Long chain Ca phenol derivatives: Human health tier II assessment

01 September 2015

Chemicals in this assessment

Chemical Name in the Inventory	CAS Number
Phenol, dodecyl-, sulfurized, carbonates, calcium salts	68784-25-8
Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased	68784-26-9
Phenol, dodecyl-, sulfurized, calcium salts	68855-45-8
Phenol, tetrapropylene-, sulfurized, calcium salts	122384-85-4
Phenol, tetrapropylene-, sulfurized, carbonates, calcium salts	122384-86-5
Phenol, tetrapropylene-, sulfurized, carbonates, calcium salts, overbased	122384-87-6

Preface

This assessment was carried out by staff of the National Industrial Chemicals Notification and Assessment Scheme (NICNAS) using the Inventory Multi-tiered Assessment and Prioritisation (IMAP) framework.

The IMAP framework addresses the human health and environmental impacts of previously unassessed industrial chemicals listed on the Australian Inventory of Chemical Substances (the Inventory).

The framework was developed with significant input from stakeholders and provides a more rapid, flexible and transparent approach for the assessment of chemicals listed on the Inventory.

Stage One of the implementation of this framework, which lasted four years from 1 July 2012, examined 3000 chemicals meeting characteristics identified by stakeholders as needing priority assessment. This included chemicals for which NICNAS already held exposure information, chemicals identified as a concern or for which regulatory action had been taken overseas, and chemicals detected in international studies analysing chemicals present in babies' umbilical cord blood.

Stage Two of IMAP began in July 2016. We are continuing to assess chemicals on the Inventory, including chemicals identified as a concern for which action has been taken overseas and chemicals that can be rapidly identified and assessed by using Stage One information. We are also continuing to publish information for chemicals on the Inventory that pose a low risk to human health or the environment or both. This work provides efficiencies and enables us to identify higher risk chemicals requiring assessment.

The IMAP framework is a science and risk-based model designed to align the assessment effort with the human health and environmental impacts of chemicals. It has three tiers of assessment, with the assessment effort increasing with each tier. The Tier I assessment is a high throughput approach using tabulated electronic data. The Tier II assessment is an evaluation of risk on a substance-by-substance or chemical category-by-category basis. Tier III assessments are conducted to address specific concerns that could not be resolved during the Tier II assessment.

These assessments are carried out by staff employed by the Australian Government Department of Health and the Australian Government Department of the Environment and Energy. The human health and environment risk assessments are conducted and published separately, using information available at the time, and may be undertaken at different tiers.

This chemical or group of chemicals are being assessed at Tier II because the Tier I assessment indicated that it needed further investigation.

For more detail on this program please visit:**www.nicnas.gov.au**

Disclaimer

ACRONYMS & ABBREVIATIONS

Grouping Rationale

All six members of this group are mixtures of oligomers of alkyl phenate molecules that are linked by one to three sulfur atoms with varying levels of unsulfurized alkyl phenate present. The alkyl phenoxy group can contain saturated branched chain C12 (tetrapropenyl) alkyl groups attached primarily at the *para* ring position. The group can be considered as calcium salts of branched C12 alkyl phenol with varying additions of calcium oxide and carbonate.

The calcium carbonate "overbased" derivative is formed by further reacting the calcium alkyl phenate sulfides with carbon dioxide and excess calcium hydroxide.

The CAS number assigned to each substance refers to the active alkyl phenol sulfide or calcium alkyl phenate sulfide component, which are never isolated from highly refined lubricant base oil. The tetrapropenyl phenol (TPP) present can vary by manufacturers from 0.1–14 %.

Import, Manufacture and Use

Australian

The following Australian industrial uses were reported under previous mandatory and/or voluntary calls for information.

The chemicals with CAS numbers 68784-25-8, 68855-45-8 and 122384-85-4 have been reported to have commercial use including:

- Lubricants and additives.

The chemicals with CAS numbers 122384-87-6, 68784-26-9 and 122384-86-5 have no known reported use in Australia.

International

The following international uses have been identified through the European Union Registration, Evaluation and Authorisation of Chemicals (EU REACH) dossiers, the Organisation for Economic Cooperation and Development Screening information data set International Assessment Report (OECD SIAR), Galleria Chemica, Substances and Preparations in the Nordic countries (SPIN) database, and other data sources via eChemPortal including the US Environmental Protection Agency's (EPA) and the Aggregated Computer Toxicology Resource (ACToR):

The chemicals from this group have reported commercial use including:

- Hydraulic fluids and additives;
- Lubricants and additives; and
- Motor and engine oils including automotive, diesel, marine and railroad.

Restrictions

Australian

No known restrictions have been identified.

International

No known restrictions have been identified.

Existing Worker Health and Safety Controls

Hazard Classification

These chemicals are components of a 'Mixture of calcium bis (C10-14 branched alkyl salicylate) and calcium bis (C18-30-alkyl salicylate) and calcium C10-14 branched alkylsalicylato-C18-30-alkyl salicylate and calcium bis (C10-14 branched alkyl phenolate) and calcium bis (C18-30-alkyl phenolate) and calcium C10-14 branched alkylphenolato-C18-30-alkyl phenolate and **C10-14 branched alkyl phenol** and C18-30-alkyl phenol' which is classified as hazardous, with the following risk phrases for human health in the Hazardous Substances Information System (HSIS) (Safe Work Australia):

Xi; R38 (Irritant)

There are no classifications for any of the individual chemicals of this group.

Exposure Standards

Australian

No specific exposure standards are available.

International

The following exposure standards are identified for CAS No.68855-45-8, CAS No. 68784-26-9, and Cas No. 68784-25-8 (Galleria Chemica):

An exposure limit (TWA - time weighted average) of 10 mg/m³ in different countries such as Canada (Ontario, Quebec), Spain and Ireland.

An exposure limit (TWA - time weighted average) of 5 mg/m³ in USA (California, Tennessee).

No specific exposure standards were found for CAS No. 122384-85-4, CAS No. 122384-87-6 and CAS No. 122384-86-5.

Health Hazard Information

Physicochemical data indicate all members have low water solubility and high octanol water partition coefficient, therefore would have low potential for absorption across the skin. In the absence of specific data on acute inhalation toxicity, data available from a saturated branched C9 (nonyl) chain substance (CAS 68515-93-5) can be used for read across as it has similar physicochemical properties and endpoints. However, their liquid form, low vapour pressure and high viscosity would also indicate inhalation as an unlikely route of exposure.

Toxicokinetics

The physicochemical properties of large molecular weight (>600), low water solubility and high lipophilicity, limit the dermal and oral absorption of the chemical (OECD, 2009). Distribution could occur in the blood, interstitial cellular and transcellular fluids and highly perfused tissues. Observations of the liver and kidney in repeat dose toxicity testing, suggested the chemical was not being transformed into toxic metabolites. It is predicted that due to the low water solubility and high lipophilicity, a significant amount of an orally administered dose would pass through the gastrointestinal tract unchanged, and eventually be eliminated in the faeces.

Acute Toxicity

Oral

The chemicals of this group exhibit low acute toxicity in animal tests as evidenced by reported oral LD50 values in rats. LD50s ranged from 5000–16000 mg/kg bw (OECD, 2009). No mortalities occurred in these studies. Observed sub-lethal effects included soft faeces, dark stained urogenital areas, and red-stained faeces.

Dermal

The chemicals of this group exhibit low acute toxicity in animal tests as evidenced by reported dermal LD50 in rats (OECD, 2009). LD50s ranged from >2000 to >15000 mg/kg bw. No mortalities occurred during these studies. During the 14 day observation period, the sub-lethal effects included a decrease in food consumption and clear ocular discharge at dose levels >4000 mg/kg.

Inhalation

Based on the similarities between the chemicals of this group and the component chemical CAS 122384-87-6, they exhibit low acute toxicity from animal tests following inhalation exposure.

The chemicals exhibit low acute toxicity in animal tests following inhalation exposure with no mortalities or systemic toxic effects observed in rodent studies (median lethal concentration LC50 >1.67 mg/L) during a one hour, nose only, exposure (OECD, 2009). In this study, five rats from each sex were exposed to the test substance as a vapour and aerosol condensate by heating the substance to 170 °C. Since the duration of exposure was only one hour as opposed to the four hours described in the OECD Test Guideline (TG) 403, it cannot be used to determine a classification.

Corrosion / Irritation

Skin Irritation

A mixture including the related chemicals is classified as hazardous with the risk phrase 'Irritating to skin' (Xi; R38) in HSIS (Safe Work Australia). The available data do not support this classification for the chemicals of the group. The chemicals in this group were not considered skin irritants, when tested for four hours under semi-occlusive conditions, according to OECD TG 404.

In a reliable skin irritation study (OECD TG 404) with test substances CAS No. 122384-85-4 and 68855-45-8, six rabbits were exposed to the chemical via dermal application for four hours (OECD, 2009). After the exposure period, the chemical was removed. Very slight to well defined erythema and slight to moderate oedema were observed at 24, 48, 72 and 96 hours after treatment. All irritation was reversible within seven days. A primary irritation index of 2.8 was obtained, indicating the chemicals were not dermal irritants.

In two reliable skin irritation studies with test substances CAS No. 122384-87-6, CAS No. 68784-26-9, CAS No. 122384-86-5 and CAS No. 68784-25-8, six to twelve rabbits were exposed to the test substances dermally for four hours (OECD, 2009). After the exposure period, the chemical was removed. In both studies, slight erythema and slight oedema were observed. The primary irritation index for one study was 1.3 and all dermal irritations were reversed after three days. In the other study, the primary irritation index was 1.6 and all irritation was reversed within 14 days, indicating the chemicals were not dermal irritants.

Eye Irritation

The chemicals in this group were reported to be slight eye irritants in animal studies (OECD, 2009), (REACH). Effects were not sufficient to warrant a hazard classification.

In an eye irritation study (OECD TG 405) with test substances CAS No. 122384-85-4 and 68855-45-8, five male and four female New Zealand White rabbits were exposed to 0.1 ml of the chemical in one eye per animal and not washed out (OECD, 2009), (REACH). Treated eyes were examined at one,

24, 48, 72 and 96 hours after treatment. Corneal opacity in one animal was observed, and a Draize score for conjunctival redness at 24 hours was 1.8 for non washed out eyes. This effect was reversed after 96 hours and considered slightly irritating to the eyes.

In several other reliable eye irritation studies with CAS No. 122384-85-4 and 68855-45-8, the eyes of six rabbits per study were exposed to the test substances (OECD, 2009). In all studies, no corneal opacity or iritis was observed, although conjunctival irritation was reported in all animals. All eyes were clear of irritation by day seven.

In an eye irritation study (OECD TG 405) with test substances CAS No. 122384-87-6, CAS No. 68784-26-9, CAS No. 122384-86-5 and CAS No. 68784-25-8, two male and four female New Zealand White rabbits were exposed to 0.1 ml of the chemical into the cupped lower conjunctival sac of each rabbit's right eye and not washed out (OECD, 2009), (REACH). Treated eyes were examined at 24, 48, 72 hours and on days four and seven. No corneal damage or iritis was observed, and conjunctival irritation was observed in all animals. The Draize score for conjunctival redness at 24 hours was 1.5 for non washed out eyes. All eyes were clear of irritation by day seven and the chemicals were considered slightly irritating to eyes.

In another older reliable eye irritation study with CAS No. 122384-87-6, CAS No. 68784-26-9, CAS No. 122384-86-5 and CAS No. 68784-25-8, the eyes of six rabbits were exposed to 0.1 ml of the test substance (OECD, 2009). No corneal opacity or iritis was observed, although conjunctival irritation was reported in all animals. Slight conjunctival irritation was present but cleared by day seven.

In another reliable eye irritation study with CAS No. 122384-87-6, CAS No. 68784-26-9, CAS No. 122384-86-5 and CAS No. 68784-25-8, the eyes of six male New Zealand White rabbits were exposed to 0.1 ml of the test substance and remained unwashed (REACH), (OECD, 2009). Although no corneal opacity or iritis was observed, conjunctival irritation was reported in all animals. Draize scores for conjunctival redness at one and 24 hours were 2.5 for non washed out eyes. On day seven, no irritation was observed, although slight conjunctival redness was observed in one animal on day ten. All eyes were clear of irritation by day 14.

Considering the previous two reliable studies, the chemicals were considered slightly irritating to eyes.

Sensitisation

Skin Sensitisation

The negative results observed for the group of chemicals in two skin sensitisation animal studies (guinea pig maximisation test and Buehler test) support a conclusion that the chemicals are not skin sensitisers.

In the only available skin sensitisation study (Buehler test) with test substances CAS No. 122384-85-4 and 68855-45-8, ten Hartley guinea pigs per sex received three dermal induction doses of the chemical diluted to 25 % (w/v) in Mineral Oil USP (OECD, 2009), (REACH). The induction doses were applied once a week, over three weeks, with dermal epicutaneous application for six hours using occlusive patches. After the exposure period, the chemical was removed. Two weeks after the induction, the animals were challenged with 5 % (w/v) test substance in Mineral Oil USP. The incidence and severity of skin reactions in test animal were equivalent to the naive control animals, indicating the chemicals were not inducing sensitisation.

In a reliable Guinea pig maximisation test following the OECD TG 406 (skin sensitisation studies with test substances CAS No. 122384-87-6, CAS No. 68784-26-9, CAS No. 122384-86-5 and CAS No. 68784-25-8), 20 female Dunkin Hartley guinea pigs received a single intradermal induction dose of 7.5 % (w/w) in Alembicol D, and a single topical induction dose of 70% (w/w) in Alembicol D (REACH) (OECD, 2009). Animals were challenged two weeks after induction, with either 20 % (w/w) or 10 % (w/w) of the test substance, in Alembicol D. No signs of mortality or toxicity were evident, although dermal reactions were reported in five of the 20 induced animals, which persisted for 72 hrs. Based on the response of test animals, the test material was not considered sensitising.

Observation in humans

Negative findings were obtained in human repeated-insult patch tests with CAS No. 122384-87-6 and CAS No. 122384-86-5, where all 128 human subjects did not show any skin sensitisation or irritation on repeated topical applications (OECD, 2009) . Overall, these substances are not considered to be sensitisers in humans.

Repeated Dose Toxicity

Oral

The negative results seen for the group of chemicals from reliable repeat dose animal studies, support a conclusion that the chemicals within this group are not considered to cause serious damage to health by repeated oral exposure, due to NOAEL >200 mg/kg bw/day.

In a 28 day repeated dose toxicity study following OECD TG 407, test substances CAS No. 122384-85-4 and 68855-45-8 were administered by oral gavage in corn oil to six animals/sex/dose of Sprague Dawley (SD) rats, treated daily at dose levels of 50, 300 or 1000 mg/kg bw/day for seven days/week for four weeks (OECD, 2009), (REACH). There was no effect on body weight or effects noted in clinical observations from serum chemistry or

urinalysis, although there was an increase (26.5 %) in mean adrenal weight in the high dose group (1000 mg/kg bw/day). A NOAEL of 300 mg/kg bw/day for males and females was reported.

In an 90 day repeated dose toxicity study following OECD TG 408, test substances CAS No. 122384-87-6 and CAS No. 68784-26-9 were administered by oral gavage in corn oil to 10 animals /sex/dose of Crl:CD(SD) rats, treated ad libitum at dose levels of 125, 250, 500 or 1000 mg/kg bw/day (REACH). There was no mortality or any effect noted in clinical observations or from serum chemistry. There were no effects noted in gross pathology, organ weights or test substance related microscopic findings from histopathology. Although there were statistically significant lower body weights in test animals compared to the control group, since the mean difference at the end of the study did not exceed 10 %, the reported body weight effects were considered to be non adverse. Given all observations were considered non adverse, the NOAEL was considered to be 1000 mg/kg bw/day.

In a reliable 28 day repeat dose oral study for test substances CAS No. 122384-87-6, CAS No. 68784-26-9, CAS No. 122384-86-5 and CAS No. 68784-25-8 (OECD, 2009), there were no toxicologically significant changes in body weight in males or females. No effects were observed from macroscopic and microscopic examinations, food consumption, or haematology, and serum chemistry parameters were unaffected by test substance administration. A slight difference in adrenal weights was seen in the high dose group (1000 mg/kg bw/day) in males compared to controls, but the differences were not statistically significant.

Dermal

Based on the similarities between the chemicals of this group and the component chemicals CAS No. 122384-87-6 and CAS No. 122384-86-5, and considering there were no-observed-adverse-effect levels (NOAELs) available from a 28 day rat study (250 mg/kg bw/d), the chemicals in this group are not considered to cause serious damage to health by repeated dermal exposure.

In a 28 day repeated dose toxicity study following OECD TG 410, test substances CAS No. 122384-87-6 and CAS No. 122384-86-5 were administered using an semi-occlusive patch to 12 animals/sex/dose of SD rats, treated daily for 28 consecutive days at dose volumes of either 20, 100 or 250 mg/kg bw/day, for six hrs/day, five days/week (OECD, 2009), (REACH). There were no treatment related effects seen on mean body weights, food consumption, serum chemistry, haematology or urinalysis parameters or organ weights. Skin irritation was observed in all dose groups, including controls, although there was a slight increase in the incidence and severity of skin irritation in male test animals compared to controls. Reported NOAEL was greater than 250 mg/kg bw/day in males and females.

Inhalation

No data are available.

Observation in humans

In a well documented study in humans, a repeated insult patch test (RIPT) was conducted with chemical substances CAS No. 122384-87-6 and CAS No. 122384-86-5. Eighty four females and 20 males between the ages of 25 and 60 received a induction dose of 0.1 ml of undiluted chemical in mineral oil, and exposed for 24 hrs under occluded patch conditions (OECD, 2009) (REACH). Induction applications occurred three times a week for three weeks. A challenge dose of 0.1 ml of undiluted test substance in mineral oil, was applied ten to 17 days after induction. Mild to moderate erythema responses were reported in response to the test material and the negative control during the challenge period. As a result, the chemicals were reported to be non-sensitising.

Genotoxicity

The chemicals in this group tested negative in a few in vitro (Bacterial Reverse Mutation Assay and Mammalian Cell Gene Mutation) and in vivo (Mammalian Erythrocyte Micronucleus) tests for gene mutation and clastogenicity.

In a reliable Bacterial Reverse Mutation Test similar to OECD TG 471, with test substances CAS No. 122384-85-4 and 68855-45-8, the chemicals were reported not to produce an increase in mutation frequency that exceeded the criteria for a mutagenic response at dose levels of 0.01 to 50 µl/plate in *Salmonella typhimurium* TA98, TA100, TA1535, TA1537 or *Escherichia coli* WP2 uvrA, with and without an S9 metabolic activation system (OECD, 2009). Similarly test substances CAS No. 122384-87-6, CAS No. 68784-26-9, CAS No. 122384-86-5 and CAS No. 68784-25-8, also reported no increase in mutation frequency that exceeded the criteria for a mutagenic response, at dose levels of 0.033 to 3.33 mg/plate in *Salmonella typhimurium* TA98, TA100, TA102 or *Escherichia coli* WP2 uvrA, with and without an S9 metabolic activation system (OECD, 2009).

In a reliable in vitro Mammalian Cell Gene Mutation Test (OECD TG 476), with test substances CAS No. 122384-87-6, CAS No. 68784-26-9, CAS No. 122384-86-5 and CAS No. 68784-25-8, no statistically significant increase in mutation frequency with or without an S9 metabolic activation system, in mouse lymphoma L5178Y cells was reported (OECD, 2009), (REACH). Doses varied from 75, 100, 150, 200, 250 and 275 ug/ml with S9 activation and from 60, 70, 80, 90, 100 and 110 µg/ml without S9 activation.

In a reliable in vivo Mammalian Erythrocyte Micronucleus Test (OECD TG 474), test substances CAS No. 122384-85-4 and 68855-45-8 were administered to Crl:CD-1®(ICR) BR mice at dose levels of 1250, 2500 or 5000 mg/kg and five animals/sex/group were sacrificed at 24, 48 and 72 hrs

(REACH), (OECD, 2009). There was no mortality and all animals appeared normal without signs of adverse effect until sacrifice. There was no statistically significant increase in the micronuclei in bone marrow polychromatic erythrocytes, which was reported as a negative result.

Carcinogenicity

No data are available.

Reproductive and Developmental Toxicity

In general, the alkyl phenate sulfides group are not developmentally toxic, as the developmental effects were only observed secondary to maternal toxicity, and OECD (2009) reported that the reproductive toxicity correlates with residual amount of unreacted tetrapropenylphenol, branched C12 alkyphenol (TPP) and the calcium salt of TPP. Furthermore, an unpublished study conducted on an analogue chemical with very low levels of unreacted TPP reported no reproductive toxicity up to test dose of 1000 mg/kg bw/day, further emphasising TPP as the causative agent for reproductive toxicity. As a result, the reduction in fertility in males and females, the reduction in mean live litter size and the reduction in the size of the male and female reproductive organs in rats, may depend on the concentration of residual TPP and CaTPP present as an impurity. Commercial blends could have varying amounts of TPP and CaTPP depending on the extent of sulfurization. The chemicals are substances of unknown or variable composition (UVCB) for which unreacted TPP and CaTPP are integral parts of the substance. Industry has reported that manufacturers can reduce the concentration of unreacted TPP to levels that have been shown in experimental studies to not cause reproductive toxicity (ATC Personal Communication, 2012). Accordingly, classification should be based on levels of unreacted TPP and CaTPP.

In a well conducted reproductive and developmental toxicity study, following OECD TG 422, the test substances CAS numbers 122384-85-4 and 68855-45-8 were administered to Sprague Dawley rats via oral gavage, to 12 animals/sex/dose for generation F0, at dose levels of 0, 50, 300 or 1000 mg/kg bw/day (OECD, 2009), (REACH, 2013). The test substance was a blend of 54 % alkyl phenate sulfide oligomers, 43 % highly refined lubricant base oil and 3 % (30 mg/kg bw/day in the highest dose group) unreacted tetrapropenyl phenol (TPP) and the calcium salt of TPP (CaTPP). F0 males were dosed daily from four weeks prior to mating period, and continuing during and post mating for a total of 70 days. F0 females were dosed daily from four weeks prior to mating period, and continuing during and post mating, gestation and through to day four of lactation. There were no effects reported from all dose levels on fertility, mean live litter size, mean testes or ovary weights or sperm counts, although there was a slight decrease in mean body weight at the highest dose level. The reproductive toxicity NOAEL was reported as 1000 mg/kg bw/day for male and female rats.

In a well conducted two generational reproductive toxicity study, following OECD TG 416, the test substance CAS No. 122384-87-6 was administered via oral gavage, to 30 animals/sex/dose for F0 of Sprague Dawley rats at dose levels of 0, 50, 300 or 1000 mg/kg bw/day (OECD, 2009), (REACH, 2013). The test substance was a blend of 43% alkyl phenate sulfide oligomers, 50.3% highly refined lubricant base oil and 6.7% (67 mg/kg bw/day in the highest dose group) unreacted tetrapropenyl phenol (TPP) and the calcium salt of TPP (CaTPP). The mean body weight, epididymis and ovary weights and fertility incidences for the F0 male and female rats in the 1000 mg/kg bw/day groups were significantly reduced compared to control groups, and a decrease in mean live litter size was also observed. The offspring (F1 litters) were potentially exposed in utero, during lactation and post weaning for a minimum of 77 days (F1 generation) or 88 days (F1 satellite cross-breeding phase). F1 satellite males were dosed for at least 114 days and F1 females were dosed for at least 118 days before sacrifice. The mean epididymis weights and mean testes weights in the high dose group for both F0 and F1 males were significantly less than the control. The mean pituitary weight in the F0 and F1 male and mean liver weight in F0 and F1 females were significantly greater than the control in the high dose groups. In the satellite group, there was an observed increase in the number of dead pups on lactation day 0 and reduced pup body weight, which was not reproduced in the F2 pups. These results were attributed to the treatment of females. No neonatal toxicity was observed in the low dose group. A NOAEL of 50 mg/kg bw/day was determined for systemic parental and neonatal toxicity. The NOAEL for toxicity in relation to fertility was 300 mg/kg bw/day.

CAS No. 122384-87-6 has a lower alkyl phenate sulfide concentration due to a high extent of overbasing and CAS No. 122384-85-4 is sulfurised to a greater degree leading to a higher yield of alkyl phenate sulfide oligomer and a lower concentration of unreacted tetrapropenyl phenol (TPP, CAS No. 74499-35-7) (OECD, 2009). The differences observed in the endpoints between the two alkyl phenate sulfides were reported to be due to the differences in the amount of unreacted tetrapropenyl phenol (TPP, CAS No. 74499-35-7) in the blended test solution, due to data from the TPP OECD SIAR for tetrapropenyl phenol (2006), which was shown to cause adverse effects on many of the same reproductive endpoints as for CAS No. 122384-87-6.

In an additional unpublished one generation oral study (Edward et al., 2012), following OECD TG 415, an analogue described as 43 % alkyl phenate sulfide oligomer, 50 % highly-refined lubricant based oil and 0.1-0.2 % wt free unreacted TPP was administered via oral gavage, to 30 animals/sex/dose to Crl:CD(SD) rats (F_0). Both sexes were dosed daily with concentrations of 0, 250, 500 or 1000 mg/kg bw/day for approximately 70 consecutive days prior to mating. Males were dosed daily and euthanased after 84 treatments. Female rats were dosed through mating, gestation, lactation and until euthanased after 127 treatments. There were no effects reported at any dose level on fertility index, mean testes or ovary weights, mean live litter size and no microscopic findings in the F_0 or F_1 males and females after scheduled necropsy. The reproductive toxicity NOAEL was reported as >1000 mg/kg bw/day for male and female rats. In the absence of neonatal toxicity at all dose levels, a NOAEL for neonatal toxicity was reported as >1000 mg/kg bw/day. This study further emphasised the importance of the amount of unreacted TPP or CaTPP as the causative agent for the adverse reproductive effects seen with some commercial blends.

A recent study on TPP for reproductive toxicity in rats gives clear evidence of toxicity to fertility (ECHA, 2013). However, this IMAP assessment has not reviewed the relevant TPP reproductive toxicity data to determine the appropriate cut-off concentrations for hazard classification purposes. Following public comment, industry has provided data on TPP and a proposed specific concentration cut-off limit for evaluation.

Risk Characterisation

Critical Health Effects

The main critical effects to human health are reproductive toxicity, due to the varying content of residual amounts of unreacted TPP and the calcium salt of TPP in the commercial blends.

Public Risk Characterisation

Members of the public are most likely to be exposed to small amounts of the members of this category when adding lubricant oil to automotive crankcases, or when changing their own automotive engine oil. Due to the low volatility and low water solubility of this chemical group, and the short period of exposure during finished lubricant oil changes, the risk of adverse health effects to the public is expected to be minimal.

Occupational Risk Characterisation

During product formulation, dermal and ocular exposure of workers to the chemicals may occur, particularly where manual or open processes are used. These may include transfer and blending activities, quality control analysis, cleaning and maintenance of equipment. Worker exposure to the chemicals at lower concentrations may also occur while using formulated products containing the chemicals. The level and route of exposure will vary depending on the method of application and work practices employed.

Given the critical systemic long-term health effects, the chemicals may pose an unreasonable risk to workers unless adequate control measures to minimise dermal, and ocular exposure to the chemical are implemented. The chemical should be appropriately classified and labelled to ensure that a person conducting a business or undertaking (PCBU) at a workplace (such as an employer) has adequate information to determine appropriate controls.

The data available support an amendment to the hazard classification in HSIS (refer to **Recommendation section**).

NICNAS Recommendation

The chemicals are recommended for Tier III assessment to determine the concentration of TPP that would lead to classification of these chemicals for reproductive toxicity.

Regulatory Control

Work Health and Safety

The chemicals in this group are UVCB substances for which the unreacted TPP and CaTPP are integral parts of the substances. The reproductive toxicity of the chemicals appears to be due to the presence of TPP/CaTPP in the chemicals. Industry has advised that the chemicals may be manufactured with varying amounts of unreacted TPP. Therefore, classification should be based on levels of unreacted TPP and CaTPP.

While NICNAS undertakes a Tier III assessment to determine the appropriate concentration cut-off for TPP for classification purposes, an advisory recommendation is made to classify those chemicals or products containing these chemicals that do contain ≥ 0.5 % unreacted TPP/CaTPP under the current Approved Criteria and adopted Globally Harmonized System of Classification and Labelling of Chemicals (GHS) as below. This is based on classification rules in the Approved Criteria (NOHSC: 1008(2004)) for chemicals with known reproductive toxicity. Chemicals with low unreacted TPP/CaTPP of < 0.5 % do not require classification for reproductive toxicity. This recommendation should be considered by manufacturers of the chemicals, taking into account any available data on reproductive toxicity of the specific UVCB substance, and any safety assessment undertaken on TPP and CaTPP.

The Tier III assessment will take into account new information provided by industry together with the evaluation undertaken by the European Chemicals Agency (ECHA) Risk Assessment Committee (RAC).

This does not consider classification of physical hazards and environmental hazards.

Hazard	Approved Criteria (HSIS)[a]	GHS Classification (HCIS)[b]
Reproductive and Developmental Toxicity	Repro. Cat 3 - Possible risk of impaired fertility (Xn; R62)	Suspected of damaging fertility - Cat. 2 (H361f)

[a] Approved Criteria for Classifying Hazardous Substances [NOHSC:1008(2004)].

[b] Globally Harmonized System of Classification and Labelling of Chemicals (GHS) United Nations, 2009. Third Edition.

[*] Existing Hazard Classification. No change recommended to this classification

Advice for consumers

Products containing the chemical should be used according to the instruction on the label.

Advice for industry

Control measures

Control measures to minimise the risk from oral exposure to the chemicals should be implemented in accordance with the hierarchy of controls. Approaches to minimise risk include substitution, isolation and engineering controls. Measures required to eliminate or minimise risk arising from storing, handling and using a hazardous chemical depend on the physical form and the manner in which the chemical is used. Examples of control measures which may minimise the risk include, but are not limited to:

- using closed systems or isolating operations;
- health monitoring for any worker who is at risk of exposure to the chemical if valid techniques are available to monitor the effect on the worker's health;
- minimising manual processes and work tasks through automating processes;
- work procedures that minimise splashes and spills;
- regularly cleaning equipment and work areas; and
- using protective equipment that is designed, constructed, and operated to ensure that the worker does not come into contact with the chemical.

Guidance on managing risks from hazardous chemicals are provided in the *Managing Risks of Hazardous Chemicals in the Workplace—Code of Practice* available on the Safe Work Australia website.

Personal protective equipment should not solely be relied upon to control risk and should only be used when all other reasonably practicable control measures do not eliminate or sufficiently minimise risk. Guidance in selecting personal protective equipment can be obtained from Australian, Australian/New Zealand or other approved standards.

Obligations under workplace health and safety legislation

Information in this report should be taken into account to assist with meeting obligations under workplace health and safety legislation as adopted by the relevant state or territory. This includes, but is not limited to:

- ensuring that hazardous chemicals are correctly classified and labelled;
- ensuring that (material) safety data sheets ((m)SDS) containing accurate information about the hazards (relating to both health hazards and physicochemical (physical) hazards) of the chemical are prepared; and
- managing risks arising from storing, handling and using a hazardous chemical.

Your work health and safety regulator should be contacted for information on the work health and safety laws in your jurisdiction.

Information on how to prepare an (m)SDS and how to label containers of hazardous chemicals are provided in relevant codes of practice such as the *Preparation of Safety Data Sheets for Hazardous Chemicals— Code of Practice* and *Labelling of Workplace Hazardous Chemicals—Code of Practice*, respectively. These codes of practice are available from the Safe Work Australia website.

A review of the physical hazards of the chemical has not been undertaken as part of this assessment.

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REACH Dossier 2013. Phenol, dodecyl-, sulfurized, carbonates, calcium salts (68784-25-8). Accessed March 2013 at http://echa.europa.eu/web/guest/information-on-chemicals/registered-substances

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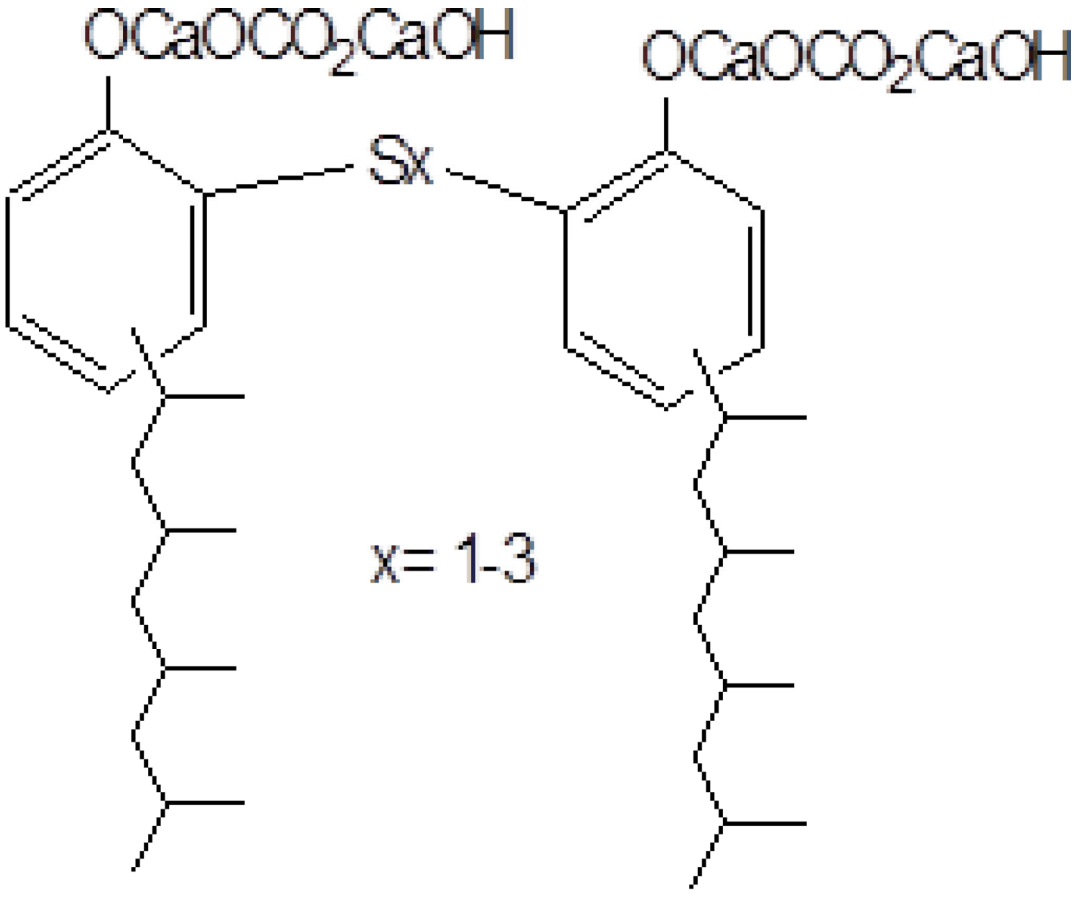
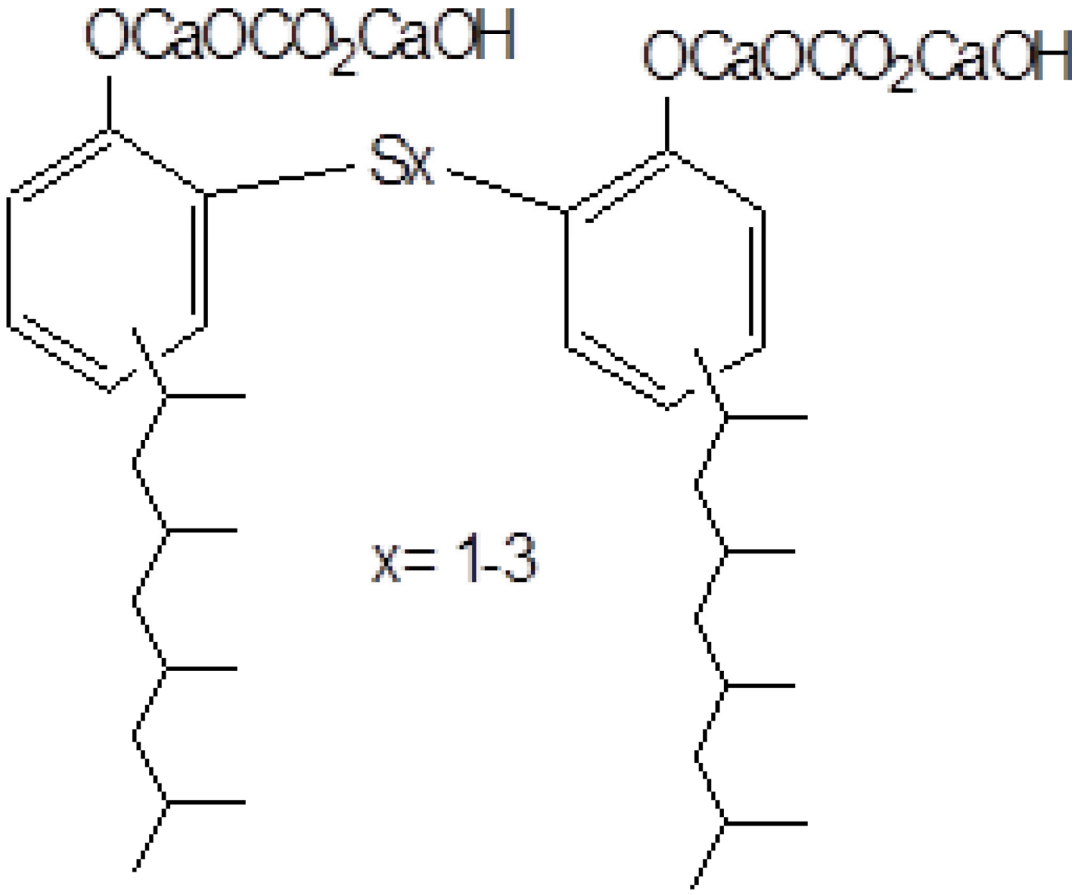
Last Update 01 September 2015

Chemical Identities

Chemical Name in the Inventory and Synonyms	**Phenol, dodecyl-, sulfurized, carbonates, calcium salts** dodecylphenol, calcium salt, sulfurized, carbonated tetrapropenyl phenate sulfide carbonates
CAS Number	68784-25-8
Structural Formula	
Molecular Formula	Unspecified

Molecular Weight	667.1 (S = 1) to 731.2 (S = 3)

Chemical Name in the Inventory and Synonyms	**Phenol, dodecyl-, sulfurized, carbonates, calcium salts, overbased** dodecylphenol, calcium salt, overbased, sulfurized, carbonated tetrapropenyl phenate sulfide carbonates, overbased
CAS Number	68784-26-9
Structural Formula	
Molecular Formula	Unspecified
Molecular Weight	667.1 (S = 1) to 731.2 (S = 3)

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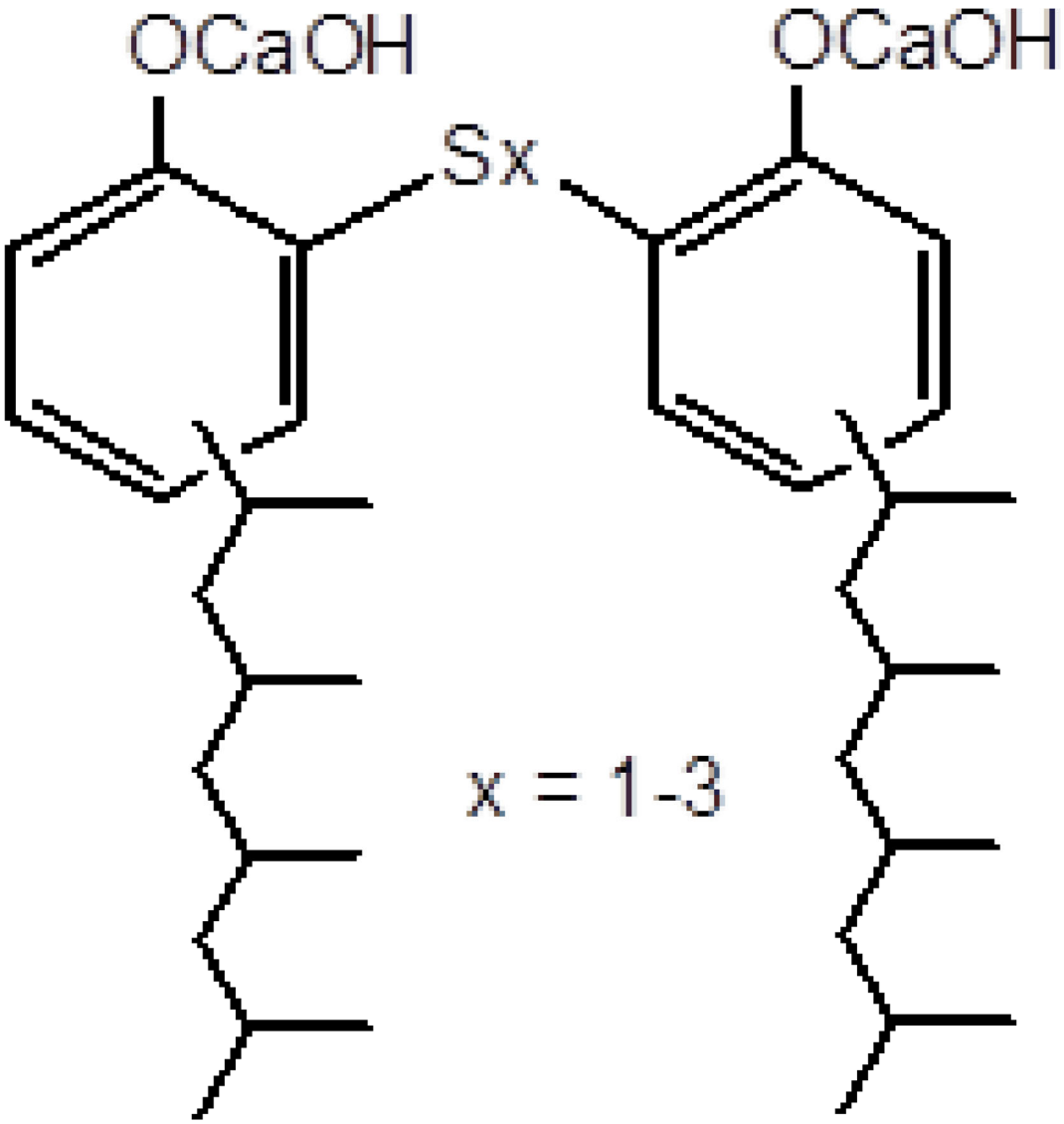
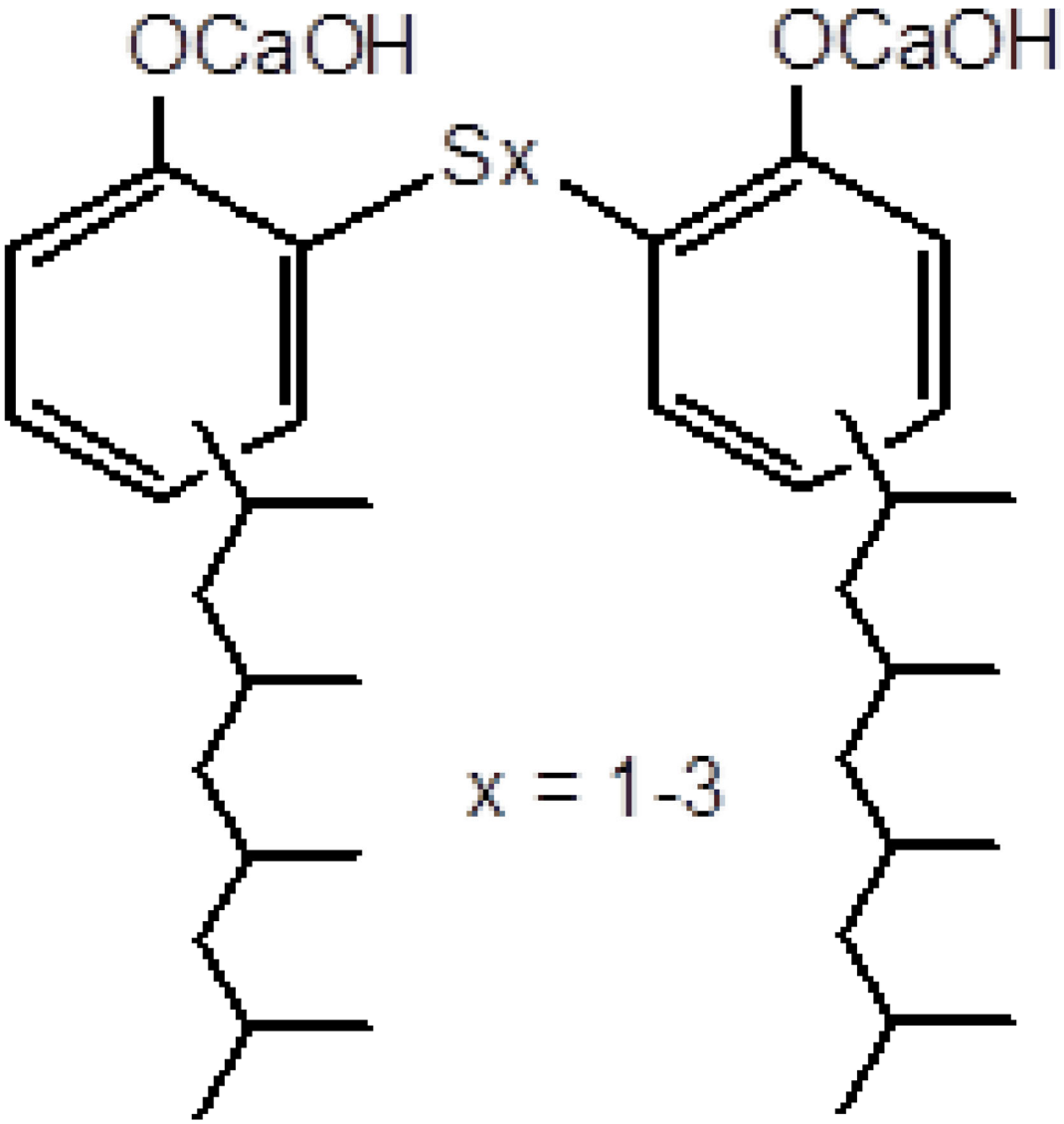
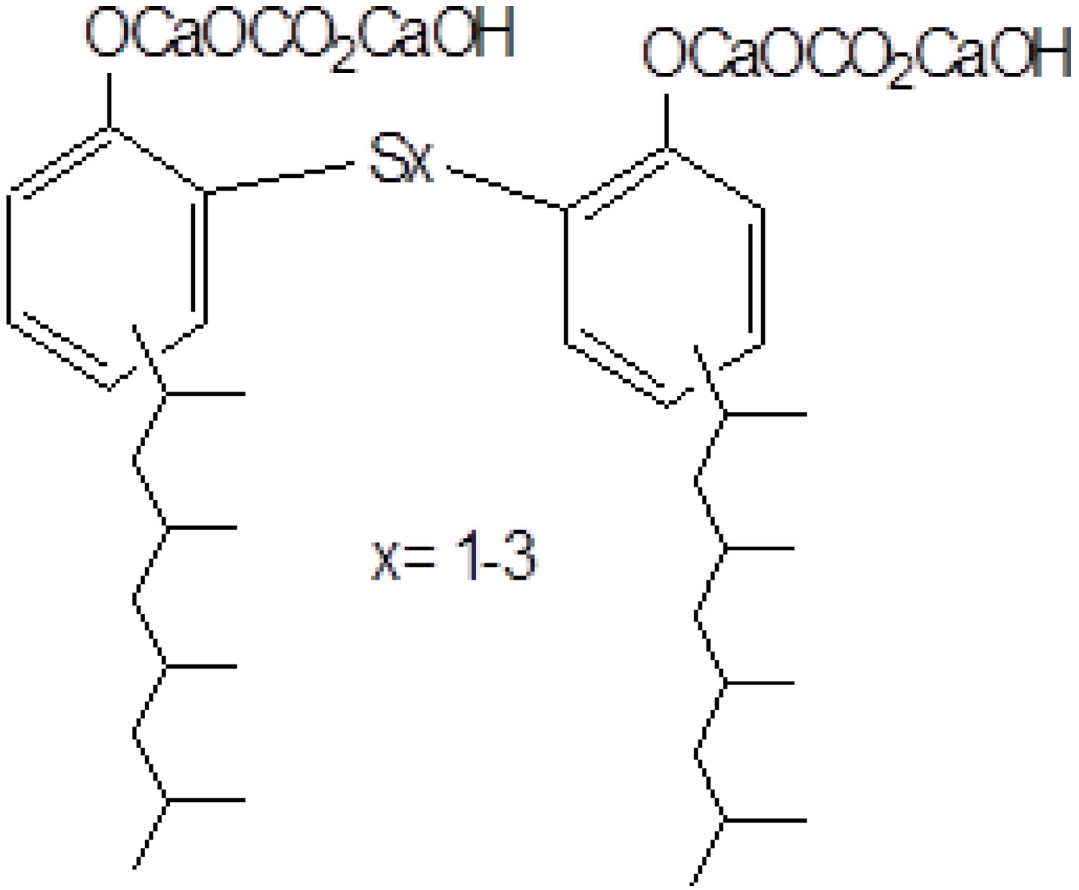
CAS Number	68855-45-8
Structural Formula	

	
Molecular Formula	Unspecified
Molecular Weight	667.1 (S = 1) to 731.2 (S = 3)

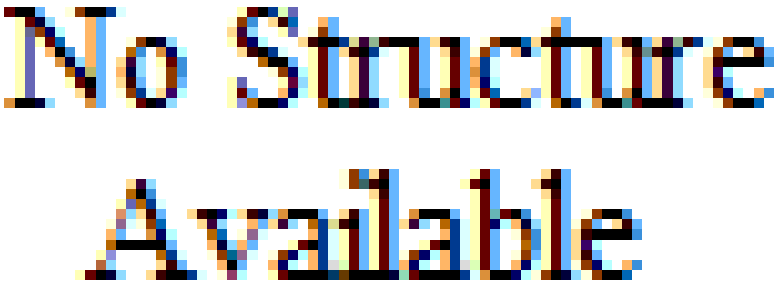
Chemical Name in the Inventory and Synonyms	**Phenol, tetrapropylene-, sulfurized, calcium salts** tetrapropenyl phenate sulfide
CAS Number	122384-85-4
Structural Formula	

	
Molecular Formula	Unspecified
Molecular Weight	667.1 (S = 1) to 731.2 (S = 3)

Chemical Name in the Inventory and Synonyms	**Phenol, tetrapropylene-, sulfurized, carbonates, calcium salts** tetrapropenyl phenate sulfide carbonates
CAS Number	122384-86-5
Structural Formula	

	
Molecular Formula	Unspecified
Molecular Weight	667.1 (S = 1) to 731.2 (S = 3

Chemical Name in the Inventory and Synonyms	**Phenol, tetrapropylene-, sulfurized, carbonates, calcium salts, overbased** tetrapropenyl phenate sulfide carbonates, overbased
CAS Number	122384-87-6
Structural Formula	

	
Molecular Formula	Unspecified
Molecular Weight	667.1 (S = 1) to 731.2 (S = 3

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