HIGH PRODUCTION VOLUME (HPV) CHEMICAL CHALLENGE PROGRAM

Fatty Acids, Lithium & Calcium Salts
used as
Lubricating Grease Thickeners

CATEGORY ANALYSIS AND HAZARD CHARACTERIZATION

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EXECUTIVE SUMMARY

The lithium and calcium salts of fatty acids in this category are used by the lubricants industry to thicken greases. For this use they are not synthesized as the "pure" compounds and seldom exist except in the presence of the oil matrix. One or more fatty acids are dissolved in mineral oil and then a metal hydroxide such as calcium hydroxide or lithium hydroxide is added. The metal hydroxide and fatty acid react to form the insoluble metal salt of the fatty acid. The resulting compounds gel the mineral oil into a functional grease. Greases typically contain from 1 to 14 % thickener by mass. Since the fatty acids used to make the salts in this category are edible themselves or closely related to edible fats and oils, hazard characterization is focused on the metal ions, calcium and lithium. However, greases thickened with aluminum, calcium or lithium soaps have been widely and safely used in industry for several decades.

Physical-chemical values for substances in the grease thickeners category were derived for fatty acid salts as if they existed outside the grease matrix. Because thickeners are created within the grease matrix, their physical-chemical properties should be interpreted with this understanding. The data show that in general, grease thickeners have melting points above 180°C and thus exist as solids under ambient conditions. Water solubility varies depending on the carbon chain length of the fatty acid molecule, but these substances would not dissolve out of the grease matrix into water. Grease thickeners have low vapor pressure and little or no tendency to partition into air. They are not susceptible to hydrolysis or direct/indirect photolysis under environmental conditions. Environmental partitioning will be primarily to soil and/or sediment. Fatty acids are known to be used by microorganisms as a source of energy, and their calcium and lithium salts are expected to be inherently if not readily biodegradable. Grease thickeners do not bleed out of the grease matrix, and this severely limits environmental exposures.

Test data on whole greases and lithium hydroxystearate indicate that grease thickeners have minimal to no toxicity to aquatic organisms. No toxicity was observed when rainbow trout were exposed to mechanical dispersions of lithium hydroxystearate up to 2000 mg/L. Tests exposing rainbow trout to whole grease did not show any acute toxicity at 12,500 mg/L. Invertebrates were not sensitive to water accommodated fractions (WAFs) of whole greases thickened with calcium hydroxystearate (EC50 >1000 mg/L loading rate). Exposures of algae to WAF solutions showed either no toxicity (EL50 >1000 mg/L loading rate) or only slight inhibition (EL50 >100 mg/L loading rate). Modeled

acute toxicity endpoints for the fatty acids were consistent with the measured data and provided additional evidence of a general low toxicity of these substances to aquatic organisms.

Results from testing lithium fatty acid salts, fatty acid salts compositionally similar to salts in this category (e.g. magnesium stearate), and greases containing thickeners from this category demonstrate that these materials are not acutely toxic by the oral or dermal route, are not irritating to the eyes or skin, and do not induce skin sensitization. Repeat dose studies in rats by the oral route (Mg stearate, castor oil, lithium complex grease), or with dermal treatment (Calcium complex grease, lithium complex grease) did not show any significant adverse effects. The range of NOAEL values for greases administered dermally is 500-2100mg/kg/day. For oral treatment the NOAEL range was comprised of the highest doses tested, 1000 – 2500mg/kg/day. Treatment with a lithium grease dermally for 2 years did not cause skin cancer in C3H mice. Mutations were not induced in bacterial assays by fatty acids used to make salts in this category. Soluble lithium salts were not mutagenic *in vitro*, and slight chromosomal effects occurred only from a very high dose of soluble lithium citrate administered intraperitoneally. Considering, along with these data, the low solubility of salts of fatty acids in the grease thickeners category, the compounds are not likely to be mutagenic. A developmental toxicity study of a lithium complex grease demonstrated no evidence of reproductive or developmental toxicity even at a maximum dose of 2000mg/kg/day that induced maternal toxicity. A calcium complex grease and a lithium grease administered dermally for 90 days did not induce adverse effects on the male reproductive system or on sperm morphology or number. The dermal developmental NOAEL = 2000mg/kg/day. Magnesium stearate (structurally similar to calcium stearate) did not induce developmental effects in orally treated pregnant rabbits.

Overall it can be concluded that calcium or lithium grease thickeners do not present a human or environmental health hazard.

1. DESCRIPTION OF GREASE THICKENERS

Fatty acids, calcium & lithium salts are used by the lubricant industry to thicken mineral oil to make greases. Greases are used in the lubrication of bearings and other moving parts in virtually every segment of transportation and industry. Most finished lubricants are mixtures of oils and additives but greases are one of the few types of lubricants that involve an actual chemical reaction during their manufacture. Although a few greases are thickened with viscous petroleum products similar to asphalt, most are made by the formation of a “soap” within a mineral oil matrix. Thickeners are not commonly synthesized as pure compounds; instead they generally exist only in the presence of the oil matrix.

1.1. Composition and Structure

Synthesis of the grease thickeners in this category is typically done by dissolving one or more fatty acids in mineral oil and then adding a metal hydroxide such as calcium hydroxide or lithium hydroxide. The metal hydroxide and fatty acid molecules react to form the insoluble metal salt of the fatty acid. The resulting compounds gel the mineral oil into a functional grease. Thickeners in greases form a mesh framework with an appearance similar to steel wool; the more fluid components of the grease are in the cavities within this mesh [see Figure 1]. Greases containing these compounds typically contain from 1-14% thickener on a mass basis.

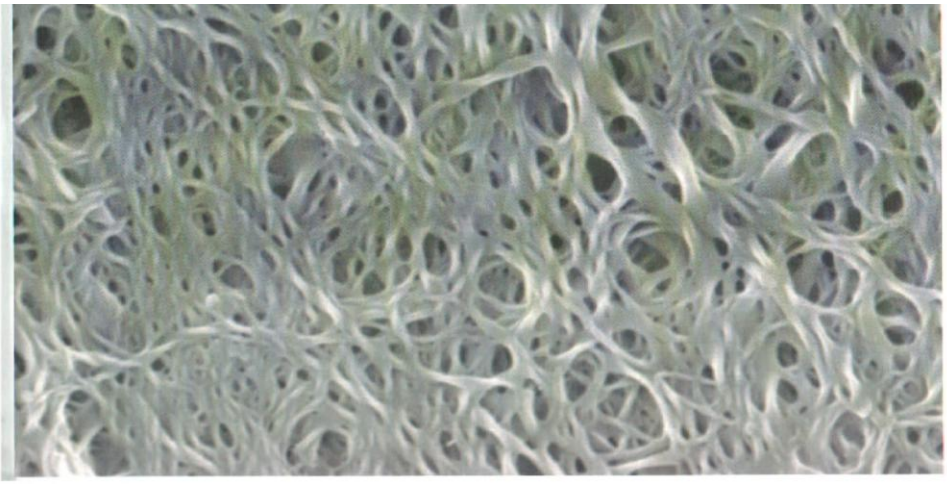

Figure 1. Scanning electron micrograph of lithium grease thickener.

If fatty acids or triglycerides are reacted with metal hydroxide outside of a mineral oil matrix, the resulting compounds are called soaps, hence the use of this term relative to grease thickeners of this type. Water or methanol is usually formed during the reaction depending on whether the fatty acid or its methyl ester, respectively, was used as a starting reactant. Only a very small percentage of greases is made with soaps formed without the presence of mineral oils. Therefore toxicity studies on formulated greases containing thickeners produced in the presence of mineral oil were considered appropriate for the assessment of potential effects of grease thickeners. This approach is explained further on subsequent pages.

The fatty acids used to make greases are derived from edible animal fats or vegetable oils. The fatty acids used as starting materials in this category are mostly monocarboxylic acids and include stearic acid (C_{18}), 12-hydroxystearic acid, docosanoic acid (C_{22}), hydrogenated castor oil (comprised of ricinoleic and similar acids, C_{18}), and methyl esters of oxidized hydrocarbon waxes ($C_{\geq 18}$). One lithium salt of a dicarboxylic acid (azelaic, C_9) is included in the category as it is commonly used in lithium complex greases. Azelaic acid (nonanedicarboxylic acid) is manufactured from ricinoleic acid (castor oil).

The metal salts in this HPV category are lithium or calcium. Some greases are thickened with the lithium salts of two different fatty acids and the resulting greases may be called “lithium complex” greases. Greases thickened with aluminum, calcium or lithium soaps have been widely and safely used for several decades.

Additional performance additives such as extreme pressure agents and antioxidants may be added to a grease before or after thickening. Therefore many of the formulated greases used for toxicity tests contain such additives.

1.2. Typical Compositional Properties

Table 1 summarizes the typical physical and chemical properties that characterize the calcium and lithium thickeners in this category and some closely-related compounds. With the exception of magnesium stearate, the related compounds are not discussed in this text but are included here to provide perspective on the characteristics of similar salts.

Table 1: Physical-Chemical Properties of Fatty Acid Salts Used as Grease Thickeners and Related Compounds

Compound	Carbon Number	Molecular wt.	Melting point (°C)	Water[1] Solubility (mg/L)	Reference
Category Members:					
CAS 3159-62-4 Calcium 12-hydroxystearate	36	639.03	320	9.7 x 10E-9 (6.4 x 10E-7)	US EPA (2000)
CAS 1592-23-0 Calcium stearate	36	607.04	179	40 @ 15 deg C	HSDB (2005a)
CAS 64755-01-7 Fatty acids, tallow, calcium salts	14 - 18	>490			
CAS 68603-11-2 Hydrocarbon waxes, petroleum, oxidized, methyl esters, calcium salts	>18	>600			
CAS 4485-12-5 Lithium stearate	18	290.42	249	4.1 (0.002)	US EPA (2000)
CAS 7620-77-1 Lithium 12-hydroxystearate	18	306.42	264	222 (0.1)	US EPA (2000)
CAS 64754-95-6 Castor oil, hydrogenated, lithium salt	>16	>260			
CAS 68783-36-8 Fatty acids, C16-22, lithium salts	16 - 22	approx 263 - 347			
CAS 4499-91-6 Lithium docosanoate	22	346.53	271	0.04 (2.0 x 10E-5)	US EPA (2000)
CAS 38900-29-7 Dilithium azelate	9	200.09	186	(877)	US EPA (2000)
Related Compounds:					
Sodium stearate	18	307.53		"slowly soluble"	HSDB (2005c)
Magnesium stearate	36	591.27	88	30 @ 15 deg C	HSDB (2005b)
Zinc stearate	36	632.34	130	"insoluble"	HSDB (2005d)
Sodium oleate	18	305.46	232 - 235	10,000 @ 12 deg C	HSDB (2003a)
Potassium oleate	18	321.56	235 - 240	25,000 @ cold water	HSDB (2002)
Sodium palmitate	16	278.41	270	"insoluble"	HSDB (2003b)

Docosanoic acid	22	340.58	79.95	0.016 @ 25°C	UNEP (2001)

[1] EPI Suite™ (US EPA, 2000) provides two estimates for water solubility values. The first value presents the estimate using the relationship with Kow (Meylan and Howard, 1994) while the value in parentheses was calculated by the fragment constant method (Meylan and Howard, 1995).

The hazard of this category of grease thickeners is low not only because of their composition (fatty acids, calcium, and lithium) but also by their stability in the oil matrix. While there is no test to measure the release of the "soap" from grease, a property measured to ensure product quality can also provide insight into the bioavailability of the grease thickener. The "dropping point" test (ASTM D 2265) determines the temperature at which the grease passes from a semisolid to a liquid. Although a thickener can have a definite melting point, the resulting grease does not. As the temperature is raised to the "dropping point", the grease softens to the extent that it loses its self-supporting characteristic, the structure collapses, and the grease flows under its own weight. The dropping point for typical anhydrous calcium and lithium greases is 285F to 400F. Complex greases have dropping points over 500F. This high temperature stability indicates that the grease thickener structure is robust and resistant to diffusion out of the oil.

2. CATEGORY DEFINITION AND JUSTIFICATION

The grease thickeners category contains 11 substances as distinguished by CAS numbers. They are all calcium or lithium salts of long-chain fatty acids with carbon numbers between C9 and C22. Within the oil matrix their bioavailability is quite limited and testing on greases has demonstrated minimal environmental or human health hazards. Outside the oil matrix only the lithium ion presents any environmental or human health hazard and because lithium (carbonate) is a licensed pharmaceutical, those hazards are well characterized. Data on the components and selected members of the category can be used to read-across to any untested category member or endpoint.

Some of the substances were included in the original list sponsored by the API in 1999 based on the EPA 1990 IUR, and other non-HPV materials have been added to provide additional information due to their structural similarities. The 11 category members are listed in Table 2. Two compounds in the category have different CAS numbers and slightly different names but are chemically the same. Lithium 12-hydroxystearate is formed from both the methyl ester of 12-hydroxy octadecanoic acid and from the acid itself. If the methyl ester is used, then methyl alcohol is formed as a byproduct instead of water.

Two other compounds in this category [Octadecanoic acid, calcium salt (CAS #1592-23-0) and Fatty acids, tallow, calcium salts (CAS #64755-01-7)] are considered adequately characterized relative to the Screening Information Data Set. These two compounds are designated "1" and the EPA has concluded that the "Chemical is not considered a candidate for testing under the HPV Challenge Program, based on preliminary EPA review indicating that testing using the SIDS base set would not further our understanding of this chemical's properties" (EPA HPV Challenge Program Chemical List).

Table 2: HPV Lubricating Grease Thickeners Category

CAS #	Name	Synonym
3159-62-4	Octadecanoic acid, 12-hydroxy-, calcium salt (2:1)	Calcium 12-hydroxystearate
38900-29-7	Nonanedioic acid, dilithium salt	Dilithium azelate
4485-12-5	Octadecanoic acid, lithium salt	Lithium stearate
4499-91-6	Docosanoic acid, lithium salt	Lithium docosanoate
53422-16-5	Octadecanoic acid, 12-hydroxy-, methyl ester, lithium salt	Lithium 12-hydroxystearate (same as 7620-77-1)
64754-95-6	Castor oil, hydrogenated, lithium salt	
68783-36-8	Fatty acids, C_{16-22}, lithium salts	
7620-77-1	Octadecanoic acid, 12-hydroxy-, monolithium salt	Lithium 12-hydroxystearate (same as 53422-16-5)
1592-23-0	Octadecanoic acid, calcium salt	Calcium stearate
64755-01-7	Fatty acids, tallow, calcium salts	
68603-11-2	Hydrocarbon waxes, petroleum, oxidized, Me esters, calcium salts	

All of the substances in this category are the lithium or calcium salt of similar fatty acids. All of the fatty acids are similar in size (14 carbons long or longer) with the exception of nonanedioic acid (azelaic), which contains 9 carbons. Stearic acid is found in food and, similarly to castor oil, is used in cosmetics and pharmaceuticals. These and the other fatty acids have similar chemical characteristics. Several of these fatty acids are HPV chemicals sponsored by other chemical manufacturers. The salts of these fatty acids are typically synthesized "in situ" in a mineral oil matrix

and their biological activity is low because of high molecular weight and insolubility. Therefore data for any one of the substances individually can be used to predict the likely effects of other category members.

3. PHYSICAL-CHEMICAL PROPERTIES

Although some data for substances in this category exist, not all of these endpoints are defined and a consensus database for chemicals that represent substances in this category does not exist. Therefore, calculated and measured representative data have been identified and a technical discussion provided, where appropriate. The "EPI Suite™ ©" computer model, as discussed in the US EPA document entitled "The Use of Structure-Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program", has been used to calculate physical-chemical properties of substances in this category (U.S. EPA, 2000). When measured data cannot be found for substances in this category, data for similar substances and modeled data have been used to describe the physicochemical and environmental fate endpoints.

The data presented in the robust summaries are for the fatty acid salts as if they existed outside the grease matrix, a significant distinction to keep in mind. As provided in the description of the grease thickeners category, the grease thickening agents in this category do not normally exist outside of the grease matrix, but are synthesized during the production of the grease by reacting fatty acids (e.g., stearic acid, docosanoic acid, etc.) and metal hydroxides (e.g., lithium, calcium) to form an insoluble metal salt of the fatty acid within the grease. Such "in situ" generation of the thickening agents limits the potential for environmental exposure to these substances since they are entrained within the grease matrix. In addition, the fatty acid salts used in greases have been selected partly due to their resistance to "bleed-out" (i.e., dispersion from the grease matrix), as this would compromise the performance characteristics of the grease. Thus, dissolution of the grease thickeners from the grease into water is very unlikely due to two factors. First, the thickeners generally are poorly water soluble. Second, the thickeners are embedded in the hydrophobic grease matrix and thus less likely to leach out.

3.1. Physical-Chemical Screening Information Data Set (SIDS)

The physical-chemical endpoints in the HPV chemicals program include the following:

- Melting Point
- Boiling Point
- Vapor Pressure
- Octanol/Water Partition Coefficient
- Water Solubility

Grease thickeners included in this category are all calcium or lithium salts of fatty acids. The hydrocarbon chain lengths vary from nine carbon atoms (nonanedioic acid, dilithium salt; CAS #38900-29-7) to greater than 18 (hydrocarbon waxes, oxidized, methyl esters, calcium salts, CAS #68603-11-2, and fatty acids, C_{16-22}, lithium salts, CAS #68783-36-8). Physicochemical data for members of the grease thickeners category are represented by measured data where available and estimations derived from structure activity models ("EPI Suite™" US EPA, 2000). Data in the robust summaries are given for thickeners composed of single fatty acid compounds. Thickeners created using mixtures of fatty acids are expected to have similar physicochemical properties to those of the single fatty acids because the mixtures contain fatty acids with similar numbers of carbon atoms. Thus, the physicochemical attributes for the four category members having variable composition in their fatty acid moieties (i.e., fatty acids, tallow, calcium salts (CAS #64755-01-7), hydrocarbon waxes, petroleum, oxidized, methyl esters, calcium salts (CAS #. 68603-11-2), castor oil, hydrogenated, lithium salt (CAS #64754-95-6), and fatty acids, C_{16-22}, lithium salts (CAS #68783-36-8)) would be expected to be defined by the data provided for the other members of the category.

3.1.1. Melting Point

Both calcium and lithium salts of fatty acids exist as solids [soaps] at ambient temperatures. Measured and/or estimated melting points fall within a range from 179°C to 320°C (see Table 1)

3.1.2. Boiling Point:

Estimated boiling points for various lithium salts of C9 to C22 fatty acids ranged from 484°C to 624°C. For calcium salts, boiling point estimates for calcium stearate and calcium hydroxystearate were 661°C and 730°C, respectively.

3.1.3. Vapor pressure

Vapor pressures of these substances are extremely low and not within the range measurable by standard guideline methods (OECD, 1995). Estimated vapor pressures ranged from 1×10^{-21} to 2×10^{-9} hPa

3.1.4. Partition coefficient

Partition coefficients (log Kow) estimated by "EPI Suite™" ranged from -3.56 to 14.3. The partition coefficient model (KOWWIN) that calculates log Kow treats ion pairs (e.g., salts) as an ionized acid, and reports values for the dissociated form (US EPA, 2004). Because partition coefficients vary with pH, the given Kow values would be expected to change in accordance with environmental pH. However, these estimates indicate that for the category members of grease thickeners, partition coefficients are expected to range broadly and increase with the number of carbon atoms in the fatty acid (e.g., C9 nonanedioic acid, dilithium salt = -3.56 and C22 docosanoic acid, lithium salt = 6.1). Estimated values for the log Kow for calcium salts of fatty acids are extremely high and exceed the upper value that is considered to be a reliable estimate by EPA (e.g., log Kow >6.0;US EPA, 1999).

3.1.5. Water solubility

Water solubility values also vary with the molecular weight of the thickening agent (see Table 1) Thus, wide ranges in solubility measurements or estimates occur with the category members. Estimated water solubility values ranged from 9.7×10^{-9}mg/L (for the C36 octadecanoic acid, 12-hydroxy calcium salt) to 877mg/L (for the C9 di-acid, nonanedioic acid, dilithium salt). However, regardless of the fatty acid chain length, grease thickeners are unlikely to bleed out of the grease matrix.

3.2 Assessment Summary for Physical-Chemical Endpoints

Physicochemical values were provided for members of the grease thickeners category using either measured or modeled data. The above data describe the thickeners as if they existed outside the grease matrix. However, thickeners are created by the reaction of alkali metals and edible fats and oils (or similar fatty acids) within an oil base with the resulting entrainment in the grease matrix. Therefore, interpretation and use of these data should be done with caution and with this understanding. The hydrocarbon components of the greases have very low water solubility, low vapor pressure and little or no tendency to partition into environmental media (e.g., soil, water, and air).

4. ENVIRONMENTAL FATE

4.1 Environmental Fate Endpoints

The Environmental Fate endpoints in the HPV chemicals program include the following:

- Photodegradation
- Stability in water [Hydrolysis]
- Transport Between Environmental Compartments [Fugacity/Distribution]

Biodegradation

Although the grease thickeners do not normally exist independent of the grease matrix, environmental fate endpoints were assessed as though these substances were free of the petroleum fraction. However, the manner in which these thickening agents are created and used in greases would be expected to influence the environmental fate properties to a great extent. Therefore, the environmental fate characteristics described herein should be viewed and interpreted in light of this qualification.

4.1.1. Photodegradation:

4.1.1.1 Direct

Direct photodegradation requires one or more bonds within a chemical to absorb ultraviolet light in the 290nm to 750nm wavelength range. Wavelengths longer than 750nm do not contain sufficient energy to break chemical bonds, while wavelengths below 290 nm are shielded from the earth by the stratospheric ozone layer (Harris, 1982). Therefore, for direct photodegradation to occur, light of the appropriate wavelengths and energy must reach the chemical bonds for any potential transformation to be possible. Grease thickeners would not be expected to undergo direct photodegradation due to their extremely low volatility and low water solubility when in the grease matrix. These characteristics and the fact that they are created and retained in the grease matrix indicate that direct photodegradation is not an important fate process for grease thickeners.

4.1.1.2 Indirect

Indirect photodegradation occurs in the atmosphere when organic chemicals react with photosensitized oxygen in the form of hydroxyl radicals (OH^-). Atmospheric oxidation as a result of hydroxyl radical attack is not direct photochemical degradation but an indirect degradation process. The photodegradation potential of grease thickeners was evaluated using the AOPWIN© subroutine of "EPI Suite™" (US EPA, 2000). The model indicated that these substances are capable of being degraded by reaction with photosensitized hydroxyl radicals in the atmosphere. However,

entrainment of these substances in the grease matrix and their extremely low vapor pressures indicate that photodegradation will not likely be a significant fate pathway.

Conclusion: Direct and Indirect photodegradation is not an important fate process for grease thickeners.

4.1.2. Stability in water

Hydrolysis is not expected to occur, as the metal salts of fatty acids do not contain functional groups that undergo hydrolysis.

Conclusion: Hydrolysis is not an important degradative pathway for grease thickeners.

4.1.3. Distribution in the Environment:

Fugacity-base equilibrium modeling using the EQC Level 1 model (Mackay, 1998) shows that if these substances, independent of the grease matrix, are released to the environment, most category members would partition to the soil. Those with the highest water solubility could distribute to the aqueous compartment. Interpretation of the fugacity modeling should take into account that these estimates were based on the pure thickener compounds and in reality the thickening agents are part of the grease matrix, which would limit environmental exposure.

Conclusion: Pure components of grease thickeners would partition primarily into soil or sediment. However the thickening agents are entrained in the grease matrix and environmental release would be severely limited.

4.1.4 Biodegradation:

A typical grease may contain 90% petroleum product consisting of base oil stocks (NLGI, 1996), with the thickening constituting the balance. Therefore, consideration of biodegradability of whole greases must take into account the carbon chain length and hydrocarbon classes that make up the petroleum fraction. A discussion of the biodegradability potential of the petroleum fraction used in formulated greases may be found in the HPV test plan for the Lubricating Oil Basestocks Category (API, 2003). For the thickening agents themselves, the hydrocarbon moieties of the calcium or lithium salts are expected to be inherently if not readily biodegradable in the environment. This was shown by several studies on category members and fatty acid salt analogs to the category members.

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Using the OECD 301B method (modified Sturm test), de Morsier et al. (1987) conducted six tests with calcium stearate (CAS #1592-23-0) using various combinations of dispersion and/or agitation of the test medium or dosing stocks. Biodegradation ranged from 55% to 99%, and five of the six tests passed the criteria for ready biodegradability status. Two additional tests by the same authors using the OECD 301C method (MITI I test) also passed the ready biodegradability criteria with final biodegradation levels of 91% and 93% (de Morsier et al., 1987). Lithium 12-hydroxystearate (CAS #53422-16-5 or 7620-77-1) was assessed for biodegradation using a 28-day shake flask method and a mixture of activated sludge and soil as inoculum (Stonybrook Laboratories, 1991). The extent of biodegradation achieved was 74.7% which met the criteria for ready biodegradability status. In a similar experiment with calcium hydroxystearate (CAS #3159-62-4), biodegradation achieved levels of 61.5% and 67.6% in duplicate test flasks (Stonybrook Laboratories, 1994). Although the ready biodegradation criterion of 60% was exceeded, it failed to attain that level within the 10-day criterion (i.e., within 10 days of exceeding 10% biodegradation). Therefore, this study did not meet the definition of readily biodegradable.

Biodegradability studies for other fatty acids and/or salts having 16 to 22 carbon atoms provided a range of 48% to 96% biodegradation when tested under different OECD ready biodegradation methods (Procter and Gamble Chemicals, 2003; Pine Chemicals Association, 2001; UNEP, 2001). Overall, these studies provide reasonably consistent biodegradation rates using different standardized test methods. Together, they indicate that members of the grease thickeners category, if considered as independent of the grease matrix, are easily degraded by aerobic microbes. Free calcium or lithium ions resulting from the dissociation of the salt from the fatty acid would not degrade *per se*, but would engage in chemical reactions with other naturally occurring anions in a manner predictable within the thermodynamic processes specific to these cations.

Conclusion: Fatty acids used in grease thickeners are known to be used by microorganisms as a source of energy and the calcium and lithium salts are expected to be inherently if not readily biodegradable.

4.2 Assessment Summary for Environmental Fate

Substances in the grease thickeners category can be considered environmentally innocuous due to their origin from alkali metals and edible fats and oils (or similar fatty acids). The hydrocarbon components of the greases have very low water solubility and little or no tendency to partition into air. They are not susceptible to hydrolysis or direct photolysis under environmental conditions and will partition primarily to soil and sediment. Entrainment of thickeners in the grease matrix severely limits

environmental exposure. Fatty acids and their calcium and lithium salts are expected to be inherently if not readily biodegradable.

5. ENVIRONMENTAL EFFECTS

5.1 AQUATIC TOXICITY

As explained in Section 1, grease thickening agents included in this category do not typically exist outside of the grease matrix. The "*in situ*" generation of the thickening agents limits the potential for environmental exposure to these substances since they are entrained within the grease matrix. In addition, fatty acids and alkali metals used in these products are resistant to "bleed-out" (i.e., disperse from the grease matrix), as this would compromise the performance characteristics of the grease. The fatty acid moiety is derived from edible animal fats or vegetable oils and would not be expected to be overtly hazardous to aquatic organisms. Calcium is a common and essential element in all living organisms, and it is not known to be toxic to aquatic organisms. Lithium is widely distributed in nature, and trace amounts are found in many soils and natural waters (HSDB, 2008). A review of EPA's ECOTOX database indicated that lithium toxicity to aquatic organisms generally lies in a range 10 - >100 mg/L (US EPA, 2007a).

5.1.1 Aquatic Endpoints – Acute Toxicity

The HPV Chemical Test Program includes acute toxicity to a freshwater fish, an invertebrate (*Daphnia magna*), and an alga. Grease thickeners would not be expected to pose a hazard to aquatic organisms based on the low bioavailability of these substances while in the grease matrix. The manner in which the thickeners are produced *in situ* and the low solubility of the grease also limits the potential for aquatic exposures. Nevertheless, aquatic hazard data are presented for the following:

- Measured toxicity of whole grease prepared using a calcium soap thickener,
- Measured toxicity of whole grease prepared using calcium 12-hydroxystearate thickener,
- Measured toxicity of lithium hydroxystearate thickener, and
- Measured or estimated toxicity of various fatty acids and their salts.

The endpoint values for experimental data cited in the robust summaries and described below for the three trophic levels reflect the loading rates of the test substance added to exposure solutions (i.e., milligrams of test substance per liter of water). For the fish studies, test solutions were prepared by

direct addition of test substance to the test vessel. Invertebrate and algal studies utilized water accommodated fraction (WAF) testing methods to prepare exposure solutions at specific loading rates.

5.1.2. Acute Toxicity to Aquatic Vertebrates

5.1.2.1 Whole Grease

No toxicity was seen in rainbow trout exposed for seven days to a grease prepared with calcium soap thickener or to one prepared with calcium 12-hydroxystearate and tallow thickener (HydroQual Laboratories, 2003). Both tests were run as limit exposures at 12,500 mg/L. Exposure solutions were prepared by spreading grease onto glass plates, then immersing the plates in each test chamber. For each grease tested in this manner, LL50 values were >12,5000 mg/L, expressed as the loading rate of whole grease (i.e., 12,500 mg grease/L water).

Conclusion: The results of these studies indicate that greases thickened with calcium salts are not toxic to freshwater fish.

5.1.2.2 Lithium hydroxystearate

Lithium hydroxystearate was tested against rainbow trout using a mechanical dispersion technique to maintain a suspension of test substance in the water column (Stonybrook Laboratories, 1992). The 96-hour LC50 was determined to be >2000 ppm. Exposure solutions exceeded the estimated water solubility value, and observations of test product in the exposure solutions verified that the solubility limit was exceeded in the test.

Conclusion: Based on the mechanical dispersion exposure technique, it is reasonable to conclude that lithium hydroxystearate is not toxic to freshwater fish at the limit of its water solubility.

5.1.3. Acute Toxicity to Aquatic Invertebrates

5.1.3.1 Whole Grease

Acartia tonsa were exposed to water accommodated fractions (WAFs) prepared at a loading rate of 1000 mg/L under static conditions of grease thickened with calcium 12-hydroxystearate. Two tests were run on the same grease and both tests resulted in an EL50 of >1000 mg/L WAF (Shell Research, 1995a,b). Organism immobilization was 13% and 20% respectively in each study.

Conclusions: The results of these studies indicate that a WAF of whole grease thickened with calcium salts is not toxic to aquatic invertebrates.

5.1.4. Toxicity to Aquatic Plants (e.g. Algae)

5.1.4.1 Whole Grease

The alga, *Skeletonema costatum*, was exposed under similar WAF conditions in two tests of whole grease prepared with calcium hydroxystearate thickener. In one test a slight growth inhibition was observed, resulting in a 72-h E_bL50 of between 100 and 1000 mg/L WAF, and a 72-h E_rL50 of between 320 and 1000 mg/L WAF (Shell Research, 1995a). The second test with the same grease did not show any effects, and both the 72-h E_bL50 and 72-h E_rL50 were >1000 mg/L WAF (Shell Research, 1995b).

Conclusions: The results of these studies indicate that a grease prepared with calcium hydroxystearate thickener demonstrates little or no toxicity to aquatic plants.

5.1.5. ECOSAR Modeled Toxicity

The aquatic hazards of grease thickeners were assessed using fish, invertebrate, and algal toxicity data estimated using the ECOSAR (US EPA, 2000) model. Estimates of the acute LC/EC50 values for fish, invertebrates, and algae for nonanedioic acid, dilithium salt, stearic acid, calcium salt, and docosanoic acid, lithium salt indicated no acute toxicity at the limits of their water solubility. Only octadecanoic acid, 12-hydroxy-lithium salt showed any potential acute toxicity for fish. The 96-h LC50 was estimated to be 123 mg/L.

Conclusions: Estimated acute toxicity values for various grease thickeners showed little or no toxicity at the limit of the water solubility for these substances.

Aquatic toxicity data for free lithium ion as a compound of interest are summarized in Appendix A.

5.2 Assessment Summary for Environmental Effects

Test data on whole greases, lithium hydroxystearate, other fatty acids having similar molecular weights and chemical structure (independent of the grease matrix) indicate that grease thickeners have minimal to no toxicity to aquatic organisms. No toxicity was observed when rainbow trout were exposed to mechanical dispersions of lithium hydroxystearate up to 2000 mg/L. Tests exposing rainbow trout to whole grease did not show any acute toxicity at 12,500 mg/L. Testing of water accommodated fractions (WAF) of whole grease at 1000 mg/L also did not reveal any acute toxicity to aquatic invertebrates. Exposures of algae to WAF solutions showed either no toxicity (EL50 >1000 mg/L) or only slight inhibition (EL50 >100 mg/L). Modeled acute toxicity endpoints for the fatty acids

were consistent with the measured data and provided additional evidence of a general low toxicity of these substances to aquatic organisms. Overall, acute toxicity to aquatic organisms is not likely to occur at the limits of the solubility of these substances.

6.0 HUMAN HEALTH ENDPOINTS

The calcium and lithium salts of fatty acids used as grease thickeners in this category are considered very low in toxicity based on their physical and chemical properties, toxicity tests in laboratory animals, and extensive use without reports of significant toxicity for many decades. Frequent dermal exposure occurs while using greases for the lubrication of bearings and other moving parts in virtually every segment of transportation and industry.

The fatty acids used to produce the compounds in this category are either edible or similar in structure to edible fatty acids. These fatty acids in their free state are readily absorbed from the gastrointestinal tract and readily metabolized. Calcium is common in all living systems and is essential to life. Free lithium ion is used pharmacologically to treat bipolar disorder (therapeutic range 0.6 – 1.2 mmol/l serum), however some neurotoxicity may be seen in sensitive patients at the upper end of the therapeutic range. Lithium has significant bioavailability only when administered as partially soluble salts such as lithium carbonate which are not used in grease thickener manufacture.

The calcium and lithium salts of the fatty acids that are formed in the presence of mineral oil or synthetic oil, however, have very low bioavailability; their function is to maintain the oils within a gel-like state in contact with the surfaces being lubricated. High resistance to water wash-out is a desirable technical property of most grease.

Toxicological studies of calcium and lithium salts of fatty acids in their pure form and studies with greases thickened with these salts are both considered relevant to an assessment of their hazards.

Dermal exposure is the route by which humans are most likely to come in contact with the salts of fatty acids in greases. Dermal absorption studies of partially soluble lithium compounds indicate low dermal absorption. A summary of studies with lithium compounds by various routes of exposure is located in Appendix A. The insolubility of the metal salts used as grease thickeners and their entrainment in the grease matrix make it unlikely that significant dermal absorption will occur.

Much of the data on the toxicity of grease thickeners comes from tests on greases rather than the metal-fatty acid salts by themselves. In toxicity studies the greases were often applied dermally at doses of 2,000 mg/kg; the doses of the thickeners were therefore proportionately reduced. This approach is based on the following practical realities in the production of greases.

1) The oil/grease thickener system rarely exists independent of greases. In order to achieve the desired physical properties and chemical composition during the production of a grease, the metal hydroxide (i.e., LiOH) and a fatty acid (i.e., hydroxystearate) are typically blended together in a mixed emulsion of oil and water due to their differing solubilities. Residual water can be removed from the resulting thickener, but residual oil will remain with the thickener, forming a grease.

2) Production of grease thickeners at higher concentrations (as high as 20-25%) in the final grease is possible, but the reaction product would represent a grease of very firm consistency that is not commonly used in the industry.

3) Grease thickeners made by the direct reaction of metal hydroxides and fatty acids are much more viscous than their respective oil/grease thickener system and were judged not to be representative of actual greases when tested in studies of mammalian toxicity.

4) For these reasons, plus the fact that exposures to grease thickeners are primarily expected to be via exposure to a grease and not to the thickeners alone, testing of typical greases was considered to provide the most appropriate approach for mammalian endpoints.

6.1 Human Health Effects

6.1.1 Acute Toxicity

6.1.1.1 Calcium Salts of Fatty Acids

There are no acute toxicity data for the calcium salts *per se*. However, data may be extrapolated from available information on magnesium salts such as Mg stearate (oral LD50 > 10 g/kg; CIR, 1982). Ca stearate is cleared as a direct food additive and is considered GRAS (Generally Recognized as Safe). Mg stearate was not irritating when tested on the skin or in the eyes of rabbits (CIR, 1982).

6.1.1.2 Lithium Salts of Fatty Acids

The oral LD50 of Li stearate in the rat is > 5 g/kg (CIR, 1982). A lithium complex grease containing 13.1% lithium 12-hydroxystearate and 2.6% dilithium azelate had an oral LD50 in the rat > 5 g/kg (Pharmakon, 1994a). This same grease had a dermal LD50 in the rabbit > 3 g/kg (Pharmakon, 1994b) and did not induce acute skin or eye irritation (Pharmakon, 1994 c, d).
Another lithium complex grease containing 8.8% lithium hydroxystearate and 1.8% dilithium azelate was tested for skin sensitization using a Buehler assay. This grease, which also contained several performance additives, did not cause allergic contact dermatitis (sensitization).(Pharmakon, 1997).

Conclusions: The available data demonstrate that the substances in this group are not acutely toxic by either the oral or dermal routes. They are non-irritating to the skin and eye and are not sensitizing to the skin. Both calcium and lithium stearates have been safely used in cosmetics and lithium stearate has been used in baby powders to aid in water repellency and oil absorbency (CIR, 1982).

6.1.2 Repeated Dose Toxicity

6.1.2.1 Calcium Salts of Fatty Acids

A study relevant to the potential for either the calcium and lithium salts in this category to cause systemic toxicity is a 13-week dietary study in rats and mice with castor oil conducted by the National Toxicology Program (1992). The predominant fatty acid in castor oil is ricinoleic acid (12-hydroxy-*cis*-9-octadecenoic acid) while the 12-hydroxystearic acid is 12-hydroxyoctadecanoic acid. Diets containing up to 10% castor oil did not produce any adverse effects.

Data may also be extrapolated from a study with magnesium stearate in which rats were fed up to 20% Mg stearate in the diet for 3 months (Sondergaard et al., 1980). There were no significant histopathologic changes. The NOEL was 5% Mg stearate in the diet (~ 2500 mg/kg/day).

A 13-weeks dermal toxicity study was performed on a "generic calcium complex grease" that contained 3.5% CAS No. 62-54-4 (acetic acid, calcium salt), 3.5% CAS No. 64754-97-8 (fatty acids, coco, calcium salts), 1.4% CAS No. 69012-90-4 (fatty acids, C6-12, calcium salts), and 1.2% CAS No. 66071-81-6 (fatty acids, tallow, hydrogenated, calcium salts). The structures of the thickeners in this grease were judged to be similar enough to those in the Lubricating Grease Thickeners category that the data from this study can be applied by read-across. The generic calcium complex grease contained 9.6% calcium thickeners and 9.2% additives. It was applied to the clipped backs of rats at doses of 0, 500 or 2000 mg/kg/day, 5 days/week for 13 weeks (Mobil, 1988a). The high dose of 2000 mg/kg/day is equivalent to a dermal application of 5 oz. grease/day to a 160 lb human. Slight erythema and flaking was observed at the application site. Slight but not significantly lower body

weights were observed in 2000 mg/kg/day treated animals at study termination. No specific organs were directly affected by treatment as judged by serum chemistry, clinical observation, organ weight changes, gross necropsy or histopathology. Increased liver and kidney weights relative to body weights occurred primarily in males but these organ weight changes were not associated with histopathologic changes and were not considered adverse effects of treatment. No differences in sperm morphology from 2000 mg/kg/day rats were identified. The NOAEL was 2000 mg/kg/day.

6.1.2.2 Lithium Salts of Fatty Acids:

A lithium complex grease containing 8.8 % lithium 12-hydroxystearate, 1.8% dilithium azelate and 7% performance additives was tested in a 90-day oral study in the rat (Huntingdon, 1997). There were no significant adverse effects after 90 days of oral dosing with the grease at 1000 mg/kg/day. This same grease was also tested in both 28-day and 90-day dermal studies (Huntingdon, 1997a,b) in the rat. Again, no significant adverse effects were observed after 90 days of 2100 mg/kg/day dermally in any of the measured endpoints, including hematology, clinical chemistry, organ weights, and histopathology.

A second lithium complex grease (Mobilux EP2) was tested in a 13-week dermal study in the rat. This grease containing 5.6% lithium hydroxystearate, 0.7% lithium salts of C16-C22 alkylcarboxylic acids and 7.0% performance additives was applied to the shaved backs of rats at doses of 0, 300, 1200 or 2000 mg/kg/day (Mobil, 1988b). Slight irritation of the skin characterized by erythema, flaking and thickening of the epidermis was observed. The skin penetration of radioactive dotriacontane from a dermally applied grease was <1.0% of the applied dose (Mobil, 1988c). Since the dotriacontane served as a surrogate for the more fluid portion of the grease, it is likely that dermal penetration of the more solid thickeners would be even less. No systemic toxicity was reported. Males in all treated groups and females receiving the two higher doses had slightly lower erythrocyte counts, hematocrit, and hemoglobin than the controls at weeks 5, 9, and 13. These differences were slight, the values for the treated animals were within the normal range, and the bone marrow was normal. Therefore these differences were judged not to represent toxicity. The NOAEL for the grease formulation was 2000 mg/kg/day

A third lithium grease (Mobilgrease HP) was also tested in a 13-week dermal study in rats. This grease contained 7.9% lithium hydroxystearate, 0.9% lithium salts of C16-C22 alkylcarboxylic acids, and 10.8% performance additives. It was tested at dermal doses of 0, 500 or 2000 mg/kg/day (Mobil, 1992). Body weight and body weight gain were comparable to controls. Among the hematology parameters, hemoglobin and hematocrit were slightly, but significantly, reduced in treated males, although erythrocyte counts were not affected. The values for these parameters fell within the normal

range of historical data (defined by the 10th and 90th percentiles). Increased liver weights in males at both doses and in females at 2000 mg/kg/day, and a slight increase in relative kidney weights in males at 2000 mg/kg/day were reported, without any abnormal histopathology correlates. Increases in liver weight in the absence of abnormal histopathology were not considered an adverse response and were not used in determining the NOAEL. Increased vacuolation in the adrenal cortex occurred in 4/10 males at 2000 mg/kg/day. No adverse effects were seen in evaluation of sperm and both the weight of testes and number of spermatids in testis were unaffected by treatment. The NOAEL for the grease formulation was reported to be 500 mg/kg/day due to the marginal changes with the higher dose.

A fourth lithium grease (envelope grease) was tested in a 13-week dermal study in Sprague-Dawley rats (Stonybrook, 1995). This grease also contained 7.9% lithium hydroxystearate and 0.9% lithium salts of C16-C22 alkylcarboxylic acids, but it had a markedly enhanced amount of 20.0% performance additives. It was tested at dermal doses of 0, 500 or 2000 mg/kg/day. Body weight and body weight gain were comparable to controls. Among the hematology parameters, hemoglobin and hematocrit were slightly (~6%), but significantly, reduced in treated males, and hemoglobin was similarly reduced in females. Erythrocyte counts were not affected. The values for hemoglobin fell within the normal range of historical data (defined by the 10th and 90th percentiles). Liver weights increased in males and females at 2000 mg/kg day, but no abnormal histopathology was reported. Increases in liver weight in the absence of abnormal histopathology were not considered an adverse response. Histopathological findings that were abnormal included an increased incidence of hyperplasia in the red pulp of the spleen (increased extramedullary hematopoiesis) in females receiving 2000 mg/kg/day. Hypertrophy of the follicular epithelial cells of the thyroid was noted in all treated groups. Among the parameters related to male reproduction, testicular weight was decreased relative to controls by ~6% and the number of testicular spermatids per gram testes was decreased by ~10%. The percent of abnormal epididymal sperm was less in males receiving 2000 mg/kg/day than in controls. The NOAEL for the grease formulation was reported to be <500 mg/kg/day.

Effects on reproductive organs were assessed in male F344 rats treated dermally with a "borated lithium grease" (Mobil, 1993), the same grease identified as the highly additized "envelope grease" in the 90-day study previously described. F344 males were chosen due to their susceptibility to effects on reproductive organs and the grease had a very high (noncommercial) level of additives. Males were treated dermally with 0, 500, or 2000 mg/kg/day, 5 days/week for 10 weeks. No adverse effects were seen on testes weight or testicular sperm. However weight of the epididymides decreased relative to controls with 500 mg/kg/day. At 2000 mg/kg/day, weights of the epididymides and cauda epididymis were decreased and the number of sperm per cauda was decreased. Because of

increased food consumption and decreased body weight, particularly with 2000 mg/kg/day, and also because of the lack of testicular toxicity, the effects on the epididymis may have been secondary to more general systemic toxicity. The NOAEL was <500 mg/kg/day.

Conclusions: Repeated dose studies have been conducted with greases containing calcium complex, lithium 12-hydroxystearate and/or dilithium azelate. Studies have been conducted with magnesium stearate, which is closely related to calcium stearate. A study has been conducted with castor oil (mostly ricinoleic acid) which is closely related to the larger fatty acids used to make the salts in this category. Results of reported studies on similar compounds are used for read-across to the grease thickeners in this category. Marginal changes of uncertain relevance were noted in hematocrit and hemoglobin in some studies with formulated greases. Increased liver weight, hypertrophy of follicular epithelium in the thyroid, and other organ-specific changes were reported with some greases, particularly those with a very high level of additives. Overall, it appeared that such changes may have been more related to these additives than to the thickeners in the grease. The range of NOAEL values for greases administered dermally is 500-2100 mg/kg/day. For oral treatment the NOAEL was the highest dose tested in each study, namely 1000 – 2500 mg/kg/day.

6.1.3 Genetic Toxicity [*In Vitro* and *In Vivo*]

No studies have been published/reported on the genotoxicity of either calcium or lithium salts in this category. However, castor oil and magnesium stearate have been tested in the Ames test and were not mutagenic (NTP, 1992; Litton Bionetics, 1976, respectively). Thus, there is no suggestion that the fatty acids used to make the salts in this category are genotoxic. The genotoxicity of lithium compounds has been tested and reviewed (Léonard et al., 1995). The overall evidence from several *in vitro* and *in vivo* studies with soluble lithium salts indicated no mutagenic activity and a possible effect on chromosomes only after a very high intraperitoneal dose of a soluble lithium salt, lithium citrate (2 g/kg).

Conclusions: Based on the low solubility of the lithium salts of fatty acids in this category and the existing data on lithium, it is unlikely that these materials cause gene mutations or would induce cytogenetic damage as a consequence of exposure to the grease complex.

6.1.4 Reproductive and Developmental Toxicity

Rats and mice were fed diets containing up to 10 percent castor oil for 13 weeks. No significant effects were observed in screening for male reproductive endpoints or length of female estrous cycles

(NTP, 1992).

The toxicity of a vehicle containing 5.5 percent magnesium stearate was tested orally in pregnant rabbits at a dose of 2.5 mg/kg (Gottschewski, 1967). There were no teratogenic effects.

6.1.4.1 Calcium Salts of Fatty Acids

No studies have been reported on the developmental toxicity of calcium salts of fatty acids in this category. However, a calcium complex grease administered dermally for 90 days did not induce adverse effects on the male reproductive system or on sperm morphology.

6.1.4.2 Lithium Salts of Fatty Acids

A lithium grease was applied dermally to pregnant rats on gestation days 0 –19 at concentrations of 0, 500 or 2000 mg/kg/day (Mobil, 1989). This grease contained 8.1% lithium hydroxystearate, 0.9% lithium salts of C16-C22 alkylcarboxylic acids, and 18.4% additives. It was very similar to the "envelope grease" used in a 90-day study described above, but without 2% of a borated additive in the "envelope grease". Maternal toxicity, expressed as decreased net maternal body weight (body weight excluding the gravid uterus) gain, was observed at both dose levels. No signs of developmental toxicity (e.g. increased fetal loss, resorptions or decreased fetal weight) were observed. No evidence of teratogenicity was reported during external, visceral or skeletal evaluation of rat fetuses from dams exposed to lithium complex grease. The developmental NOAEL for the grease in this study was 2000 mg/kg/day.

Conclusions: For two of the calcium salts in the category (Octadecanoic acid, calcium salt, CAS # 1592-23-0 and fatty acids, tallow, calcium salts, CAS # 64755-01-7), it has been concluded that the “Chemical is not considered a candidate for testing under the HPV Challenge Program, based on preliminary EPA review indicating that testing using the SIDS base set would not further our understanding of this chemical’s properties” (EPA HPV Challenge Program Chemical List). In addition, a 13-week dermal study of a calcium complex grease showed no significant adverse effects of treatment in any organ system or on sperm morphology [NOAEL = 2000 mg/kg/day].

The potential impact of the presence of lithium in formulated thickeners was addressed in a series of studies on greases as well as by recent publications on therapeutic soluble lithium salts that have been used in the treatment of psychological conditions which are summarized in Appendix A. The lithium salts used as grease thickeners are not considered soluble. Also, the developmental toxicity study of a lithium complex grease described above demonstrated that lithium hydroxystearate in a

grease formulation did not induce adverse reproductive or developmental effects in offspring of animals treated throughout gestation at doses high enough to induce toxicity in the dam. Decreased net maternal body weight gain confirmed absorption of some components of the grease formulation at levels sufficient to induce maternal toxicity. Regarding effects on the male reproductive system, no adverse effects or marginal effects on testes or sperm in Sprague-Dawley rats were reported in 13-week dermal studies, with these marginal effects occurring with the grease containing excessive amounts of additives. In contrast, testes were unaffected in F344 rats exposed to the same highly additized grease and the decreases in the epididymis weight and epididymal sperm count may have been secondary to more general systemic toxicity. Since these male effects were not seen in other studies with comparable grease thickener content and may related to additive content, they are not considered relevant to the evaluation of grease thickeners in this program. The Developmental NOAEL for greases administered dermally = 2000 mg/kg/day.

6.2. Health Effects Other

6.2.1. Carcinogenicity

Grease containing 7.5 percent lithium 12-hydroxystearate was tested in a chronic skin-painting study with 50 male and 50 female C3H/HeJ mice (Barkley and Stemmer, 1984). This grease also contained performance additives at a total concentration of about 12 percent. The total tumor incidence was 3/100. Based on the incidence of tumors in the negative control groups, dermal carcinogenesis studies are considered to be positive at tumor frequencies of 4% or greater. As that level was not achieved here, the results of this assay were negative for carcinogenicity.

6.3 Assessment Summary for Health Effects

Results from testing lithium fatty acid salts, fatty acid salts compositionally similar to salts in this category (e.g. magnesium stearate), and greases containing thickeners from this category demonstrate that these materials are not acutely toxic by the oral or dermal route, are not irritating to the eyes or skin, and do not induce skin sensitization. Repeat dose studies in rats by the oral route (Mg stearate – 3 months in diet; castor oil – 13 wks in diet; lithium complex greases –90 days by oral gavage), or with dermal treatment (Calcium complex grease – 13 weeks, lithium complex grease – 28 or 90 days; 13 weeks) did not show any significant adverse effects at 500mg/kg/day and above although some effects were seen in thyroid and testes in one dermal study, possibly related to high blend of additives. The general range of NOAEL values for greases administered dermally is 500 - 2100 mg/kg/day. For oral treatment the NOAEL was the highest dose tested in each study, namely

1000 – 2500 mg/kg/day. Treatment with a lithium grease dermally applied for 2 years did not cause skin cancer in C3H mice. Mutations were not induced in bacterial assays by fatty acids used to make salts in this category. In other studies soluble lithium salts [the lithium salts used to make greases are not soluble] were not mutagenic *in vitro*, and slight chromosomal effects occurred only when a very high dose of lithium citrate alone was administered intraperitoneally. Considering, along with these data, the low solubility of salts of fatty acids in the grease thickeners category, the compounds are not likely to be mutagenic. A dermal developmental toxicity study of a lithium complex grease demonstrated no evidence of reproductive or developmental toxicity even at a maximum dose of 2000mg/kg/day that induced maternal toxicity. Effects on the male reproductive system from dermal treatment with a highly additized lithium complex grease were not seen in other studies with comparable grease thickener content and may be attributed to generalized toxicity related to additive content; as such they are not considered relevant to the evaluation of grease thickeners in this program. A calcium complex grease and a lithium grease administered dermally for 90 days did not induce adverse effects on the male reproductive system or on sperm morphology or number. The dermal developmental NOAEL = 2000 mg/kg/day. Magnesium stearate (structurally similar to calcium stearate) did not induce developmental effects in orally treated pregnant rabbits. Two calcium salts in this category are not considered candidates for SIDS. Based on negative results for greases prepared with calcium and lithium thickeners, magnesium stearate or castor oil, it is unlikely that greases thickeners present developmental or reproductive hazards.

7. CATEGORY ANALYSIS CONCLUSION

The lithium and calcium salts of fatty acids in this category are used by the lubricants industry to thicken greases. Greases are used for the lubrication of bearings and other moving parts in virtually every segment of the transportation and industry. They are one of the few lubricants that involve an actual chemical reaction during their manufacture. Grease thickeners are not commonly synthesized as pure compounds and generally exist only in the presence of the oil matrix. The function of these metal-fatty acid salt compounds is to maintain the oil within a gel-like state in contact with the surfaces being lubricated. The 11 substances in this category are lithium and calcium salts of similar fatty acids. The fatty acids used to make greases are derived from animal fats and vegetable oils. Two substances in this category [Octadecanoic acid, calcium salt, CAS # 1592-23-0 and fatty acids, tallow, calcium salts, CAS # 64755-01-7] are considered ”adequately characterized” under the HPV Challenge Program. The calcium and lithium salts in this category are considered very low in toxicity based on their physical and chemical properties [high molecular weight, insolubility and typical *in situ* synthesis in a mineral oil matrix], results of animal and environmental testing, and extensive industrial

use involving extensive dermal exposure without reports of significant toxicity for many decades. Studies provided here demonstrate substantial similarities in environmental and human health effects making it possible to provide read-across values for untested substances in this category. The study endpoint measured data, and read-across values for untested category members are summarized in Appendix B. Matrix of Grease Thickeners Category Data.

Physical chemical values for substances in the grease thickeners category originate from alkali metals and edible fats and oils (or similar fatty acids). These substances have high melting points and thus exist as solids at ambient temperatures. The grease thickeners have variable water solubility depending on the length of the carbon chain in the fatty acid, but dissolution is prevented by the hydrophobic grease matrix. Grease thickeners have low vapor pressure and little or no tendency to partition into air. They are not susceptible to hydrolysis or direct/indirect photolysis under environmental conditions. Environmental partitioning will be primarily to soil and sediment. Fatty acids are known to be used by microorganisms as a source of energy, and their calcium and lithium salts are expected to be inherently if not readily biodegradable. Grease thickeners do not bleed out of the grease matrix and this severely limits environmental exposure.

Test data on whole greases, lithium hydroxystearate, and other fatty acids having similar molecular weights and chemical structure (independent of the grease matrix) indicate that grease thickeners have minimal to no toxicity to aquatic organisms. No toxicity was observed when rainbow trout were exposed to mechanical dispersions of lithium hydroxystearate up to 2000 mg/L. Invertebrates were not sensitive to water accommodated fractions (WAFs) of whole greases thickened with calcium hydroxysterate (EC50 >1000 mg/L loading rate). Tests exposing rainbow trout to whole grease did not show any acute toxicity at 12,500 mg/L. Exposures of algae to WAF solutions showed either no toxicity (EL50 >1000 mg/L) or only slight inhibition (EL50 >100 mg/L). Modeled acute toxicity endpoints for the fatty acids were consistent with the measured data and provided additional evidence of a general low toxicity of these substances to aquatic organisms.

Results from testing lithium fatty acid salts, fatty acid salts compositionally similar to salts in this category (e.g. magnesium stearate), and greases containing thickeners from this category demonstrate that these materials are not acutely toxic by the oral or dermal route, are not irritating to the eyes or skin, and do not induce skin sensitization. Repeat dose studies in rats by the oral route (Mg stearate, castor oil, lithium complex grease), or with dermal treatment (Calcium complex grease, lithium complex grease) did not show any significant adverse effects. For oral treatment the NOAEL

range was the highest dose tested in each study, namely 1000 – 2500 mg/kg/day. The range of NOAEL values for greases administered dermally is 500-2100mg/kg/day. Dermal treatment with a lithium grease for 2 years did not cause skin cancer in C3H mice. Mutations were not induced in bacterial assays by fatty acids used to make salts in this category. Soluble lithium salts (which are not used in grease thickener manufacture) were not mutagenic *in vitro*, and slight chromosomal effects occurred only from a very high dose of soluble lithium citrate administered intraperitoneally. Considering, along with these data, the low solubility of salts of fatty acids in the grease thickeners category, the compounds are not likely to be mutagenic. A calcium complex grease and a lithium grease administered dermally for 90 days did not induce adverse effects on the male reproductive system or on sperm morphology or number. The dermal developmental NOAEL is 2000 mg/kg/day. Magnesium stearate (structurally similar to calcium stearate) did not induce developmental effects in orally treated pregnant rabbits. Negative results for greases prepared with calcium and lithium thickeners, magnesium stearate or castor oil, indicate that it is unlikely that greases thickeners are developmental or reproductive hazards.

Overall based on animal and environmental studies and safe use for decades in industrial and consumer applications it can be concluded that that calcium or lithium grease thickeners do not present a human or environmental hazard.

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9. LIST OF APPREVIATIONS AND ACRONYMS

API – American Petroleum Institute
BOD – biological oxygen demand
AUGC – area under the growth curve
CAS RN/CAS #/CAS No. - Chemical Abstract Service Registry Number
^{o}C – degrees Celsius
CIR – Cosmetics Ingredients Review Panel
CONCAWE – Conservation of Clean Air and Water in Europe
d - day
DMSO – Dimethyl sulfoxide
EINECS – European Inventory of Existing Commercial Chemical Substances
EL_{50} – effective loading rate lethal to 50% of the test population
E_bL_{50} – effective loading rate that causes 50% reduction in algal cell biomass
E_rL_{50} – effective loading rate that causes 50% reduction in algal growth rate
EPA/US EPA – United States Environmental Protection Agency
g/cm^3 – grams per cubic centimeter
h - hour
HLS – Huntingdon Life Sciences
HPV – High Production Volume
HSDB – Hazardous Substances Data Bank
IRDC – International Research and Development Corporation
^{o}K – degrees Kelvin
kPa - kilopascal
LC_{50} – lethal concentration for 50% of the test population
LC_{50}– lethal dose level for 50% of the test population
LL_{50} – lethal loading rate for 50% of the test population
Loading Rate – total amount of test substance added to dilution water to prepare water accommodated fractions (WAFs) for ecotoxicity testing
LOAEL – lowest observable adverse effect level
mg/kg – milligrams per kilogram
mg/L – milligrams per liter
mg/m^3 – milligrams per cubic meter
mL - milliliter
mm - millimeter
nm - nanometer
NOAEL – no observable adverse effect level
NOEC – no observable effect concentration
NOELR – no observable effect loading rate
NTP – National Toxicology Program
OECD – Organization for Economic Cooperation and Development
OPPTS – US EPA Office of Prevention, Pesticides and Toxic Substances
PAC - Polycyclic aromatic compound
PAH – polycyclic aromatic hydrocarbon
PNA – polynuclear aromatic
ppm – part per million
SIDS – Screening Information Data Set
UNEP – United Nations Environment Program
US EPA – United States Environmental Protection Agency
UV - ultraviolet
WAF – water accommodated fraction
wt% - weight percent
μg - microgram
μg/L – microgram/liter
> greater than
< less than

10. GLOSSARY

NOTE: *The following terms are used in this document. To the extent possible definitions were taken from relevant authoritative sources such as EPA, OECD, ASTM and IUPAC.*

Bioavailability: The state of being capable of being absorbed and available to interact with the metabolic processes of an organism. Typically a function of chemical properties, physical state of the material to which an organism is exposed, and the ability of the individual organism to physiologically take up the chemical. Also, the term used for the fraction of the total chemical in the environmental which is available for uptake by organisms. **(AIHA 2000)**

Category Member: The individual chemical or substance entities that constitute a chemical category.

Category: A chemical category, for the purposes of the HPV Challenge Program, is a group of chemicals whose physicochemical and toxicological properties are likely to be similar or follow a regular pattern as a result of structural similarity. These structural similarities may create a predictable pattern in any or all of the following parameters: physicochemical properties, environmental fate and environmental effects, and/or human health effects. **(US EPA 2007b)**

Dose: The amount of a substance available for interactions with metabolic processes or biologically significant receptors after crossing the outer boundary of an organism. The **potential dose** is the amount ingested, inhaled, or applied to the skin. The **applied dose** is the amount presented to an absorption barrier and available for absorption (although not necessarily having yet crossed the outer boundary of the organism). The **absorbed dose** is the amount crossing a specific absorption barrier (e.g., the exchange boundaries of the skin, lung, and digestive tract) through uptake processes. **Internal dose** is a more general term denoting the amount absorbed without respect to specific absorption barriers or exchange boundaries. The amount of the chemical available for interaction by an particular organ or cell is termed the delivered or **biologically effective dose** for that organ or cell **(US EPA 2002).**

Dose-Response Relationship: The relationship between a quantified exposure (dose) and the proportion of subjects demonstrating specific biological changes in incidence or in degree of change (response) **(US EPA 2002).**

Ecological Effects – all endpoints (OECD definitions)

> **Fish, Acute Toxicity Test:** In a four-day exposure, acute toxicity is defined by the LC_{50}, the concentration of test substance in water which kills 50% of the test population of fish. Test methodology is described in OECD Guideline 203, in OECD Guidelines for the Testing of Chemicals.
>
> ***Daphnia* sp., Acute Immobilization Test:** In a one or two-day exposure, acute toxicity is defined by the EC_{50}, the concentration of test substance in water which causes immobilization to 50% of the test population of invertebrates. Test methodology is described in OECD Guideline 202, Part 1, in OECD Guidelines for the Testing of Chemicals.
>
> **Alga, Growth Inhibition Test:** In a three-day exposure, growth inhibition is defined by the EC_{50}, the concentration of test substance in growth medium which results in a 50% reduction in either alga cell growth or growth rate relative to a control group. Test methodology is described in OECD Guideline 201, in OECD Guidelines for the Testing of Chemicals.

Endpoint: In the context of the EPA High Production Volume Challenge Program, an endpoint is a physical-chemical, environmental fate, ecotoxicity, and human health attribute measurable by following an approved test methodology (e.g., OECD Guidelines for Testing of Chemicals). Melting point, biodegradation, fish acute toxicity, and genetic toxicity are examples of endpoints that are measured by an approved test method. **(US EPA 1999)**

Environmental Fate Effects – all endpoints (OECD definitions)

Photodegradation: The photochemical transformation of a molecule into lower molecular weight fragments, usually in an oxidation process. This process may be measured by Draft OECD Guideline, "*Phototransformation of Chemicals in Water – Direct and Indirect Photolysis*". This process also may be estimated using a variety of computer models.

Stability in Water: This environmental fate endpoint is achieved by measuring the hydrolysis of the test substance. Hydrolysis is defined as a reaction of a chemical RX with water, with the net exchange of the group X with OH at the reaction center. Test methodology for hydrolysis is described in OECD Guideline 111, in OECD Guidelines for the Testing of Chemicals.

Transport Between Environmental Compartments: This endpoint describes the distribution of a chemical between environmental compartments using fugacity-based computer models. The results of the model algorithms provide an estimate of the amount of the chemical within a specific compartment. The environmental compartments included in many models are air, water, soil, sediment, suspended sediment, and aquatic biota.

Biodegradation: Breakdown of a substance catalyzed by enzymes *in vitro* or *in vivo*. As an endpoint in EPA's HPV program, biodegradation is measured by one of six methodologies described in OECD Guidelines 301A-F, in OECD Guidelines for the Testing of Chemicals.

Exposure: Contact made between a chemical, physical, or biological agent and the outer boundary of an organism. Exposure is quantified as the amount of an agent available at the exchange boundaries of the organism (e.g., skin, lungs, gut). **(US EPA 2002).**

Feedstock: A refinery product that is used as the raw material for another process; the term is also generally applied to raw materials used in other industrial processes. **(Speight, 2007).**

Female Mating Index: Number of females with confirmed mating (sperm and/or vaginal plug)/number of females placed with males. (OECD)

Hazard Assessment: The process of determining whether exposure to an agent can cause an increase in the incidence of a particular adverse health effect (e.g., cancer, birth defect) and whether the adverse health effect is likely to occur in humans **(US EPA 2002)**.

Hazard Characterization: A description of the potential adverse health effects attributable to a specific environmental agent, the mechanisms by which agents exert their toxic effects, and the associated dose, route, duration, and timing of exposure **(US EPA 2002).**

Hazard: A potential source of harm **(US EPA 2002**).

Health Effects – all endpoints (OECD definitions, unless otherwise specified)

Acute Toxicity: The adverse effects occurring within a short time-frame of administration of a single dose of a substance, multiple doses given within 24 hours, or uninterrupted exposure over a period of 24 hours or less. Exposure may be via oral, dermal or inhalation routes as described in OECD Guidelines 401, 402, 403, and 420 in OECD Guidelines for the Testing of Chemicals.

Developmental Toxicity: Adverse effects on the developing organism that may result from exposure prior to conception (either parent), during prenatal development, or postnatally until the time of sexual maturation. The major manifestations of developmental toxicity include death of the developing organism, structural abnormality, altered growth, and functional deficiency. **(US NLM 2007)**

Genetic Toxicity *in vivo* (Chromosomal Aberrations): The assessment of the potential of a chemical to exert adverse effects through interaction with the genetic material of cells in the

whole animal. Genotoxicity may be studies in the whole animal using methods described in OECD Guideline 475, in OECD Guidelines for the Testing of Chemicals.

Genetic Toxicity *in vitro* (Gene Mutations): The assessment of the potential of a chemical to exert adverse effects through interaction with the genetic material of cells in cultured mammalian cells. Genotoxicity may be studies in cultured cells using methods described in OECD Guideline 476, in OECD Guidelines for the Testing of Chemicals.

Repeated Dose Toxicity: The adverse effects occurring due to repeated doses that may not produce immediate toxic effects, but due to accumulation of the chemical in tissues or other mechanisms, produces delayed effects. Repeated dose toxicity may be studied following methods described in OECD Guidelines 407, 410, or 412 in OECD Guidelines for the Testing of Chemicals.

Reproductive Toxicity: The occurrence of biologically adverse effects on the reproductive systems of females or males that may result from exposure to environmental agents. The toxicity may be expressed as alterations to the female or male reproductive organs, the related endocrine system, or pregnancy outcomes. The manifestation of such toxicity may include, but not be limited to, adverse effects on onset of puberty, gamete production and transport, reproductive cycle normality, sexual behavior, fertility, gestation, parturition, lactation, developmental toxicity, premature reproductive senescence, or modifications in other functions that are dependent on the integrity of the reproductive systems. **(US EPA 1996f)**

Lowest-Observed-Adverse-Effect Level (LOAEL): The lowest exposure level at which there are statistically or biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group **(US EPA 2002).**

No-Observed-Adverse-Effect Level (NOAEL): The highest exposure level at which there are no biologically significant increases in frequency or severity of adverse effects between the exposed population and its appropriate control group; some effects may be produced at this level, but they are not considered adverse or precursors to adverse effects **(US EPA 2002)**.

Portal-of- Entry Effect: A local effect produced at the tissue or organ of first contact between the biological system and the toxicant **(US EPA 1994)**.

Read Across: Read-across can be regarded as using data available for some members of a category to estimate values (qualitatively or quantitatively) for category members for which no such data exist. **(OECD 2007)**

Systemic Effects or Systemic Toxicity: Toxic effects as a result of absorption and distribution of a toxicant to a site distant from its entry point **(US EPA 2002)**.

Target Organ: The biological organ(s) most adversely affected by exposure to a chemical or physical agent **(US EPA 2002).**

Appendix A: Toxicity Data on Lithium

Aquatic Toxicity

Aquatic toxicity data for the free lithium ion were available for fish, invertebrates and algae (1). The 96-hr LC50 values for fish ranged from 22 to 315 mg/L, and the 24-hr to 96-hr EC50 values for invertebrates ranged from 0.3 to 45 mg/L. For algae, the lowest observed effect concentration (LOEC) was 160 mg/L while the no observed effect concentration (NOEC) was 80 mg/L.

Mammalian Toxicity: Laboratory Animals

Effects on Male Reproduction:

"Significant inhibition of spermatogenesis has been reported with daily subcutaneous injections of 0.3 mg (0.04 mmol) Li/kg/b.w. as lithium chloride in immature male for 15 days (2). :Lithium affected testicular function by reducing the serum levels of FSH, LH, prolactin and testosterone. Reduced activity of key enzymes in androgen biosyntheses was also observed. Administration of lithium chloride for 20 and 25 days also reduced the weights of testes, prostate and seminal vesicles. Lithium level in serum was reported to be about 0.5 mmol/1 (2)" (3). Prolactin was shown to inhibit most of these effects (4). It is worth noting that 0.5 mM Li in human serum is associated with hand tremors, increased TSH, hypothyreosis, and other signs in some people (5).

In an oral study with male Wistar rats dosed orally with 35 mg/kg/day of Li carbonate (a soluble salt) for 21 days, several ultrastructural changes were reported in the seminiferous tubules. The level of plasma lithium was not reported (6).

Thakur et al (7) used oral doses of lithium carbonate that were reported to give increased serum lithium of 0.5 to 1.2 mEq/L. The higher doses in this study resulted in changes in the epididimides, testes, prostate, number of sperm produced, and the number of abnormal sperm (Table 1).

There is no question that lithium administered orally as a soluble salt can affect the male reproductive tract of rats. The question here is whether the insoluble lithium thickeners pose a hazard by the dermal route. Information was compiled in Table 1 to compare the changes reported by Thakur et al with similar endpoints that were evaluated in dermal studies with greases. The following observations can be made from this table.

1) Dermal administration of Mobilux EP-2 and Mobilgrease HP at 2,000 mg/kg/day for 13 weeks did not cause significant changes in many of the same endpoints affected by oral lithium carbonate in Thakur et al. The grease thickeners themselves did not appear to significantly affect male reproductive endpoints in these studies.
2) Dosing of F344 or Sprague-Dawley rats with the grease containing high additive levels affected some of the same endpoints altered by lithium carbonate, but not all. The pattern of toxicity appears to be different. Therefore the effects on male reproductive parameters in F344 rats do not appear to be related to free lithium ion from the grease thickeners.

Regarding more general effects on reproduction, effects "on fertility at doses which seem to have no other effects on the animals were described in an incompletely reported study in which mice of both sexes were given drinking water containing lithium chloride (10 - 200 mmol Li/l; 69 - 1388 mg Li/l). Fewer litters and elevated mortality among the pups during the period between birth and weaning were reported in the group that received 50 mmol (347 mg) Li/l from 2 weeks before mating until the pups were weaned. The plasma level was reported to be about 0.7 mmol Li/l. When the animals received 50 mmol Li/l starting five weeks before mating, postnatal growth and development were also retarded. No reproduction was reported in animals given 100 mmol (696 mg) Li/l (8)" (3).

Developmental/Teratogenic Effects:

Soluble lithium salts have caused teratogenic effects in laboratory animals in some studies. In addition, Casarett and Doull's Toxicology cites Gralla and McIlhenny (1972) as finding no adverse effects on fetuses "in rats (4.05 mEq/kg), rabbits (1.08 mEq/kg), or primates (0.67 mEq/kg). The dose in rats was sufficient to produce maternal toxicity and effects on the pups of treated lactating dams" (9). In other "animal experiments, teratogenic effects due to administration of lithium have been reported to be dose-related. In one review (10) the NOAEL for effects on fetuses and mothers was given as 10 mg (1.4 mmol) Li/kg/b.w./day when lithium was administered during the critical periods for cell differentiation and organogenesis. Defects in the heart/circulatory system have not been observed in animal experiments (5) as have been suggested in humans in a Swedish study (see below). Additional studies with oral exposure reported reproductive toxicity in rodents and swine including reduced litter size and pup weights in rats and an increased incidence of cleft palate in mice (11-15).

Beliles (16) cited Wright et al (17) as finding teratogenic changes in rats dosed with LiCl. A dose of 50 mg/day was given i.p. on days 1, 4, 7, and 9 of gestation and was followed by 20 mg daily until day 17. with serum Li values in the therapeutic range, malformations of the eyes (62%), cleft palate (39%),

and external ear (45%) were reported. Beliles also cited the work of Szabo (15), who dosed mice with serum levels of 0.45, 1.25, and 4.26 mEq/L. Cleft palate was observed. In contrast, no abnormalities were reported in monkeys, rabbits, or rats treated with lithium carbonate at maximal subtoxic doses (18 as cited in 16).

The developmental study with a lithium complex grease administered dermally to rats from gestation day 0 to 19 did not induce developmental toxicity at the maternally toxic maximum dose of 2000 mg/kg/day. These results demonstrate that the insoluble lithium salts entrained in grease are not developmental toxicants.

Human Experience

Absorption of Lithium Ion:

Lithium has been used medicinally since the 1800's, originally for gout and more recently for bipolar disorder. Therapeutic doses of soluble Li salts (i.e., Li carbonate) are given orally and absorption from the GI tract is nearly complete. Unfortunately the therapeutic index for oral Li is small. Therapeutic serum levels are in the range of 0.75-1.25 mEq/L (19), while neurotoxicity can occur in people at levels as low as 0.5-0.75 mEq/L (5,16). A single ingestion of 40 mg/kg of Li carbonate by a sensitive patient with prior history of Li use can result in toxic levels of Li in the blood (>2 mEq/L). At that level, blurred vision, muscular weakness, dizziness, and other symptoms might occur (20).

In contrast to absorption via the GI tract, limited data on dermal absorption indicate low absorption via the skin. One study was performed with lithium succinate, a topical treatment for uremic puritus (21) and seborrheic dermatitis (22, 23). A total of 227 adult patients with seborrheic dermatitis were treated with an ointment containing 8% Li succinate self-administered twice daily for 4 weeks (24). The levels of serum lithium, measured before and at the end of topical treatment with the lithium-containing ointment, were not significantly elevated by treatment. In a second study on dermal absorption of Li ion from water in a spa, 53 participants (28 males and 25 females) spent 20 minutes per day, 4 days per week for 2 consecutive weeks in one of two assigned spas. The test spa contained 40 mg/L Li^+, simulating the maximum exposure that would be expected in a spa sanitized with lithium hypochlorite. The control spa contained only the background level of approximately 0.02 ppm. Serum Li^+ was measured before and after use of the spa by graphite-furnace atomic absorption spectroscopy with a minimum detectable level of Li^+ in serum of 2 mµg l-1 (ppb), Serum levels were not significantly increased (25).

Reproductive/Developmental Effects:

"Concerning male reproductive ability, a few early case studies have reported impotency, which disappeared when lithium was withdrawn. It is not possible to draw any valid conclusions from these studies. A decrease in sperm viability from 70 to 55%, but no significant change in sperm count or motility was found in a study on 4 patients after 3 weeks of continuous therapy with lithium carbonate (26)" (5). "As for possible effects on reproduction in men undergoing lithium treatment, existing data are too scanty to allow a conclusion (5)" (3).

Although there has been concern with possible teratogenic effects from soluble lithium salts given therapeutically, the risk appears to be low. Li is reported to cross the placental barrier (27) and there is evidence of teratogenicity in studies with lab animals (20). Goodman and Gilman's text on pharmacology states that "epidemiological data suggest that the use of Li^+ in early pregnancy may be associated with a severalfold increase in the incidence of cardiovascular anomalies of the newborn (esp. Ebstein's malformation) (Goldberg and DiMascio, 1978; Kallen and Tandberg, 1983)" (28). More specifically, "an elevated incidence of a rare heart defect (Epstein's anomaly) in children born to mothers on lithium treatment during their first trimester was reported in the 1970's. The data originated in the Lithium Baby Register, a register containing retrospective, voluntarily submitted data (28, 29)" (3).

"Later studies have indicated that lithium therapy is associated with little or no risk to fetuses.... In 1992, Jacobson *et al*. published a prospective multicentre study of pregnancy outcome after lithium exposure during the first trimester (29). Rates of major congenital malformations did not differ significantly between the lithium and control groups and the authors' conclusion was that lithium was not a major teratogen" (5).

"In 1994, Cohen et al. published a re-evaluation of all controlled epidemiological studies, which had been published since the alarming reports from the Register of lithium babies (30). They found 4 large case-control studies dealing with Ebstein's anomaly and 2 cohort studies, one register-linked from Sweden and the Jacobson *et al*. study mentioned above. In the 4 case-control studies 208 children with Ebsteins's anomaly were found. None of the mothers of these children was exposed to lithium during pregnancy. In the Swedish study from 1983 none of 59 lithium-exposed infants had Ebstein's anomaly, but the risk ratio for congenital heart defects was 7.7 (95% confidence interval 1.5-41.2). Cohen *et al*. concluded that the teratogenic risk of first-trimester lithium exposure is lower than

previously suggested (30)" (5). "In summary, there is a very low risk, if any, of teratogenic effects of lithium therapy at present therapeutic doses." (5)

"The question of whether prenatal lithium exposure affects postnatal development has been examined in a few studies. In a follow-up study of 60 children without congenital malformations from the Lithium Baby Register, no elevation in incidence of physical or mental abnormality was observed when these babies were compared with unexposed siblings (31). In a study in which "milestones in development" (e.g. sitting, crawling, talking, walking) of 22 children of mother treated with lithium were compared with controls, no difference was noted (29)" (3).

Overall, evaluation of lithium effects in humans indicates minimal dermal absorption, some toxicity in sensitive patients, limited data on possible reproductive effects in male patients and likely low risk of teratogenic effects at therapeutic doses.

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Table 1. Selected parameters of male reproduction. Except for percent abnormal sperm, numbers are percent of respective control group.

study		Ref. 7		52372	61955	64718		66155
Material		Li carbonate		Mobilux EP-2	Mobilgr. HP	env gr [a]		env gr [a]
Route		oral		dermal	dermal	dermal		dermal
Duration		13 wk		13 wk	13 wk	10 wk		13 wk
Rat strain		Wistar		SD [c]	SD [c]	F344		SD [c]
Dose	500 [b]	800 [b]	1,100 [b]	2000	2000	500	2000	2000
body weight change	no change	no change	no change	no change	no change	98	90 [d]	no
epididimides wt	108	84 [d]	73 [d]	100	95	95 [d]	94 [d]	99
cauda eipdidymis wt					88	96	89 [d]	102
testis wt	101	81 [d]	63 [d]	94	102	98	97	94 [d]
prostate wt	95	78 [d]	62 [d]	106	87	NE	NE	111
# sperm/cauda	92	62 [d]	53 [d]	NE	92	90	82 [d]	90
% abnormal sperm / control	10.9/7.3 [d]	12.4/7.3 [d]	14.1/7.3 [d]	4.3/4.6	8.7/7.7	4.8/3.4	3.9/3.4	1.9/2.9 [d]
Histopathology								
Decr. spermatids & spermatozoa/g testis	no (morphol.)	yes (morphol.)	yes morphol.)	no	no (95%)	no (100%)	no (100%)	no (90%)
Degeneration in cauda epididymis	no	yes	yes	NE	NE	no	no	NE

a) env gr = envelope grease. b) mg/kg diet. c) SD = Sprague-Dawley strain. d) Significantly different from controls.
NE = Not evaluated

Appendix B. Matrix of Grease Thickeners Category Data

Please see the accompanying Excel file titled "Grease Thickeners CAD Appendix B Data Matrix".

CAS No.	3159-62-4	1592-23-0	64755-01-7	557-04-0	Mixture[14]	4499-91-6	4485-12-5	53422-16-5	7620-77-1	68783-36-8	64754-95-6	38900-29-7	68603-11-2	
Name:	Octadecanoic acid, 12-hydroxy-, calcium salt (2:1)	Octadecanoic acid calcium salt	Fatty acids, tallow, calcium salts	Supporting Chemical: Octadecanoic acid magnesium salt	Supporting Chemical	Docosanoic acid, lithium salt	Octadecanoic acid, lithium salt	Octadecanoic acid, 12-hydroxy-, methyl ester, lithium salt	Octadecanoic acid, 12-hydroxy-, monolithium salt	Fatty acids, C_{16-22}, lithium salts	Castor oil, hydrogenated, lithium salt	Nonanedioic acid, dilithium salt	Hydrocarbon waxes, petroleum, oxidized, Me esters, calcium salts	**Read Across Range to Untested Category Members**
Synonym:	Calcium 12-hydroxystearate	Calcium stearate		Magnesium stearate	Generic calcium complex grease	Lithium docosanoate	Lithium stearate	Lithium 12-hydroxystearate (same as 7620-77-1)	Lithium 12-hydroxystearate (same as 53422-16-5)			Dilithium azelate		
Endpoint	**PHYSICAL-CHEMICAL PROPERTIES**													
Melting Point (°C)	320	179				271	249		264			186		179 to 320
Boiling Point (°C)	730	661				624	578		611			484		484 to 730
Vapor Pressure (hPa)	1 x 10E-21	6 X 10E-14				5 x 10E-14	1 x 10E-12		2 x 10E-16			2 x 10E-9		<1 x 10E-5
Partition Coefficient	11.7	14.3				6.1	4.1		2.6			-3.6		-3.6 to 14.3
Water Solubility[1] (mg/L)	9.7 x 10E-9 (6.4 x 10E-7)	40 at 15 C				0.04 (2.0 x 10E-5)	4.1 (0.002)	222 (0.1)				(877)		<0.001 to 877
	ENVIRONMENTAL FATE													
Photodegradation, OH^- reaction $T_{1/2}$ (d)	0.2	0.2				0.4	0.5		0.4			1.4		0.2 to 1.4
Stability in Water	stable	stable				stable	stable		stable			stable		stable
Environ. Distribution	<0.1% air <0.1% water 98% soil 2% sediment	<0.1% air <0.1% water 98% soil 2% sediment				<0.1% air <0.1% water 98% soil 2% sediment	<0.1% air 8% water 90% soil 2% sediment		<0.1% air 73% water 26% soil 0.6% sediment			<0.1% air >99% water <0.1% soil <0.1% sediment		air <0.1% soil <0.1% to 98% water <0.1% to 99% sediment <0.1% to 2%
Biodegradation classification	inherently	readily					readily							
	ENVIRONMENTAL EFFECTS													
Acute Fish, mg/L	LC50 >12,500	no toxicity at limits of solubility				no toxicity at limits of solubility		LC50 = 123	LC50 > 2000 mg/L			no toxicity at limits of solubility		LC50 >2000 mg/L [2]
Exposure type	whole grease	Ecosar Model thickener				Ecosar Model thickener		Ecosar Model thickener	thickener, OWD			Ecosar Model thickener		
Acute Invertebrate, mg/L	EL50 >1000	no toxicity at limits of solubility				no toxicity at limits of solubility						no toxicity at limits of solubility		EL50 >1000 mg/L [3]
Exposure type	WAF, whole grease	Ecosar Model thickener				Ecosar Model thickener						Ecosar Model thickener		
Algae, mg/L	>1000 EL_r50 = >320 to	no toxicity at limits of solubility				no toxicity at limits of solubility						no toxicity at limits of solubility		EL_b50 = >100 to >1000 mg/L [3] EL_r50 = >320 to >1000 mg/L
Exposure type	WAF, whole grease	Ecosar Model thickener				Ecosar Model thickener						Ecosar Model thickener		
	HEALTH EFFECTS													
Acute (mg/kg, oral)				LD50 >10,000				LD50 >5,000	LD50 >5,000			LD50 >5,000		LD50 >5,000
Acute (mg/kg, dermal)								LD50 >3,000 [6]	LD50 >3,000 [6]			LD50 >3,000 [6]		LD50 >2,000
Repeated-Dose (mg/kg/day, oral)				NOEL = 5% of diet (~2,500)				NOAEL = 1,000	NOAEL = 1,000			NOAEL = 1,000		NOAEL = 1,000
Repeated-Dose (mg/kg/day, dermal)					NOAEL = 2,000[14]			NOAEL = 2,100[9] NOEL = 2,100 NOEL = 2,000[1] NOAEL <500[12]	NOAEL = 2,100[9] NOEL = 2,100 NOEL = 2,000[1] NOAEL <500[12]	NOEL=2,000[1] NOAEL <500[12]		NOAEL = 2,100[7][8] NOEL = 2,100		NOAEL = 2,000
Genotoxicity, *in vitro*				negative										negative
Genotoxicity, *in vivo*														negative
Reproductive toxicity (dermal, mg/kg)														NOAEL = 2,000[13]
Developmental toxicity (dermal, mg/kg)								NOEL = 2,000[11]	NOEL = 2,000[11]	NOEL = 2,000[11]				NOAEL = 2,000
Carcinogenicity (dermal, mg, mouse skin painting)								negative (50 mg/dose)	negative (50 mg/dose)					negative

Blank cells indicate no data. Value from the read across range will be used for these cells.

Footnotes:

[1] EPI SuiteTM (US EPA, 2000) provides two estimates for water solubility values. The first value presents the estimate using the relationship with Kow (Meylan and Howard, 1994) while the value in parentheses was calculated by the fragment constant method (Meylan and Howard, 1995).

[2] Whole grease tested as an oil-water dispersion (OWD).

[3] Invertebrate and algae test ranges based on water accommodated fraction testing of a whole grease.

[5] NOAEL is for a grease that contained 13.1% CAS No. 7620-77-1 and 2.6% CAS No. 38900-29-7.

NOAEL is for a grease that contained 8.8% CAS No. 7620-77-1 and 1.8% CAS No. 38900-29-7. Study was for 90 days in rats with sample R960002575.

NOAEL is for a grease that contained 8.8% CAS No. 7620-77-1 and 1.8% CAS No. 38900-29-7. Study was for 4 weeks in rats with sample R960002575.

NOAEL is for a grease that contained 8.8% CAS No. 7620-77-1 and 1.8% CAS No. 38900-29-7. Study was for 13 weeks in rats with sample R960002575.

Test was with PARL-3093-GR-81, a grease containing 7.5% lithium 12-hydroxystearate.

[1] NOEL is for a grease that contained 5.6% CAS No. 7620-77-1 and 0.7% CAS No. 68783-36-8. Study was for 13 weeks in rats with Mobilux EP-2.

[11] NOEL is for a grease that contained 8.1% CAS No. 7620-77-1 and 0.9% CAS No. 68783-36-8. Study was in female rats with "Generic Lithium Grease".

[12] Lowest dose tested was with a grease that contained 7.9% CAS No. 7620-77-1 and 0.9% CAS No. 68783-36-8. Study was in male F344 rats with "Borated-Lithium 12-Hydroxy Complex Generic Grease". Grease contained ~20% performance additives, over twice the amount typically used in greases.

CAS No.	3159-62-4	1592-23-0	64755-01-7	557-04-0	Mixture[14]	4499-91-6	4485-12-5	53422-16-5	7620-77-1	68783-36-8	64754-95-6	38900-29-7	68603-11-2	
Name:	Octadecanoic acid, 12-hydroxy-, calcium salt (2:1)	Octadecanoic acid calcium salt	Fatty acids, tallow, calcium salts	Supporting Chemical: Octadecanoic acid magnesium salt	Supporting Chemical	Docosanoic acid, lithium salt	Octadecanoic acid, lithium salt	Octadecanoic acid, 12-hydroxy-, methyl ester, lithium salt	Octadecanoic acid, 12-hydroxy-, monolithium salt	Fatty acids, C_{16-22}, lithium salts	Castor oil, hydrogenated, lithium salt	Nonanedioic acid, dilithium salt	Hydrocarbon waxes, petroleum, oxidized, Me esters, calcium salts	**Read Across Range to Untested Category Members**
Synonym:	Calcium 12-hydroxystearate	Calcium stearate		Magnesium stearate	Generic calcium complex grease	Lithium docosanoate	Lithium stearate	Lithium 12-hydroxystearate (same as 7620-77-1)	Lithium 12-hydroxystearate (same as 53422-16-5)			Dilithium azelate		

[13] Results from repeat dose studies and developmental studies with lithium complex greases with typical additive concentrations can be used to read across to all members of category.

[14] A 13-weeks dermal toxicity study was performed on a "generic calcium complex grease" that contained 3.5% CAS No. 62-54-4 (acetic acid, calcium salt), 3.5% CAS No. 64754-97-8 (fatty acids, coco, calcium salts), 1.4% CAS No. 69012-90-4 (fatty acids, C6-12, calcium salts), and 1.2% CAS No. 66071-81-6 (fatty acids, tallow, hydrogenated, calcium salts). The structures of the thickeners in this grease were judged to be similar enough to those in the Lubricating Grease Thickeners category that the data from this study can be applied by read-across.