Barium Sulfate (CAS# 7727-43-7) GreenScreen® for Safer Chemicals (GreenScreen®) Assessment

Prepared for:

Washington State Department of Ecology

Prepared by:

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October 14, 2014

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GreenScreen® Executive Summary for Barium Sulfate (CAS #7727-43-7)

Barium sulfate is a chemical that is used to make drilling muds in the oil and gas industry, to make paints, bricks, tiles, glass, and rubber, as a chemical intermediate to prepare other barium compounds, to perform medical tests and x-rays, and as a color pigment.

Barium sulfate was assigned a GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") as it has Very High persistence (P), Moderate Group I Human Toxicity (reproductive toxicity (R)) and Moderate Ecotoxicity (chronic aquatic toxicity (CA)). This corresponds to GreenScreen® benchmark classifications 2c and 2e in CPA (2011). Data gaps (DG) exist for developmental toxicity (D), endocrine activity (E), 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), barium sulfate meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if barium sulfate were assigned a High score for the data gaps developmental toxicity (D), endocrine activity (E), or respiratory sensitization (SnR*), 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 Barium Sulfate

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**	*M*	DG	DG	**L**	DG	**L**	DG	**L**	**L**	DG	**L**	**L**	**M**	*M*	*vH*	*L*	*L*	*L*

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 Barium Sulfate (CAS #7727-43-7)

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

Chemical Name: Barium sulfate

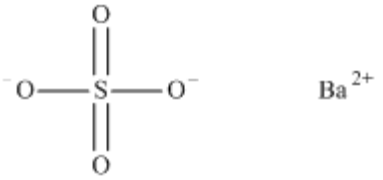
CAS Number: 7727-43-7

GreenScreen® Assessment Prepared By:
Name: Jennifer Rutkiewicz, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: September 25, 2014
Assessor Type: Licensed GreenScreen® Profiler

Quality Control Performed By:
Name: Bingxuan Wang, Ph.D.
Title: Toxicologist
Organization: ToxServices LLC
Date: October 14, 2014

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

Chemical Structure(s):



Also called: Pigment white 21; Sulfuric acid, barium salt (1:1); CI 77120; Barium sulphate (ChemIDplus 2014)

Chemical Structure(s) of Chemical Surrogates Used in the GreenScreen®:
Very few data were identified for barium sulfate. The REACH dossier for this chemical (ECHA 2014) identified barium chloride dihydrate as a read-across chemical for barium sulfate, based on the assumption that toxic effects result from the barium ion rather than the chloride or sulfate ions. Barium chloride hexahydrate was also selected as a representative barium compound for the U.S. EPA's toxicological review and RfD derivation of barium and its compounds (U.S. EPA 2005). Compared to barium sulfate, which has only slight water solubility of 3.1 mg/L (ECHA 2014), barium chloride is moderately soluble in water at 375 mg/L (U.S. EPA 2005). Barium sulfate is generally considered to be of low toxicity as it is not soluble in the gastrointestinal tract and is therefore an inefficient source of the Ba^{2+} ion. The Ba^{2+} ion in barium chloride is more bioavailable (ATSDR 2007), and thus scores based on data for this chemical are conservative and are not likely to underestimate the effects of barium sulfate. Confidence in scores other than Low assigned based on data for the surrogate are considerered to be low due to different physicochemical properties of the two compounds.

[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

Barium chloride dihydrate (CAS# 10326-27-9)

Identify Applications/Functional Uses:
1. Drilling muds
2. Paints
3. Bricks
4. Tiles
5. Glass
6. Rubber
7. Chemical intermediate
8. Medical tests and x-rays (ATSDR 2007)
9. Color pigment (ChemIDplus 2014)

GreenScreen® Summary Rating for Barium Sulfate[4]: Barium sulfate was assigned a GreenScreen® Benchmark Score of 2 ("Use but Search for Safer Substitutes") as it has Very High persistence (P), Moderate Group I Human Toxicity (reproductive toxicity (R)) and Moderate Ecotoxicity (chronic aquatic toxicity (CA)). This corresponds to GreenScreen® benchmark classifications 2c and 2e in CPA (2011, 2012a). Data gaps (DG) exist for developmental toxicity (D), endocrine activity (E), 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), barium sulfate meets requirements for a GreenScreen® Benchmark Score of 2 despite the hazard data gaps. In a worst-case scenario, if barium sulfate were assigned a High score for the data gaps developmental toxicity (D), endocrine activity (E), or respiratory sensitization (SnR*), it would be categorized as a Benchmark 1 Chemical.

Figure 1: GreenScreen® Hazard Ratings for Barium Sulfate

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	*M*	DG	DG	L	DG	L	DG	L	L	DG	L	L	M	*M*	*vH*	*L*	*L*	*L*

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. Barium sulfate is a stable inorganic chemical and is expected to persist in the environment. No transformation products are expected.

Introduction

Barium sulfate is a naturally occurring barium compound found in underground ore deposits. It is used to make drilling muds in the oil and gas industry, to make paints, bricks, tiles, glass, and rubber, as a chemical intermediate to prepare other barium compounds, to perform medical tests and x-rays (ATSDR 2007), and as a color pigment (ChemIDplus 2014).

ToxServices assessed barium sulfate 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 barium sulfate can be found in Appendix C and a summary of the results can be found below:

- Developmental Toxicity:
  - German MAK - List of Substances (MAK) Pregnancy Risk Group C

- Mammalian Toxicity:
  - Environment Canada - Domestic Substances List (DSL) Inherently Toxic to Humans: DSL substances that meet human health categorization criteria
  - U.S. DOT Hazard Class 6.1 Packing Group II

- Persistence:
  - Environment Canada - Domestic Substances List (DSL) DSL substances that are Persistent

PhysicoChemical Properties of Barium Sulfate

Barium sulfate is a solid at room temperature. It is slightly soluble in water based on its water solubility of 3.1 mg/L and decomposes without melting at 1600 °C. It has a relative density of 3.07-3.91. No additional physicochemical properties were identified.

[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 Barium Sulfate (CAS #7727-43-7)		
Property	**Value**	**Reference**
Molecular formula	Ba-S-O4	ChemIDplus 2014
SMILES Notation	[O-]S(=O)(=O)[O-].[Ba+2]	ChemIDplus 2014
Molecular weight	233.392	ChemIDplus 2014
Physical state	Solid	ECHA 2014
Appearance	White crystalline powder	ECHA 2014
Melting point	1600°C (decomposes)	ECHA 2014
Vapor pressure	Not identified	
Water solubility	3.1 mg/L at 20°C	ECHA 2014
Dissociation constant	Not identified	
Density/specific gravity	3.07-3.97 at 19°C	ECHA 2014
Partition coefficient	Not identified	

Hazard Classification Summary Section:

Group I Human Health Effects (Group I Human)

Carcinogenicity (C) Score (H, M, or L): L
Barium sulfate was assigned a score of Low for carcinogenicity based on negative results in oral carcinogenicity studies of the surrogate barium chloride dihydrate in rats and mice. GreenScreen® criteria classify chemicals as a Low hazard for carcinogenicity when adequate data are available and are negative for carcinogenicity, and the chemical is not present on authoritative or screening lists (CPA 2012a).

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

Barium sulfate (CAS# 7727-43-7)

- No data were identified

Barium chloride dihydrate (CAS# 10326-27-9)

- ECHA 2014, NTP 1994
    - Barium chloride dihydrate was negative in a 2-year oral carcinogenicity study in male and female F344/N rats conducted by NTP. Animals (60/sex/dose) were administered barium chloride dihydrate (>99% purity) in drinking water at concentrations of 0, 500, 1,250, or 2,500 ppm (corresponding to daily doses of 15, 30, or 60 mg barium/kg for males and 15, 45, or 74 mg barium for females) for 104 weeks (males) or 105 weeks (females). No evidence of carcinogenicity was seen. Authors identified a NOAEL of 2,500 ppm for carcinogenicity, which corresponds to barium doses of 60 mg/kg/day (males) and 75 mg/kg/day (females).
    - Barium chloride dihydrate was negative in a 2-year oral carcinogenicity study in male and female B6C3F1 mice conducted by NTP. Animals (60/sex/dose) were administered barium chloride dihydrate (>99% purity) in drinking water at concentrations of 0, 500, 1,250, or 2,500 ppm (corresponding to daily doses of 30, 75, or 160 mg barium/kg for males and 40, 90, or 200 mg barium/kg for females) for 103 weeks (males) or 104 weeks (females). No evidence of carcinogenicity was seen. Authors identified a NOAEL of 2,500 ppm for carcinogenicity, which corresponds to barium doses of 160 mg/kg/day (males) and 200 mg/kg/day (females).

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

Barium sulfate was assigned a score of Low for mutagenicity/genotoxicity based on negative results in *in vitro* bacterial and mammalian cell mutagenicity assays and an *in vitro* chromosome aberration assay for the surrogate barium chloride dihydrate. GreenScreen® criteria classify chemicals as a Low hazard for mutagenicity/genotoxicity when adequate data are available and are negative for both mutagenicity and clastogenicity, and the chemical is not present on authoritative or screening lists (CPA 2012a).

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

Barium sulfate (CAS# 7727-43-7)

- No data were identified

Barium chloride dihydrate (CAS# 10326-27-9)

- ECHA 2014
    - Barium chloride dihydrate was negative in a GLP-compliant *in vitro* mammalian chromosome aberration test according to OECD Guideline 473 in Chinese hamster Ovary (CHO) cells when tested at concentrations up to 2,000 µg/mL without metabolic activation and 5,000 µg/mL with metabolic activation.
    - Barium chloride dihydrate was negative in a GLP-compliant Ames reverse mutation assay according to OECD Guideline 471 in *S. typhimurium* strains TA1535, TA1537, TA98, TA100, and TA97 when tested in duplicate at concentrations of 100, 333, 1,000, 3,333, 10,000 µg/plate with and without metabolic activation. No increase in revertants was seen in any strain at any dose.
    - Barium chloride dihydrate was negative in a GLP-compliant *in vitro* mammalian cell gene mutation assay according to OECD Guideline 476 in mouse lymphoma L5178Y cells when tested at concentrations of 250-2,082 µg/mL with and without metabolic activation (experiment 1) or 100-1,400 µg/mL without metabolic activation and 200-1,400 µg/mL with metabolic activation (experiment 2). No evidence of mutagenicity was seen at any concentration, including toxic or precipitating concentrations, in two independent experiments.

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

Barium sulfate was assigned a score of Moderate for reproductive toxicity based on effects on litter size in 1-generation oral studies of the surrogate barium chloride dihydrate in rats and mice. GreenScreen® criteria classify chemicals as a Moderate hazard for reproductive toxicity when there is limited or marginal evidence of reproductive toxicity (CPA 2012a).

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

Barium sulfate (CAS# 7727-43-7)

- No data were identified

Barium chloride dihydrate (CAS# 10326-27-9)

- U.S. EPA 2005
    - In a 1-generation mating trial study in F344/N rats, animals (20/sex/dose) were administered barium chloride dihydrate in drinking water at concentrations of 0, 1,000, 2,000, or 4,000 ppm (equivalent to 0, 65, 110, or 200 mg/kg/day for males and 0, 65, 115, or 180 mg/kg/day for females) for 60 days (males) or 30 days (females). At the conclusion of treatment, animals were mated during an 8 day mating period. Length of pregnancy, number of implantation sites, number of live and dead offspring, pup weights at birth postnatal day 5,

external abnormalities of pups, gross examination of the vagina, cervix, oviduct, and uterus of the F_0 dams, and evaluation of sperm density, morphology, and motility, and reproductive organ weights of the F_0 males were assessed. There were no effects on gestation length, pup survival, or external abnormalities of pups. Litter sizes were marginally but not statistically significantly reduced at the high dose. The number of implants per dam was marginally but not statistically significantly reduced at this dose as well. Live pup weight at birth was reduced at the high dose, but no reduction was observed at postnatal day 5.

- In a 1-generation mating trial study in B6C3F1 mice, animals (20/sex/dose) were administered barium chloride dihydrate in drinking water at concentrations of 0, 500, 1,000, or 2,000 ppm (equivalent to 0, 55, 100, or 205 mg/kg/day for males and 0, 60, 110, or 200 mg/kg/day for females) for 60 days (males) or 30 days (females). At the conclusion of treatment, animals were mated during an 8 day mating period. Length of pregnancy, number of implantation sites, number of live and dead offspring, pup weights at birth postnatal day 5, external abnormalities of pups, gross examination of the vagina, cervix, oviduct, and uterus of the F_0 dams, and evaluation of sperm density, morphology, and motility, and reproductive organ weights of the F_0 males were assessed. No effects on weight gain, gestation length, pup survival, or pup weights were seen. Average litter size on days 0 and 5 was significantly reduced in the 1,000 ppm dose group but not at the high dose of 2,000 ppm. There were no effects on sperm counts, sperm motility, sperm morphology, testicular or epididymal weights, or vaginal cytology.

- Based on the weight of evidence, a conservative score of Moderate was assigned. Reductions in litter sizes in the rat study were not statistically significant, but a similar result was seen in the mouse study. Similar effects on pup weight at day 0 were seen in both species as well. Although effects in both studies were of low magnitude, transient and/or not dose related, a score of Moderate was conservatively assigned as GreenScreen® criteria specify a score of Moderate when there is limited or marginal evidence of reproductive toxicity in animals.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M, or L): DG
Barium sulfate was assigned a score of Data Gap for developmental toxicity based on a lack of data for this endpoint (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:*
    - German MAK - List of Substances (MAK) Pregnancy Risk Group C
  - *Screening:* Not present on any screening lists

<u>Barium sulfate (CAS# 7727-43-7)</u>

- No data were identified

<u>Barium chloride dihydrate (CAS# 10326-27-9)</u>

- No data were identified

Endocrine Activity (E) Score (H, M, or L): DG
Barium sulfate was assigned a score of Data Gap for endocrine disruption 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.

Barium sulfate (CAS# 7727-43-7)
- No data were identified

Barium chloride dihydrate (CAS# 10326-27-9)
- 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

Barium sulfate was assigned a score of Low for acute toxicity based on an oral LD_{50} of 307-364 g/kg in rats. GreenScreen® criteria classify chemicals as a Low hazard for acute toxicity when oral LD50 values are greater than 2,000 mg/kg (CPA 2012a).

- Authoritative and Screening Lists
  - *Authoritative:*
    - U.S. DOT Hazard Class 6.1 Packing Group II (as barium compounds n.o.s.)
  - *Screening:* Not present on any screening lists

Barium sulfate (CAS# 7727-43-7)
- ECHA 2014
  - *Oral*: LD_{50} (rat, male Wistar) = 307-364 g/kg
- Based on the weight of evidence, a score of Low was assigned. The U.S. DOT classifies barium compounds not otherwise specified as hazard class 6.1 Packing Group II, which corresponds to a score of Very High. However this is a generic classification for barium compounds, and while soluble barium salts are known to have toxic effects in the body, the insoluble salt barium sulfate is considered to be nontoxic as it is not an efficient form of the Ba^{2+} ion (NTP 1994, ATSDR 2007). Therefore the generic DOT classification was not considered relevant to barium sulfate. The oral LD_{50} of 307-364 g/kg corresponds to a score of Low.

Systemic Toxicity/Organ Effects incl. Immunotoxicity (ST)

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

Barium sulfate was assigned a score of Data Gap for systemic toxicity (single 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

Barium sulfate (CAS# 7727-43-7)
- No data were identified

Barium chloride dihydrate (CAS# 10326-27-9)
- No data were identified

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

Barium sulfate was assigned a score of Low for systemic toxicity (repeated dose) based on subchronic and chronic oral toxicity studies of the surrogate barium chloride dihydrate in rats and mice. GreenScreen® criteria classify chemicals as a Low hazard for systemic toxicity (repeated dose) when

adequate data are available and systemic toxicity is not seen below the guidance value of 100 mg/kg/day for an oral study (CPA 2012a).

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

Barium sulfate (CAS# 7727-43-7)

- No data were identified

Barium chloride dihydrate (CAS# 10326-27-9)

- U.S. EPA 2005, NTP 1994
    - *Oral*: In a subchronic oral toxicity study conducted by NTP, male and female F344/N rats were administered ministered barium chloride dihydrate (>99% purity) in drinking water at concentrations of 0, 125, 500, 1,000, 2,000, or 4,000 ppm (corresponding to daily barium doses of 10, 30, 65, 110, or 200 mg/kg for males and 10, 35, 65, 115, or 180 mg/kg for females) for 13 weeks. Mortality (3 males and 1 female) was observed only at the high dose. At the high dose, water consumption decreased by 30% and body weights were reduced by 13% in males and 8% in females. Absolute and relative kidney weights were increased in females at the two highest doses, and mean thymus weight was decreased by 22% at the high dose. Mean absolute liver weight was decreased in males at the high dose. Nephropathy (minimal to mild, focal to multifocal areas of dilatation of the proximal convoluted tubules) was seen in 3/10 males and 3/10 females only at the high dose. Lymphoid depletion of the spleen and thymus was seen in the high dose animals that died. No treatment related biologically significant changes in clinical chemistry or hematology were seen. A significant increase in serum phosphorus levels in females at doses of >500 ppm and males at > 2,000 ppm were considered by NTP not to be relevant as statistical significance was due to a control value lower than historical controls. No effects on a cardiovascular assessment (heart rate, EKG readings, or blood pressure) were seen. Authors identified a NOAEL of 110 mg/kg/day barium based on effects at the high dose. The equivalent dose of barium sulfate is 187 mg/kg/day[6].
    - *Oral*: In the 2-year oral carcinogenicity study in male and female F344/N rats described above for carcinogenicity, hematology and clinical chemistry were assessed at a 15 month interim evaluation, and 10 animals/sex/dose were sacrificed for organ weight and histopathological assessments. Survival of treated males was increased relative to controls, and survival of females was not affected. Body weights of males at the high dose were reduced by 5% and weights of females at the two highest doses were reduced by 6% and 11%. No treatment-related effects were seen on bone density. In females at the 1,250 and 2,500 ppm doses, relative kidney weights were increased by 6% and 15% and absolute kidney weights were increased by 3% and 4%. In males at these doses, relative kidney weights were decreased by 7% and 9% and absolute kidney weights were not affected. Absolute liver weight was decreased in females at all treatment groups. Statistical significance was not reported. Nephropathy was observed in both control and treated animals, and was not found to be treatment-related. Authors identified a NOAEL of 30 mg/kg/day and LOAEL of 60 mg/kg/day barium (male doses) based on effects on body weight at the high dose. The equivalent doses of barium sulfate are 51 mg/kg/day and 102 mg/kg/day (for males).
    - *Oral*: In a subchronic oral toxicity study conducted by NTP, male and female B6C3F1 mice (10/sex/dose) were administered barium chloride dihydrate (>99% purity) in drinking water

[6] 110 mg/kg/day * 233.392/137.33 = 187 mg/kg/day (based on molecular weights of 137.33 for barium and 233.392 for barium sulfate)

at concentrations of 0, 125, 500, 1,000, 2,000, or 4,000 ppm (corresponding to daily barium doses of 15, 55, 100, 205, and 450 mg/kg for males and 15, 60, 110, 200, and 495 mg/kg for females) for 13 weeks. High mortality (6/10 males and 7/10 females) was seen in the high dose group, and water consumption decreased by 18% in males. Body weights were reduced by 30-50% in both sexes at the high dose. In males at this dose, absolute and relative kidney weights were decreased by 23% and 12%, and in females at this dose, absolute kidney weights were decreased by 21%, and relative kidney weights were increased by 40%. Absolute and relative thymus weights were decreased in both sexes. Absolute and relative liver weights were decreased in both sexes at concentrations of 1,000 ppm and above. Statistical significance was not reported. Histologically, nephropathy (tubule dilatation, renal tubule atrophy, tubule cell regeneration, and presence of crystals in the lumen of the renal tubules) was seen in all males and 9/10 females at the high dose. Atrophy of the spleen (diminution of the hematopoietic elements of red pulp and depletion of lymphocyctes in the periarteriolar lymphoid sheath) and thymus (necrotic or moderate to marked depletion of thymic lymphocytes) was seen in animals at the high dose. Authors identified a NOAEL of 2,000 ppm and LOAEL of 4,000 ppm (200 mg/kg/day and 450 mg/kg/day barium). The equivalent doses of barium sulfate are 340 and 764 mg/kg/day[7].

- *Oral*: In the 2-year oral carcinogenicity study in male and female B6C3F1 mice described above for carcinogenicity, 6-10 animals/sex/dose were sacrificed for a 15-month interim evaluation and the remainder were evaluated at the conclusion of the study. Organ weights and clinical chemistry were assessed at the interim evaluation and hematology and histopathology were evaluated at both time points. Survival was significantly reduced in both sexes at the high dose and mean body weights were reduced by 8% in males and 12% in females. At the interim evaluation, in the high dose group absolute and relative spleen weights were reduced in females and mean and relative thymus weights were reduced in males. Several males at the high dose had increased levels of BUN, alanine aminotransferase, and creatine kinase and several females had increased levels of BUN (statistical significance not reported). Histologically, moderate to marked nephropathy was seen in 19/60 males and 37/60 females at the high dose and 2/58 males and 1/60 females at the mid dose. Irregularly shaped brown crystals were seen in the renal tubules and interstitium. At the high dose, lymphoid depletion was apparent in the spleen, thymus, and lymph nodes. Authors identified a LOAEL of 160 mg/kg/day barium based on the significant increase in renal lesions at the high dose. They considered the low dose of 30 mg/kg/day barium to be the NOAEL, as a low level of renal lesions was seen at the mid dose of 750 mg/kg/day barium. ToxServices conservatively considers 75 mg/kg/day to be the LOAEL, based on the small number of animals with nephropathy at this dose. The doses of 30 mg/kg/day and 75 mg/kg/day barium are equivalent to 51 mg/kg/day and 127.46 mg/kg/day barium sulfate.

- Based on the weight of evidence, a score of Low was assigned. The most conservative LOAELs identified were equivalent to 102 mg/kg/day barium sulfate based on effects on body weight in the 2-year drinking water study in rats and 127.46 mg/kg/day barium sulfate based on effects on the kidney in the 2-year drinking water study in mice. In its evaluation of barium and barium compounds, U.S. EPA considered treatment-related nephropathy to be the critical toxic effect of barium exposure, and identified the 2-year drinking water study in mice to be the key study. Considering the lack of effects on the kidney and small magnitude of effects on body weight (5-11%) in the 2-year study in rats, ToxServices weighed the remaining NTP studies that reported

[7] 200 mg/kg/day * 233.392/137.33 = 340 mg/kg/day (based on molecular weights of 137.33 for barium and 233.392 for barium sulfate)

kidney toxicity more heavily in the assessment. While the LOAEL of 127.46 mg/kg/day in the mouse study is above the guidance value of 100 mg/kg/day, the NOAEL of 51 mg/kg/day falls below it. Therefore these data are insufficient to determine if effects would be seen below the guidance value. However, NOAEL values in the subchronic oral toxicity studies in rats and mice were equivalent to 187 mg/kg/day and 340 mg/kg/day. Considering that these values are above the guidance value and that barium chloride dihydrate is a conservative surrogate for barium sulfate, a score of Low was assigned.

Neurotoxicity (N)

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

Barium sulfate was assigned a score of Data Gap for neurotoxicity (single 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).

Barium sulfate (CAS# 7727-43-7)

- No data were identified

Barium chloride dihydrate (CAS# 10326-27-9)

- No data were identified

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

Barium sulfate was assigned a score of Low for neurotoxicity (repeated dose) based on a NOAEL equivalent to 187 mg/kg/day barium sulfate for neurotoxic effects from a subchronic oral toxicity study of the surrogate barium chloride dihydrate. GreenScreen® criteria classify chemicals as a Low hazard for neurotoxicity (repeated dose) when adequate data are available and no neurological effects are seen below the guidance value of 100 mg/kg/day for an oral toxicity study (CPA 2012a).

- 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).

Barium sulfate (CAS# 7727-43-7)

- No data were identified

Barium chloride dihydrate (CAS# 10326-27-9)

- U.S. EPA 2005, NTP 1994
  - *Oral*: In the subchronic oral toxicity study in male and female F344/N rats conducted by NTP described above for systemic toxicity, neurobehavioral assessments (spontaneous motor activity, forelimb and hind limb grip strength, thermal sensitivity, and startle response to acoustic and air-puff stimulus) were performed before exposure and at days 45 and 91. The magnitude of undifferentiated motor activity at day 90 was significantly decreased at the high dose of 4,000 ppm and marginally decreased at all doses other than 1,000 ppm. No effects were seen on other neurobehavioral endpoints. Authors noted that effects were inconsistent, and may be due to the general condition of animals at high doses. ToxServices identified a NOAEL of 2,000 ppm based on statistically significant effects on motor activity at the high dose, which corresponds to 110 mg/kg/day barium. The equivalent dose of barium sulfate is

187 mg/kg/day[8].

- *Oral*: In the subchronic oral toxicity study in male and female B6C3F1 mice conducted by NTP described above for systemic toxicity, neurobehavioral assessments (undifferentiated motor activity, thermal sensitivity judged by a tail flick latency test, startle response to acoustic and air-puff stimuli, forelimb and hind limb grip strength, and hind limb foot splay) were performed on all animals on days 0, 45, and 90. Forelimb grip strength was significantly reduced in females at the high dose of 4,000 ppm, but no other neurobehavioral endpoints were affected by treatment. ToxServices identified a NOAEL of 2,000 ppm, which corresponds to 200 mg/kg/day barium. The equivalent dose of barium sulfate is 340 mg/kg/day[9].

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

Barium sulfate was assigned a score of Low for skin sensitization based on negative results in a LLNA for the surrogate barium chloride dihydrate. GreenScreen® criteria classify chemicals as a Low hazard for skin sensitization when adequate data are available and are negative for sensitization, and the chemical is not present on authoritative or screening lists (CPA 2012a).

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

Barium sulfate (CAS# 7727-43-7)

- No data were identified

Barium chloride dihydrate (CAS 10326-27-9)

- Barium chloride dihydrate was negative in a GLP-compliant mouse LLNA according to OECD Guideline 429 in female CBA mice. The stimulation indices (SI) at 5%, 10%, and 25% were 1.3, 1.5, and 1.2, respectively. The substance was considered to be non-sensitizing since none of the concentrations produced an SI>3.

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

Barium sulfate 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

Barium sulfate (CAS# 7727-43-7)

- No data were identified

Barium chloride dihydrate (CAS# 10326-27-9)

- No data were identified

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

Barium sulfate was assigned a score of Low for skin irritation/corrosivity based on negative results in an *in vitro* dermal irritation study for the surrogate barium chloride dihydrate. GreenScreen® criteria classify chemicals as a Low hazard for skin irritation/corrosivity when adequate data are available and are negative for irritation, and the chemical is not present on authoritative or screening lists (CPA 2012a).

[8] 110 mg/kg/day * 233.392/137.33 = 187 mg/kg/day (based on molecular weights of 137.33 for barium and 233.392 for barium sulfate)

[9] 200 mg/kg/day * 233.392/137.33 = 340 mg/kg/day (based on molecular weights of 137.33 for barium and 233.392 for barium sulfate)

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

Barium sulfate (CAS# 7727-43-7)

- No data were identified

Barium chloride dihydrate (CAS# 10326-27-9)

- ECHA 2014
    - In a GLP-compliant *in vitro* dermal irritation study according to EC No. 440/2008 B.46 in the EPISKIN Standard Model, mean tissue viability for barium chloride dihydrate was 80%. Authors concluded that the substance is a non-irritant.

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

Barium sulfate was assigned a score of Low for eye irritation/corrosivity based on negative results in a GLP-compliant ocular irritation study in rabbits. GreenScreen® criteria classify chemicals as a Low hazard for eye irritation/corrosivity when adequate data are available and are negative for irritation, and the chemical is not present on authoritative or screening lists (CPA 2012a).

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

Barium sulfate (CAS# 7727-43-7)

- ECHA 2014
    - Barium sulfate was not irritating in a GLP-compliant ocular irritation study according to OECD Guideline 405 in 3 male Himalayan rabbits. Secretion and mild conjunctival redness (grade 1) was seen in all animals 1 hour post-instillation and resolved by the 24 hour observation. No irritation was seen in any animal at the 24, 48, or 72 hour observation.

Ecotoxicity (Ecotox)

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

Barium sulfate was assigned a score of Moderate for acute aquatic toxicity based on an EC_{50} of 32 mg/L in daphnia. GreenScreen® criteria classify chemicals as a Moderate hazard for acute aquatic toxicity when the most conservative LC/EC_{50} value is between 10 and 100 mg/L (CPA 2012a).

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

Barium sulfate (CAS# 7727-43-7)

- ECOTOX 2014
    - 96-hour LC_{50} (*Poecilia sp.*, mollies) > 59 g/L
    - 48-hour EC_{50} (*Daphnia magna*, water flea) = 32 mg/L
    - 48-hour EC_{50} (*Cypris subglobosa*, ostracod) = 634 mg/L

Barium chloride dihydrate (CAS# 10326-27-9)

- ECHA 2014

  Note: due to the large number of studies available in the REACH dossier, only those reported with a Klimisch score of 1 or 2 for reliability were considered in the assessment.
    - 96-hour LC_{50} (*Danio rerio*, zebrafish) > 174 mg/L (nominal)
    - 48-hour EC_{50} (*Daphnia magna*, water flea) = 14.5 mg/L (nominal)
    - 72-hour EC_{50} (*Pseudokirchnerella subcapitata*, green algae) > 100 mg/L (nominal)

Chronic Aquatic Toxicity (CA) Score (vH, H, M, or L): *M*
Barium sulfate was assigned a score of Moderate for chronic aquatic toxicity based on an estimated NOEC of 2.9 mg/L in daphnia for the surrogate barium chloride dihydrate. GreenScreen® criteria classify chemicals as a Moderate hazard for chronic aquatic toxicity when the most conservative chronic aquatic toxicity value is between 1 and 10 mg/L (CPA 2012a).

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

Barium sulfate (CAS# 7727-43-7)

- No data were identified

Barium chloride dihydrate (CAS# 10326-27-9)

- ECHA 2014
  Note: due to the large number of studies available in the REACH dossier, only those reported with a Klimisch score of 1 or 2 for reliability were considered in the assessment.
    - 21-day NOEC (Daphnia magna, water flea) = 2.9 mg/L (nominal) (reproduction, estimated NOEC derived from EC_{16})
    - 72-hour NOEC (*Pseudokirchnerella subcapitata*, green algae) = 100 mg/L (nominal)
- Based on the weight of evidence, a score of Moderate was assigned. No data were identified for barium sulfate, but barium chloride has an estimated NOEC of 2.9 mg/L in daphnia. In aquatic toxicity tests of barium sulfate, daphnia were the most sensitive species. Since barium chloride dihydrate has much higher water solubility than barium sulfate, the NOEC for barium sulfate is not likely to be lower than 2.9 mg/L. Therefore a score of Moderate was assigned.

Environmental Fate (Fate)

Persistence (P) Score (vH, H, M, L, or vL): *vH*
Barium sulfate was assigned a score of Very High for persistence based on expert judgment, as it is in insoluble inorganic compound that is expected to persist in the environment. GreenScreen® criteria classify chemicals as a Very High hazard for persistence when the chemical is recalcitrant (CPA 2012a).

- Authoritative and Screening Lists
    - *Authoritative:* Not present on any authoritative lists
    - *Screening:*
        - Environment Canada - Domestic Substances List (DSL) DSL substances that are Persistent

Barium sulfate (CAS# 7727-43-7)

- ATSDR 2007
    - Barium compounds that do not dissolve well in water persist in the environment. Other barium compounds typically react with sulfate or carbonate in the environment, resulting in production of the longer-lasting forms.
- Based on the weight of evidence, a score of Very High was assigned. As an inorganic compound that is insoluble in water, barium sulfate is expected to be recalcitrant.

Bioaccumulation (B) Score (vH, H, M, L, or vL): *L*
Barium sulfate was assigned a score of Low for bioaccumulation based on a reported BCF of 129 for barium in freshwater fish. GreenScreen® criteria classify chemicals as a Low hazard for bioaccumulation when the most conservative BCF is between 100 and 500 (CPA 2012a).

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

- *Screening:* Not present on any screening lists

Barium (CAS# 7440-39-3)

- ECHA 2014
  - Bioconcentration factors of 1.2-74.4 have been measured in bluegills (*Lepomis macrochirus*) in a field study of tributaries of the San Joaquin River.
- ATSDR 2007
  - A bioconcentration factor of 100 for barium has been reported in marine animals.
  - A bioconcentration factor of 129 for barium has been estimated in freshwater fish when the concentration of barium in water was 0.07 mg/L.
- No standard bioaccumulation studies are available for barium sulfate or other barium compounds, but reports from field studies suggest that barium compounds do not have a high bioaccumulation potential. A score of Low was assigned based on the highest reported BCF of 129. Confidence in this score is reduced as no standard bioaccumulation studies were available, and few details were provided in reports from field studies.

Physical Hazards (Physical)

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

Barium sulfate was assigned a score of Low for reactivity based on a report that it is not explosive. GreenScreen® criteria classify chemicals as a Low hazard for reactivity when the chemical is not explosive or otherwise reactive, and the chemical is not present on authoritative or screening lists (CPA 2012a).

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

Barium sulfate (CAS# 7727-43-7)

- ESIS 2000
  - Barium sulfate is not explosive.

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

Barium sulfate was assigned a score of Low for flammability based on a report that it is not combustible. GreenScreen® criteria classify chemicals as a Low hazard for flammability when available data indicate that the chemical does not warrant GHS classification as a flammable solid, and the chemical is not present on authoritative or screening lists (CPA 2012a).

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

Barium sulfate (CAS# 7727-43-7)

- ATSDR 2007
  - Barium sulfate is not combustible.

References

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United States Department of Transportation (U.S. DOT). 2008b. Classification Criteria. 49 CFR § 173. Available at: http://www.ecfr.gov/cgi-bin/text-idx?c=ecfr&tpl=/ecfrbrowse/Title49/49cfr173_main_02.tpl.

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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 Barium Sulfate (CAS #7727-43-7)

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**
Yes	**Barium sulfate**	**7727-43-7**	**L**	**L**	*M*	DG	DG	**L**	DG	**L**	DG	**L**	**L**	DG	**L**	**L**	**M**	*M*	*vH*	*L*	*L*	*L*

Table 3: Hazard Summary Table

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

Table 4

Chemical Name	Preliminary GreenScreen® Benchmark Score
Barium sulfate	**2**

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

Table 6

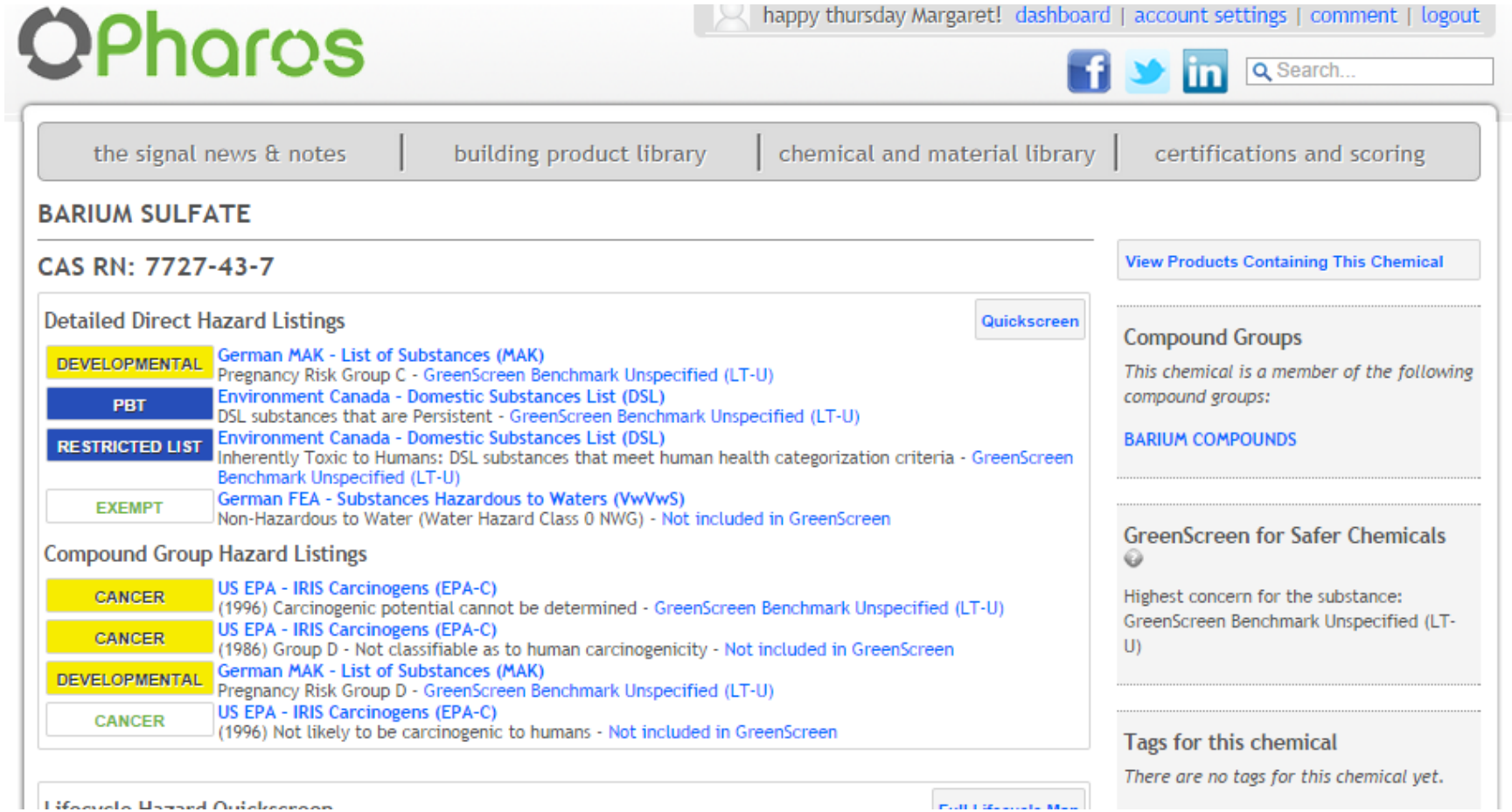
Chemical Name	Final GreenScreen® Benchmark Score
Barium sulfate	**2**

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 Barium Sulfate (CAS #7727-43-7)



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

Barium Sulfate GreenScreen® Evaluation Prepared by:

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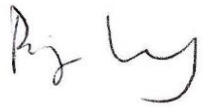
Barium Sulfate GreenScreen® Evaluation QC'd by:



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