CPSC Staff Statement on University of Cincinnati Report
"Toxicity Review for Phenyl Esters of C10-C18
Alkylsulfonic Acid Esters (ASE)"[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 ASE follows. Based on the research conducted by the University of Cincinnati, the animal data support the conclusion that ASE does not fit the designation of acutely toxic under the FHSA following single oral exposure. Limited data suggest low acute dermal toxicity. No studies of acute toxicity via inhalation were found.

[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

PHENYL ESTERS OF C10-C18 ALKYLSULFONIC ACIDS (ASE)

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

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1 Introduction

This report summarizes available data on the identity, physicochemical properties, manufacture, supply, use, toxicity, and exposure associated with phenyl esters of C10-C18 alkylsulfonic acid esters; henceforth identified as alkylsulfonic phenyl esters (ASE). The available toxicological studies on ASE[1] (which at the time was a potential candidate for use in children's articles) were briefly identified in a previous contractor report to CPSC (Versar, 2010).

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, due to the complex nature of the ASE mixture, as well as the complexity of the nomenclature and synonyms. 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 ASE 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/)

[1] Identified as Mesamoll®. At the time, no toxicity data for Mesamoll® were identified.

- 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 web searching via Google was conducted in February, 2019. Supplemental searching also determined that the ASE data on the ECHA website are not listed under the CAS numbers provided in Table 1. Instead, the ASE data are posted under the EC number, 701-257-8. Additional information on the identity and components of ASE are provided in Section 2.

2 Identity and Physico-Chemical Characteristics

The material referred to as ASE is a complex mixture of closely-related materials. In addition, different related mixtures are referred to as ASE. The main components of the ASE mixture are esters of phenol and alkyl (C10-C21) sulfonic acid. Further complicating the situation, the list of synonyms includes chains lengths of C10-C21, as well as C10-C18. Mono-, di- and tri-esters are included (see Figure 1). The material also contains alkylsulfonic acids and phenol (these are variously listed as integral components or contaminants), as well as alkanes and chloroalkanes as impurities (EFSA, 2009, as cited by DEZA, 2013).

Although the web sites that were sources of physical/chemical properties listed only the straight-chain alkyl derivatives, ECHA (2019) lists all ASE information under the EC number for the secondary acid esters (see Figure 2); no CAS number is associated with this structure. ECHA defines its listing as “C14-C17 alkanes, sec-mono- and disulfonic acid phenyl esters”. However, it is not clear which form(s) are associated with the provided test data.

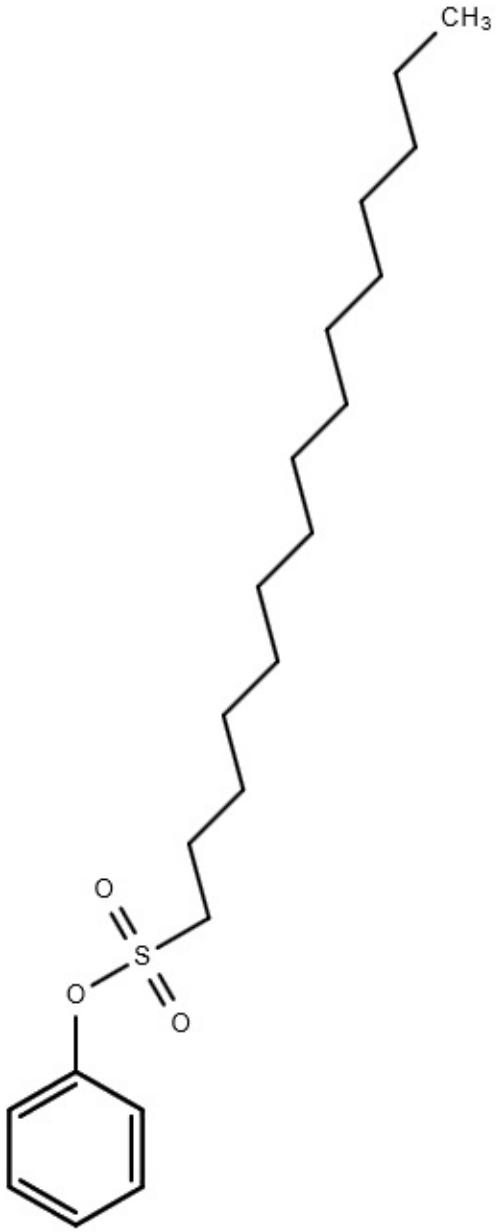
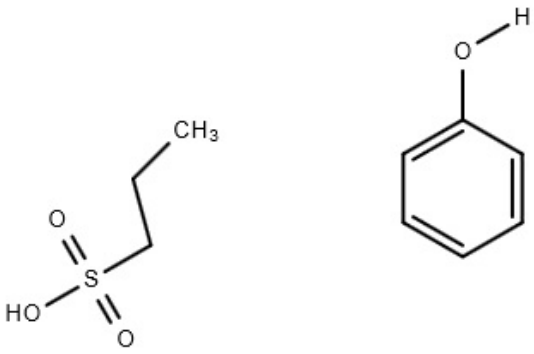
DEZA (2013) noted that somewhat different forms of ASE are available on the market under variants of the Mesamoll® name. Specifically, DEZA noted Mesamoll®, Mesamoll® II, and Mesamoll® TP LXS 51067, but stated that all three products share the same CAS number and that limited information is available in the literature to distinguish among these products. According to company literature, Mesamoll® II has lower volatility than Mesamoll® (Lanxess,

2005, as cited by DEZA, 2013), and Mesamoll® TP LXS 51067 is a "fast-solvating plasticizer for (polyvinyl chloride) PVC processing, particularly suitable for producing plastic floor coverings and wall coatings" (Lanxess, 2010, as cited by DEZA, 2013).

Some physical and chemical properties of ASE are summarized below in Table 1.

Table 1: Physicochemical Properties and Identification Information for ASE

Chemical Name	Sulfonic acids, C10-21-alkane, phenyl esters	Sulfonic acid, C10-18-alkane phenyl ester
Synonyms	Phenyl esters of C10-C18 alkylsulfonic acids; Mesamoll® II; C10-18-Alkane sulfonic acids phenyl esters; Phenyl (C10-C18) alkylsulfonate; Sulfonic acids, C10-18-alkane, Ph esters; Sulfonic acids, C10-18-alkane, phenyl esters; phenyl esters C10-18 alkane sulfonic acids; phenyl esters C10-21 alkane sulfonic acids; Sulfonic acids, C10-21-alkane, Ph esters; Sulfonic acids, C10-21-alkane, phenyl esters	Phenyl esters of C10-C18 alkylsulfonic acids; propane-1-sulfonic acid-phenol;C10-18-Alkane sulfonic acids phenyl esters; phenol; propane-1-sulfonic acid (Pubchem, 2018)
CAS Number	91082-17-6	70775-94-9

Chemical Name	Sulfonic acids, C10-21-alkane, phenyl esters	Sulfonic acid, C10-18-alkane phenyl ester
Structure	 (Representative structure, redrawn from PubChem, 2018)	 (Representative structure, redrawn from PubChem, 2018)
Chemical Formula	Mono-ester: C16H26O3S-C27H48O3S Di-ester: C22H34O9S3-C39H56O9S3 Tri-ester: C28H34O9S3-C39H56O9S3	$C_9H_{14}O_4S$
Molecular Weight	Varies	Varies

Chemical Name	Sulfonic acids, C10-21-alkane, phenyl esters	Sulfonic acid, C10-18-alkane phenyl ester
Physical State	Liquid	Liquid
Color	Yellow	Not applicable
Melting Point	<-150°C	Not applicable
Boiling Point	300 - 400°C at 101.3 kPa (accompanied by decomposition)	Not applicable
Vapor Pressure	2.94 10^{-4} Pa at 20°C	Not applicable
Water Solubility	2.2 mg/L at 20°C	Not applicable
Log Kow	10.4	Not applicable
Flashpoint	210 - 240°C	Not applicable
Density	1.05 g/cm^3	Not applicable
Sources	DEZA (2013), unless otherwise stated	PubChem (2018), unless otherwise stated

Log K_{ow} is the octanol-water partition coefficient. See Appendix 2 for more detail

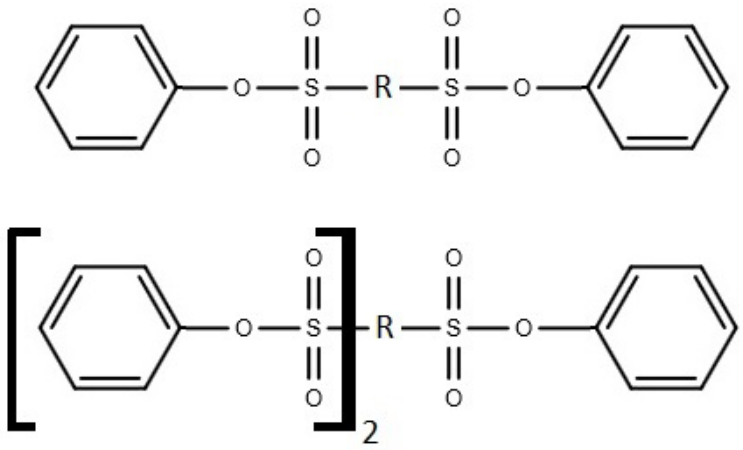


Figure 1. Di- and tri- esters of ASE (adapted from DEZA, 2013)

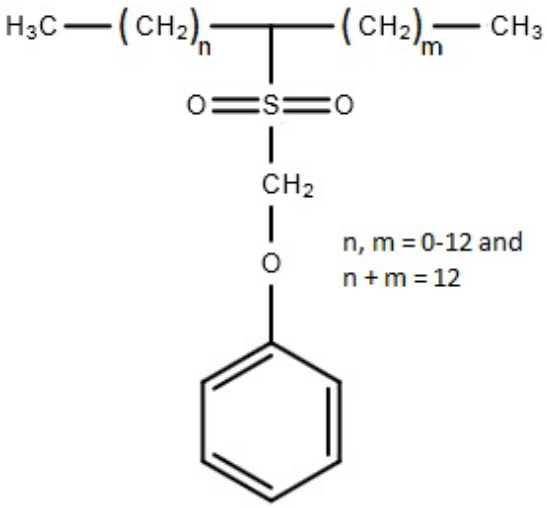


Figure 2. Secondary disulfonic acid phenyl esters

3 Manufacture, Supply, and Use

Manufacture and Supply

ASE is a high production volume chemical with U.S. manufacture and imports reported between 10 million and 50 million pounds (5,000 to 25,000 tons) per year for 2015 (U.S. EPA, 2019).

Use

ASE has been used in production of polyvinyl chloride (PVC) for over 60 years (Haslam et al., 1951, as cited by ECHA, 2012) and are reported to be used as a substitute for butyl benzyl phthalate (BBP), dibutyl phthalate (DBP), and Di(2- ethylhexyl) phthalate (DEHP) in polymer and non-polymer applications (ECHA, 2012). ASE is compatible with PVC, polyurethanes, natural rubber, and synthetic rubbers and has outstanding resistance to light and weathering and high saponification resistance (Maag et al., 2010). In consumer products, ASE is used in adhesives and sealants, paints and coatings, and plastic and rubber products. Industrial uses include as a plasticizer, processing aid, and solvent (PubChem, 2018).

US producers/importers have reported that ASE is intended for use in products intended for children (U.S. EPA, 2019), and it was developed specifically for use in "sensitive applications" such as children's toys and medical tubing (Versar, 2010). Its use in toys has been reported by Danish manufacturers (Maag et al., 2010). The Household Products Database indicates that a paste with less than 1% ASE content is used in masonry and concrete sealants, and blacktop and roofing filler/sealants (NLM, 2019). It has been used in waterbed linings and is reported as a possible substitute in PVC-coated textile fabrics (e.g., tents, tarps, rainwear, workwear) (Nilsson

et al., 2002; Hansen and Lejre, 2002, both as cited by ECHA, 2012). ASE is approved for use in PVC food contact articles in the U.S and Europe.

4 Toxicokinetics

Toxicokinetic data for ASE are limited. Greim (1994) noted that bioaccumulation is expected for C10-21 alkylsulfonic acid-phenyl esters along with other sulfonic acid compounds with a $LogP_{OW} > 6$. As described in the following paragraph, the available toxicokinetic data confirm that ASE distributes to the fat, with elimination requiring weeks.

The oral toxicokinetics of a commercial formulation of ASE were assessed in male Wistar rats (Schmidt, 1975, as reported by ECHA, 2018). Both gavage and feeding studies were performed. By gavage, 30 rats/dose were given a single dose of 0, 100, or 1000 mg/kg ASE and concentration was measured in fat and liver tissue 1, 3, 7, 14, 21, and 34 days post-exposure. The peak concentrations in fat were measured on day 3 and day 1 in the 100 and 1000 mg/kg groups, respectively. The half-life in fat tissue was 8 days. No accumulation was seen in the liver, and 20-30% of the total dose was excreted via feces within 24 hours. In the feeding portion of the study, rats were provided 100 or 1000 ppm in the feed (approx. 9 or 90 mg/kg-day) for 49 days. The low-dose group (30 animals) were assessed at 1, 3, 7, 14, 21, and 43 days of feeding and ASE accumulated linearly in fat for the duration of feeding. In the high-dose group (50 animals), assessed at day 1, 3, 7, 14, 21, 28, 35, 42, and 49, ASE accumulated in fat linearly until day 21 (232 µg/g fat), and accumulated slower thereafter (maximum 290 µg/g fat). In an additional experiment, 50 rats were fed 90 mg/kg-day ASE in the diet for 27 days and assessed on days 1, 3, 7, 14, 28, and 43. The half-life of ASE after cessation of dietary exposure was 15 days.

5 Hazard Information

5.1 Acute Single Dose Toxicity

5.1.1 Acute Oral Toxicity

Based on various reports, ASE has a low level of acute toxicity via the oral route.

A commercial formulation of ASE was administered to male Wistar rats (10/dose) via gavage at doses of 5.0 and 15.0 mL/kg (approximately 5300 and 15,900 mg/kg, respectively) in an acute toxicity study (Loser et al., 1975, as cited by ECHA, 2018). The observation period was 14 days. Signs of intoxication (behavior, ruffled fur, and diarrhea) were observed in 10/10 animals in the high-dose group, and no animals in the low-dose group. No deaths were observed at any dose, and an LD_{50} was not determined.

An additional citation (Bornmann, 1956, as cited by ECHA, 2018) reported an LD_{50} of 26,380-31,650 mg/kg following exposure via gavage in rats. The strain, sex, and sample size was not available.

5.1.2 Acute Dermal Toxicity

Loser et al. (1975, as cited by ECHA, 2018) applied 1 mL of a commercial formulation of ASE to the skin of male and female Wistar rats (5/sex) and observed the rats for 7 days. The dose was equivalent to 1055 mg/kg and no signs of toxicity were seen.

5.1.3 Acute Inhalation Toxicity.

No studies of acute toxicity via inhalation were found.

5.1.4 Irritation/Sensitization

Limited data indicate that ASE is not irritating, corrosive, or sensitizing.

Data from two skin irritation/corrosion tests for ASE are available (both Loser et al., 1975, as cited by ECHA, 2018). ASE (undiluted commercial formulation, dose not reported) was tested on seven volunteers (sex not given) via 24-hour application to the skin followed by a 7-day observation period. No effects were observed. In a second experiment, ASE was tested on male and female New Zealand white rabbits (one per sex). Approximately 0.5 mL ASE was applied to the skin of the ear for 24 hours and observed for 7 days. No effects were observed. Although the rabbit study is limited by the small sample size, it supports the conclusion that ASE is not irritating. One further citation (Anonymous, 1975, as cited by ECHA, 2018) reported no effects in two volunteers when ASE was applied to the forearm for 8 hours followed by a 7 day observation period. (No other details were provided.)

Eye irritation/corrosion was tested in rabbits (sex/strain/number of animals not given) (Loser et al., 1975, as cited by ECHA, 2018). A volume of 100 µL ASE was applied to the conjunctival sac followed by a 7-day observation period. No effects were observed.

Sensitization was tested in a guinea pig maximization test performed according to OECD 406 in a GLP-compliant study (Vohr, 2002, as cited by ECHA, 2018). Female HSD POC:DH guinea pigs (10 controls, 20 treated animals) were exposed to ASE (commercial formulation, “72% purity”) via intradermal injection and topical application at concentrations of 5 and 12%, respectively, in polyethylene glycol 400 (all treated animals received both treatments). Topical challenge with a 3% solution 48 and 72 hours later did not elicit any observed effects.

5.2 Repeated Dose Toxicity

Oral

A 25-day range-finding study (Anonymous, 1986, as cited in ECHA, 2018) exposed female Bor:WISW rats (10/dose) to 0, 3000, or 10,000 ppm ASE (commercial formulation) in the diet.

(The corresponding approximate doses are 0, 309, or 1030 mg/kg-day[2].) Increases in water consumption and absolute and relative liver weights were seen at the highest dose, and were considered adaptive by the authors. No other effects were seen in behavior, body weight, appearance, hematology, or histology of a broad range of organs.

A 6-week study (Bornmann et al., 1956, as cited by ECHA, 2018) exposed male and female rats (strain and sample size not given) to 530 mg/kg-day ASE via gavage in an olive oil vehicle. No effects on body weight, food and water consumption, or organ histology were observed. ECHA (2018) attributed another report to the same reference, describing a 1-year study in rats, but the study details are unclear and no useful conclusions can be drawn.

A 90-day feeding study (Ramm and Eiben, 1987, as cited by ECHA, 2018) was reported in male and female Wistar (Bor:WISW) rats (10/sex/dose) in a GLP-compliant study performed according to OECD Guideline 408. The concentration of ASE in diet was 0, 750, 3000, or 12,000 ppm. The corresponding doses calculated by the study authors were approximately 0, 55, 228, and 985 mg/kg-day for males, and 0, 69, 283, and 1489 mg/kg-day for females. A comprehensive range of endpoints was examined. Decreased growth was observed in the 12,000 ppm dose group for both males and females. Kidney weight was also increased at this dose, and males consumed more water, while females consumed more food. Hematology tests showed that males also had a slightly increased thromboplastin time at the high dose. Liver weights were described as dose-dependently increased at all dose levels, but the study authors did not consider the change to be adverse. No quantitative data were provided, making it impossible to independently evaluate the results. The study authors considered 228 mg/kg-day to be the study NOAEL. A brief summary of the same study by EFSA (2010) named a NOAEL of 55 mg/kg-day based on increased liver weights and increased lactate dehydrogenase activity "at higher doses in both sexes."

Inhalation and Dermal

No studies of repeat-dose toxicity via inhalation or dermal exposure were identified.

5.3 Chronic Toxicity/Carcinogenicity

No data evaluating the carcinogenicity of ASE was found.

5.4 Reproductive Toxicity

ASE does not appear to affect fertility, although maternal effects on body weight/growth may eventually affect reproduction. In addition to a well-documented guideline study reported below, information was available on a three-generation reproductive study.

Eiben and Rinke (2002, as cited by ECHA, 2018) conducted a GLP-compliant one-generation reproductive toxicity study in Wistar rats according to OECD Guideline 415. Rats (25/sex/dose) were fed ASE (commercial formulation, C10-21, purity "100.1%") at dietary concentrations of 0,

[2] Based on a default food factor of 0.103 kg food/kg bw-day (https://www.tera.org/Tools/ratmousevalues.pdf)..

600, 3000, or 15,000 ppm (approximately 0, 47, 234, and 1172 mg/kg-day for males, and 0, 68, 339, and 1697 mg/kg-day for females) for 10 weeks prior to mating until 4 weeks after birth (17-20 weeks total). Clinical signs, body weight, food intake, and histopathological examination of a limited number of organs was reported for the adults. The reproductive evaluation assessed mating performance, fertility, duration of pregnancy, estrus cycling, sperm parameters, implantation sites, number of live births, and histopathology of selected organs. Food intake was increased among females in the 3000 and 15,000 ppm groups, but body weights were decreased in females during gestation and lactation in the high-dose group, indicating decreased food efficiency. Liver weights were increased in females at 3000 ppm and higher. Kidney weights were also increased at the same doses in both sexes. The authors considered these changes non-adverse as these tissues appeared normal under microscopic examination. "Altered follicular colloid in the thyroids" was seen in males (15/25, 16/25, 22/25, and 23/25 animals at 0, 600, 3000 and 15000 ppm, respectively) and follicular cell hypertrophy was increased at 15000 ppm. Altered follicular colloid appearance was seen in females at an incidence of 1/25, 4/25, 4/25, and 5/25 in the 0, 600, 3000, and 15000 ppm groups, respectively. These effects were considered an "unspecific expression of adaptive physiological changes" by the authors, implying they were not necessarily adverse. No effects on reproduction were observed up to the maximum dose (1172 and 1697 mg/kg-day for males and females, respectively). Gross appearance, litter size, sex ratio, pup weight, viability, organ weights, and developmental milestones were assessed in offspring. Growth retardation was observed in offspring of the 3000 and 15,000 ppm groups. Delayed developmental milestones (balano-preputial separation and vaginal opening) were also observed and considered to be secondary to the growth retardation. No other test-related effects were seen in offspring. The study authors considered 600 ppm (68 mg/kg-day in females) to be the study NOAEL, based on the developmental changes of growth retardation and associated delayed developmental milestones at 339 mg/kg-day. The corresponding maternal NOAEL was 339 mg/kg-day, based on decreased body weight gain during gestation and lactation. The highest dose tested, 1172 mg/kg-day for males and 1697 mg/kg-day for females, was the reproductive NOAEL. Changes in liver and kidney weight were not considered adverse. There was a thyroid NOAEL of 234 mg/kg-day and LOAEL of 1172 mg/kg-day in males, based on follicular cell hypertrophy.

A three-generation reproductive study in rats (Bornmann et al., 1956, as cited by ECHA, 2018, and Maag et al, 2010) gavaged female rats (8/dose, strain not given) with 0 or 530 mg/kg-day ASE in olive oil for 6 weeks prior to mating with unexposed males. No effects on body weight gain, estrus cycling, or fertility were seen in F0, F1, F2, or F3 rats. No other details were given, and it was not clear if generations after F0 received exposure.

5.5 Prenatal, Perinatal, and Post-natal Toxicity

Based on the results of two studies, ASE does not induce structural developmental effects but may result in delayed fetal growth, as noted in the one-generation study summary in Section 5.4 (Eiben and Rinke, 2002, as cited by ECHA, 2018).

Developmental toxicity was assessed in a GLP-compliant study performed according to OECD Guideline 414 (Klaus, 2002, as cited by ECHA, 2018). Pregnant Wistar rats (26-27/dose) were administered 0, 100, 300, or 1000 mg/kg-day ASE (commercial formulation, C10-C21, purity 97.2%) via gavage in polyethylene glycol on gestation days (GD) 6-19. F1 fetuses were examined on day 20 of gestation. Sex ratio, fetal weight, development, and external, visceral, and skeletal malformations were assessed. No treatment-related effects were observed in fetuses at any dose. However, maternal feed consumption and body weight gain were reduced at 1000 mg/kg-day. The maternal NOAEL was 300 mg/kg-day and the LOAEL was 1000 mg/kg-day, based on decreased body weight gain. The developmental NOAEL was the high dose of 1000 mg/kg-day.

5.6 Genotoxicity

ASE (commercial formulation) was tested for mutagenicity in *Salmonella typhimurium* reverse mutation (Ames) and mammalian gene mutation (HPRT) assays. Ames tests were negative when carried out at up to 12.5 mg/plate in strains TA1535, TA100, TA1537, and TA98, with or without exogenous metabolic activation (Herbold , 1981, as cited by ECHA, 2018).

A commercial formulation of ASE was also not mutagenic up to 5 mg/mL (with or without exogenous metabolic activation) in an HPRT assay using V79 (Chinese hamster lung) cell cultures (Brendler-Schwaab, 1996, as cited by ECHA, 2018). The maximum dose in this study was the limit of solubility of the test article.

ASE (commercial formulation) was tested for clastogenicity in lung cells from female Chinese hamsters (Nakagawa, 2003, as cited by ECHA, 2018). Chromosomal aberrations were not seen in cultures exposed to up to 5 mg/mL, with or without S9. In a 1996 GLP-compliant study done according to OECD Guideline 473 in V79 cell culture (likely Brendler-Schwaab, 1996, as cited by ECHA, 2018), no chromosomal aberrations were seen at ASE concentrations up to 1000 µg/mL in the absence of S9. A non-significant increase of structural aberrations was seen when exogenous metabolic activation was included.

5.7 Mechanistic Studies

No mechanistic studies were located for ASE.

5.8 Mode of Action

Based on the limited body of data, it is not possible to describe a mode of action for ASE. A handful of reports document increased feeding in rats concurrent with decreases in body weight, suggesting that ASE may interfere with some aspect of nutritional absorption (all available studies are via the oral route in rat).

Some speculation is also possible regarding the MOA for the reported thyroid changes. As described by Dellarco et al. (2006), induction of liver metabolic enzymes (as suggested by the observation of increased liver weight in several studies) can lead to increased metabolism of the

thyroid hormones T3 and T4, leading to decreased serum levels of these hormones and compensatory increases in thyroid stimulating hormone (TSH). The increased TSH can lead to changes in follicular colloid, and ultimately to follicular cell hypertrophy. This hypothesized MOA is plausible in rats exposed to ASE, but currently is purely speculative in the absence of measurements of thyroid hormones. It is noted, however, that although thyroid tumors resulting from this MOA are not considered relevant to humans, neurodevelopmental effects can result from the changes in thyroid hormones associated with this MOA and are considered relevant to humans (Zoeller and Crofton, 2005). This suggests that it would be useful to conduct such hormone evaluations in treated rats, and if effects are observed, to evaluate the potential neurodevelopmental toxicity of ASE.

5.9 Lowest Hazard Endpoints by Organ System and Exposure Duration

Available toxicity studies demonstrate that the repeat dose toxicity of ASE is low. The primary observed effects were decreased body weight gain and increased liver and kidney weight. Interpretation of the data is limited because none of the primary studies were available, and almost no quantitative data were provided to aid in determining whether the degree of change would be considered adverse.

Decreased body weight was reported in male and female rats ingesting diets containing 12,000 ppm ASE (985 mg/kg-day for males and 1489 mg/kg-day for females) for 90 days (Ramm and Eiben, 1987, as cited by ECHA, 2018). This finding was supported by decreased feed consumption and maternal body weight gain in a developmental study in rats at 1000 mg/kg-day (Klaus, 2002, as cited by ECHA, 2018), and decreased body weight compared to controls during gestation and lactation at 15,000 ppm in diet (1697 mg/kg-day) in the one-generation reproductive toxicity study (Eiben and Rinke, 2002, as cited by ECHA, 2018).

Liver weights were consistently increased, but were not accompanied by histopathology changes or clinical chemistry indications of liver damage, and so the liver weight changes were not considered adverse. Increased liver weight was reported in female rats receiving 10,000 ppm ASE in the diet (about 1030 mg/kg-day) for 25 days (Anonymous, 1986, as cited by ECHA, 2018), and a dose related increase was seen in male and female rats beginning at 750 ppm ASE in the diet (about 55 mg/kg-day for males and 69 mg/kg-day for females) for 90 days (Ramm and Eiben, 1987, as cited by ECHA, 2018). Increased liver weight was not reported in males in the one-generation reproductive study at dietary levels up to 15,000 ppm (1172 mg/kg-day), but was reported in females in that study at 3000 ppm (339 mg/kg-day) (Eiben and Rinke, 2002, as cited by ECHA, 2018). The reason for the lower apparent effect level in the 90-day study is not clear, but may simply reflect the authors' apparent focus on where the dose-response began, as opposed to where statistically significant differences began.

Increased kidney weights were reported in both the 90-day study (Ramm and Eiben, 1987, as cited by ECHA, 2018) and the one-generation reproductive toxicity study (Eiben and Rinke, 2002, as cited by ECHA, 2018), for which the exposure was of a similar duration. In the former study, increased kidney weight was seen at 12,000 ppm in the feed (985 mg/kg-day for males and 1489 mg/kg-day for females), and in the latter study it was seen at 3000 ppm in the feed (234

mg/kg-day in males and 339 mg/kg-day in females). As for the liver weight, the changes in kidney weight were not considered adverse in the absence of histopathology correlates.

There was no evidence of reproductive toxicity in the one-generation study (Eiben and Rinke, 2002, as cited by ECHA, 2018) up to 15,000 ppm in diet (1172 mg/kg-day for males and 1697 mg/kg-day for females), and no evidence of reproductive organ effects in the subchronic toxicity study at dietary concentrations up to 12,000 ppm (Ramm and Eiben, 1987, as cited by ECHA, 2018). There was also no developmental toxicity in the offspring of rats gavaged on GD 6-19 with doses up to 1000 mg/kg-day (Klaus, 2002, as cited by ECHA, 2018). However, postnatal growth retardation and delayed markers of sexual maturation were seen in the offspring of rats fed 3000 ppm ASE in the diet (339 mg/kg-day) in the one-generation study.

Two other effects were seen in only one study. Slightly increased thromboplastin time was reported in males only in the 90-day study at 12,000 ppm (985 mg/kg-day) (Ramm and Eiben, 1987, as cited by ECHA, 2018). Although this endpoint is a potentially adverse one, no effect was observed in the females, nor were other related blood-clotting endpoints affected (assuming they were evaluated). The second change was increased thyroid follicular cell hypertrophy in the one-generation study (Eiben and Rinke, 2002, as cited by ECHA, 2018), in males that consumed 15,000 ppm in diet (1172 mg/kg-day). Although hypertrophy was not seen in the females, the suggestion that ASE can affect the thyroid is supported by changes in the thyroid follicular colloid in males at 234 mg/kg-day and in females with a marginally increased incidence over controls at all doses.

ASE was adequately tested and was negative for gene mutations in the Ames assay (Herbold , 1981, as cited by ECHA, 2018) and in V79 cell cultures (Brendler-Schwaab, 1996, as cited by ECHA, 2018). It was also negative for clastogenicity in lung cells from female Chinese hamsters (Nakagawa, 2003, and Brendler-Schwaab, 1996, both as cited by ECHA, 2018).

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

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[3]	Toxicological Basis	Comments
Bor:WISW [Wistar] rats (F) 10/dose Anonymous, 1986, as cited by ECHA, 2018	25 days Diet 0, 3000, 10,000 ppm 0, 309, 1030 mg/kg-day	Liver	NOEL = N/A LOEL = 1030 (F)	Increased absolute and relative liver weights	Behavior, body weight, appearance, hematology, and histology of a broad range of organs assessed Dose conversions based on food factor defaults for Wistar rats
Unknown strain rat (M & F) Sample size not given Bornmann et al., 1956, as cited by ECHA, 2018	6 weeks Oral gavage 0, 530 mg/kg-day	Systemic	NOAEL = 530 (M, F) LOAEL = N/A (M, F)	No effects	Body weight, food and water consumption, and organ histology assessed Limited study details
Wistar rats (M/F) 10/sex/dose Ramm and Eiben, 1987,	90 days Diet 0, 750, 3000, 12,000 ppm	Body weight	NOAEL = 228 (M) LOAEL = 985 (M) NOAEL = 283 (F) LOAEL = 1489 (F)	Decreased growth	OECD Guideline 408, GLP-compliant Comprehensive range of endpoints examined
		Kidney	NOAEL = 228 (M) LOAEL = 985 (M)	Increased kidney weight	

[3] All effect levels as identified by the authors of this assessment. Effect levels identified by previous assessments, when different or of note, are in the comments section.

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[3]	Toxicological Basis	Comments
as cited by ECHA, 2018	M: 0, 55, 228, 985 mg/kg-day F: 0, 69, 283, 1489 mg/kg-day		NOAEL = 283 (F) LOAEL = 1489 (F)		Water consumption increased in males and food consumption increased in females at 985 and 1489 mg/kg-day (high dose group), respectively 228 mg/kg-day was considered the study NOAEL by authors; EFSA (2010) considered the NOAEL to be 55 mg/kg-day.
		Liver	LOEL = 55 (M) LOEL = 69 (F)	Increased liver weight dose-dependently "at all dose levels", was not considered adverse change by the authors	
		Hematology	NOAEL = 228 (M) LOAEL = 985 (M) NOAEL = 1489 (F) LOAEL = N/A (F)	Slightly increased thromboplastin time	
Wistar rats (M/F) 25/sex/dose Eiben and Rinke, 2002, as cited by ECHA, 2018	17-20 weeks (10 weeks before mating, 3-6 weeks mating and gestation, 4 weeks post-natal) Diet 0, 600, 3000, 15,000 ppm M: 0, 47, 234, 1172 mg/kg-day	Reproductive	NOAEL = 1172 (M) NOAEL = 1697 (F) LOAEL = N/A (M, F)	No effects	OECD Guideline 415, GLP-compliant Full range of organs examined in F0 histopathology was not given Food consumption was increased among females at 339 mg/kg-day and above, which the authors considered non-adverse
		Liver	NOAEL = 1172 (M) LOAEL = N/A (M) NOEL = 68 (F) LOEL = 339 (F)	Increased liver weight, not considered adverse	
		Kidney	NOEL = 47 (M) LOEL = 234 (M) NOEL = 68 (F) LOEL = 339 (F)	Increased kidney weight, not considered adverse	
		Thyroid	NOAEL = 234 (M) LOAEL = 1172 (M) NOAEL = 1697 (F) LOAEL = N/A (F)	Follicular cell hypertrophy; changes in follicular colloid considered adaptive	
		Maternal	NOAEL = 339 (F) LOAEL = 1697 (F)	Decreased body weight during	

Species (Sex), Reference	Exposure Regimen	Effect Category	Toxicological Endpoint (mg/kg-day)[3]	Toxicological Basis	Comments
	F: 0, 68, 339, 1697 mg/kg-day			gestation and lactation	
		Developmental	NOAEL = 68 LOAEL = 339	Postnatal growth retardation in offspring and delayed developmental milestones	
Unknown strain rat (F) 8/dose Bornmann et al., as cited by ECHA, 2018, and Maag et al., 2010	6 weeks (prior to mating) Oral gavage 0, 530 mg/kg-day	Reproductive	NOAEL = 530 (F) LOAEL = N/A	No effects	Three-generation study (not clear if generations after F0 received exposure) No effects on body weight gain, estrus cycling, or fertility seen in F0, F1, F2, or F3 generations Limited study details
Wistar rats (F) 26-27/dose Klaus, 2002, as cited by ECHA, 2018	GD 6-19 Oral (gavage) 0, 100, 300, 1000 mg/kg-day	Maternal	NOAEL = 300 (F) LOAEL = 1000 (F)	Decreased feed consumption and body weight gain	OECD Guideline 414, GLP-compliant Maternal and fetal endpoints were examined at GD 20
		Developmental	NOAEL = 1000	No effects	

5.10 Uncertainties and Data Gaps

Several uncertainties of varying importance were identified in this assessment.

Database:

The overall database on ASE includes many of the key studies. Guideline-compliant studies are available for subchronic systemic toxicity (Ramm and Eiben, 1987, as cited by ECHA, 2018), as well as a one-generation study (Eiben and Rinke, 2002, as cited by ECHA, 2018) in rats and a developmental toxicity study (Klaus, 2002, as cited by ECHA, 2018). However, studies are available only in rats, and no studies beyond acute duration are available for the inhalation or dermal routes. Adequate data are available for genotoxicity (Herbold, 1981; Brendler-Schwaab, 1996; Nakagawa, 2003, all as cited by ECHA, 2018).

Another key limitation to the database is that all of the studies were available only from secondary sources, and none of the secondary sources provided detailed quantitative results. This substantially limited the potential for independent evaluation of the results. Finally, as noted in the context of the MOA, there is some indication that ASE affects the thyroid by disrupting thyroid hormone metabolism. This suggests that it would be useful to evaluate thyroid hormone levels in treated rats, and if effects are observed, to evaluate the potential neurodevelopmental toxicity of ASE.

Hazard:

For all of the observed effects, there is at least some uncertainty regarding the adversity of the observed change, due to the absence of quantitative results.

Body weight: There is uncertainty whether the reported changes are adverse, in the absence of quantitative information on the magnitude of the difference from controls.

Liver weight: There is uncertainty as to whether the liver weight changes occurring in the absence of other supporting changes would be considered adverse in a modern risk assessment context. Recent guidance by U.S. EPA (2002) provides that hepatocellular hypertrophy and/or liver size/weight changes should not be considered adverse unless there is a known mode of action for toxicity and/or the other study data (e.g., clinical chemistry and histopathology) indicate adverse changes.

Kidney weight: There is uncertainty in interpreting the kidney weight changes in the absence of quantitative data.

Hematology: There is uncertainty regarding the toxicological significance of the slight increase in thromboplastin time (Ramm and Eiben, 1987, as cited by ECHA, 2018), in the absence of similar changes in females or effects on other clotting-related endpoints.

Thyroid: There is uncertainty regarding the significance and mode of action of the observed thyroid changes (Eiben and Rinke, 2002, as cited by ECHA, 2018). There is some evidence of a dose-response, with incidence and severity increasing with dose in males, and some support from females in the same study. Thyroid effects were not observed in the

subchronic study (Ramm and Eiben, 1987, as cited by ECHA, 2018), but that study did not test doses as high as in the reproductive toxicity study in which the thyroid effects were seen.

6 Exposure

The use of ASE in consumer products has been described in Section 3 of this report. The general population may be exposed to ASE via ingestion of foods when used in food contact and packaging materials. Consumers may be exposed dermally through products made of polymers or rubbers that contain ASE. Infants and children may ingest ASE via mouthing of products (e.g., children's toys) containing ASE or from ingestion of dust contaminated with ASE. Occupational exposure may occur during manufacturing.

Limited information on migration of ASE from polymers was found. Nielsen et al. (2014) in a Danish EPA report notes that compared to DEHP, the extraction rate of ASE from PVC into water is greater and that ASE has low migration into ethanol (no reference citations provided). ASE is approved for use in PVC food contact articles in the U.S., with the maximum level not to exceed 46% by weight (FDA, 2018). In Europe, the Scientific Panel on Food Contact Materials, Enzymes, Flavourings and Processing Aids (CEF) limits ASE to migration rates no greater than 0.05 mg/kg food and does not allow ASE use in contact with fatty foods (EFSA, 2010). A Japanese study measured ASE in two of four PVC food contact gloves tested (concentrations of 40% and 38%) (Kawamura et al., 2002).

Only one study was located that measured ASE in a consumer-relevant medium. Fromme et al. (2017) measured dust samples collected from the bags of the regularly-used vacuum cleaners from 25 German residences (in 2015) and 25 German daycare centers (in 2011 and 2012) (contents sieved to <63 µm before analysis). In the daycare center samples, the median concentration in the dust for the sum of tetra- to heptadecylphenyl esters was 19.6 mg/kg (95^{th} percentile of 216 mg/kg, maximum of 551 mg/kg). In the residences, the dust concentrations were lower, with a median of 7.6 mg/kg (95^{th} percentile of 171 mg/kg, maximum of 208 mg/kg). Fromme and colleagues discussed potential sources of this contamination and conclude that product use indoors is a significant contributor to indoor dust contamination with ASE.

To estimate a daily intake from contaminated dust, Fromme and colleagues (2017) used the median and 95^{th} percentile values of the dust samples (the text did not specify whether these values were for residence or daycare, or a combination of the two). They calculated a median intake of 0.08 µg/kg-day and a 95^{th} percentile intake of 0.86 µg/kg-day. They assumed an average intake of 60 mg dust/day for children one to six years old, and 100% absorption by the gastro-intestinal tract. The authors noted that these intakes are well below a tolerable daily intake value of 0.1 mg/kg-day set by the EU Scientific Committee for Food (SCF, 1995, as cited by Fromme et al., 2017), but that their risk characterization is uncertain, due to assumptions about absorption and the potential for exposure from other sources.

7 Discussion

7.1 Toxicity Under FHSA

Animal data support the conclusion that ASE **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. Multiple rat studies have reported rat oral LD_{50} values as greater than 5000 mg/kg (Loser et al., 1975; Bornmann, 1956, both as cited by ECHA, 2018). No rabbit dermal LD_{50} is available for ASE, but Loser et al. (1975, as cited by ECHA, 2018) reported no signs of toxicity in rats treated dermally with 1055 mg/kg, indicating that the rat LD_{50} is above this dose.

ASE was not irritating to the skin when tested on volunteers, or in a study with rabbits limited by the small sample size (Anonymous, 1975, Loser, 1975, both as cited by ECHA, 2018). ASE was also not irritating to the eyes of rabbits (Loser et al., 1975, as cited by ECHA, 2018). ASE was also not sensitizing in a guinea pig maximization test (Vohr, 2002, as cited by ECHA, 2018).

The systemic toxicity of ASE is low, with reproducible effects occurring at relatively high doses, and primarily limited to changes in body weight, and liver and kidney weight (Ramm and Eiben, 1987; Eiben and Rinke, 2002, both as cited by ECHA, 2018). There may also be effects on thromboplastin and on the thyroid, but there are some uncertainties in understanding the toxicological significance of the observed changes.

ASE did not cause reproductive toxicity in a one-generation study (Eiben and Rinke, 2002, as cited by ECHA, 2018), and there was no developmental toxicity in the developmental toxicity study (Klaus, 2002, as cited by ECHA, 2018). However, postnatal growth retardation and delayed markers of sexual maturation were seen in the offspring of rats fed ASE in the one-generation study.

ASE was adequately tested and was negative for gene mutations in bacterial and mammalian cells (Herbold , 1981; Brendler-Schwaab, 1996; both as cited by ECHA, 2018). It was also negative for clastogenicity in lung cells from female Chinese hamsters (Nakagawa, 2003, and Brendler-Schwaab, 1996, both as cited by ECHA, 2018).

No chronic/carcinogenicity studies are available for ASE.

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APPENDIX 1

Search Terms Used

Original Search (June, 2018)

Toxline	(91082-17-6)
Pubmed	"C10-18-Alkane sulfonic acids phenyl esters" OR "Sulfonic acids, C10-18-alkane, phenyl esters" OR "phenyl esters C10-21 alkane sulfonic acids" OR "Sulfonic acids, C10-21-alkane, phenyl esters"

Supplemental Search (February, 2018)

Toxline	“Phenyl (C10-C18) alkylsulfonate” OR “Sulfonic acids, C10-18-alkane, Phenyl esters” OR “Propane-1-sulfonic acid- phenol(1:1)” OR “C10-18-Alkane sulfonic acids phenyl esters” OR “phenol; propane-1-sulfonic acid” OR “mesamoll” OR (70775-94-9)
	“Phenyl 1-pentadecane sulfonate” OR “1-Pentadecane sulfonic acid phenyl ester” OR “1-Pentadecanesulfonic acid phenyl ester” OR “1-Pentadecane sulfonic acid, phenyl ester” OR “C10-21 alkanesulfonic acids phenyl esters” OR “Sulfonic acids, C10-21-alkane, Phenyl esters” OR “alkylsulfonic phenyl ester” OR (91082-17-6)
Pubmed	“Phenyl (C10-C18) alkylsulfonate” OR “Sulfonic acids, C10-18-alkane, Phenyl esters” OR “Propane-1-sulfonic acid- phenol(1:1)” OR “C10-18-Alkane sulfonic acids phenyl esters” OR “phenol; propane-1-sulfonic acid” OR “mesomoll” OR (70775-94-9)
	“Phenyl 1-pentadecane sulfonate” OR “1-Pentadecane sulfonic acid phenyl ester” OR “1-Pentadecanesulfonic acid phenyl ester” OR “1-Pentadecane sulfonic acid, phenyl ester” OR “C10-21 alkanesulfonic acids phenyl esters” OR “Sulfonic acids, C10-21-alkane, Phenyl esters” OR “alkylsulfonic phenyl ester” OR (91082-17-6)

APPENDIX 2

Explanation of Physico-chemical Parameters

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).