 2013
    - Based on examination of the structure, ToxServices determined that dibutoxymethane is not an organic peroxide, does not contain reactive groups associated with self-reactive substances, and is not an organometallic substance that may produce flammable gases on contact with water.
- UN 2010
    - Based on examination of the structure, ToxServices determined that dibutoxymethane does not have any alerts for explosivity (Appendix G).
- Sigma Aldrich 2014
    - Dibutoxymethane was assigned an HMIS rating of 0 for physical hazards. This corresponds to "Materials that are normally stable, even under fire conditions, and will NOT react with water, polymerize, decompose, condense, or self-react. NonExplosives (Paint.org 2015)."

Flammability (F) Score (vH, H, M, or L): M
Dibutoxymethane was assigned a score of Moderate for flammability based on an experimental flash point of 62.4°C. GreenScreen® criteria classify chemicals as a Moderate hazard for flammability when available data indicate that the chemical warrants classification to GHS Category 4 for flammable liquids (CPA 2012a). Confidence in the score is high because it is based on an experimental flash point.

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:* Not present on any screening lists
- ECHA 2016a
    - Flash point = 62.4°C (ASTM D93 non-equilibrium closed cup)

- Based on the weight of evidence, a score of Moderate was assigned as the experimental flash point of 62.4°C falls between the guidance values of 60°C and 93°C for GHS Category 4 classification (UN 2015).

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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 Dibutoxymethane (CAS #2568-90-3)

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	Dibutoxymethane	2568-903	DG	*M*	DG	*L*	DG	**L**	*L*	*L*	**M**	DG	**L**	DG	**L**	**L**	*M*	*M*	*M*	**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	Yes	No	No
3	STOP						
4	STOP						

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Dibutoxymethane	2

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

Table 6

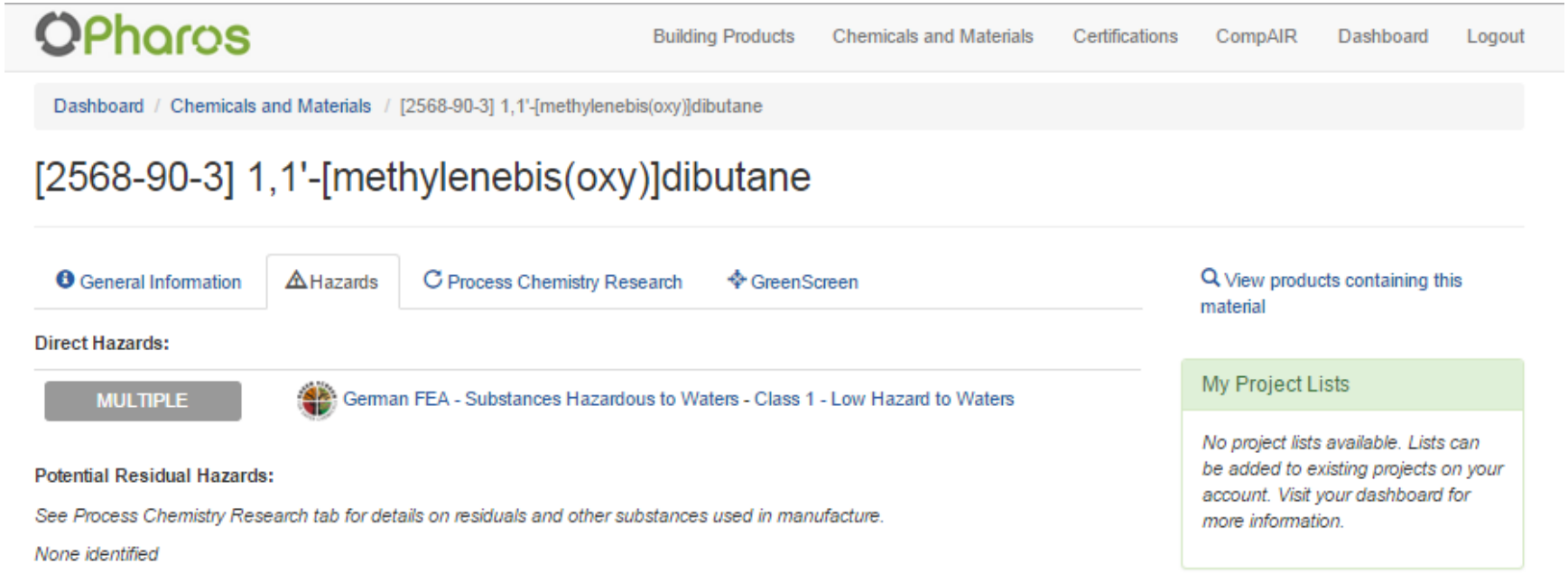
Chemical Name	Final GreenScreen® Benchmark Score
Dibutoxymethane	U

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

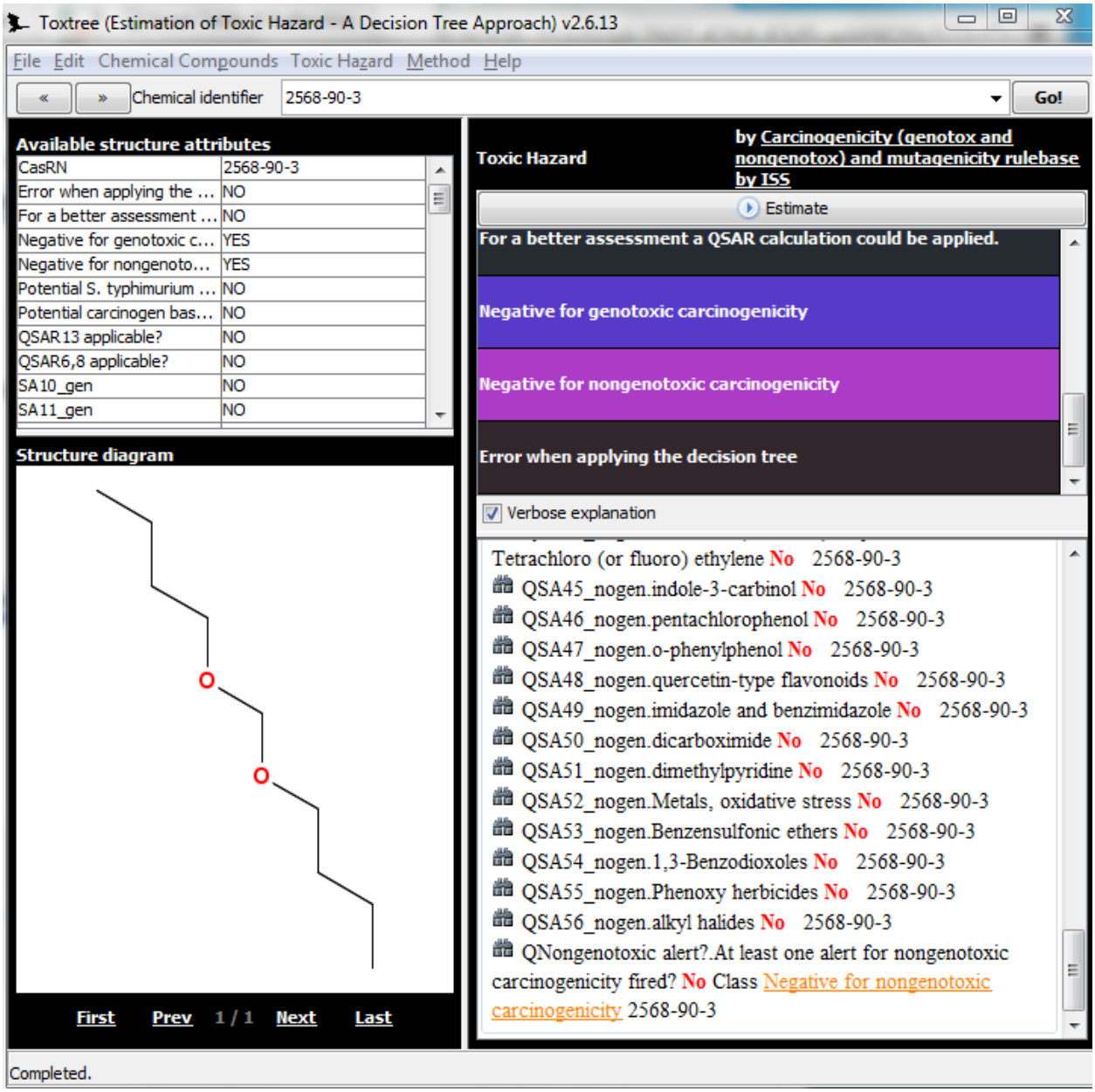
Table 5: Data Gap Assessment Table

Datagap Criteria	a	b	c	d	e	f	g	h	i	j	bm4	End Result
1												
2	No	Yes	Yes	Yes	Yes							U
3												
4												

APPENDIX C: Pharos Output for Dibutoxymethane (CAS #2568-90-3)



APPENDIX D: Toxtree Skin Sensitization Results for Dibutoxymethane (CAS #2568-90-3)



APPENDIX E: ECOSAR Modeling Results for Dibutoxymethane (CAS #2568-90-3)

ECOSAR Version 1.11 Results Page

SMILES : O(CCCC)COCCCC
CHEM : Butane, 1,1 -[methylenebis(oxy)]bis-
CAS Num: 002568-90-3
ChemID1:
MOL FOR: C9 H20 O2
MOL WT : 160.26
Log Kow: 2.752 (EPISuite Kowwin v1.68 Estimate)
Log Kow: 2.770 (User Entered)
Log Kow: (PhysProp DB exp value - for comparison only)
Melt Pt: 182.50 (deg C, User Entered for Wat Sol estimate)
Melt Pt: -58.10 (deg C, PhysProp DB exp value for Wat Sol est)
Wat Sol: 19.34 (mg/L, EPISuite WSKowwin v1.43 Estimate)
Wat Sol: 222.5 (mg/L, User Entered)
Wat Sol: (PhysProp DB exp value)

Values used to Generate ECOSAR Profile

Log Kow: 2.770 (User Entered)
Wat Sol: 222.5 (mg/L, User Entered)

Available Measured Data from ECOSAR Training Set

No Data Available

ECOSAR v1.1 Class-specific Estimations

Neutral Organics

ECOSAR Class	Organism	Duration	End Pt	Predicted mg/L (ppm)
Neutral Organics	: Fish	96-hr	LC50	26.785
Neutral Organics	: Daphnid	48-hr	LC50	16.329
Neutral Organics	: Green Algae	96-hr	EC50	16.320
Neutral Organics	: Fish		ChV	2.847
Neutral Organics	: Daphnid		ChV	1.941
Neutral Organics	: Green Algae		ChV	5.007
Neutral Organics	: Fish (SW)	96-hr	LC50	33.876

Neutral Organics	: Mysid	96-hr	LC50	14.944
Neutral Organics	: Fish (SW)		ChV	5.884
Neutral Organics	: Mysid (SW)		ChV	1.028
Neutral Organics	: Earthworm	14-day	LC50	231.832 *

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

Class Specific LogKow Cut-Offs

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

Neutral Organics:

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

APPENDIX F: EPISuite Modeling Results for Dibutoxymethane (CAS #2568-90-3)

CAS Number: 2568-90-3
SMILES : O(CCCC)COCCCC
CHEM : Butane, 1,1 -[methylenebis(oxy)]bis-
MOL FOR: C9 H20 O2
MOL WT : 160.26
---------- EPI SUMMARY (v4.11) ----------
Physical Property Inputs:
Log Kow (octanol-water): 2.77
Boiling Point (deg C) : 182.50
Melting Point (deg C) : -59.40
Vapor Pressure (mm Hg) : 0.59
Water Solubility (mg/L): 222.5
Henry LC (atm-m3/mole) : ------

Log Octanol-Water Partition Coef (SRC):
Log Kow (KOWWIN v1.68 estimate) = 2.75

Boiling Pt, Melting Pt, Vapor Pressure Estimations (MPBPVP v1.43):
Boiling Pt (deg C): 187.20 (Adapted Stein & Brown method)
Melting Pt (deg C): -20.93 (Mean or Weighted MP)
VP(mm Hg,25 deg C): 1.18 (Mean VP of Antoine & Grain methods)
VP (Pa, 25 deg C) : 157 (Mean VP of Antoine & Grain methods)
MP (exp database): -58.1 deg C
BP (exp database): 179.2 deg C

Water Solubility Estimate from Log Kow (WSKOW v1.42):
Water Solubility at 25 deg C (mg/L): 543.8
log Kow used: 2.77 (user entered)
melt pt used: -59.40 deg C

Water Sol Estimate from Fragments:
Wat Sol (v1.01 est) = 717.76 mg/L

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

Henrys Law Constant (25 deg C) [HENRYWIN v3.20]:
Bond Method : 2.77E-004 atm-m3/mole (2.81E+001 Pa-m3/mole)
Group Method: 1.47E-003 atm-m3/mole (1.49E+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: 5.592E-004 atm-m3/mole (5.666E+001 Pa-m3/mole)
VP: 0.59 mm Hg (source: User-Entered)
WS: 223 mg/L (source: User-Entered)

Log Octanol-Air Partition Coefficient (25 deg C) [KOAWIN v1.10]:
Log Kow used: 2.77 (user entered)
Log Kaw used: -1.946 (HenryWin est)
Log Koa (KOAWIN v1.10 estimate): 4.716
Log Koa (experimental database): None

Probability of Rapid Biodegradation (BIOWIN v4.10):
Biowin1 (Linear Model) : 0.1934
Biowin2 (Non-Linear Model) : 0.0803
Expert Survey Biodegradation Results:
Biowin3 (Ultimate Survey Model): 3.4244 (days-weeks)
Biowin4 (Primary Survey Model) : 4.1352 (days)
MITI Biodegradation Probability:
Biowin5 (MITI Linear Model) : 0.5850
Biowin6 (MITI Non-Linear Model): 0.6749
Anaerobic Biodegradation Probability:
Biowin7 (Anaerobic Linear Model): -0.2911
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): 78.7 Pa (0.59 mm Hg)
Log Koa (Koawin est): 4.716
Kp (particle/gas partition coef. (m3/ug)):
Mackay model : 3.81E-008
Octanol/air (Koa) model: 1.28E-008
Fraction sorbed to airborne particulates (phi):
Junge-Pankow model : 1.38E-006
Mackay model : 3.05E-006
Octanol/air (Koa) model: 1.02E-006

Atmospheric Oxidation (25 deg C) [AopWin v1.92]:
Hydroxyl Radicals Reaction:
OVERALL OH Rate Constant = 28.1080 E-12 cm3/molecule-sec
Half-Life = 0.381 Days (12-hr day; 1.5E6 OH/cm3)
Half-Life = 4.566 Hrs
Ozone Reaction:
No Ozone Reaction Estimation
Fraction sorbed to airborne particulates (phi):
2.21E-006 (Junge-Pankow, Mackay avg)
1.02E-006 (Koa method)
Note: the sorbed fraction may be resistant to atmospheric oxidation

Soil Adsorption Coefficient (KOCWIN v2.00):
Koc : 47.76 L/kg (MCI method)
Log Koc: 1.679 (MCI method)

Koc : 188.8 L/kg (Kow method)
Log Koc: 2.276 (Kow 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 = 1.495 (BCF = 31.24 L/kg wet-wt)
Log Biotransformation Half-life (HL) = -0.4154 days (HL = 0.3842 days)
Log BCF Arnot-Gobas method (upper trophic) = 1.647 (BCF = 44.33)
Log BAF Arnot-Gobas method (upper trophic) = 1.647 (BAF = 44.33)
log Kow used: 2.77 (user entered)

Volatilization from Water:
Henry LC: 0.000559 atm-m3/mole (calculated from VP/WS)
Half-Life from Model River: 2.617 hours
Half-Life from Model Lake : 134.7 hours (5.613 days)

Removal In Wastewater Treatment:
Total removal: 22.78 percent
Total biodegradation: 0.09 percent
Total sludge adsorption: 3.55 percent
Total to Air: 19.13 percent
(using 10000 hr Bio P,A,S)

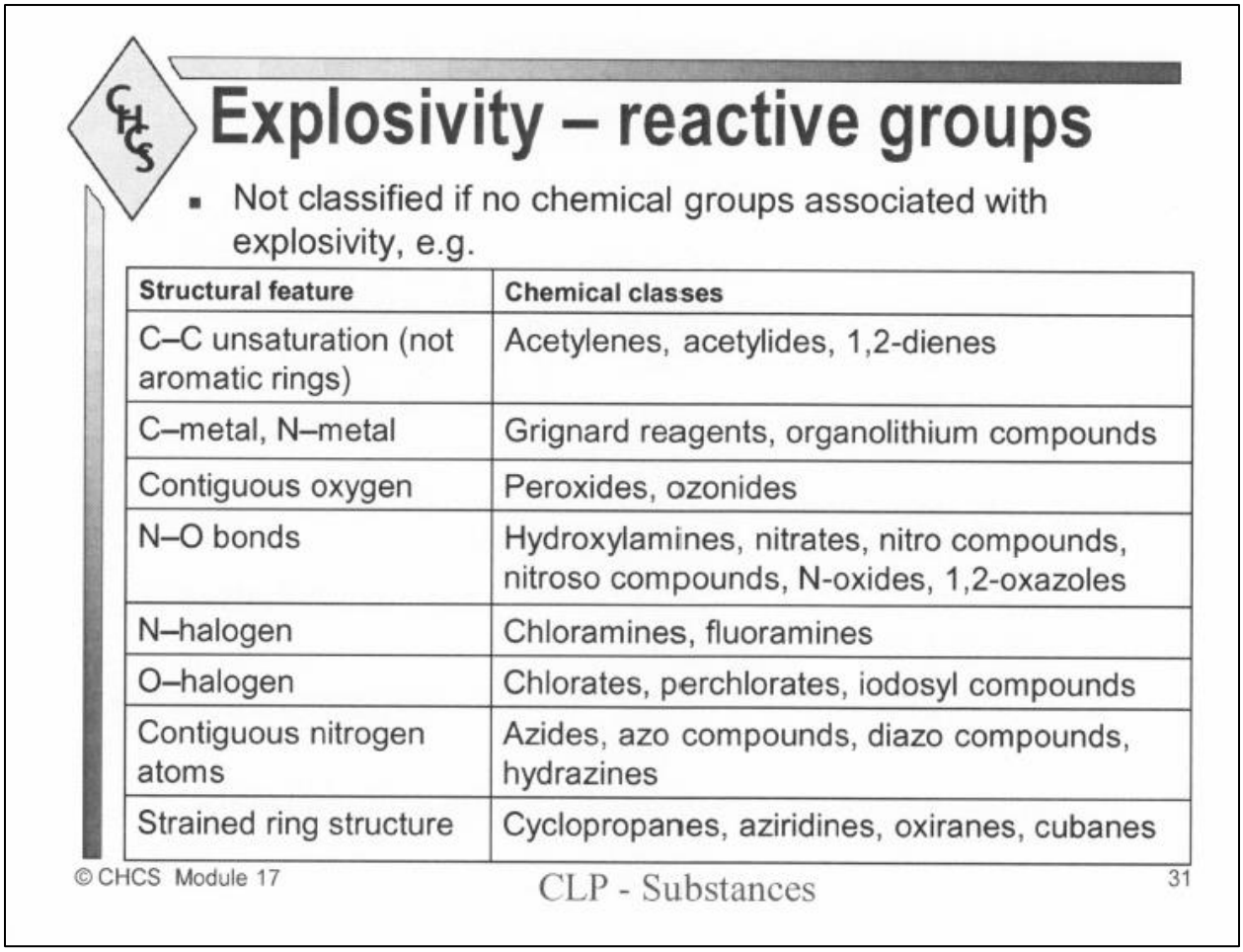
Level III Fugacity Model:

	Mass Amount (percent)	Half-Life (hr)	Emissions (kg/hr)
Air	3.61	7.57	1000
Water	36	208	1000
Soil	60.3	416	1000
Sediment	0.123	1.87e+003	0

Persistence Time: 161 hr

APPENDIX G: Known Structural Alerts for Reactivity

Explosivity – Abbreviated List



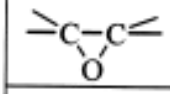
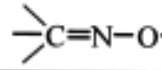
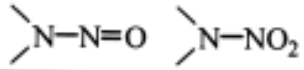
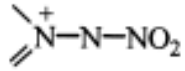
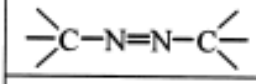
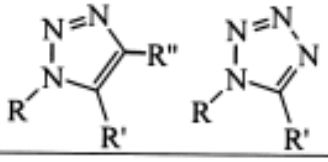
Explosivity – reactive groups

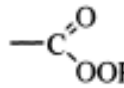
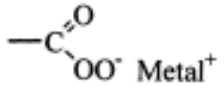
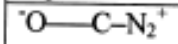
- Not classified if no chemical groups associated with explosivity, e.g.

Structural feature	Chemical classes
C–C unsaturation (not aromatic rings)	Acetylenes, acetylides, 1,2-dienes
C–metal, N–metal	Grignard reagents, organolithium compounds
Contiguous oxygen	Peroxides, ozonides
N–O bonds	Hydroxylamines, nitrates, nitro compounds, nitroso compounds, N-oxides, 1,2-oxazoles
N–halogen	Chloramines, fluoramines
O–halogen	Chlorates, perchlorates, iodosyl compounds
Contiguous nitrogen atoms	Azides, azo compounds, diazo compounds, hydrazines
Strained ring structure	Cyclopropanes, aziridines, oxiranes, cubanes

Explosivity – Full List

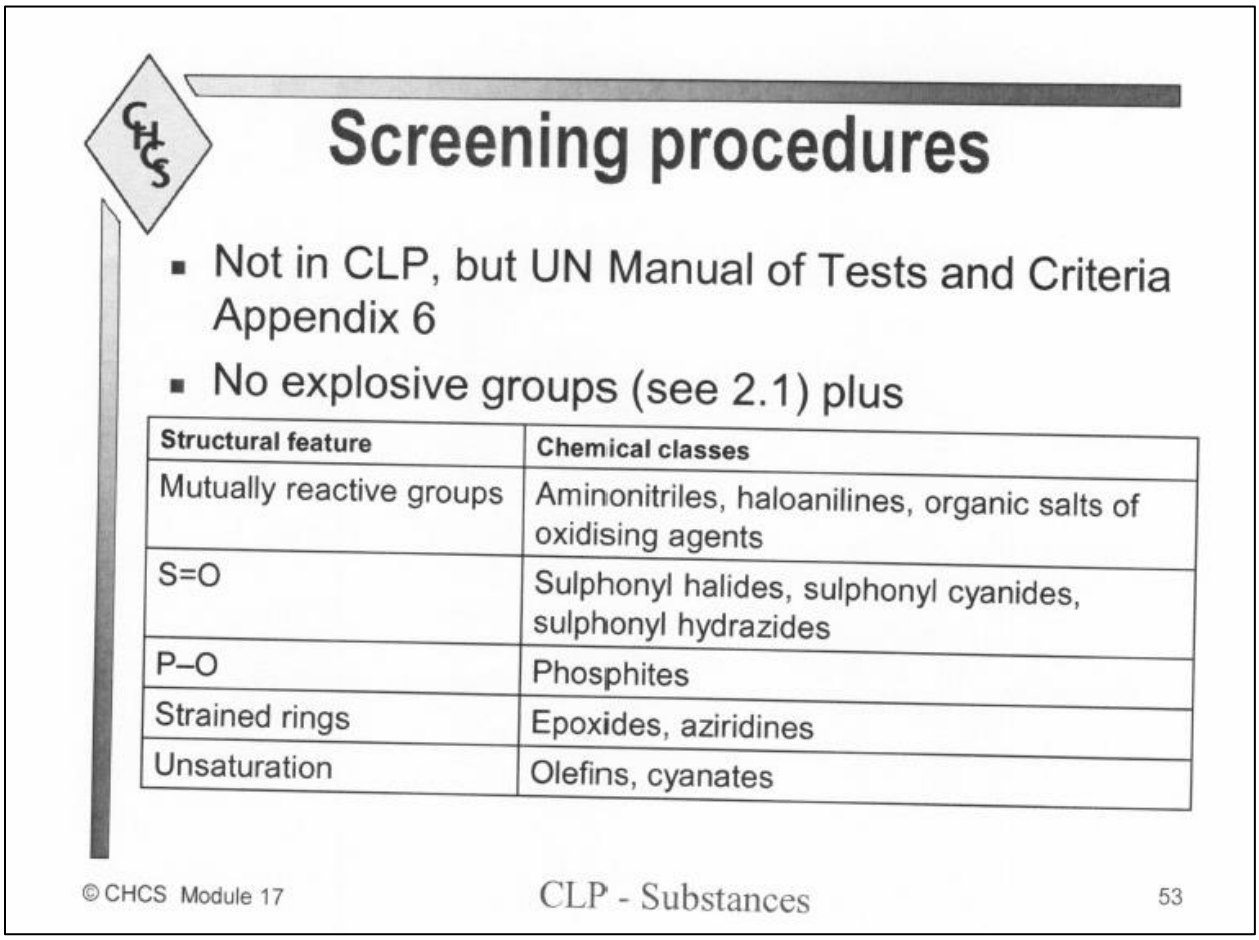
Table R.7.1-28 Chemical groups associated with explosive properties

Chemical group	Chemical Class
-C≡C- -C≡C-Metal -C≡C-Halogen	Acetylenic Compounds Metal Acetylides Haloacetylene Derivatives
	Diazo Compounds
-N=O -NO_2	Nitroso and Nitro Compounds,
R-O-N=O R-O-NO_2	Acyl or Alkyl Nitrites and Nitrates
	1,2-Epoxides
	Metal Fulminates or *aci*-Nitro Salts
	N-Metal Derivatives (especially heavy metals)
	N-Nitroso and N-Nitro Compounds
	N-Azolium Nitroimidates
	Azo Compounds
Ar-N=N-O-Ar	Arene Diazoates
$(ArN=N)_2O$, $(ArN=N)_2S$	Bis-Arenediazo Oxides and Sulfides
RN=N-NR'R''	Triazines
	High-nitrogen Compounds: e.g. Triazoles, Tetrazoles

Chemical group	Chemical Class
[1] ROOR', [2] 	Peroxy Compounds: [1] Alkyl hydroperoxides (R'=H), Peroxides (R'=organic); [2] Peroxo acids (R'=H), Peroxyesters (R'=organic)
[1] ROOMetal, [2] 	Metal peroxides, Peroxoacids salts
$-N_3$	Azides e.g. PbN_6, CH_3N_3
	Arenediazonium oxides i.e. inner diazonium salts in which the counter ion is an oxide
Ar-N=N-S- Ar-N=N-S-Ar	Diazonium sulfides and derivatives, Arenediazo Aryl Sulfides
XO_n	Halogen Oxide: e.g. percholrates, bromates, etc
NX_3 e.g. $NC1_3$, $RNC1_2$	N-Halogen Compounds

Adapted from Bretherick (Bretherick's Handbook of Reactive Chemical Hazards 6th Ed., 1999, Butterworths, London)

Self-Reactive Substances



Licensed GreenScreen® Profilers

Dibutoxymethane GreenScreen® Evaluation Prepared by:

Jennifer Rutkiewicz, Ph.D.
Toxicologist
ToxServices LLC

Dibutoxymethane GreenScreen® Evaluation QC'd by:

Bingxuan Wang, Ph.D., D.A.B.T.
Toxicologist
ToxServices LLC