Bis(2-ethylhexyl)azelate (DOZ) (CAS #103-24-2)
GreenScreen™ Assessment

October 9th, 2012

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

TABLE OF CONTENTS

TABLE OF FIGURES

GreenScreen™ Assessment for Bis(2-ethylhexyl) azelate (DOZ) (CAS #103-24-2)

GreenScreen™ Version 1.2 Verified Assessment

Date of Verification:	**October 17, 2012**
Expiration Date:	**October 17, 2015**
Uses:	This complete report may be freely published and distributed by the Green Chemistry and Commerce Council (GC3).
Restrictions:	Clean Production Action does not confer licensing rights or authorize the use of the GreenScreen trademark on public or promotional materials for individual products comprised of the chemical assessed in this report. Any promotional use of the GreenScreen trademarks must be covered under a separate license agreement.

Chemical Name: Bis(2-ethylhexyl) azelate (DOZ)

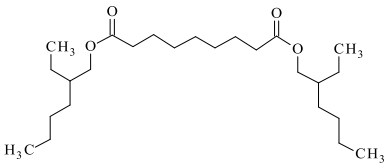
GreenScreen™ Assessment Prepared By:
Name: Chris Schlosser, M.F.S.

Title: Associate Toxicologist
Organization: ToxServices LLC
Date: October 9, 2012

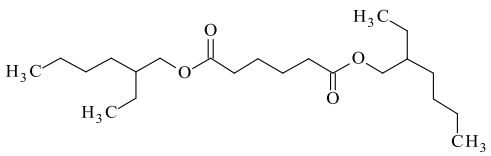
Quality Control Performed By:
Name: Dr. Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.S.B., E.R.T., D.A.B.T.
Title: Managing Director and Chief Toxicologist
Organization: ToxServices LLC
Date: October 9, 2012

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

Chemical Structure(s):



Bis(2-ethylhexyl) azelate (DOZ)
(CAS #103-24-2)



Bis(2-ethylhexyl) adipate
(CAS #103-23-1)

Chemical Surrogates, analogs or moieties used in this assessment (CASs #): Limited human health and environmental toxicity data were identified for DOZ. In order to address data gaps for specific hazard endpoints, data on bis(2-ethylhexyl) adipate (DEHA) (CAS #103-23-1) were used. DEHA was chosen as a chemical surrogate as it contains the same functional groups and differs only in the length of central carbon chain. The U.S. EPA's Robust Summaries for Aliphatic Esters – Diesters HPV Test Plan indicates that DEHA is an acceptable surrogate for diester substances such as DOZ (U.S. EPA 2010). Additionally, the ChemIDplus similarity search identified DOZ and DEHA as 98% similar in structure.

[1] Every chemical in a material or formulation should be assessed if it is:
1. intentionally added and/or
2. present at greater than or equal to 100 ppm

Identify Applications/Functional Uses:
Bis(2-ethylhexyl) azelate (DOZ) is a plasticizer for cellulosics, polystyrene, and vinyl plastics, and is especially used as a low-temperature plasticizer (HSDB 2002).

GreenScreen™ Summary Rating for DOZ[2]: DOZ was assigned a GreenScreen™ Benchmark Score of U (Unspecified) based on data gaps being assigned to both Carcinogenicity (C) and Endocrine Activity (E) endpoints. As outlined in CPA (2011c) Section III(1)(Benchmarking Chemicals With Data Gaps), permissible data gaps for Group I Human Health endpoints may only include Endocrine Activity and either Reproductive (R) or Developmental (D) Toxicity.

It should be noted that DOZ was assigned a Moderate (M) for Dermal Irritation/Corrosion (IrS). Based on this endpoint and if no data gaps were present and DOZ received a Low score for Carcinogenicity (C), DOZ would be assigned a GreenScreen™ Benchmark score of 3 ("Use but Search for Safer Substitutes"). This corresponds to a hypothetical GreenScreen™ Benchmark classification 3c in CPA 2011a, and demonstrates that datagaps in this chemical's health effects dataset affects the overall GreenScreen™ score. In a worst-case hazard benchmarking scenario, if DOZ were assigned a High (H) score for C or E it would be assigned a GreenScreen™ Benchmark score of 1 ("Avoid- Chemical of High Concern").

Figure 1: GreenScreen™ Hazard Ratings for Bis(2-ethylhexyl) azelate (DOZ)

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	*L*	**L**	**L**	dg	**L**	dg	**L**	dg	dg	*L*	dg	*M*	*L*	**L**	**L**	**vL**	**vL**	*L*	**L**

Note: Hazard levels (Very High (vH), High (H), Moderate (M), Low (L), Very Low (vL)) in *italics* reflect estimated values and lower confidence. Hazard levels in **BOLD** font reflect values based on test data (See Guidance).
Note: Please see Appendix A for a glossary of hazard acronyms.

Transformation Products and Ratings[3]:
Identify relevant fate and transformation products (i.e., dissociation products, transformation products, valence states) **and/or moieties of concern[4]**

Functional Use	Life Cycle Stage	Transformation Pathway	Transformation Products	CAS #	On CPA Red List[5]?	Green Screen Rating[6]
N/A	End of Life	Combustion	Carbon monoxide	630-08-0	Reproductive/developmental toxicant, neurotoxicant (CPA 2009)	End of Life
N/A	End of	Combustion	Carbon	124-38-9	Not present on the Red List	End of

[2] For inorganic chemicals with low human and ecotoxicity across all hazard endpoints and low bioaccumulation potential, persistence alone will not be deemed problematic. Inorganic chemicals that are only persistent will be evaluated under the criteria for Benchmark 4.
[3] Products that contain phthalates or phthalate alternatives are often plastics. Plastics are often disposed of via incineration. Therefore, health and environmental effects associated with combustion byproducts are of particular concern.
[4] 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.
[5] The CPA "Red List" refers to chemicals: 1) flagged as Benchmark 1 using the GreenScreen™ List Translator, or 2) flagged as Benchmark 1 or 2 using the GreenScreen™ List Translator and further assessed and assigned as Benchmark 1. The most recent version of the GreenScreen™ List Translator should be used (CPA 2011b).
[6] GreenScreen reviews of transformation products depend on the GreenScreen Benchmark Score of the parent chemical (See Guidance in CPA 2011c).

	Life		dioxide		of chemicals (CPA 2009)	Life

Introduction

Bis(2-ethylhexyl) azelate (DOZ) is a plasticizer for cellulosics, polystyrene, and vinyl plastics, including use as a low-temperature plasticizer (HSDB 2002). DOZ is produced from azelaic acid and 2-ethylhexanol as starting materials. DOZ production is carried out in a closed and batch system. Initial product mixtures are subject to distillation under reduced pressure in order to purify DOZ. A typical commercial DOZ product contains normally up to 2% of bis(2-ethylhexyl) adipate (CAS No. 103-23-1) in addition to numerous azelate isomers having similar boiling points/ranges, which are hard to remove. Residual non-reacted raw materials and by-products are recovered from the reactor tank after distillation and are applied for re-distillation and/or incineration (UNEP 2006).

The primary use (up to 95%) of DOZ produced in the United States or imported into the United States is as a plasticizer for cellulosics, polystyrene, and vinyl plastics in order to improve a plastic's resistance and to minimize plastic cracking at low temperatures. DOZ is also used as a lubricant at a small number of industrial sites (UNEP 2006).

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 2012). Pharos (Pharos 2012) is an online list-searching tool that is used to screen chemicals against the List Translator electronically. The output indicates benchmark or possible benchmark scores for each human health and environmental endpoint. No output was identified in Pharos for DOZ.

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

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

DOZ has been assigned a data gap for carcinogenicity. Although it is not a known carcinogen, carcinogenicity testing has not performed on the chemical.

- Not listed as a known carcinogen by IARC, NTP, U.S. EPA, or CA Prop 65.
- No relevant data were identified for DOZ or structurally related chemicals.

Cancer data for the chemical surrogate bis(2-ethylhexyl) adipate were insufficient to address the endpoint of carcinogenicity, as described below:

Bis(2-ethylhexyl) adipate (CAS #103-23-1)

- NTP 1982
    - The NTP conducted a GLP-compliant 2-year oral carcinogenicity study using male and female F344 rats and B6C3F1 mice (50/sex/dose). Rats and mice were administered doses of 0, 600, and 1,250 mg/kg and 0, 1,080, and 3,750 mg/kg of the test substance in the diet, respectively. An increased incidence of hepatocellular carcinoma and adenoma were observed in female mice in the 1,080 and 3,750 mg/kg groups (combined total: 3/100 control, 19/100 mid-dose, and 18/98 high dose) and male mice in the 3,750 mg/kg group (15/49 versus 6/50 in control). Hepatocellular tumor incidence did not increase in rats. No other statistically significant increases in treatment-related tumors were reported. The increased incidence of hepatocellular carcinomas and adenomas in mice were found to be due to peroxisome proliferation (induced growth or numbers of peroxisomes) and not to be relevant to human exposure (U.S. EPA 2008). Furthermore, IARC classified bis(2-ethylhexyl) adipate as a Group 3 substance (Not classifiable as to its carcinogenicity to humans) (IARC 2000). Additionally, IARC does not consider peroxisome proliferation to be relevant to human exposure as outline in their technical publication on Peroxisome Proliferation and its Role in Carcinogenesis (WHO 1994).

ToxServices concurs with the U.S EPA's and IARC's conclusion that peroxisome proliferation is not relevant to assessing human health risks from exposure to this class of chemicals.

In the absence of cancer data on DOZ, and without further study details to verify the relevance of tumors in mice exposed to the chemical surrogate bis(2-ethylhexyl) adipate, DOZ is assigned a data gap for carcinogenicity.

Mutagenicity/Genotoxicity (M) Score (H, M or L): *L*
DOZ was assigned a score of Low for mutagenicity based on negative *in vitro* mutagenicity and clastogenicity assays in prokaryotic and eukaryotic cells. A low confidence score was assigned for this hazard endpoint, as no *in vivo* assays were identified.

- U.S. EPA 2010 –
    - *In vitro* – A GLP-compliant Bacterial Reverse Mutation assay (OECD 471) was conducted utilizing *Salmonella typhimurium* tester strains TA98, TA100, TA1535, TA1537, and *E. coli* tester strain WP2 uvrA with and without metabolic activation (S9-mix) at concentrations of 0, 312.5, 625, 1,250 and 5,000 µg/plate of DOZ (77.2% purity). DOZ was negative for mutagenicity under the test conditions.
    - *In vitro* – A GLP-compliant Chromosomal Aberration assay (OECD 473) was conducted utilizing Chinese hamster lung (CHL/IU) cells with and without metabolic activation (S9-mix) at concentrations of 0, 37.5, 75, 150, 300, 600, 1,200, 2,400 µg/ml of DOZ (77.2% purity). DOZ was negative for clastogenicity and polyploidy under the test conditions.
- UNEP 2006
    - *In vitro:* DOZ was not genotoxic with or without an exogenous metabolic activation system in a bacterial test and in a chromosomal test. No other information was provided.

Reproductive Toxicity (R) Score (H, M, or L): L
DOZ was assigned a score of Low for reproductive toxicity. Based on data from a combined repeated dose with reproductive/developmental toxicity screening test, the NOAEL for reproductive toxicity was determined to be 1,000 mg/kg bw/day. No treatment-related adverse effects on reproduction were noted at any dose tested; therefore this chemical is not classified as a GHS 1 or 2 substance (UN 2009).

- UNEP 2006
    - A GLP-compliant Combined Repeated Dose with Reproductive/Developmental toxicity screening study (OECD 422) was conducted using male and female Sprague-Dawley rats (13 rats/sex/dose). Rats were administered doses by gavage of 0, 100, 300 and 1,000 mg/kg DOZ (77.2% purity) for 42 days beginning 14 days before mating in males, and 42 to 53 days in females, beginning 14 days before mating to day 4 of lactation throughout mating and pregnancy. No deaths were reported for any of the dose groups in either sex. As part of the reproductive/developmental screening test, histopathological examination of the testes, epididymis and ovaries was performed and showed no toxicological changes. There were no adverse effects on copulation index, fertility index, precoital interval, gestation length, gestation index or number of corpora lutea. No significant changes were observed in numbers of implantations and pups and live pups, and in indexes for implantation, delivery, birth and live birth. There were no treatment-related changes in body weight, external appearance or necropsy findings in offspring of rats. The NOAEL for reproductive and developmental toxicity was established to be 1,000 mg/kg bw/day.

Developmental Toxicity incl. Developmental Neurotoxicity (D) Score (H, M or L): L
DOZ was assigned a score of Low for developmental toxicity. Based on data from a combined repeated dose with reproductive/developmental toxicity screening test (OECD 422), the NOAEL for developmental toxicity was determined to be 1,000 mg/kg bw/day. No treatment-related adverse effects on development were noted at any dose tested; therefore this chemical is not classified as a GHS 1 or 2 substance (UN 2009).

- UNEP 2006
    - A GLP-compliant Combined Repeated Dose with Reproductive/Developmental toxicity screening study (OECD 422) was conducted using male and female Sprague-Dawley rats (13 rats/sex/dose). Rats were administered doses by gavage of 0, 100, 300 and 1,000 mg/kg DOZ (77.2% purity) for 42 days beginning 14 days before mating in males, and 42 to 53 days in females, beginning 14 days before

mating to day 4 of lactation throughout mating and pregnancy. No deaths were reported for any of the dose groups in either sex. As part of the reproductive/developmental screening test, histopathological examination of the testes, epididymis and ovaries was performed and showed no toxicological changes. There were no adverse effects on copulation index, fertility index, precoital interval, gestation length, gestation index or number of corpora lutea. No significant changes were observed in numbers of implantations and pups and live pups, and in indexes for implantation, delivery, birth and live birth. There were no treatment-related changes in body weight, external appearance or necropsy findings in offspring of rats. A 1,000 mg/kg bw/day NOAEL for reproductive and developmental toxicity was assigned by the study authors.

Endocrine Activity (E) Score (H, M or L): dg
DOZ was assigned a data gap for endocrine activity. Although it is not a known endocrine disruptor, endocrine disruption testing has not performed on the chemical.

- 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.
- Not listed as a potential endocrine disruptor on the Red List of Chemicals (CPA 2011d).
- ACD/Labs 2012 –
    - ACD/I-Lab Estrogen Receptor Binding Affinity predicts that DOZ is not expected to bind to the estrogen receptor. Please refer to Appendix B for the ACD/I-Lab prediction report.
- QSAR modeling indicates that no potential effects on the endocrine system are expected. However, a full two-generation reproductive toxicity study, developmental toxicity study or 90-day repeat dose toxicity study were not available to assess potential androgenic and thyroid effects.

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
DOZ was assigned a score of Low for acute mammalian toxicity based on two oral and one dermal LD_{50} values greater than 2,000 mg/kg, which is the cut off for low acute mammalian toxicity (CPA 2011a).

- UNEP 2006
    - *Oral* LD_{50} (Sprague-Dawley rat) > 2,000 mg/kg (GLP-compliant OECD 401)
    - *Oral* LD_{50} (Wistar rat) = 8,000 mg/kg (No further details provided)
    - *Dermal* LD_{50} (New Zealand white rabbit) = 18,300 mg/kg (No further details provided)

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

- No relevant data were identified for DOZ or structurally related chemicals.

Group II* Score (repeated dose)**(H, M, L): L**
DOZ was assigned a score of Low for systemic toxicity/organ effects (repeated dose). Based on available data, DOZ has a repeat dose LOAEL of 444 mg/kg bw/day and is therefore not categorized as a GHS Category 1 or 2 chemical. Guidance values for Category 2 chemicals are between 10 and 100 mg/kg (UN 2009).

- UNEP 2006
    - A GLP-compliant Combined Repeated Dose with Reproductive/Developmental toxicity screening study (OECD 422) was conducted using male and female Sprague-Dawley rats (13/sex/dose). Rats were administered doses by gavage of 0, 100, 300 and 1,000 mg/kg DOZ (77.2% purity) for 42 days beginning 14 days before mating in males, and 42 to 53 days in females, beginning 14 days before mating to day 4 of lactation throughout mating and pregnancy. No deaths were reported for any of the dose groups in either sex. Body weight gain was suppressed in males at 1,000 mg/kg bw/day. No changes in general conditions, food consumption, detailed clinical observations or neurobehavioral tests

were found in males and females in any group treated with this chemical. Decreases in the number of white blood cells and calcium levels were observed in females at 1,000 mg/kg bw/day. The albumin/globulin (A/G) ratio was increased at 1,000 mg/kg bw/day in both sexes and at 300 mg/kg bw/day in females. The increase in the A/G ratio in females at 300 mg/kg bw/day was not considered an adverse effect because no changes were observed in total protein or albumin at this dose. Lowered total protein was found in females at 1,000 mg/kg bw/day. Increases in relative weight of the liver in males and females, in absolute and relative weights of the kidney in males, and in relative weight of the kidney in females were noted at 1,000 mg/kg bw/day. In histopathological examinations, a tendency of increased incidence of hypertrophy of the centrilobular hepatocytes was observed in males at 1,000 mg/kg bw/day. Based on these findings, the NOAEL and LOAEL for repeated dose toxicity were considered to be 300 and 1,000 mg/kg bw/day in male and female rats, respectively.

- GHS (2009) guidance values are based on studies of 90-day duration. Therefore, in order to adjust for a shorter study duration, a LOAEL of 466 mg/kg[7] was derived.

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

- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- Not listed as a potential neurotoxicant on the Red List of Chemicals (CPA 2011d).
- No relevant data were identified.

Group II* Neurotoxicity Score (repeated dose)**(H, M, L):** dg
DOZ was assigned a data gap for neurotoxicity. Although a combined repeated dose with reproductive and developmental toxicity screening test also included neurobehavioral tests, insufficient data were disclosed in the OECD 422 study to facilitate an assessment as to this chemical's potential neurotoxicity.

- Not classified as a developmental neurotoxicant (Grandjean and Landrigan 2006).
- Not listed as a potential neurotoxicant on the Red List of Chemicals (CPA 2011b).
- UNEP 2006
    - A GLP-compliant Combined Repeated Dose with Reproductive/Developmental toxicity screening study (OECD 422) was conducted using male and female Sprague-Dawley rats (number not reported). Rats were administered doses of 0, 100, 300 and 1,000 mg/kg of DOZ (77.2% purity) for 42 days in males, and 42 to 53 days in females. Examinations performed include: clinical observations; neurobehavioral tests; body weights; food consumption; hematology; clinical chemistry; and reproductive and developmental parameters. No significant differences were reported in the neurobehavioral examinations conducted as part of the OECD screening test. No detailed data were provided.

Skin Sensitization (SnS) Group II* Score (H, M or L): *L*
DOZ was assigned a score of Low for sensitization based on negative sensitization studies reported for the surrogate, bis(2-ethylhexyl) adipate, as described below.

- No relevant data were identified for DOZ or structurally related chemicals.

<u>Bis(2-ethylhexyl) adipate (CAS #103-23-1)</u>

- ESIS 2000 -
    - Bis(2-ethylhexyl) adipate was reported as being non-sensitizing following a Draize test utilizing guinea pigs and a repeated patch test utilizing rabbits. No further details were provided for these studies, such as test design or GLP status.
- UNEP 2000 -
    - Ten male guinea pigs were treated with intracutaneous injections of 0.1% bis(2-ethylhexyl) adipate in olive oil. Animals were injected 3 times a week for 3 weeks and were challenged after a two week rest period. This substance was found to be not sensitizing. The GLP status of this study is unknown.

[7] Normalized dose for 42 day study duration ≈ 466 mg/kg (1,000 mg/kg dose x (42 days/90 days))

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

- No relevant data were identified for DOZ or structurally related chemicals.

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

DOZ was assigned a score of Moderate for corrosion/irritation based on study details indicating that structurally similar chemical Bis(2-ethylhexyl) adipate showed mild, reversible skin irritation that lasted 72 hours, as detailed below. Based on GHS criteria, a substance that produces mild irritation in at least two of the treated animals that persists to the end of the observation period is classified as a Category 3 irritant (UN 2009). GHS Category 3 skin irritants are assigned a hazard score of moderate (CPA 2011a).

- No relevant data were identified for DOZ.

Bis(2-ethylhexyl) adipate (CAS #103-23-1)

- ESIS 2000 -
    - Bis(2-ethylhexyl) adipate was reported as being non-irritating the skin and eyes of rabbits. No further details were provided for these studies such as test design or GLP status.
- UNEP 2000 -
    - Bis(2-ethylhexyl) adipate was applied neat to the abraded and intact skin of 6 albino rabbits for 24 hours and the irritation was observed for 48 hours after patch removal. The entire trunk of the animal was wrapped with rubberized cloth. Slight erythema was observed when the patch was removed, and the severity decreased in all animals by 72 hours. There was no apparent difference between abraded and intact skin. The primary irritation index was 0.83 and this substance was classified as being slightly irritating to irritating.

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

DOZ was assigned a score of Low for corrosion/irritation based on negative ocular irritation studies for DOZ and its surrogate, bis(2-ethylhexyl) adipate. The hazard score was reported as low confidence, as detailed study data were only identified for the surrogate chemical.

- HSDB 2002 –
    - DOZ is not irritating to the eyes of rabbits. No other details were provided.

Bis (2-ethylhexyl) adipate (CAS #103-23-1)

- ESIS 2000 -
    - Bis(2-ethylhexyl) adipate was reported as being non-irritating the skin and eyes of rabbits. No further details were provided for these studies.
- UNEP 2000 -
    - Rabbits (sex, strain and number not reported) were treated with 0.5 mL of undiluted bis(2-ethylhexyl) adipate and the area of corneal necrosis was scored. The results showed slight irritation but the substance was classified as being not irritating to the eyes of rabbits.
    - A solution of 0.1 mL bis(2-ethylhexyl) adipate was instilled into one eye of 6 albino rabbits. The other eye remained untreated. The eyes were examined at 24, 48, and 72 hours after treatment. No ocular irritation was observed at any point throughout treatment.

Ecotoxicity (Ecotox)

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

DOZ was assigned a score of Low for acute aquatic toxicity based on the test substance's absence of solubility, which prevents it from reaching sufficiently high concentrations in water.

- UNEP 2006 –
    - DOZ has reported L/EC_{50} values of > 0.072 mg/L (*Oryzias latipes*, fish 96-hr), >0.093 mg/L (*Daphnia magna*, 48-hr), and > 0.08 mg/L (*Pseudokirchneriella subcapitata*, algae 72-hr).

  - DOZ has limited solubility in water (< 0.0004 mg/L at 20˚C), which is less than the reported acute aquatic toxicity values. Therefore, no adverse effects in aquatic organisms are expected at saturation levels.
- U.S. EPA 2010 –
  - The U.S. EPA Task Group for the Diesters HPV Test plan reported that aquatic toxicity of diesters have reported L/EC_{50} values that clearly exceed the water solubility of this class of chemicals. The authors reported that it would be more appropriate to classify this endpoint as exceeding the maximum water solubility limit (WSL) for the test material. Based on the existing aquatic toxicity data and the limited water solubility of DOZ and structurally related diesters, the existing data suggest that aquatic toxicity is not expected.

- U.S. EPA 2011 –
  - The "No Effects at Saturation" (NES) occurs for solids when effect concentration is one order of magnitude (≥ 10x) less than the water solubility.

Chronic Aquatic Toxicity (CA) Score (vH, H, M or L): L
DOZ was assigned a score of Low for chronic aquatic toxicity based on not being soluble enough to reach limits of toxicity.
- UNEP 2006 –
  - DOZ has reported NOEC values of > 0.064 mg/L (*Daphnia magna*, 21-day), and > 0.08 mg/L (*Pseudokirchneriella subcapitata*, algae 72-hr).
  - DOZ has limited solubility in water (< 0.0004 mg/L at 20˚C) which is less than the reported chronic aquatic toxicity values. Therefore, no adverse effects are expected at saturation levels.
- U.S. EPA 2010 –
  - The U.S. EPA Task Group for the Diesters HPV Test plan reported that aquatic toxicity of diesters have reported L/EC_{50} values that clearly exceed the water solubility of this class of chemicals. The authors reported that it would be more appropriate to classify this endpoint as exceeding the maximum water solubility limit (WSL) for the test material. Based on the existing aquatic toxicity data and the limited water solubility of DOZ and structurally related diesters, the existing data suggest that aquatic toxicity is not expected.
- U.S. EPA 2011 –
  - The "No Effects at Saturation" (NES) occurs for solids when effect concentration is one order of magnitude (≥ 10x) less than the water solubility.

<u>Environmental Fate (Fate)</u>

Persistence (P) Score (vH, H, M, L, or vL): vL
DOZ was assigned a score of Very Low for persistence based on results that indicate this substance is "readily biodegradable." Substances classified as being "readily biodegradable" (i.e. meet the 10-day biodegradation window), are assigned a hazard score of very low (CPA 2011a).
- UNEP 2006
  - A GLP-compliant biodegradation assay (OECD 301C "Ready Biodegradability: Modified MITI Test") was conducted. DOZ was found to have 80-84% biodegradation in 14 days and 94-95% biodegradation in 28 days. Under the conditions of the test, DOZ meets the criteria to be considered readily biodegradable.

Bioaccumulation (B) Score (vH, H, M, L, or vL): vL
DOZ was assigned a score of Very Low for bioaccumulation based on a calculated bioconcentration factor (BCF) of 0.5, which is below than the 100 guidance value for very low bioaccumulation (CPA 2011a).
- UNEP 2006 –
  - DOZ has a calculated BCF of 0.5 based on a log K_{ow} of 11.9. GreenScreen guidance indicates that chemical with a log K_{ow} greater than 5 are designated as Very High for bioaccumulation. However,

chemicals with a very high log K_{ow} are no longer bioavailable and result in a low bioaccumulation potential as indicated by the BCF of 0.5 reported in the SIDS document. Therefore, DOZ will be assigned a low hazard as this chemical is not expected to be bioavailable to aquatic organisms[8].

Physical Hazards (Physical)

Reactivity (Rx) Score (vH, H, M or L): *L*
DOZ was assigned a score of Low for reactivity based on information from an MSDS sheet. No other data were identified.

- HB Chemical 2008 –
    - DOZ is stable under normal conditions.

Flammability (F) Score (vH, H, M or L): L
DOZ was assigned a score of Low for flammability based not being classifiable as a flammable liquid under the GHS criteria (CPA 2011a).

- BASF 2011 –
    - DOZ has a flash point of 212°C (415°F). Liquids with a flashpoint above 93°C are not classified as flammable by GHS (UN 2011).

[8] $LogK_{ow}$, or the octanol-water coefficient, is a measure of how a chemical will partition between an organic or aqueous environment. At low K_{ow} values above 10, no bioavailability is expected (U.S. EPA 2009). Chemicals with a high $LogK_{ow}$ are expected to be highly hydrophobic, and will not be available for absorption.

References

Clean Production Action (CPA). 2011a. The GreenScreen™ for Safer Chemical Version 1.2. Available: http://www.cleanproduction.org/Greenscreen.v1-2.php

Clean Production Action (CPA). 2011b. Red List of Chemicals. Available: http://www.cleanproduction.org/library/greenScreenv1-2/GS_v_1_2_Benchmark_1_Lists.pdf

Clean Production Action (CPA). 2011c. The GreenScreen™ for Safer Chemicals v 1.2 Guidance for Hazard Assessment and Benchmarking Chemicals. 10/18/2011. http://www.cleanproduction.org/library/greenScreenv1-2/DRAFT_GreenScreen_v1-2_Guidance_2011_1018_v2.pdf

European Chemical Substances Information System (ESIS). 2000. IUCLID Dataset for Di(2-ethylhexyl) adipate. European Commission Joint Research Centre. Available: http://esis.jrc.ec.europa.eu/doc/existing-chemicals/IUCLID/data_sheets/103231.pdf

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

Hazardous Substances Data Bank (HSDB). 2002. Entry for Bis (2-ethylhexyl) azelate (DOZ). United States National Library of Medicine. Available: http://toxnet.nlm.nih.gov/cgi-bin/sis/search/r?dbs+hsdb:@term+@rn+@rel+103-24-2

HB Chemical Corporation. 2008. Material Safety Data Sheet for Di 2-ethylhexyl azelate. Available: http://www.hbchemical.com/admin/uploads/DOZ%20MSDS+.pdf

International Agency for Research on Cancer (IARC). 2000. Summaries & Evaluations for Di(2-ethylhexyl) adipate. Available: http://monographs.iarc.fr/ENG/Monographs/PDFs/index.php

National Institute for Occupational Safety and Health (NIOSH). 1998. International Chemical Safety Card for bis(2-ethylhexyl) adipate. Centers for Disease Control. Available: http://www.cdc.gov/niosh/ipcsneng/neng1292.html

National Toxicology Program (NTP). 1982. Carcinogenesis Bioassay of Di(2-ethylhexyl) adipate: F344 Rats and B6C3F1 Mice (Feed Study). Available: http://ntp.niehs.nih.gov/ntp/htdocs/LT_rpts/tr212.pdf

United Nations (UN). 2011. Globally Harmonized System (GHS) of Classification and Labeling of Chemicals, Fourth Revised Edition.

United Nations Environmental Programme (UNEP). 2000. Screening Information Dataset (SIDS) for Bis (2-ethylhexyl) adipate (DEHA). Organisation for Economic Development (OECD). Available: http://www.chem.unep.ch/irptc/sids/OECDSIDS/103231.pdf

United Nations Environmental Programme (UNEP). 2006. Screening Information Dataset (SIDS) for Bis (2-ethylhexyl) azelate (DOZ). Organisation for Economic Development (OECD). Available: http://webnet.oecd.org/Hpv/UI/handler.axd?id=4ed45505-d58f-4388-bb4f-36ea8b7c2e80

United States Environmental Protection Agency (U.S. EPA). 2008. Interpretative Assistance Document for Discrete Organic Chemicals. Available: http://www.epa.gov/opptintr/sf/pubs/iad_discretes_092009.pdf

United States Environmental Protection Agency (U.S. EPA). 2009. Supporting Documents for Initial Risk-Based Prioritization of High Production Volume Chemicals. Available: http://www.epa.gov/hpvis/rbp/Cat_Diesters_Web_SuppDocs_Sept2008.pdf

United States Environmental Protection Agency (U.S. EPA). 2010. Robust Summaries for Substances in the HPV Test Plan for the Diesters Category of the Aliphatic Esters Chemicals. Available: http://epa.gov/HPV/pubs/summaries/alipestr/c13466rr8.pdf

United States Environmental Protection Agency (U.S. EPA). 2011. Interpretive Assistance Document for Assessment of Discrete Organic Chemicals. Available: http://www.epa.gov/oppt/sf/pubs/iad_discretes_092011.pdf

World Health Organization (WHO). 1994. Peroxisome Proliferation and its Role in Carcinogenesis. IARC Technical Publication No. 24. Available: http://monographs.iarc.fr/ENG/Publications/techrep24/IARCrep24.pdf

APPENDIX A: Hazard Benchmark Acronyms
(in alphabetical order)

(AA) Acute Aquatic Toxicity

(AT) Acute Mammalian Toxicity

(B) Bioaccumulation

(C) Carcinogenicity

(CA) Chronic Aquatic Toxicity

(Cr) Corrosion/ Irritation (Skin/ Eye)

(D) Developmental Toxicity

(E) Endocrine Activity

(F) Flammability

(IrE) Eye Irritation/Corrosivity

(IrS) Skin Irritation/Corrosivity

(M) Mutagenicity and Genotoxicity

(N) Neurotoxicity

(P) Persistence

(R) Reproductive Toxicity

(Rx) Reactivity

(SnS) Sensitization- Skin

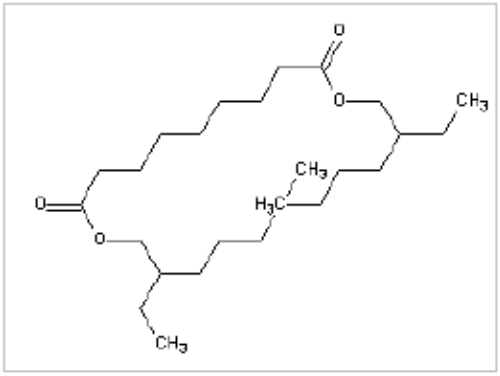
(SnR) Sensitization- Respiratory

(ST) Systemic/Organ Toxicity

APPENDIX B: ACD/I Lab Output

ACD/Labs
I-Lab 2.0 - ilab.acdlabs.com
Tuesday 9th of October 2012 09:33:46 PM. Algorithm Version: v5.0.0.184

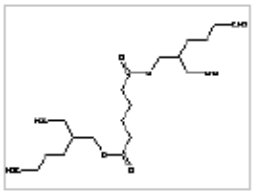
Compound structure



No binding to Estrogen Receptor alpha (LogRBA<-3)

Probability of Estrogen Receptor Binding:
LogRBA > -3: 0.12
LogRBA > 0: 0.02

Experimental Values for Similar Structures



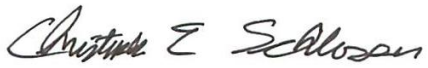
bis(2-ethylhexyl)adipate
CAS: 103-23-1

no binding
Species: human
References:

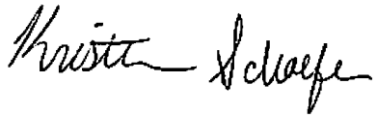
- Risk Assessment of Endocrine Disrupters (METI). Ministry of Economy, Trade and Industry, Japan. 2003.

Authorized Reviewers

Bis(2-ethylhexyl) azelate (DOZ) GreenScreen™ Evaluation Prepared By:

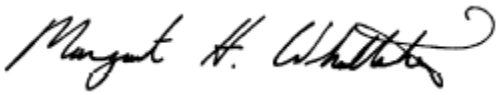


Chris Schlosser, M.F.S.
Associate Toxicologist
ToxServices LLC



Kristen Schaefer, M.F.S.
Associate Toxicologist
ToxServices LLC

Bis(2-ethylhexyl) azelate (DOZ) GreenScreen™ Evaluation QC'd By:



Margaret H. Whittaker, Ph.D., M.P.H., CBiol., F.S.B., E.R.T., D.A.B.T.
Managing Director and Chief Toxicologist
ToxServices LLC