CPSC Staff Statement on University of Cincinnati Report
"Toxicity Review for Glycerides, Castor-oil-mono-, Hydrogenated, Acetates (COMGHA)"[1]

June 2019

The U.S. Consumer Product Safety Commission (CPSC) contracted with the University of Cincinnati to conduct toxicology assessments for nine dialkyl o-phthalate (o-DAP) substitutes: phenyl esters of C10-C18 alkylsulfonic acid esters (ASE); glycerides, castor-oil-mono-, hydrogenated, acetates (COMGHA); dibutyl adipate (DBA) and di-isobutyl adipate (DiBA); di (2-ethylhexyl) sebacate (DEHS)/dioctyl sebacate (DOS); a mixture of 98% di-2-ethylhexyl terephthalate (DEHT) and 2% 2-ethylhexyl methyl terephthalate (2-EHMT); dibutyl sebacate (DBS); diisononyl adipate (DINA); epoxidized soybean oil (ESBO); and tributyl citrate (TBC). The reports will be used to inform staff's assessment of products that may contain these compounds and is the first step in the risk assessment process.

CPSC staff assesses a product's potential health effects to consumers under the Federal Hazardous Substances Act (FHSA). The FHSA is risk-based. To be considered a "hazardous substance" under the FHSA, a consumer product must satisfy a two-part definition. First, it must be "toxic" under the FHSA, or present one of the other hazards enumerated in the statute. Second, it must have the potential to cause "substantial personal injury or substantial illness during or as a proximate result of any customary or reasonably foreseeable handling or use." Therefore, exposure and risk must be considered in addition to toxicity when assessing potential hazards of products under the FHSA.

The first step in the risk assessment process is hazard identification, which consists of a review of the available toxicity data for the chemical. If it is concluded that a substance may be "toxic," then CPSC staff will pursue a quantitative assessment of exposure and risk to evaluate whether a specified product may be considered a "hazardous substance."

The toxicity review for COMGHA follows. Based on the research conducted by the University of Cincinnati, it appears that COMGHA does not fit the designation of acutely toxic under the FHSA following single oral or dermal exposure. No acute inhalation toxicity studies were located, however the potential for exposure via the inhalation route is low due to the physical properties of COMGHA.

[1] This statement was prepared by the CPSC staff, and the attached report was produced by the University of Cincinnati for CPSC staff. The statement and report have not been reviewed or approved by, and do not necessarily represent the views of, the Commission.

TOXICITY REVIEW FOR GLYCERIDES, CASTOR-OIL-MONO-, HYDROGENATED, ACETATES (COMGHA)

Contract No. CPSC-D-17-0001
Task Order No. 61320618F1002

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April 11, 2019

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1 Introduction

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure associated with glycerides, castor-oil-mono-, hydrogenated, acetates (COMGHA). COMGHA was noted in a previous contractor report to CPSC (Versar, 2010) as a potential food contact substance, but limited toxicity information was available at the time.

Literature searches for physico-chemical, toxicological, exposure, and risk information were performed in June 2018 using the CAS number and synonyms (see Appendix 1 for the full list of search terms), and using the following databases:

- EPA SRS
- PUBMED
- RTECS
- TSCATS (included in TOXLINE)
- TOXNET databases, including
    - TOXLINE
    - CCRIS
    - DART/ETIC
    - GENE-TOX
    - HSDB

Searches were conducted for studies indexed to PubMed and Toxline databases from all dates to the date of the search (June, 2018). As the project proceeded, however, it became apparent that additional supplemental searching was needed to capture all of the synonyms and components of COMGHA. This searching was conducted in February, 2019, for all dates up to the date of the search. The search terms for this supplemental search are also provided in Appendix 1.

Other databases and websites were also used to identify additional key information, particularly authoritative reviews. Authoritative reviews for general toxicity and physicochemical information were identified in the following databases using the CAS number for COMGHA and synonyms. Downloaded documents were saved as PDFs. Websites searched included:

- ANSES Information on Chemicals (https://www.anses.fr/en)
- ChemIDPlus (https://chem.nlm.nih.gov/chemidplus/)
- ECHA Information on Chemicals (https://echa.europa.eu/information-on-chemicals)
- EFSA (https://www.efsa.europa.eu/)

- EPA chemistry dashboard (https://comptox.epa.gov/dashboard)
- EPA Chemview (https://chemview.epa.gov/chemview)
- EPA (https://www.epa.gov/)
- EPA IRIS (https://www.epa.gov/iris)
- FDA (https://www.fda.gov/)
- Health Canada (https://www.canada.ca/en/health-canada.html)
- IARC (https://www.iarc.fr/)
- INCHEM (http://www.inchem.org/)
- JEFCA (http://www.who.int/foodsafety/areas_work/chemical-risks/jecfa/en/)
- NICNAS (https://www.nicnas.gov.au/)
- NTP (https://ntp.niehs.nih.gov/)
- OECD (http://www.oecd.org/)
- WHO (http://www.who.int/en/)

Some limited supplemental searching using Google was conducted in February, 2019.

2 Physico-Chemical Characteristics

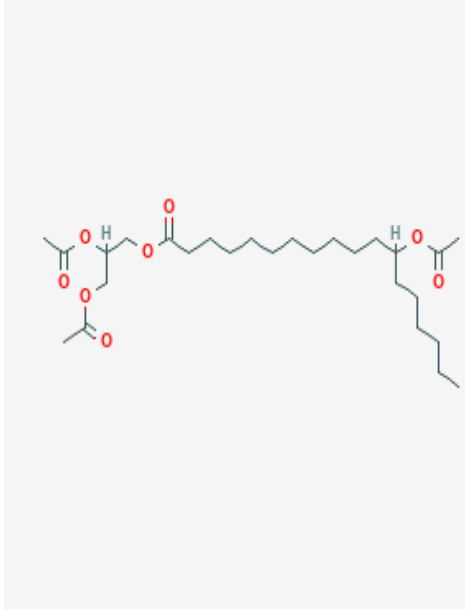
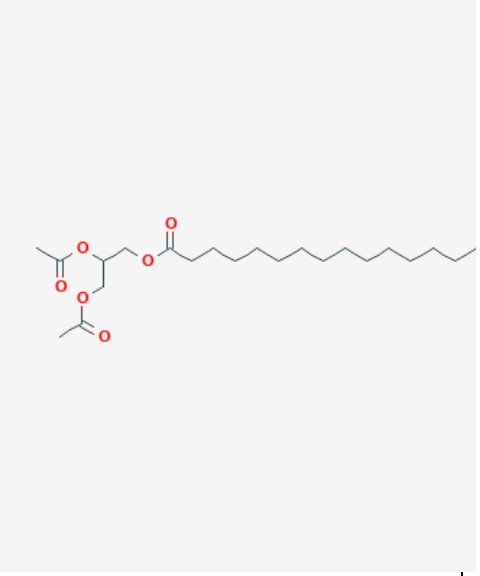
COMGHA is a fully acetylated monoglyceride derived from castor oil. COMGHA is a mixture with two primary components, each of which exists in multiple isomers, with some minor contaminants.

Various secondary references reflect somewhat different compositions of COMGHA, although the basis of these differences is not clear. NICNAS (2009) describes the main components of COMGHA as being acetylated monoglycerides of 12-hydroxy octadecanoic acid, octadecanoic acid (also known as stearic acid), and hexadecanoic acid (also known as palmitic acid). NICNAS (2009) did not provide information on the relative contributions of the different primary components. It lists the primary impurities (% by weight) as (1) Octadecanoic acid, 12-(acetyloxy)-, 2-hydroxy-, 3-acetyloxypropyl ester (2%); (2) Octadecanoic acid, 12-oxy, 2,3-bis(acetyloxy) propyl ester (1.5%); (3) Octadecanoic acid, 12-(acetyloxy)-, 2-(acetyloxy)-1,3-propanediyl ester (1.1%); and (4) Octadecanoic acid, 3-(acetyloxy)-2-hydroxypropyl ester (1%).

ECHA (2012) describes the primary component of COMGHA as the acetylated monoglyceride of 12-hydroxystearic acid (83-86% of total product composition). It lists two isomers of this primary component: 12-acetoxy-octadecanoic acid 2,3-diacetoxypropyl ester and 12- acetoxy-octadecanoic acid 2-acetoxy-1-acetoxymethyl-ethyl ester. ECHA lists the second major component (approximately 10% of total product composition) as fully acetylated monoglycerides of stearic and palmitic acid (i.e., without the 12-acetoxy group). Four isomers were listed: Octadecanoic acid 2,3-diacetoxy-propyl ester, Octadecanoic acid 2-acetoxy-1-acetoxymethyl-ethyl ester, Hexadecanoic acid 2,3-diacetoxy- propyl ester and Hexadecanoic acid 2-acetoxy-1-acetoxymethyl-ethyl ester.

Table 1: Physical-Chemical Characteristics and Identity of COMGHA

Chemical Name	12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester (84%), octadecanoic acid, 2,3-(bis(acetoxy)propyl ester (10%)	12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester	Octadecanoic acid, 2,3-bis(acetoxy)propyl ester
Synonyms	Grinsted Soft-N-Safe; COMGHA (PubChem, 2018); TS-ED 532, AMG-HCO, ACETEM CAO 90-00 (NICNAS, 2009)	12-Acetoxyoctadecanoic acid 2,3-diacetoxypropyl ester; Octadecanoic acid, 12-(acetyloxy)-, 2,3-bis(acetyloxy)propyl ester (PubChem, 2018)	2,3-diacetoxypropyl stearate; 2,3-diacetyloxypropyl octadecanoate; Octadecanoic acid, 2,3-bis(acetyloxy)propyl ester; 2,3-Diaceto-1-stearin; 1,2-diacetyl-3-stearoylglycerol; 2,3-Bis(acetyloxy)propyl stearate; Glycerin 1,2-diacetate 3-stearate; Glycerol, 1-octadecanoate, diacetate; Stearic acid, 3-dihydroxypropyl ester diacetate; Octadecanoic acid, 3-bis(acetyloxy)propyl ester, Octadecanoic acid; 2,3-bis (acetyloxy)propyl ester
CAS Number	736150-63-3	330198-91-9	33599-07-4

Structure	See components		
Chemical Formula	See components	$C_{27}H_{48}O_8$ (PubChem, 2018)	$C_{25}H_{46}O_6$ (PubChem, 2018)
Molecular Weight	500.50 g/mol (Bui et al., 2016)	500.673 g/mol (PubChem, 2018)	442.637 g/mol (PubChem, 2018)
Physical State	Liquid (NICNAS, 2009)	Liquid (NICNAS, 2009)	Liquid (NICNAS, 2009)
Color	Clear (NICNAS, 2009)	Clear (NICNAS, 2009)	Clear (NICNAS, 2009)
Melting Point	-21.5ºC (Bui et al., 2016)	-10.7ºC (predicted median)	8.97ºC (predicted median)
Boiling Point	>300ºC (decomposes) (NICNAS, 2009)	449ºC (predicted average)	425ºC (predicted average)
Vapor Pressure	$4.8x10^{-8}$ Pa at 25ºC (Bui et al., 2016)	$9.27x10^{-9}$ mmHg (predicted average)	$4.51x10^{-8}$ mmHg (predicted average)

Water Solubility	<0.1 mg/L (Bui et al., 2016)	$4.19x10^{-6}$ mol/L (predicted average)	$9.27x10^{-6}$ mol/L (predicted average)
Log Kow	6.4 at 25ºC (Bui et al., 2016)	6.70 (predicted average)	7.56 (predicted average)
Log Koc	5.4 at 25°C (NICNAS, 2009)	2.07×10^4 L/kg (predicted average)[1]	1.01×10^4 L/kg (predicted average)[1]
Henry's Law	Not available	$4.9x10^{-8}$ atm-m^3/mole (predicted average)	$2.85x10^{-7}$ atm-m^3/mole (predicted average)
Flashpoint	244 ºC at 101.3 kPa (NICNAS, 2009)	218ºC (predicted average)	205ºC (predicted average)
Density	1.00 g/cm^3 (Bui et al., 2016)	1.01 g/cm^3 (predicted average)	0.963 g/cm^3 (predicted average)
BCF	981 ± 330 (measured) (ECHA, 2012)	20.3 (predicted average)	29.9 (predicted average)
Source	As stated	U.S. EPA (2019a), unless otherwise stated	U.S. EPA (2019b), unless otherwise stated

Log K_{ow} is the octanol-water partition coefficient. Henry's Law is Henry's Law Constant. Log Koc is soil adsorption coefficient. BCF is bioconcentration factor. See Appendix 2 for more details.

[1]It appears that these values are actually the Koc, not the Log Koc, based on their magnitude, and by comparison to the value for the mixture.

ECHA (2012) noted that COMGHA is a glyceride, and so is readily metabolized. This means that COMGHA is not expected to bioaccumulate, despite the relatively high BCF.

Rather than being listed by the individual CAS numbers, toxicity data for the REACH dossier are listed under the legal entity TS-ED 532, which is described as being the "reaction mass of 1,3-diacetoxypropan-2-yl 12-acetoxyoctadecanoate and 2,3-diacetoxypropyl 12-acetoxyoctadecanoate." The toxicity and toxicokinetics studies with COMGHA were all conducted with a specific formulation of COMGHA, TS-ED 532 (ECHA, 2018), and so the test material is identified as that formulation for all of the studies in Sections 4 and 5 of this report. TS-ED 532 is described as consisting of three constituents. The first two constituents are the same as the two isomers that ECHA (2012) listed as the primary component. The third constituent is listed as a combination of CAS No. 33599-07-4; 55401-62-2, 55268-70-7, and 55268-69-4 (all similar to the primary component as derivatives of octadecanoic acid or hexadecanoic acid, but without the 12-acetoxy group). Because the specific formulations used for products and materials containing COMGHA to which people may be exposed are not known, the simple term COMGHA is used in the other sections of this report or when describing the general toxicity information.

3 Manufacture, Supply, and Use

Information on U.S. production volumes of COMGHA was not located. One producer/importer is listed in the U.S. EPA Chemical Data Reporting system but the production volumes are withheld (U.S. EPA, 2019c). In the European Economic Area, COMGHA is manufactured and/or imported at a rate of 1,000 tons to 10,000 tons per year (ECHA, 2019).

Primary uses of COMGHA are in polyvinyl chloride (PVC) products, with consumer product applications such as food contact materials (e.g., film wraps, storage containers, microwave oven trays), tubes, bottles, medical devices, flooring, carpet backing, coated fabrics, sealants and adhesives, textile dyes, fillers, putties, plasters, cosmetics and personal care products, wire and cable applications, plastisol applications, toys, and medical devices (NICNAS, 2009; ECHA, 2012; SCENIHR, 2016; Lowell Center, 2011; DEZA, 2013; ECHA, 2019). SCENIHR (2016) noted that COMGHA could also be used in other polymers, such as polyolefins, styrenics, and polyethylene terephthalate (PET).

4 Toxicokinetics

Toxicokinetic information for TS-ED 532 is only available for the oral route in rats. The available data from a radiolabel-based experiment support the conclusion that TS-ED 532 is absorbed, distributed, and metabolized similarly to other fatty acid esters. However, it appears likely that significant metabolism occurs in the GI tract prior to absorption.

A Good Laboratory Practices (GLP)-compliant toxicokinetic study was performed according to OECD Guideline 417 (Anonymous, 2004a, as cited by ECHA, 2018). Male Crl:CD(SD)BR rats (24/dose) were administered COMGHA (as TS-ED 532) via daily gavage at doses of 500 or 5000 mg/kg-day for 5 days. The following day, rats received radio-labeled TS-ED 532 in the form of 12-[1-^{14}C] acetoxy-octadecanoic acid-2,3-diacetoxy-propyl ester at the same dosages

and methods. Animals were switched back to unlabeled TS-ED 532 the following day, and exposure continued as above for 6 further days. Radiolabel was quantified in urine, feces, blood, plasma, serum and other tissues, adipose tissue (perirenal), gastrointestinal (GI) tract and contents, kidneys and adrenals, liver, and thymus at 1, 3, 6, 12, 24, 48, 72 and 168 hours following the radio-labeled dose (3 animals/dose level/time point). In rats given 500 mg/kg or 5000 mg/kg radio-labeled TS-ED 532, absorption was rapid, with peak blood concentrations reached within 3 hours and 6 hours, respectively. The peak concentrations represented an estimated 1.3% and 0.3% of the administered dose at the sampling time for the low- and high-dose groups. The distribution of radiolabel was broad. The highest concentrations beyond the GI tract were seen in the liver (representing 1.29% of dose) at 24 hours, kidneys (representing 0.23% of dose) at 6 hours, and thymus (representing 0.026% of dose) at 12 hours. Elimination half-time from plasma was slow and ranged from 55.6 to 51.9 hours in the low- and high-dose groups, respectively.

An additional group of 5 male rats received 5000 mg/kg-day as above, and these were kept in metabolic cages. Urine and feces were collected at 6, 12, 24, 48 and 72 hours following radio-labeled TS-ED 532, and expired CO_2 was collected at the same time points (a 3-hour sample was also included). Total reactivity in these samples over 72 hours represented 108.5% of the total dose. The greatest fraction of this total was recovered in expired CO_2 (77.0%), followed by feces (24.6%) and urine (6.5%). Of the total radioactivity recovered, 97.5% was excreted within 24 hours of dosing.

A noteworthy aspect of these results is the rapid excretion of the label, primarily as CO_2, contrasted with the long half-life in plasma and generally low concentrations in plasma and tissues. The study authors explained these observations by suggesting that metabolism begins with the hydrolytic cleavage of the 12-acetyl moiety[1] in the stomach, followed by catabolism to CO_2. They suggested that there is no significant absorption of the unchanged TS-ED 532 from the GI tract, explaining the low concentrations in tissue and the carcass.

ECHA (2018) also cited other studies that were included in the submittal packet but are not available online. Based on these studies, the study authors concluded that TS-ED 532 is extensively but not completely hydrolyzed in the intestine to glycerol and the constituent acids. They suggested that some of the acetic acid formed from the release of the acetoxy groups is absorbed, and further metabolized to CO_2, but that the 12-acetoxy group is the least labile to hydrolysis. Hydrolysis products were reported to be released in the feces mainly as 12-acetoxystearic acid, and 12-hydroxyoctadecanoic acid, along with minor amounts of 12-acetoxy-octadecanoic acid 2,3-bis(hydroxy)propyl ester and 12-hydroxy-octadecanoic acid 2,3-

[1]Note that other acetyl groups could not be followed in this study, because only the 12-acteyl carbon was radiolabeled.

bis(hydroxy)propyl ester. The potential for further metabolism of the hydroxylated fatty acid via beta-, alpha-and omega-oxidation was also noted.

ECHA (2018) stated that the vapor pressure of TS-ED 53 is low, and aerosol formation is not expected, and so the potential for exposure via the inhalation route is low. Given the high molecular weight, low water solubility, and high K_{OW} of TS-ED 532, dermal absorption is also not likely to be significant.

5 Hazard Information

5.1 Acute Single Dose Toxicity

5.1.1 Acute Oral Toxicity

No oral toxicity studies of COMGHA were identified. ECHA (2018) inferred an LD_{50} in rats of >5000 mg/kg, based on the finding of a NOAEL of 5000 mg/kg-day in a subchronic feeding study (Anonymous, 2004b, as cited by ECHA, 2018).

5.1.2 Acute Dermal Toxicity

The dermal toxicity of TS-ED 532 was tested (Anonymous, 2003a, as cited by ECHA, 2018) in male and female Wistar rats (5/sex). Animals were exposed to a volume of 4 mL/kg TS-ED 532 diluted in corn oil via semi-occlusive application to 10% of the total body surface for 24 hours. The total dose was 2000 mg/kg. No effects on mortality, bodyweights, or macroscopic appearances were seen over a 14-day observation period. Therefore, the authors concluded that the dermal LD_{50} of TS-ED 532 in rats is >2000 mg/kg.

5.1.3 Acute Inhalation Toxicity

No acute inhalation toxicity studies were located.

5.1.4 Irritation/Sensitization

Skin irritation/corrosion was tested in a GLP-compliant study performed according to OECD Guideline 404 (Anonymous, 2003b, as cited by ECHA, 2018). Undiluted TS-ED 352 (0.5 mL) was applied to the clipped skin of New Zealand White rabbits (one male and two females) for 4 hours and the area was examined 1, 24, 48, 72, and 168 hours following removal. Mild erythema and edema was observed, and resolved within 168 hours (7 days) following treatment. The edema (severity 1 on a scale of 4) was observed only at the 24-hour time point. Erythema up to severity 2 (on a scale of 4) was observed at the first two time points, and decreased to severity 1 after that. No corrosive effects were observed. The authors considered TS-ED 532 to be non-irritating based on the slight severity and reversibility of effects, but a better characterization that accounts for the initial reaction would be that TS-ED 532 is slightly irritating.

Eye irritation/corrosion was tested in a GLP-compliant study performed according to OECD Guideline 405 (Anonymous, 2003c, as cited by ECHA, 2018). Undiluted TS-ED 352 (0.1 mL) was applied to the left eyes of New Zealand White rabbits (one male, two females) and responses were assessed 1, 24, 48, and 72 hours following exposure. No washing was performed after initial application. There was no effect on corneal opacity or on the iris. Mild reddening of the conjunctivae (score 1 on a scale of 3), discharge (severity grade not reported), and chemosis (score 1 on a scale of 4) were observed. Redding of the sclera was also observed at 1 hour (score 1 on a scale of 3). All effects resolved within 48 hours. No corrosive effects were seen. The authors considered TS-ED 532 to be non-irritating based on the mildness and reversibility of effects, but the transient effects observed at the first 24 hours suggest that it might be better to describe TS-ED 532 as mildly irritating.

Skin sensitization was assessed in a GLP-compliant study using the mouse local lymph node assay (LLNA) according to OECD Guideline 429 (Anonymous, 2007a, as cited by ECHA, 2018). Female CBA/CaOlaHsd mice (5/dose) were treated for 3 successive days on the dorsal surface of the ear with a 25 µL solution of 0, 10, 25, or 50% TS-ED 532 diluted in an acetone/olive oil (4:1 v/v) vehicle for 3 days, followed by iv injection of 3H-thymidine 5 days after the first treatment. The test was negative for all doses (proliferation in local lymph nodes was unchanged from control). Two other reports of GLP-compliant LLNA studies were available but disregarded by ECHA due to deficiencies. Both used the same experimental design as above according to OECD Guideline 429. In one disregarded report (Anonymous, 2007b, as cited by ECHA, 2018), four different batches of TS-ED 532 ("TS-ED 532") tested negative as sensitizers but the study was disregarded due to unusually weak responses in the positive control (α-hexylcinnamaldehyde) group. In a second disregarded report (Anonymous, 2003d, as cited by ECHA, 2018), test article-related positive results were observed but disregarded because requirements of the test guideline were not fulfilled, including the use of dimethyl sulfoxide (DMSO) as the vehicle.

5.2 Repeated Dose Toxicity

Oral

A 90-day feeding study (Anonymous, 2004b, as cited by ECHA, 2018) exposed male and female Hsd:Sprague Dawley rats (20/sex/dose) to 0, 0.4, 1.2, or 3.6% TS-ED 532 in the diet (corresponding to target doses of 0, 500, 1600, and 5000 mg/kg-day) in a GLP-compliant study performed according to OECD Guideline 408. A comprehensive range of endpoints was examined, including a functional observation battery, but histopathology and organ weights were evaluated only in the control and 5000 mg/kg-day groups. Blood was sampled at days 30, 60 and at termination for hematology and clinical chemistry evaluation. No toxicologically-meaningful changes related to the treatment were seen at any dose. Sporadic and/or non-dose-related changes in endpoints such as body weight, food consumption, liver weight, and alkaline phosphatase were not considered by the authors to be biologically meaningful. Liver homogenates were

assayed for peroxisomal enzyme activity. Small non-adverse increases in hepatic palmitoyl-CoA oxidation and carnitine acetyltransferase activity (related to fat metabolism) were seen with increasing dose. The study NOAEL was the high dose of 5000 mg/kg-day.

A 1-year feeding study (Anonymous, 2011a, as cited by ECHA, 2018) exposed male and female Wistar rats (21/sex/dose) to 0, 1500, 6000, or 15,000 ppm TS-ED 532 in the diet. This study was GLP-compliant, and conducted according to OECD Guideline 452. In order to achieve a high dose of approximately 1000 mg/kg-day, the high dose was adjusted upwards to 25,000 ppm on week 10 and 30,000 ppm on week 41. Incorporating the dose escalation, approximate mean doses reported by the authors, based on actual food consumption and body weights, were 0, 87.1, 348.5, and 1116.5 mg/kg-day (males) and 0, 109.3, 435.0, and 1549.8 mg/kg-day (females). A comprehensive range of endpoints was examined, including functional observations, hematology, clinical chemistry, and urinalysis. No effects were observed at any dose, and so the high dose of 1116.5 mg/kg-day (males) and 1549.8 mg/kg-day (females) was the NOAEL.

Inhalation, Dermal

No repeat-dose inhalation or dermal studies were available.

5.3 Chronic Toxicity/Carcinogenicity

No data on carcinogenicity was available.

5.4 Reproductive Toxicity

SafePharm Laboratories (2009b[2], as cited by ECHA, 2018, NICNAS, 2009) conducted a GLP-compliant range-finding one-generation reproductive toxicity study to set dose levels for the two-generation study and to conduct endocrine disruptor screening tests. In this study, male and female Sprague-Dawley rats (10/sex/dose) were given TS-ED 532 in the diet at levels of 0, 10,000, or 20,000 ppm for 2 weeks prior to mating until post-natal day (PND) 21. F1 offspring were exposed to the same dose level until sexual maturation. Diethylhexyl phthalate (DEHP) at 5000 ppm in the diet was included as a positive control. The study authors calculated the mean doses for mature F0 males and females, and during gestation and lactation for females. The mean doses for the males were: 0, 387, and 1105 mg/kg-day (F0 males) and 0, 1107, and 2228 mg/kg-day (F1 males). For females, the dose range (including during gestation and lactation) in each group was: 0, 68-1498, and 1360-2746 mg/kg-day, with the highest doses occurring during lactation. Because of a procedural error, the low-dose group was exposed to 1000 ppm (instead of 10,000 ppm) for the initial 2-week exposure period (i.e., during the premating and mating phases). Parental body weight and clinical signs, reproductive performance and related indices, and gross developmental pathology were examined. No effects were seen at any dose level. There was also no effect on male nipple counts, ano-genital distance, or age of sexual maturation. However, there was also no effect on male nipple counts or ano-genital distance in

[2]Cited by ECHA (2018) as a 2010 report.

the DEHP-exposed group, although sexual maturation was delayed in the F1 males exposed to DEHP. The high dose of 20,000 ppm was a NOAEL.

In a GLP-compliant 2-generation reproductive study consistent with OECD Guideline 416 and Guideline 426 (developmental neurotoxicity) (Anonymous, 2011b, as cited by ECHA, 2018), male and female Sprague-Dawley rats (F0: 28/sex/dose; F1: 24/sex/dose) were given 0, 1500, 6000, or 25,000 ppm TS-ED 532 in the diet beginning 10 weeks prior to mating. Dietary exposure continued throughout mating, and continued during gestation, and lactation in females. F1 offspring continued to receive dietary exposure throughout maturation and breeding at about 14 weeks of age. The F2 animals were sacrificed at weaning. The high-dose F0 group was initially dosed at 15,000 ppm and escalated to 20,000 ppm and then 25,000 ppm during the initial 10-week exposure, after which the F1 animals were maintained at this dietary level. DEHP (10,000 ppm in diet) was included as a positive control for endpoints related to endocrine disruption. The study authors calculated the mean doses for F0 and F1 males, and the F0 and F1 females during maturation, gestation, and lactation. The mean doses for males were: 0, 82, 324, and 1159 mg/kg-day (F0 males); and 0, 109, 435, 1342 mg/kg-day (F1 males). For females, the dose ranges from maturation through gestation and lactation in each group were: 0, 106-231, 411-919, and 1392-3544 mg/kg-day (F0 females); and 0, 108-238, 434-918, and 1493-3596 mg/kg-day (F1 females). The range of endpoints included clinical observations (body weight, feeding, behavior), a full range of reproductive parameters in males and females (including estrous cyclicity, evaluation of oocyte number in F1 females, and sperm parameters), development and maturation of offspring (including ano-genital distance and nipple counts for each sex), and histological examination of a broad range of tissues in all adult animals and selected pups from the F1 and F2 litters. Both absolute and relative spleen weight were significantly decreased in both the F1 and F2 female pups. The trend was dose-related in the F1 pups, but not consistently dose-related in the F2 pups; the maximum decrease at the high dose was by 20% in the F1 generation and 27% in the F2 generation. The consistency of the observation between generations suggests that this was a treatment-related effect. However, the adversity of the change is unclear. The study authors did not consider the change to be adverse, since there was no effect on spleen weight in the adult F1 females. In support of this conclusion, there were no effects on spleen weight or hematology in the 90-day study (Anonymous, 2004b, as cited by ECHA, 2018) at target doses up to 5000 mg/kg-day. However, it is possible that there was a transient adverse effect on the pups, especially since the dose to the dams during lactation was substantially higher than the dose at maturation to the F1 females. Based on these considerations, the high dose of 20,000 ppm was a NOAEL for reproductive, developmental, and systemic toxicity, with the exception of spleen effects in pups, for which the high dose was an LOEL.

This study also included assessments for developmental neurotoxicity using OECD Guideline 426. F1 and F2 pups were evaluated pre-weaning for surface righting, air righting, and motor activity. The F1 pups selected for the postweaning developmental neurotoxicity test received

basal diet from weaning on postnatal (PND) day 21 through study termination at PND 70. Endpoints evaluated post-weaning included motor activity, grip strength, rotor rod performance, learning assessment, startle response, and microscopic histopathological changes in multiple sections of the brain and nervous system. No effects related to treatment were seen at any dose level, and 20,000 ppm was a NOAEL for developmental neurotoxicity.

5.5 Prenatal, Perinatal, and Post-natal Toxicity

In a GLP-compliant study performed according to OECD Guideline 414 (Harlan Laboratories, 2009b[3], as cited by ECHA, 2018, NICNAS, 2009), pregnant Sprague-Dawley rats (24/dose) were given 0, 100, 300, or 1000 mg/kg-day TS-ED 532 via gavage in arachis oil BP grade on gestation days (GD) 5-19. No maternal effects were noted. No effects were seen in uterine parameters, fetal viability and growth, skeletal development, or microscopic examination of fetal viscera. All treated groups had a statistically significant increase in the percent of fetuses with bilateral/unilateral wavy 13th rib(s), and the incidence was highest at the high dose. The incidence of affected litters was also markedly increased in all treated groups, although the authors did not conduct statistical analyses based on affected litters (the preferred unit of measure). However, this variation was not considered adverse in the absence of other supporting changes (decreased fetal body weight, decreased ossification of skull bones or metatarsals/metacarpals). The doses in the definitive study were chosen based on a range-finding/optimization study (SafePharm Laboratories, 2009a[4], as cited by ECHA, 2018, NICNAS, 2009) that was carried out as above with 8 pregnant rats/dose given 0, 250, 500, or 1000 mg/kg-day. Maternal toxicity and developmental effects were evaluated, but the examination of fetuses was limited to external observations. No maternal or developmental effects were seen at any dose level. Therefore, the maternal and developmental NOAEL was 1000 mg/kg-day in both the range-finding and the definitive study; no LOAEL was identified.

In a GLP-compliant study in rabbits conducted in accordance with OECD Guideline 414 (Anonymous, 2011c, as cited by ECHA, 2018), pregnant New Zealand White rabbits (24/dose) were given 0, 100, 300, or 1000 mg/kg-day TS-ED 532 via gavage in 1% carboxymethyl cellulose on GD 3-28. No maternal effects were noted. No effects were seen in uterine parameters, fetal viability and growth, skeletal development, or microscopic examination of fetal viscera and heads. The doses in the definitive study were chosen based on a range-finding/optimization study (Harlan Laboratories, 2009a[5], as cited by ECHA, 2018, NICNAS, 2009) that was carried out as above in 6 pregnant rabbits/dose given 0, 250, 500, or 1000 mg/kg-day. Maternal toxicity and developmental effects were evaluated, but the examination of fetuses was limited to external observations. No maternal or developmental effects were seen at any dose level. Therefore, the maternal and developmental NOAEL was 1000 mg/kg-day in both the range-finding and the definitive study; no LOAEL was identified.

[3]Cited by ECHA (2018) as a 2010 report
[4]Cited by ECHA (2018) as a 2010 report
[5]Cited by ECHA (2018) as a 2010 report

5.6 Genotoxicity

TS-ED 532 has been tested in bacterial and mammalian gene mutation assays *in vitro*, and in *in vitro* and *in vivo* tests for clastogenicity. All of the studies were negative.

TS-ED 532 was tested in *Salmonella typhimurium* strains TA1535, TA1537, TA98, TA100, and TA102. Tests were negative at levels up to 5000 µg/plate with or without exogenous metabolic activation (Anonymous, 2004c, as cited by ECHA, 2018).

TS-ED 532 was tested in mouse lymphoma L5178Y cells at concentrations up to 5000 µg/mL (first trial) in the absence of S9 activation, with exposure for 4 hours (first trial) or 24 hours (second trial). In the presence of exogenous metabolic activation, exposure was for 3 hours in both trials, with testing up to 5000 µg/mL in the first trial and 3600 µg/mL in the second trial. The study author reported that there was no biologically or statistically significant increase in mutant colonies at any dose. Although primary data were not reported, the absence of a statistically significant response at any dose, coupled with testing to both the limit dose (5000 µg/mL) and to cytotoxic concentrations, supports the authors' conclusions.[6] (Scantox Laboratories, 2002, as cited by ECHA, 2018, NICNAS, 2009).

An *in vitro* chromosome aberration test was carried out using primary lymphocytes from two healthy male volunteers. The *in vitro* exposure duration was 3 hours for both trials in the presence of S9. In the absence of S9, exposure was for 3 hours in the first trial and 20 hours in the second trial. Cells were harvested 20 hours after the start of treatment. In all of the trials, TS-ED 532 was tested up to 5000 µg/mL. Metaphase analysis was conducted on three doses/test.

Doses for metaphase analysis were reportedly selected based on cytotoxicity, but primary cytotoxicity data and details on selection criteria were not given. There was no evidence of clastogenicity at any dose evaluated, but the adequacy of testing cannot be independently evaluated in the absence of the primary cytotoxicity data for each dose (Anonymous, 2004d, as cited by ECHA, 2018).

In an *in vivo* micronucleus assay, male CD-1 mice (7/dose/time point) were given 0 or 2000 mg/kg TS-ED 532 in arachis oil via intraperitoneal injection. Bone marrow was collected 24 and 48 hours following exposure and the incidence of micronuclei in erythrocytes was assessed. There was no effect on the polychromatic erythrocyte (PCE)/normochromatic erythrocyte (NCE) ratio, and no increase in the frequency of micronucleated PCEs (Anonymous, 2008, as cited by ECHA, 2018).

5.7 Mechanistic Studies

As noted in Section 5.2, there were small increases in peroxisomal enzyme activity in the livers of Sprague Dawley rats treated with TS-ED 532 in the diet. Such increases are consistent with increased fat metabolism, but were not accompanied by other markers of peroxisome

[6]There are some inconsistencies in reporting of this study, with the criteria for a positive result and other sections referring to the frequency of metaphases with aberrant chromosomes, rather than the incidence of mutant colonies. However, the summary and data tables do appear to be for the correct study.

proliferation, such as increased liver weight. In addition, binding to the peroxisome proliferator-activated receptor (PPAR) has not been investigated.

5.8 Mode of Action

No adverse effects have been seen in any of the studies with TS-ED 532, and so no mode of action (MOA) can be ascertained. However, the available toxicokinetic data suggest that low oral absorption of COMGHA contributes to its low toxicity (Anonymous, 2004a, as cited by ECHA, 2018).

5.9 Lowest Hazard Endpoints by Organ System and Exposure Duration

The available toxicity studies indicate that the toxicity of TS-ED 532 is very low. Aside from studies reporting slight skin and eye irritation (Anonymous, 2003b, 2003c, as cited by ECHA, 2018), there has been no clear identification of adverse effects. TS-ED 532 has been tested in guideline-compliant 90-day and 1-year studies in rats (Anonymous, 2004b, 2011a, as cited by ECHA, 2018), a 2-generation reproduction study that included special testing for neurodevelopmental toxicity (Anonymous, 2011b, as cited by ECHA, 2018), and developmental toxicity studies in rats (Harlan Laboratories, 2009b, as cited by ECHA, 2018, NICNAS, 2009) and rabbits (Anonymous, 2011c, as cited by ECHA, 2018).

The only reported effect was decreased spleen weight (by as much as 26%) in female F1 and F2 pups in the 2-generation study. This effect was seen at a LOEL of 1665 mg/kg-day, which was the lower of the maternal doses for the gestational periods of the two generations.

5.10 Uncertainties and Data Gaps

Database:

As noted, the database for the COMGHA formulation TS-ED 532 is almost complete, with a number of guideline-compliant studies. Specifically, the database includes guideline-compliant 90-day and 1-year studies in rats (Anonymous, 2004b, 2011a, as cited by ECHA, 2018), a 2-generation reproduction study that included special testing for neurodevelopmental toxicity (Anonymous, 2011b, as cited by ECHA, 2018), and developmental toxicity studies in rats (Harlan Laboratories, 2009b, as cited by ECHA, 2018, NICNAS, 2009) and rabbits (Anonymous, 2011c, as cited by ECHA, 2018). The only missing key studies are a systemic toxicity study in a second species, and a chronic/carcinogenicity study. However, in light of the negative results for *in vitro* and *in vivo* gene mutation and chromosome damage studies (Anonymous, 2004c, 2004d, 2008, as cited by ECHA, 2018; Scantox Laboratories, 2002, as cited by ECHA, 2018, NICNAS, 2009), and in the absence of other evidence of toxicity, it appears unlikely that COMGHA is carcinogenic.

A key uncertainty regarding the database is that all of the toxicity studies summarized in this assessment were available only in secondary sources or from robust summaries, without primary data, making it difficult to independently evaluate the toxicological significance of the reported

effects. However, tables of key data were reported for the reproductive and developmental toxicity studies.

Hazard:

Spleen: The only uncertainty regarding interpretation of results relates to the toxicological significance of the decreased spleen weight in the female pups in the 2-generation reproductive toxicity study (Anonymous, 2011b, as cited by ECHA, 2018). The changes appear to be treatment-related, based on the general dose-response and consistency across generations. In addition, the magnitude of the change (decreases of 20-27% in absolute weight) indicates that the change is real. However, the adversity is uncertain in the absence of changes in spleen weight in the F1 adult females in the reproduction study, or in the 90-day study at a much higher dose. In addition, hematology changes indicative of adverse changes in the spleen were not seen in the 90-day study. Unfortunately, no hematology evaluation was conducted in the 2-generation study.

Table 2. Summary of NOAELs/LOAELs Identified for COMGHA by Organ System

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg day)[7]	Toxicological Basis	Comments
Sprague-Dawley rats (M & F) 20/sex/dose Anonymous, 2004b, as cited by ECHA, 2018	90 days Diet 0, 0.4, 1.2, or 3.6% 0, 500, 1600, or 5000 mg/kg-day (target)	Systemic	NOAEL = 5000 (M,F) LOAEL = N/A	No adverse effects	GLP-compliant, OECD Guideline 408 Liver homogenates showed non-adverse dose-related increases in palmitoyl-CoA oxidation and carnitine acetyltransferase
Wistar rats (M & F) 21/sex/dose Anonymous, 2011a, as cited by ECHA, 2018	1 year Diet 0, 1500, 6000, and 15,000-30,000 ppm M: 0, 87.1, 348.5, and 1116.5 mg/kg-day F: 0, 109.3, 435.0, and	Systemic	NOAEL = 1116.5 (M) NOAEL = 1549.8 (F) LOAEL = N/A	No effects	A comprehensive range of clinical, hematological, and histological endpoints was examined The high dose group started at 15,000 ppm, increased to 25,000 ppm on week 10, and increased to 30,000 ppm on week 41. Final mg/kg-day conversion is an average calculated by authors

[7] All effect levels as identified by the authors of this assessment.

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg day)[7]	Toxicological Basis	Comments
	1549.8 mg/kg-day				
Sprague-Dawley rats (M & F) 10/sex/dose Range-finding SafePharm, 2009b, as cited by ECHA, 2018, NICNAS 2009	2 weeks prior to mating until PND 21 (exposure continued in F1 until maturation) Diet 0, 10,000, or 20,000 ppm M: 0, 387, and 1105 mg/kg-day (F0); 0, 1107, and 2228 mg/kg-day (F1) F – range across F0 and F1: 0, 68-1498, and 1360-2746 mg/kg-day	Systemic (F0)	NOAEL = 1105 (M) NOAEL = 1360 (F)	No effects	Only clinical signs and body weight evaluated for systemic toxicity; female NOAEL based on maturation period and developmental NOAEL based on maternal gestational exposure. GLP-compliant, non-guideline Due to error, the low-dose group was exposed at 1000 ppm diet for the initial 2-week exposure; the dose was corrected to 10,000 ppm thereafter Systemic and reproductive NOAELs are listed based on the lowest dose over time for the respective sex, while developmental NOAEL is based on maternal exposure during gestation. Dose conversions given by authors. For the females, the ranges are based on the span of doses achieved during maturation, gestation, and lactation in F0 and in mature F1 females.
		Reproductive	NOAEL = 1105 (M) NOAEL = 1360 (F) LOAEL = N/A	No effects	
		Developmental	NOAEL = 1467 LOAEL = N/A	No effects	

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg day)[7]	Toxicological Basis	Comments
Sprague-Dawley rats (M & F) 28/sex/dose (F0) 24/sex/dose (F1) Anonymous, 2011b, as cited by ECHA, 2018	10 weeks prior to mating until weaning, exposure continued in F1 offspring Diet 0, 1500, 6000, or 15,000-25,000 ppm M: 0, 82, 324, and 1159 mg/kg-day (F0); 0, 109, 435, 1342 mg/kg-day (F1) F: 0, 106-231, 411-919, and 1392-3544 mg/kg-day	Systemic	NOAEL = 1159 (M) NOAEL = 1392 (F) LOAEL = N/A	No effects	GLP-compliant, OECD Guideline 416 (2-generation reproductive study) Endpoints included neurodevelopmental assessment according to OECD Guideline 426 High-dose group initially started at 15,000 ppm diet and escalated to 20,000 and 25,000 ppm during initial 10-week exposure Dose conversions given by authors. For the females, the ranges are based on the span of maturation, gestation, and lactation. Systemic and reproductive NOAELs are listed based on the lowest dose over time for the respective sex, while developmental NOAEL is based on maternal exposure during gestation. Developmental neurotoxicity doses based on F1 males and F1 females during maturation
		Reproductive	NOAEL = 1342 (M) NOAEL = 1493 (F) LOAEL = N/A	No effects	
		Developmental - Spleen	NOAEL = 1665 (M pups) NOAEL = 411 (F pups) LOEL = 1665 (F pups)	Decreased absolute and relative spleen weight in female F1 and F2 pups	
		Developmental - Other	NOAEL = 1665 LOAEL = N/A	No effects	

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg day)[7]	Toxicological Basis	Comments
	(F0); 0, 106-231, 434-918, and 1493-3596 mg/kg-day (F1)	Developmental neurotoxicity	NOAEL = 1342 (M) NOAEL = 1493 (F) LOAEL = N/A	No effects	
Sprague-Dawley rats (F) 24/dose Harlan Laboratories, 2009b[8], as cited by ECHA, 2018, NICNAS, 2009	GD 5-19 Gavage in arachis oil (BP grade) 0, 100, 300, or 1000 mg/kg-day	Maternal	NOAEL = 1000 LOAEL = N/A	No effects	GLP-compliant, OECD Guideline 414
		Developmental	NOAEL = 1000 LOAEL = N/A	No effects	
Sprague-Dawley rats (F) 8/dose	GD 5-19 Gavage in arachis oil (BP grade)	Maternal	NOAEL = 1000 LOAEL = N/A	No effects	GLP-compliant, range-finding study, conducted equivalent to OECD Guideline 414 except for sample size and fetal endpoints (fetal examination limited to external observations)

[8]Cited by ECHA (2018) as a 2010 report

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg day)[7]	Toxicological Basis	Comments
SafePharm Laboratories, 2009a[9], as cited by ECHA, 2018, NICNAS, 2009	0, 250, 500, or 1000 mg/kg-day	Developmental	NOAEL = 1000 LOAEL = N/A	No effects	
New Zealand White rabbits (F) 24/dose Anonymous, 2011c, as cited by ECHA, 2018	GD 3-28 Gavage in 1% carboxymethyl cellulose 0, 100, 300, or 1000 mg/kg-day	Maternal	NOAEL = 1000 LOAEL = N/A	No effects	GLP-compliant, OECD Guideline 414
		Developmental	NOAEL = 1000 LOAEL = N/A	No effects	
New Zealand White rabbits (F) 6/dose Harlan Laboratories, 2009a[10], as cited by ECHA 2018,	GD 3-28 Gavage in 1% carboxymethyl cellulose 0, 250, 500, 1000 mg/kg-day	Maternal	NOAEL = 1000 LOAEL = N/A	No effects	GLP-compliant, range-finding, conducted equivalent to OECD Guideline 414 except for sample size and fetal endpoints (fetal examination limited to external observations)
		Developmental	NOAEL = 1000 LOAEL = N/A	No effects	

[9]Cited by ECHA (2018) as a 2010 report
[10]Cited by ECHA (2018) as a 2010 report

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg day)[7]	Toxicological Basis	Comments
NICNAS, 2009					

6 Exposure

The use of COMGHA in consumer products has been described in Section 3 of this report. The general population may be exposed to COMGHA via ingestion of food when it is used in food contact and packaging materials. Infants and children may ingest COMGHA via mouthing of products (e.g., children's toys) made with COMGHA. Worker exposure is not expected from importation, transport, and storage unless packaging is breached; workers could experience dermal or ocular exposure during blending and cleaning, if personal protective equipment is not in use (NICNAS, 2009). Its low vapor pressure makes it unlikely that COMGHA will partition into air (NICNAS, 2009) and aerosol formation is not expected, so the potential for exposure via the inhalation route is low (ECHA, 2018). While consumers may be exposed dermally through products made of polymers that contain COMGHA, the high molecular weight, low water solubility, and high K_{OW} of COMGHA mean that dermal absorption is also not likely to be significant.

NICNAS (2009) reported that when used as a plasticizer, the concentrations of COMGHA in final products range from 2% to 34%, and when used as a colorant carrier for textiles and plastics, the concentration in the final product ranges from 0.1 to 0.5%.

While COMGHA is expected to be used in consumer products, including toys, no studies were located that documented levels of the chemical in toys, childcare articles, or other consumer products.

A study of the migration of COMGHA from PVC food film wrap showed that, following contact with sunflower oil at 40°C for 10 days, a large fraction of the plasticizer migrated into the oil, with an average migration of 10.3 mg/dm^2 of film sample (Development Laboratories Emulsifiers, 2005; as cited by NICNAS, 2009). Another study by the same laboratory used aqueous food simulants, again at 40°C for 10 days, and measured migration rates of 0.010 mg/dm^2 film sample for a 3% w/v aqueous acetic acid simulant, and 0.011 mg/dm^2 film sample for a 15% v/v aqueous ethanol simulant (Development Laboratories Emulsifiers, 2005; as cited by NICNAS, 2009). NICNAS (2009) noted that migration of COMGHA out of consumer products would be lower at lower temperatures. They concluded that human exposure to consumer products that do not come into contact with food would be low (NICNAS, 2009).

7 Discussion

7.1 Toxicity Under FHSA

It appears that COMGHA **does not fit the designation of acutely toxic under the Federal Hazardous Substances Act (FHSA) (16 CFR§1500.3(c)(2)(i)(A))** following single oral exposures, although the testing does not meet the criteria prescribed in the FHSA. No acute oral LD_{50} is available, but no adverse effects were seen in a 90-day feeding study in rats at doses up

to 5000 mg/kg-day (Anonymous, 2004b, as cited by ECHA, 2018), indicating that the acute LD_{50} would also be >5000 mg/kg. Similarly, the data suggest that **COMGHA does not fit the designation of acutely toxic under the Federal Hazardous Substances Act (FHSA) (16 CFR§1500.3(c)(2)(i)(A))** following single dermal exposures, based on a dermal LD_{50} in rats of >2000 mg/kg (Anonymous, 2003a, as cited by ECHA, 2018), but no data on acute dermal toxicity are available in rabbits.

COMGHA was slightly irritating to the skin and eyes of rabbits (Anonymous, 2003b, 2003c, as cited by ECHA, 2018), but the observed effects were transient. COMGHA did not cause skin sensitization in mice, based on the results of the LLNA (Anonymous, 2007a, as cited by ECHA, 2018).

Based on results from repeated-dose toxicity studies, as well as the 2-generation reproductive toxicity study in rats that included special testing for neurodevelopmental toxicity (Anonymous, 2011b, as cited by ECHA, 2018) and developmental toxicity studies in rats (Harlan Laboratories, 2009b, as cited by ECHA, 2018, NICNAS, 2009) and rabbits (Anonymous, 2011c, as cited by ECHA, 2018), COMGHA does not appear to be toxic under the FHSA. No adverse effects were seen in guideline-compliant studies conducted up to the respective limit doses. The only potential effect was decreased spleen weight in the female pups of the 2-generation study, but there was no effect on spleen weight in the F1 female adults, and no effect on spleen weight or hematology parameters at a higher dose in the 90-day study (Anonymous, 2004b, 2011, as cited by ECHA, 2018).

COMGHA has not been tested for carcinogenicity, but it appears that it is unlikely that COMGHA is carcinogenic, in light of the negative results for *in vitro* and *in vivo* gene mutation and chromosome damage studies (Anonymous, 2004c, 2004d, 2008, as cited by ECHA, 2018; Scantox Laboratories, 2002, as cited by ECHA, 2018, NICNAS, 2009), and in the absence of other evidence of toxicity.

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APPENDIX 1

Search Terms Used

Search Terms Used – June 2018

Toxline	"Soft-n-safe - 12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester (84%), octadecanoic acid, 2,3-bis(acetoxy)propyl ester" OR "Glycerides, castor-oil mono-, hydrogenated, acetates" OR "COMGHA" OR "AMG-HCO" OR "hydrogenated castor-oil mono-acectates glycerides" OR (736150-63-3)
Pubmed	"Soft-n-safe - 12-(Acetoxy)-stearic acid, 2,3-bis(acetoxy)propyl ester (84%), octadecanoic acid, 2,3-bis(acetoxy)propyl ester" OR "Glycerides, castor-oil mono-, hydrogenated, acetates" OR "COMGHA" OR "AMG-HCO" OR "hydrogenated castor-oil mono-acectates glycerides" OR (736150-63-3)

Search Terms Used – February 2019

Pubmed	"Soft-n-safe" OR (330198-91-9) OR (33599-07-4) OR "acetylated monoglyceride" OR (acetoxy stearic,2,3-bis (acetoxy) propyl) OR (octadecanoic, 2,3-bis (acetoxy) propyl) OR (acetoxyoctadecanoyl diacetoxypropyl) OR (octadecanoic, 12- (acetyloxy) , 2,3-bis (acetyloxy) propyl) OR (diacetoxypropyl stearate) OR (diacetyloxypropyl octadecanoate) OR (stearic, 2,3-dihydroxypropyl diacetate) OR (diaceto stearic) OR (diacetyl stearoylglycerol) OR (2,3-Bis (acetyloxy) propyl stearate) OR (glycerin 1,2-diacetate 3-stearate) OR (glycerol, octadecanoate, diacetate) OR (stearic, 3-dihydroxypropyl diacetate) OR (octadecanoic, 3-bis (acetyloxy) propyl) OR (octadecanoic, 2,3-bis (acetyloxy) propyl)
Toxline	"Soft-n-safe" OR (330198-91-9) OR (33599-07-4) OR "acetylated monoglyceride" OR (acetoxy stearic,2,3-bis (acetoxy) propyl) OR (octadecanoic, 2,3-bis (acetoxy) propyl) OR (acetoxyoctadecanoyl diacetoxypropyl) OR (octadecanoic, 12- (acetyloxy) , 2,3-bis (acetyloxy) propyl) OR (diacetoxypropyl stearate) OR (diacetyloxypropyl octadecanoate) OR (stearic, 2,3-dihydroxypropyl diacetate) OR (diaceto stearic) OR (diacetyl stearoylglycerol) OR (2,3-Bis (acetyloxy) propyl stearate) OR (glycerin 1,2-diacetate 3-stearate) OR (glycerol, octadecanoate, diacetate) OR (stearic, 3-dihydroxypropyl diacetate) OR (octadecanoic, 3-bis (acetyloxy) propyl) OR (octadecanoic, 2,3-bis (acetyloxy) propyl)

APPENDIX 2

Explanation of Physico-chemical Parameters

The organic carbon normalized solid-water partition coefficient (K_{oc}), also known as the organic carbon adsorption coefficient, is defined as the ratio of the chemical's concentration in a state of sorption (i.e. adhered to soil particles) and the solution phase (i.e. dissolved in the soil water). K_{oc} is crucial for estimating a chemical compound's mobility in soil and the prevalence of its leaching from soil. For a given amount of chemical, the smaller the K_{oc} value, the greater the concentration of the chemical in solution. Thus, chemicals with a small K_{oc} value are more likely to leach into groundwater than those with a large K_{oc} value (http://www.acdlabs.com/products/phys_chem_lab/logd/koc.html).

Henry's law, one of the gas laws formulated by William Henry, states that "at a constant temperature, the amount of a given gas dissolved in a given type and volume of liquid is directly proportional to the partial pressure of that gas in equilibrium with that liquid (http://en.wikipedia.org/wiki/Henry's_law)." Henry's Law Constants characterize the equilibrium distribution of dilute concentrations of volatile, soluble chemicals as the ratio between gas and liquid phases.

The octanol/water partition coefficient (K_{ow}) is defined as the ratio of a chemical's concentration in the octanol phase to its concentration in the aqueous phase of a two-phase octanol/water system. In recent years, this coefficient has become a key parameter in studies of the environmental fate of organic chemicals. It has been found to be related to water solubility, soil/sediment adsorption coefficients, and bioconcentration factors for aquatic life. Because of its increasing use in the estimation of these other properties, K_{ow} is considered a required property in studies of new or problematic chemicals (http://www.pirika.com/chem/TCPEE/LOGKOW/ourlogKow.htm).

The bioconcentration factor (BCF) is the concentration of a particular chemical in a tissue per concentration of chemical in water (reported as L/kg). This property characterizes the accumulation of pollutants through chemical partitioning from the aqueous phase into an organic phase, such as the gill of a fish. The scale used to determine if a BCF value is high, moderate or low will depend on the organism under investigation. The U.S. EPA generally defines a high potential BCF as being greater than 5,000; a BCF of moderate potential as between 5,000 and 100; a low potential BCF as less than 100 (http://en.wikipedia.org/wiki/Bioconcentration_factor; http://sitem.herts.ac.uk/aeru/footprint/en/Quest/ecotox.htm).