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**HIGH PRODUCTION VOLUME (HPV)  
CHEMICAL CHALLENGE PROGRAM**

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**FINAL SUBMISSION**

**For**

**ZINC DIALKYLDITHIOPHOSPHATE CATEGORY**

**Prepared by**

**The American Chemistry Council  
Petroleum Additives Panel  
Health, Environmental, and Regulatory Task Group**

**April 19, 2005**

**LIST OF MEMBER COMPANIES IN THE  
HEALTH, ENVIRONMENTAL AND REGULATORY TASK GROUP**

The Health, Environmental, and Regulatory Task Group (HERTG) of the American Chemistry Council Petroleum Additives Panel includes the following member companies:

Afton Chemical (formerly Ethyl Corporation)

Chevron Oronite Company, LLC

Crompton Corporation

ExxonMobil Chemical Company

Ferro Corporation

Infineum

The Lubrizol Corporation

Rhein Chemie Corporation

SNPE

## EXECUTIVE SUMMARY

The American Chemistry Council Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG), and its member companies submitted a test plan on November 11, 2002, for review and public comment for the “*Zinc dialkyldithiophosphate*” (ZDDP) category of chemicals under the United States Environmental Protection Agency High Production Volume (HPV) Chemical Challenge Program. The test plan discussed available public and company data and identified additional testing to be conducted in order to characterize the Screening Information Data Set (SIDS) for human health, environmental fate and effects, and physicochemical property endpoints for the ZDDP category. The HERTG has now completed the proposed testing and submits this final report. This report includes data previously described in the Test Plan for these substances as well as newly acquired data in conjunction with scientific judgment and analysis. As discussed in this report, all SIDS endpoints now have reliable and adequate data.

### **Zinc dialkyldithiophosphate Category-**

Consistent with EPA guidance document on “Development of Chemical Categories in the HPV Challenge Program,” in which use of chemical categories is encouraged, the following twelve closely related chemicals constitute the ZDDP chemical category:

- Phosphorodithioic acid, mixed O,O-bis(1,3-dimethylbutyl and iso-propyl) esters, zinc salts – (CAS # 84605-29-8), referred to as “mixed isopropyl and 1,3-dimethylbutyl derivative”
- Phosphorodithioic acid, mixed O,O-bis(iso-butyl and pentyl) esters, zinc salts – (CAS # 68457-79-4), referred to as “mixed isobutyl and pentyl derivative”
- Phosphorodithioic acid, mixed O,O-bis(sec-butyl and 1,3-dimethylbutyl) esters, zinc salts – (CAS # 68784-31-6), referred to as “mixed sec-butyl and 1,3-dimethylbutyl derivative”
- Phosphorodithioic acid, mixed O,O-bis(sec-butyl and isooctyl) esters, zinc salts – (CAS # 113706-15-3), referred to as “mixed sec-butyl and isooctyl derivative”
- Phosphorodithioic acid, O-(2-ethylhexyl) O-isobutyl ester, zinc salt – (CAS # 26566-95-0), referred to as “mixed isobutyl and 2-ethylhexyl derivative”
- Phosphorodithioic acid, mixed O,O-bis(iso-butyl and isooctyl and pentyl) esters, zinc salts – (CAS # 68988-46-5), referred to as “mixed isobutyl, pentyl and isooctyl derivative”
- Phosphorodithioic acid, O,O-bis(1,3-dimethylbutyl) ester, zinc salt – (CAS # 2215-35-2), referred to as “1,3-dimethylbutyl derivative”
- Phosphorodithioic acid, O,O-bis(2-ethylhexyl) ester, zinc salt – (CAS# 4259-15-8), referred to as “2-ethylhexyl derivative”
- Phosphorodithioic acid, O,O-bis(isooctyl) ester, zinc salt – (CAS# 28629-66-5), referred to as “isooctyl derivative”
- Phosphorodithioic acid, O,O-diisodecyl ester, zinc salt – (CAS # 25103-54-2), referred to as “diisodecyl derivative”
- Phenol, dodecyl-, hydrogen phosphorodithioate, zinc salt – (CAS # 54261-67-5), referred to as “dodecylphenol derivative”

- Phenol, tetrapropenyl-, hydrogen phosphorodithioate, zinc salt – (CAS # 11059-65-7), referred to as, “tetrapropenylphenol derivative”.

It should be noted that additive manufacturers synthesize the *branched* alkaryl C<sub>12</sub> tetrapropenyl congener using propylene tetramer. Propylene tetramer is a distilled product manufactured from oligomerization of 1-propene under acid catalysis conditions. Commercial propylene tetramer is a range of C<sub>10</sub>-C<sub>15</sub> olefins with the C<sub>12</sub> propylene tetramer isomer being ~60 wt-% of the total. Although study reports may identify the dodecyl derivative as the test article, the tetrapropenyl derivative is and always has been the prepared chemical. Consequently, data submitted in this report for CAS # 54261-67-5 and 11059-65-7 should be considered interchangeable and referred to as the same chemical species.

***Structural Similarity.*** A key factor supporting the classification of these chemicals as a category is their structural similarity. Zinc dialkyldithiophosphates are used as multi-functional anti-wear and anti-oxidation inhibitor performance components in passenger motor oils, diesel engine oils and industrial oils such as hydraulic lubricants. All substances in this category consist of alkyl (C<sub>3</sub>-C<sub>12</sub>) or alkaryl (C<sub>12</sub> alkylphenol) substituted phosphorodithioic acid structures complexed with zinc. Zinc dialkyldithiophosphates are manufactured and distributed in commerce in highly refined lubricant base oil (IP 346 DMSO extractables < 3%). The oil is added during the neutralization of the dithiophosphate alkyl esters intermediate with zinc oxide. The oil acts as a solvent in the reaction, manages the viscosity and improves consistency of the final product. The zinc dialkyldithiophosphates are never isolated from base oil at any time during their life cycle. Hence, all testing for environmental fate, aquatic toxicity and health effects was performed on zinc dialkyldithiophosphates in highly refined lubricant base oil.

***Physicochemical Properties.*** The similarity of the physicochemical properties of these substances parallels their structural similarity. Zinc dialkyldithiophosphates are amber colored viscous liquids containing 10-15 wt-% highly refined lubricating base oil (representative lubricating base oil CAS registry numbers are 64742-54-7 and 64741-88-4). The physicochemical properties of zinc dialkyldithiophosphates largely reflect those of base oil. These materials have limited water solubility, low vapor pressure, high viscosity and partition preferentially into the hydrophobic (oil) phase.

***Fate and Transport Characteristics.*** The zinc dialkyldithiophosphates are formulated for use in oils and have low water solubility. Solubility testing was conducted on representative low and high molecular weight members of this category which shows an upper solubility limit of 0.0158 grams/liter (g/L) for the lower molecular weight member (CAS # 84605-29-8) and a solubility of 0.00018 g/L for the higher molecular weight member (CAS # 11059-65-7). Members of this category have been shown to be poorly biodegradable (<10% in 28 days). Adequate biodegradation data exist for two commercial oil-based samples of the zinc dialkyldithiophosphate which represents both the low and high molecular weight members of this category. Bridging was used to fill the remaining data gaps for the other ten substances. Available literature and historical information indicates that these materials are stable and are not susceptible to hydrolysis under normal conditions. These materials are known to be thermally labile at temperatures >120°C. This decomposition mechanism is key to how they provide anti-wear and anti-oxidation performance enhancements in engine oils. A search of the chemical

literature has shown no known photochemical pathways; therefore photodegradation is not expected to cause significant physical degradation of zinc dialkyldithiophosphates. To further confirm this, ultraviolet (UV) absorption data was collected on 2 representative members of the category to evaluate if direct photolysis is feasible. The UV absorption data indicates that these chemicals will not absorb light in the wavelengths (290 – 750 nm) where photolysis could occur which further shows that photolysis is not a significant fate mechanism for the ZDDPs.

***Aquatic and Mammalian Toxicity.*** The zinc dialkyldithiophosphates have a long history of use in lubricants and published and unpublished aquatic toxicity data is available for many of the members in this category. Additional aquatic toxicity testing was conducted which provides a robust hazard evaluation of the members of this category. Review of existing published and unpublished mammalian toxicity test data for commercial samples of zinc dialkyldithiophosphates in highly refined lubricant base oil suggest that the toxicity profiles of these materials are similar. Both aquatic and mammalian toxicity endpoints are further discussed below.

***Aquatic Toxicity:*** Existing inter and intra- company data on the ZDDPs indicated variability in aquatic toxicity profile for the ZDDPs which was attributed to use of old test methodology which was not optimized for the presence of mineral oil. Acute fish, invertebrate, and alga toxicity testing was therefore conducted on representative low and high molecular weight members for zinc dialkyldithiophosphates in highly refined lubricant base oil to adequately characterize the toxicity of this category. The study results show aquatic toxicity consistent with the molecular weight and water solubility.

The lower molecular weight member (CAS # 84605-29-8) with alkyl group  $<C_8$  was most toxic to fish with 96-hour median lethal concentration ( $LC_{50}$ ) of 1 - 10 mg/L. It was relatively less toxic to invertebrates and algae with median effects concentration ( $EC_{50}$ ) in 10 – 100 mg/L range. This data will be bridged to the other relatively lower molecular weight members ( $<C_8$  alkyl chains) as illustrated in the table. The  $C_8$  ethylhexyl derivative (CAS # 4259-15-8) which has a lower solubility and higher molecular weight compared to CAS # 84605-29-8 was moderately toxic to fish with  $LC_{50}$  values in the 10 – 100 mg/L range and relatively less toxic to invertebrates and algae with  $EC_{50}$  values of  $>100$  mg/L. The high molecular weight member with  $C_{12}$  alkyl groups (CAS # 11059-65-7) was relatively non-toxic to fish and algae ( $LC/EC_{50}$  values of  $>100$  and  $>1000$  mg/L respectively). It was moderately toxic to invertebrates with  $EC_{50}$  value of 75 mg/L. These data indicate that the ZDDPs with ( $<C_8$ ) alkyl groups are toxic to aquatic species. Comparatively, ZDDPs with alkyl groups of  $C_8$  and higher are relatively less toxic to aquatic species.

***Mammalian Toxicity - Acute:*** Data on acute mammalian toxicity of zinc dialkyldithiophosphates in highly refined lubricant base oil were reviewed, and the findings indicate a low concern for acute toxicity.

***Mammalian Toxicity - Mutagenicity:*** Data from bacterial reverse mutation assays, *in vitro* mutation assays in mammalian cells and *in vivo* chromosome aberration studies were reviewed. Findings indicate that commercial samples of zinc

dialkyldithiophosphates in highly refined lubricant base oil have a low potential for inducing genetic toxicity. Due to the similarity of structure and physicochemical properties, the existing data were bridged to the other members of the category where information is lacking. As a result, the category is adequately tested for mutagenicity.

***Mammalian Toxicology - Systemic Toxicity:*** Data from several repeated-dose toxicity studies using commercial samples of zinc dialkyldithiophosphates in highly refined lubricant base oil were reviewed. Repeated dermal exposure to experimental animals resulted in moderate-to-severe dermal irritation, behavioral distress, body weight loss and emaciation, reduction in hematological parameters and adverse effects on male reproductive organs. Oral administration caused significant gastric irritation and related gastrointestinal disturbances, signs of distress but with no evidence of adverse effects on male reproductive organs. Bridging was used to satisfy repeated dose data gaps for those zinc dialkyldithiophosphates in highly refined lubricant base oil where the carbon chain lengths/molecular weights are similar, yet lack subchronic toxicity information. No additional repeated-dose systemic toxicity testing was conducted.

***Mammalian Toxicity - Reproductive and Developmental Toxicity:*** Data from a study on the 2-ethylhexyl derivative in highly refined lubricant base oil indicates a low concern for reproduction/ developmental toxicity. Furthermore, an epidemiological study on workers exposed to oil-based zinc dialkyldithiophosphates (range C<sub>4</sub>-C<sub>8</sub>) in an additive manufacturing plant revealed no adverse effects on worker reproductive health. Review of the available information underscores the similarity of clinical and pathological findings in repeated-dose dermal toxicity studies with C<sub>4</sub>-C<sub>10</sub> zinc dialkyldithiophosphates, as well as the absence of reproduction and developmental toxicity and the lack of untoward findings in a human epidemiological investigation. In light of the irritant properties that zinc dialkyldithiophosphates in highly refined lubricant base oil have on skin and gastrointestinal mucosa, any additional repeated dose testing would cause unnecessary distress and suffering in experimental animals, and would add no additional insight into the hazard assessment of this category of substances. Therefore, the HERTG concludes that the existing information is adequate to characterize the reproduction/developmental toxicity profile of the entire zinc dialkyldithiophosphate category.

***Conclusion.*** Based upon the data reviewed for this test plan, the physicochemical, environmental toxicity and fate, and toxicological properties of the zinc dialkyldithiophosphate category members in highly refined lubricant base oils are similar and/ follow a regular, predictable pattern. This report presents a comprehensive evaluation of the physicochemical, environmental fate and toxicity and health hazard of the members of this category. The SIDS data needs for all category members are covered by collecting additional test data on representative members and by bridging data to make read-across assessments. This resourceful use of existing and new data has helped to minimize the use of animals for testing while effectively assessing the potential hazards of the category members.

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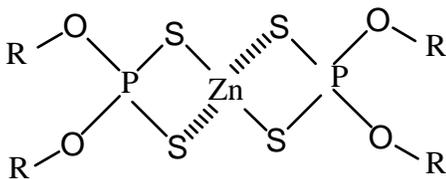
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## 1.0 INTRODUCTION

In March 1999, the American Chemistry Council (formerly the Chemical Manufacturers Association) Petroleum Additives Panel Health, Environmental, and Regulatory Task Group (HERTG), and its participating member companies committed to address data needs for certain chemicals listed under the Environmental Protection Agency (EPA) High Production Volume (HPV) Chemical Challenge Program. A Test Plan was submitted on November 11, 2002, which discussed publicly available and company data and identified additional testing to be conducted in order to characterize the Screening Information Data Set (SIDS) for human health, environmental fate and effects, and physicochemical property endpoints for the ZDDP category. The HERTG has now completed the proposed testing and submits this final report. This report includes data previously described in the Test Plan as well as newly acquired data in conjunction with scientific judgment and analysis on the 12 substances included in Table 1.

### 1.1 Identity and Chemistry of Zinc Dialkyldithiophosphates

Zinc dialkyldithiophosphates consist of a phosphorodithioic acid structure with alkyl or alkaryl ester substituent groups. The alkyl groups are saturated hydrocarbon chains that vary in length ( $C_3$ - $C_{10}$ ) and in the extent of branching. An idealized structure for the zinc dialkyldithiophosphate component is shown below.



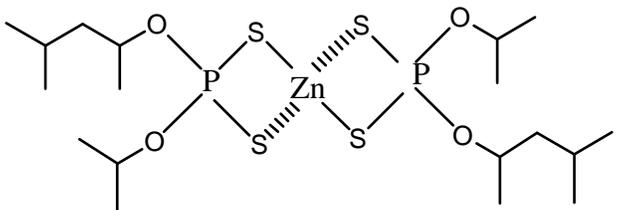
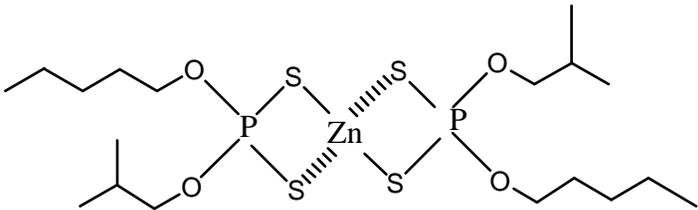
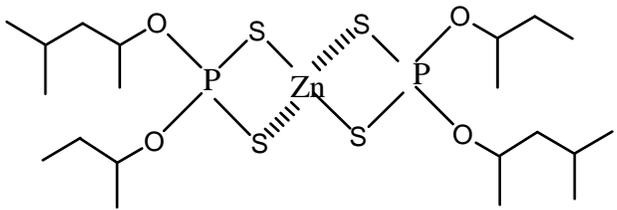
R =  $C_3$  –  $C_{10}$  (linear and/or branched) alkyl or  $C_{12}$  (branched) alkaryl

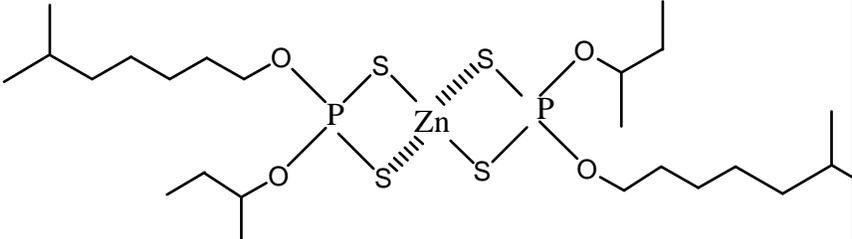
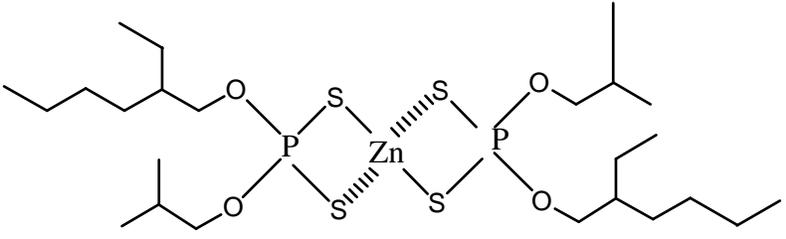
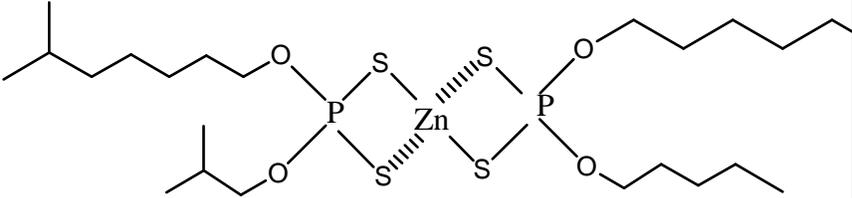
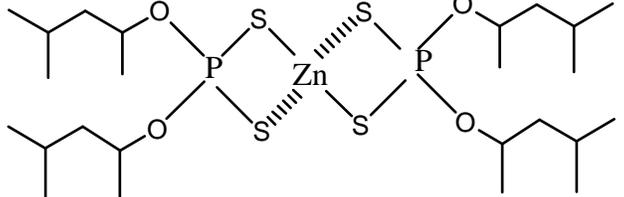
The chemical names and CAS numbers for the members of the zinc dialkyldithiophosphate category are presented in Table 1. These substances are prepared by reacting phosphorous pentasulfide ( $P_2S_5$ ) with one or more primary or secondary  $C_3$ - $C_{10}$  branched or linear alcohols to form the phosphorodithioic acid ester. The only exception is the alkaryl dithiophosphate where the alcohol moiety is tetrapropenylphenol. The dithiophosphoric acid ester is further diluted with 10-15 wt-% highly refined lubricating base oil (typical CAS #s 64742-54-7 and 64741-88-4) before it is neutralized with zinc oxide. The oil acts as a solvent in the neutralization reaction, manages the viscosity of the final product and improves consistency. The zinc complex that is formed upon neutralization is not a salt in the traditional sense, since the Zn-S bond is more coordinate covalent in character than ionic.

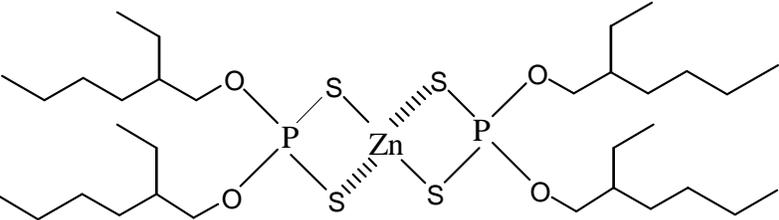
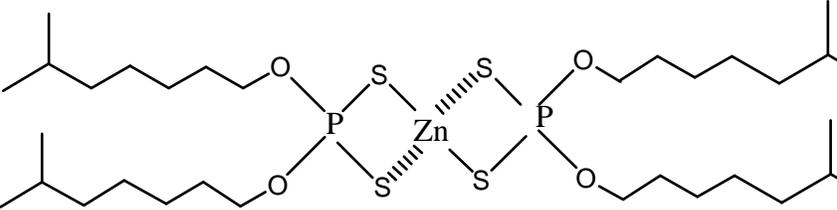
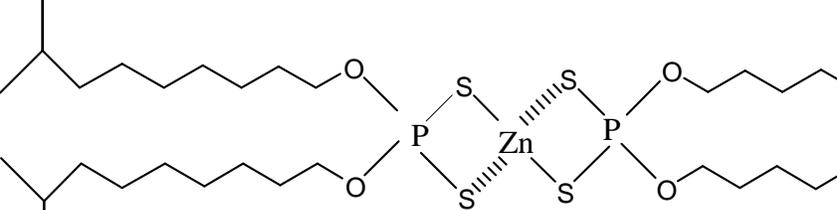
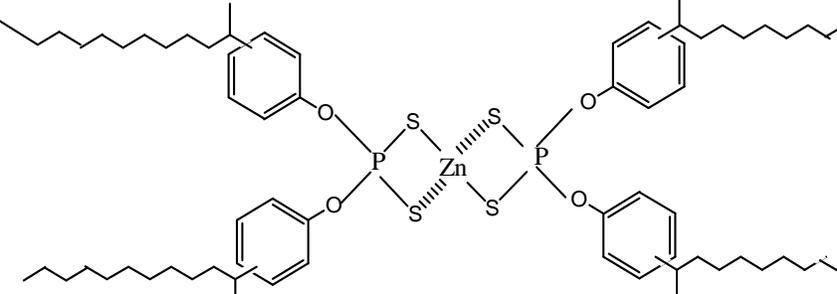
Although the TSCA Inventory Update Rule (IUR) reports list 1990 production volumes for “Phenol, dodecyl (*straight-chain*  $C_{12}$ )-, hydrogen phosphorodithioate, zinc salt” (CAS # 54261-67-5), it is typical for additive manufacturers to synthesize the *branched*  $C_{12}$  tetrapropenyl (CAS # 11059-65-7) congener using propylene tetramer. Propylene tetramer is a distilled product manufactured from oligomerization of 1-propene under acid catalysis conditions. Commercial

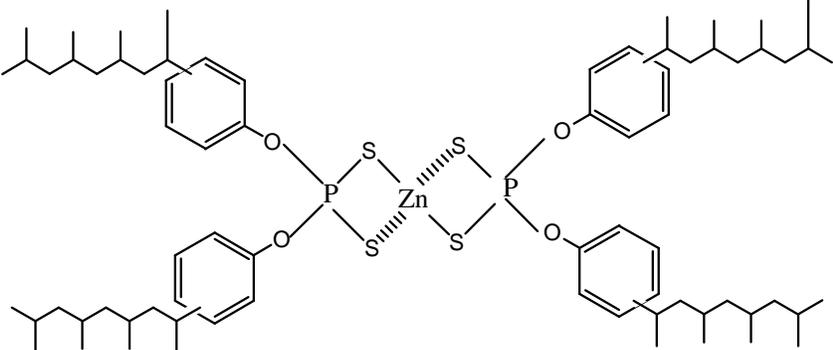
propylene tetramer is a range of C<sub>10</sub>-C<sub>15</sub> olefins with the C<sub>12</sub> propylene tetramer isomer being ~60 wt-% of the total. Although study reports may identify the dodecyl derivative as the test article, the tetrapropenyl derivative is and always has been the prepared chemical. Therefore, in this test plan the presented data for CAS registry numbers 54261-67-5 and 11059-65-7 should be considered interchangeable and referred to as the same chemical species.

**Table 1. Chemical Structures and nomenclature of Zinc Dialkyldithiophosphates**

CAS Number & Simplified Chemical Name	Chemical Structure and Nomenclature
<p>84605-29-8</p> <p>Mixed isopropyl and 1, 3-dimethylbutyl derivative</p>	 <p><u>Phosphorodithioic acid, mixed O,O-bis(1,3-dimethylbutyl and iso-propyl) esters, zinc salts</u></p>
<p>68457-79-4</p> <p>Mixed isobutyl and pentyl derivative</p>	 <p><u>Phosphorodithioic acid, mixed O,O-bis(iso-butyl and pentyl) esters, zinc salts</u></p>
<p>68784-31-6</p> <p>Mixed sec-butyl and 1,3-dimethylbutyl derivative</p>	 <p><u>Phosphorodithioic acid, mixed O,O-bis(sec-butyl and 1,3-dimethylbutyl) esters, zinc salts</u></p>

CAS Number & Simplified Chemical Name	Chemical Structure and Nomenclature
<p>113706-15-3</p> <p>Mixed sec-butyl and 1,3-isooctyl derivative</p>	 <p><u>Phosphorodithioic acid, mixed O,O-bis(sec-butyl and isooctyl) esters, zinc salts</u></p>
<p>26566-95-0</p> <p>Mixed isobutyl and 2-ethylhexyl derivative</p>	 <p><u>Phosphorodithioic acid, O-(2-ethylhexyl) O-isobutyl ester, zinc salt</u></p>
<p>68988-46-5</p> <p>Mixed isobutyl, pentyl and isooctyl derivative</p>	 <p><u>Phosphorodithioic acid, mixed O,O-bis(iso-butyl and isooctyl and pentyl) esters, zinc salts</u></p>
<p>2215-35-2</p> <p>1,3-dimethylbutyl derivative</p>	 <p><u>Phosphorodithioic acid, O,O-bis(1,3-dimethylbutyl) ester, zinc salt</u></p>

CAS Number & Simplified Chemical Name	Chemical Structure and Nomenclature
<p>4259-15-8</p> <p>2-ethylhexyl derivative</p>	 <p><u>Phosphorodithioic acid, O,O-bis(2-ethylhexyl) ester, zinc salt</u></p>
<p>28629-66-5</p> <p>Isooctyl derivative</p>	 <p><u>Phosphorodithioic acid, O,O-bis(isooctyl) ester, zinc salt</u></p>
<p>25103-54-2</p> <p>Diisodecyl derivative</p>	 <p><u>Phosphorodithioic acid, O,O-diisodecyl ester, zinc salt</u></p>
<p>54261-67-5</p> <p>Dodecyl derivative</p>	 <p><u>Phenol, dodecyl-, hydrogen phosphorodithioate, zinc salt</u></p>

CAS Number & Simplified Chemical Name	Chemical Structure and Nomenclature
11059-65-7 Tetrapropenylphenol derivative	 <p data-bbox="630 779 1365 810"><u>Phenol, tetrapropenyl-, hydrogen phosphorodithioate, zinc salt</u></p>

## 1.2 Physical-Chemical Properties

The physical-chemical properties of the members of the zinc dialkyldithiophosphate category are presented in Table 2. Zinc dialkyldithiophosphate produced for use as lubricating petroleum additive are manufactured and distributed in 10-15 wt-% highly refined lubricating base oils. The highly refined lubricating base oil used in the manufacture of the zinc dialkyldithiophosphates cannot be removed without altering the structural and physicochemical character of the zinc dialkyldithiophosphate molecules. Therefore, many of the physicochemical properties presented are qualitative estimates.

**Table 2. Physicochemical Properties of Zinc Dialkyldithiophosphates**

CAS Number	Average Molecular Weight (g/mol)	Alcohol Carbon Number Range	Specific Gravity <sup>1</sup> (g/ml)	Viscosity <sup>2</sup> (cSt)	Melting Point °C	Boiling Point °C	Vapor Pressure <sup>3</sup> (Pa)	Water Solubility (g/L)
84605-29-8	578.1	C12-C24	1.145	11.0 @ 100°C	NA	Decomp. @ 120°C	1.7 x 10 <sup>-4</sup>	0.0158
68457-79-4	578.1	C16-C20	1.120	115.0 @ 40°C	NA	Decomp. @ 120°C	1.7 x 10 <sup>-4</sup>	Bridging <sup>4</sup>
68784-31-6	606.2	C16-C24	1.080	8.0 @ 100°C	NA	Decomp. @ 120°C	1.7 x 10 <sup>-4</sup>	Bridging <sup>4</sup>
113706-15-3	662.3	C16-C32	No data	No data	NA	Decomp. @ 120°C	1.7 x 10 <sup>-4</sup>	Bridging <sup>4</sup>
26566-95-0	648.3	C16-C32	1.135	12.5 @ 100°C	NA	Decomp. @ 120°C	1.7 x 10 <sup>-4</sup>	Bridging <sup>4</sup>
68988-46-5	634.2	C16-C32	No data	No data	NA	Decomp. @ 120°C	1.7 x 10 <sup>-4</sup>	Bridging <sup>4</sup>

CAS Number	Average Molecular Weight (g/mol)	Alcohol Carbon Number Range	Specific Gravity <sup>1</sup> (g/ml)	Viscosity <sup>2</sup> (cSt)	Melting Point °C	Boiling Point °C	Vapor Pressure <sup>3</sup> (Pa)	Water Solubility (g/L)
2215-35-2	662.3	C24	No data	No data	NA	Decomp. @ 120°C	1.7 x 10 <sup>-4</sup>	Bridging <sup>4</sup>
4259-15-8	774.5	C32	1.099	15.0 @ 100°C	NA	Decomp. @ 120°C	1.7 x 10 <sup>-4</sup>	0.00109
28629-66-5	774.5	C32	No data	No data	NA	Decomp. @ 120°C	1.7 x 10 <sup>-4</sup>	Bridging <sup>5</sup>
25103-54-2	886.7	C40	1.015	18.0 @ 100°C	NA	Decomp. @ 120°C	1.7 x 10 <sup>-4</sup>	Bridging <sup>5</sup>
54261-67-5	1303.3	C72	0.998	30.0 @ 100°C	NA	Decomp. @ 120°C	1.7 x 10 <sup>-4</sup>	Bridging <sup>5</sup>
11059-65-7	1303.3	C72	No data	No data	NA	Decomp. @ 120°C	1.7 x 10 <sup>-4</sup>	0.00018

<sup>1</sup>ASTM D1298-99, Standard Test Method for Density, Relative Density (Specific Gravity), or API Gravity of Crude Petroleum and Liquid Petroleum Products by Hydrometer Method

<sup>2</sup>ASTM D 445-97, Standard Test Method for Kinematic Viscosity of Transparent and Opaque Liquids (the Calculation of Dynamic Viscosity)

<sup>3</sup> “De-oiled” zinc dialkyldithiophosphates are solid, data in table is for lubricating base oil.

<sup>4</sup>Bridging data from CAS # 84605-29-8

<sup>5</sup>Bridging data from CAS # 4259-15-8

NA – Not applicable for liquids at ambient temperature

### 1.2.1 Alkyl Chain Length and Molecular Weight

As discussed above, the members of the zinc dialkyldithiophosphate category contain alkyl chain lengths that range from C<sub>3</sub>-C<sub>10</sub>, or tetrapropenylphenol (range = C<sub>10</sub>-C<sub>15</sub>, C<sub>12</sub> enriched). It is common for zinc dialkyldithiophosphates to contain mixed alkyl esters (e.g., C<sub>4</sub>, C<sub>5</sub>), although derivatives with single chain lengths (e.g., C<sub>8</sub>) are included in the category. Alkyl groups can be linear or branched. Two members of the category contain alkylphenol ester side-chains. As a result of this diversity in alkyl side chain length, the molecular weight distribution for the members of the category is broad, 578 to 1303 g/mol. Due to the predominant influence of carbon chain length on molecular weight, the members of the category are arrayed in all tables in order of increasing carbon chain length.

### 1.2.2 Melting Point and Boiling Point

Zinc dialkyldithiophosphates, as manufactured and distributed in commerce in highly refined lubricating base oil, are high viscosity liquids at ambient temperature. However, at elevated temperatures (> 120°C), zinc dialkyldithiophosphates become unstable and degrade.

### 1.2.3 Vapor Pressure

Due to the technical difficulty of isolating intact zinc dialkyldithiophosphates from the highly refined lubricating base oil, vapor pressure has not been measured on the pure chemical. De-oiled zinc dialkyldithiophosphates are solid so the vapor pressure of ZDDPs is therefore equivalent to that of the base oil. The vapor pressure of lubricating base oils is expected to be

negligible. Vapor pressure was experimentally measured for solvent-dewaxed heavy paraffinic distillate base oil and was found to be  $1.7 \times 10^{-4} \text{ Pa}^1$ .

#### 1.2.4 Water Solubility and Octanol-Water Partition Coefficients

The zinc dialkyldithiophosphates are formulated for use in oils and have very low water solubility. Unpublished company data for a commercial zinc dialkyldithiophosphate with an alkyl group less than  $C_8$  indicates a water solubility of  $1.6 \text{ mg/L}^2$ . Historically, the zinc dialkyldithiophosphates are generally regarded to be poorly soluble in water. In order to adequately define the solubility range of the members of this category, water solubility testing was conducted on both the low and high molecular weight members of this category as described below:

- the mixed isopropyl and 1,3-dimethylbutyl derivative (CAS# 84605-29-8) in highly refined lubricating base oil, which contains the lowest molecular weight substance and the shortest alkyl side chain ( $C_3$ ) in the category. A solubility of  $0.0158 \text{ g/L}$  was determined for this substance. This data will be bridged to other members with alkyl side chains of  $<C_8$  in the category.
- the 2-ethylhexyl derivative (CAS # 4259-15-8) in highly refined lubricating base oil which represents a higher molecular weight member ( $C_8$  alkyl side chain) of this category. A solubility of  $0.00109 \text{ g/L}$  was determined for this substance. This data will be bridged to the  $C_8$  and  $C_{10}$  alkyl side chain derivatives.
- the tetrapropenylphenol derivative (CAS # 11059-65-7) in highly refined lubricating base oil which represents a higher molecular weight alkaryl member ( $C_{12}$  alkyl side chain) of this category. A solubility of  $0.00018 \text{ g/L}$  was determined for this substance. This data applies to both the dodecyl and tetrapropenyl derivatives.

Unpublished company data on a commercial zinc dialkyldithiophosphate with a carbon chain length of less than eight yielded an octanol/water partition coefficient ( $\log K_{ow}$ ) value of  $2.49^1$ . Longer chain materials are likely to have higher octanol/water partition coefficients. The  $\log K_{ow}$  is a measure of the lipophilicity of a substance and is used as a surrogate indicator of the potential of a chemical substance to bioaccumulate in aquatic organisms. While  $\log K_{ow}$  is a good predictor of bioaccumulation for nonpolar organic compounds, the mechanisms for uptake and depuration of metals and metal compounds are very complex and variable. For metal compounds, the  $\log K_{ow}$  data are not indicative of the bioaccumulation potential. In view of the above, no further testing for  $\log K_{ow}$  was conducted.

### 1.3 Category Justification

An analysis of the available data on these chemicals supports the designation of the zinc dialkyldithiophosphates as a “chemical category” as provided in the EPA guidance document entitled, “Development of Chemical Categories in the HPV Challenge Program”. This document provides the basis for that determination, indicates the findings and data gaps of the data review process, and provides results on additional studies that were proposed on the ZDDP Test Plan to

<sup>1</sup> HPV Chemical Challenge Program - Test Plan for Lubricating Oil Basestocks Category submitted to the US EPA by the Petroleum HPV Testing Group. March 24, 2003.

<sup>2</sup> Information Review: Zinc Dialkyl Dithiophosphates. CRCS, Inc. Prepared under EPA Contract No. 68-01-6650 for TSCA Interagency Testing Committee. October 31, 1984.

satisfy parts of the required test battery for endpoints without data that would be considered adequate under the HPV program.

EPA guidance on the HPV Chemical Challenge Program indicates that the primary purpose of the program is to encourage “the chemical industry . . . to voluntarily compile a Screening Information Data Set (SIDS) on all chemicals on the US HPV list.” (EPA, “Development of Chemical Categories in the HPV Challenge Program,” p. 1) At the same time, EPA recognizes that the “large number of chemicals to be tested [about 2800 HPV chemicals] makes it important to reduce the number of tests to be conducted, *where this is scientifically justifiable.*” (*Id.*, p. 1) [emphasis added] The next part of the guidance explains where this would be scientifically justifiable:

One approach is to test closely related chemicals as a group, or category, rather than test them as individual chemicals. In the category approach, *not every chemical needs to be tested for every SIDS endpoint.* However, *the test data finally compiled* for the category must prove adequate to support a screening level hazard-assessment of the category and its members. That is, the *final data set* must allow one to estimate the hazard for the untested endpoints, *ideally* by interpolation between and among the category members. In certain cases, where toxicity is low and no upward trend is expected, extrapolation to the higher category members may be acceptable. (*Id.*, p. 1) [emphasis added].

EPA guidance goes on to state, “The use of categories is encouraged in the Challenge Program and will have a number of benefits.” (*Id.*, p. 1) Among the benefits identified in the guidance for the use of categories are “a reduction in testing will result in fewer animals used to test a category of chemicals as opposed to doing each test on each individual chemical,” and “there will be . . . economic savings since less testing may be needed for chemicals considered as a category.” (*Id.*, p. 1) That guidance also states that categories “accomplish the goal of the Challenge Program – to obtain screening level hazard information – through the strategic application of testing to the category.” (*Id.*, p. 2)

A similarly stated intent “to reduce the number of tests to be conducted, *where this is scientifically justifiable*” was articulated by the Agency in its draft guidance document titled, “The Use of Structure Activity Relationships (SAR) in the High Production Volume Chemicals Challenge Program.” [emphasis added].

The EPA “Chemical Categories” guidance sets forth a definition of what constitutes a “chemical category, for the purposes of the Challenge Program”. Specifically, that definition states that a chemical category under 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.*” (*Op. Cit.*, p. 2) [emphasis added].

According to the guidance, what is important is that the “structural similarities [among members of the group] *may* create a predictable pattern *in any* or all of the following parameters: physicochemical properties, environmental fate and effects, and human health effects.” (*Id.*, p. 2) [emphasis added]. Thus, it is not necessary for the chemicals in a category to be similar in all respects. Nor must there be conclusive proof that the chemicals in the postulated category will behave identically across all relevant parameters. All that is required for an acceptable category

under the HPV Challenge Program is that there is a *likelihood* of similarity of physicochemical and toxicological properties or a *likelihood* that the chemicals will in some pertinent respect follow a regular pattern as a result of their structural similarity.

In identifying the zinc dialkyldithiophosphate category, the six-step process set out in the EPA guidance on category development was followed. As the information below indicates, the zinc dialkyldithiophosphate chemicals clearly satisfy the standards established in that guidance for use of a chemical category:

Step 1: group structurally similar chemicals into a putative category

Step 2: gather relevant published and unpublished literature for each member of the category

Step 3: evaluate the compiled data for adequacy in accordance with the EPA guidance documentation

Step 4: construct matrices of SIDS endpoints versus category members arranged so as to indicate the structural progression of the category (in this case, by increasing molecular weight)

Step 5: evaluate the data to determine whether there is a correlation between category members for each SIDS endpoint

Step 6: make available to EPA, and to the public for review, this test plan including the foregoing category definition and rationale and the following data assessment with the proposed testing scheme for the zinc dialkyldithiophosphates.

All the above elements have been satisfied and the data presented in this report shows that reliable and adequate data are available for all SIDS endpoints.

## 2.0 GENERAL INFORMATION ON EXPOSURE

The ZDDP's are manufactured primarily from three basic raw materials, alkyl or alkaryl alcohols, phosphorus pentasulfide and zinc oxide. The alcohols which are liquids are typically handled in bulk and range widely in viscosity and flash point whereas the other raw materials are solids and require different handling and storage requirements. Phosphorus pentasulfide is a flammable solid and reacts with moisture to produce H<sub>2</sub>S gas, it is therefore stored in a moisture free inert atmosphere. The manufacture of ZDDPs involves a two-step process where the intermediate dithiophosphoric acid is prepared first and subsequently neutralized with zinc oxide. Generally, the acid intermediates are typically neutralized on the same site where they are manufactured. ZDDPs are typically manufactured and processed in contained systems and stored in closed vessels connected to gas removal and treatment systems designed to prevent exposure to H<sub>2</sub>S. Automated processes (closed piping/pumping systems) are designed to minimize exposure to product and any off-gas. At ZDDP manufacturing facilities, proper personal protective equipment, H<sub>2</sub>S detectors and other containment measures are employed to minimize worker exposure. Due to their limited water solubility and blending in mineral oil, ZDDPs

partition preferentially into the sludge in the wastewater treatment plant and emissions into the water are minimal.

## 2.1 Use Patterns

Zinc dialkyldithiophosphates are used to formulate finished lubricating oils including all types of automotive and diesel engine crankcase, industrial oils and hydraulic fluids. They are used as anti-wear inhibitors to reduce wear in engines and hydraulic equipment parts, and also act as antioxidants. Zinc dialkyldithiophosphates are generally sold to finished oil blenders in additive packages, where the concentration ranges from 1 to 20 wt-%. These additive packages are then blended into finished oils where the typical concentration of zinc dialkyldithiophosphate ranges from 0.1 to 10 wt-% in the finished oil.

Zinc dialkyldithiophosphates are manufactured and blended into additive packages at plants owned by members of the HERTG. Finished lubricants are blended at facilities owned by HERTG customers. Additive packages are shipped to customers in ships, iso-containers, railroad tank cars, tank trucks or in 55-gallon steel drums. The additive packages are stored in bulk storage tanks at the customer blending sites. Finished oils are blended by pumping the lubricating oil blend stocks and the additive package from their storage tanks through computer controlled valves that meter the precise delivery of the components into a blending tank. After blending, the finished lubricant products are sold in bulk and shipped in tank trucks to large industrial users, such as manufacturing facilities and facilities that service truck fleets and passenger motor vehicles. Finished lubricants are also packaged into 55-gallon drums, 5-gallon pails and one-gallon and one-quart containers for sale to smaller industrial users. Sales of lubricants in one-gallon and one-quart containers to consumers at service stations or retail specialty stores also occur.

Based on these uses, the potentially exposed populations include (1) workers involved in the manufacture of zinc dialkyldithiophosphates, blending them into additive packages, and blending the additive packages into finished lubricants; (2) quality assurance workers who sample and analyze these products to ensure that they meet specifications; (3) workers involved in the transfer and transport of zinc dialkyldithiophosphates, additive packages or finished lubricants that contain them; (4) mechanics who may come into contact with both fresh and used lubricants while working on engines or equipment; (5) gasoline station attendants and consumers who may periodically add lubricating oil to automotive crankcases; and (6) consumers who may change their own automotive engine oil. The most likely route of exposure for these substances is skin and eye contact. Manufacturing, quality assurance and transportation workers will likely have access to engineering controls and wear protective clothing to minimize exposure. Mechanics wear protective clothing but often work without gloves or eye protection. Gasoline station attendants and consumers often work without gloves or other protective equipment. The most likely source of environmental exposure is accidental spills at manufacturing sites and during transport.

### 3.0 ENVIRONMENTAL FATE DATA

Available environmental fate data for the ZDDPs are summarized in Table 3A and briefly discussed in the following sections.

**Table 3A: Environmental Fate Data**

CAS Number	Biodegradation	Hydrolysis	Photolysis
84605-29-8	5.9%	No testing needed	UV absorption maxima of 1.0957 AU @ 202 nm
68457-79-4	Bridging <sup>1</sup>	No testing needed	No testing needed
68784-31-6	Bridging <sup>1</sup>	No testing needed	No testing needed
113706-15-3	Bridging <sup>1</sup>	No testing needed	No testing needed
26566-95-0	Bridging <sup>1</sup>	No testing needed	No testing needed
68988-46-5	Bridging <sup>1</sup>	No testing needed	No testing needed
2215-35-2	Bridging <sup>1</sup>	No testing needed	No testing needed
4259-15-8	Bridging <sup>1</sup>	No testing needed	No testing needed
28629-66-5	Bridging <sup>1</sup>	No testing needed	No testing needed
25103-54-2	Bridging <sup>1</sup>	No testing needed	No testing needed
54261-67-5	5.9% 4.2%	No testing needed	No testing needed
11059-65-7	Bridging <sup>2</sup>	No testing needed	No testing needed

<sup>1</sup>Bridge data from CAS # 84605-29-8.

<sup>2</sup>Bridge data from CAS # 54261-67-5.

#### 3.1 Biodegradability

The Modified Sturm Test (OECD Guideline 301B, *CO<sub>2</sub> Evolution Test*) was used to evaluate the biodegradability of the mixed isopropyl and 1,3-dimethylbutyl derivative (CAS # 84605-29-8) in highly refined lubricating base oil. After the 28-day test, the extent of biodegradation was 5.9% based on carbon dioxide evolution.

The biodegradability of the dodecylphenol derivative (CAS # 54261-67-5) in highly refined lubricating base oil was evaluated using the Modified Sturm Test (OECD Guideline 301B, *CO<sub>2</sub> Evolution Test*) and the *Manometric Respirometry Test* (OECD Guideline 301F). After 28 days in each test, the extent of biodegradation was 5.9% based on carbon dioxide evolution and 4.2% based on theoretical oxygen demand, respectively.

Adequate biodegradation data exist for two of twelve substances in the zinc dialkyldithiophosphate category representing both the lower (CAS# 84605-29-8) and higher molecular weight (CAS# 54261-67-5) members. The results indicate that these substances are poorly biodegraded irrespective of molecular weight. Therefore, these data are bridged to all intermediate molecular weight category members, thereby characterizing the biodegradability of the entire category.

### 3.2 Hydrolysis

Zinc dialkyldithiophosphates are formulated in oil and are hydrolytically stable under normal conditions. This is documented in various studies that have been conducted to study the hydrolytic stability and hydrolysis pathways for the zinc dialkyldithiophosphates. The studies were carried out by heating the zinc dialkyldithiophosphates at 85°C to achieve hydrolysis<sup>3</sup>. These substances have little, if any, potential for hydrolysis under environmentally relevant conditions.

Since available literature information and historical use of these substances in petroleum additive formulations indicates that these materials are not subject to hydrolytic degradative mechanisms under normal conditions, no hydrolysis testing was conducted.

### 3.3 Photodegradation

Photodegradation can occur as a result of direct and indirect mechanisms. A prerequisite for direct photodegradation is the ability of one or more bonds within a chemical to absorb ultraviolet (UV)/visible light in the 290 to 750 nm range. Light wavelengths longer than 750 nm do not contain sufficient energy to break chemical bonds and wavelengths below 290 nm are shielded from the earth by the stratospheric ozone layer. In order to evaluate if direct photolysis is a relevant fate mechanism for ZDDPs, the UV light absorption spectra was taken for the mixed isopropyl and 1,3-dimethylbutyl derivative (CAS # 84605-29-8). The absorbance maxima for CAS # 84605-29-8 was 1.0957 AU at 202 nm which indicates that direct photolysis is not a relevant pathway for members of this category. No photodegradation studies were therefore conducted. Indirect photodegradation as a result of hydroxyl radical interaction is not a significant pathway as these substances are not volatile and will not exist in a vapor phase.

### 3.4 Fugacity Modeling

Fugacity-based multimedia fate modeling compares the relative distribution of chemicals among environmental compartments. A widely used model for this approach is the EQC model<sup>4</sup>. There are multiple levels of the EQC model. The EQC Level I model predicts the equilibrium distribution of a fixed quantity of chemical, in a closed environment at equilibrium. The medium receiving the emission is unimportant because the chemical is assumed to become instantaneously distributed to an equilibrium condition. The Level III model assumes that a chemical is continuously discharged at a constant rate and achieves a steady state condition in which input and output rates are equal. Equilibrium between media is not assumed and each medium is at a different fugacity. Level III modeling is appropriate where the amount of potential discharge into a media is known and reaction half-life estimates are available for air, water, soil, sediment etc.

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<sup>3</sup> Burn A.J. et al. Analysis of the Hydrolytic Stability of Zinc(II) O,O-Dialkyl Dithiophosphates as a Function of the Nature of the Alkyl Groups by <sup>31</sup>P NMR Spectroscopy. *J. Chem. Soc. Perkin Trans. 2*, 1992.

<sup>4</sup> Mackay, D., A. Di Guardo, S. Paterson, and C. E. Cowan. 1996. Evaluating the Environmental Fate of a Variety of Types of Chemicals Using the EQC Model. *Environ.*

Since inputs for Level III are not known, the Level I model was utilized to evaluate the distribution of the ZDDP in the environment. As summarized in table 3B, fugacity modeling was conducted on representative ZDDPs which cover both the low and high molecular weight members. The results show that the ZDDPs will partition preferentially into the soil and sediment compartment. This is consistent with the physical-chemical properties (low solubility and low vapor pressure) and the fact that ZDDPs are manufactured and processed in petroleum base oils.

**Table 3B: Environmental Distribution of Representative ZDDPs Modeled by EQC Level I**

CAS #	Air (%)	Water (%)	Soil (%)	Sed. (%)	Sus.Sed. (%)	%Fish	Fugacity ( $\mu$ Pa)
84605-29-8	7E-04	0.576	97.2	2.16	0.067	5.5E-03	3.0E-05
4259-15-8	0.021	1.8E-4	97.7	2.172	0.068	5.5E-03	1.2E-03
11059-65-7	0.029	1.1E-11	97.7	2.172	0.068	5.5E-03	1.03E-03

## 4.0 AQUATIC TOXICITY DATA

The zinc dialkyldithiophosphates have a long history of use in lubricants and published and unpublished aquatic toxicity data is available for many of the members in this category. Existing inter and intra- company data on the ZDDPs indicated variability in aquatic toxicity profile for the ZDDPs which was attributed to use of old test methodology which was not optimized for the inherent low water solubility of these materials and dispersal in mineral oil. Test methodology used in older studies appears to be a significant factor in the variability seen in the data. As discussed earlier, the zinc dialkyldithiophosphates are sparingly soluble in water and direct addition of these chemicals to the exposure solution is not feasible. In some of the studies, the test material was added directly above its water solubility resulting in the presence of undissolved test material including oil droplets and surface sheen in the exposure solution. It is apparent in some of the studies that physical fouling (coating of the fish gills and trapping of smaller invertebrates) contributed to the toxicity and erratic dose response was seen. For example, higher mortality/effects were seen in the lower test concentration compared to the higher test concentration. In other studies, even though water accommodated fraction (WAF) was used for testing, proper techniques for separating the soluble components in the water phase were not used resulting in oil sheen in the exposure solutions. It also appears that a very vigorous stirring technique was used in some studies that resulted in an inseparable emulsion of oil in water, which significantly contributed to adverse effects in test organisms. In some of the older studies, use of a co-solvent and dissolution of the test material above its water solubility limit may have contributed to toxicity that would not be associated with the test material under normal, environmentally relevant exposure conditions.

### 4.1 Acute Toxicity Test Results

Acute fish, invertebrate and alga toxicity testing was conducted on representative low and high molecular weight members for zinc dialkyldithiophosphates in highly refined lubricant base oil to adequately characterize the toxicity of this category. As summarized in the table 4.0, the

study results show aquatic toxicity consistent with the molecular weight and water solubility of the chemicals.

**Table 4.0 - Summary of Ecotoxicity Data**

CAS Number	Chemical Name	MW (g/mol)	Water Solubility (g/L)	Toxicity Data		
				Fish LC50 (mg/L)	Invertebrates EL50 (mg/L)	Algae EL50 (mg/L)
84605-29-8	Mixed isopropyl and 1,3-dimethylbutyl derivative	578.1	0.0158	4.5	23	21
68457-79-4	Mixed isobutyl and pentyl derivative	578.1	Bridging <sup>1</sup>	Bridging <sup>1</sup>	Bridging <sup>1</sup>	Bridging <sup>1</sup>
68784-31-6	Mixed sec-butyl and 1,3-dimethylbutyl derivative	606.2	Bridging <sup>1</sup>	Bridging <sup>1</sup>	Bridging <sup>1</sup>	Bridging <sup>1</sup>
113706-15-3	Mixed sec-butyl and isooctyl derivative	662.3	Bridging <sup>1</sup>	Bridging <sup>1</sup>	Bridging <sup>1</sup>	Bridging <sup>1</sup>
26566-95-0	Mixed isobutyl and 2-ethylhexyl derivative	648.3	Bridging <sup>1</sup>	Bridging <sup>1</sup>	Bridging <sup>1</sup>	Bridging <sup>1</sup>
68988-46-5	Mixed isobutyl, pentyl and isooctyl derivative	634.2	Bridging <sup>1</sup>	Bridging <sup>1</sup>	Bridging <sup>1</sup>	Bridging <sup>1</sup>
2215-35-2	1,3-dimethylbutyl derivative	662.3	Bridging <sup>1</sup>	Bridging <sup>1</sup>	Bridging <sup>1</sup>	Bridging <sup>1</sup>
4259-15-8	2-ethylhexyl derivative	774.5	0.00109	47	>100	260
28629-66-5	Isooctyl derivative	774.5	Bridging <sup>2</sup>	Bridging <sup>2</sup>	Bridging <sup>2</sup>	Bridging <sup>2</sup>
25103-54-2	Diisodecyl derivative	886.7	Bridging <sup>2</sup>	Bridging <sup>2</sup>	Bridging <sup>2</sup>	Bridging <sup>2</sup>
54261-67-5	Dodecylphenol derivative	1303.3	Bridging <sup>2</sup>	Bridging <sup>2</sup>	Bridging <sup>2</sup>	Bridging <sup>2</sup>
11059-65-7	Tetrapropenylphenol derivative	1303.3	0.00018	>100	75	>1000

<sup>1</sup>Indicates bridging data from CAS # 84605-29-8.

<sup>2</sup>Indicates bridging data from CAS # 4259-15-8

The acute toxicity studies were conducted using water accommodated fraction which consists of a water-soluble extract of test material, but it can also include a stable micro-emulsion or contain small amounts of suspended matter. The lower molecular weight member (CAS # 84605-29-8) with alkyl group <C<sub>8</sub> was acutely toxic to fish with 96-hour median lethal concentration (LC<sub>50</sub>) of 4.5 mg/L. It was relatively less toxic to invertebrates and algae with median effects concentration (EC<sub>50</sub>) in 10 – 100 mg/L range. This data will be bridged to the other relatively lower molecular weight members (<C<sub>8</sub> alkyl chains) as illustrated in table 4.

The C<sub>8</sub> ethylhexyl derivative (CAS # 4259-15-8), which has a lower solubility and higher molecular weight compared to CAS # 84605-29-8, was moderately toxic to fish with LC50 values in the 10 – 100 mg/L range and relatively less toxic to invertebrates and algae with EC50 values of >100 mg/L.

The high molecular weight member with C<sub>12</sub> alkyl groups (CAS # 11059-65-7) was relatively non-toxic to fish and algae with LC/EC<sub>50</sub> values of >100 and >1000 mg/L respectively. It was

moderately toxic to invertebrates with EC<sub>50</sub> value of 75 mg/L. These data indicate that the ZDDPs with (<C<sub>8</sub>) alkyl groups are toxic to aquatic species. Comparatively, ZDDPs with alkyl groups of C<sub>8</sub> and higher are relatively less toxic to aquatic species.

## 5.0 MAMMALIAN TOXICITY DATA

### 5.1 Acute Mammalian Toxicity

Acute toxicity data for commercial samples of zinc dialkyldithiophosphates in highly refined lubricating base oil is summarized in Table 5A. Ten members of the category have been tested by either the oral or dermal route of administration and demonstrate a low order of acute toxicity.

**Table 5A - Acute Toxicity Data**

CAS Number	ACUTE ORAL TOXICITY <sup>1</sup>	ACUTE DERMAL TOXICITY <sup>1</sup>
84605-29-8	LD <sub>50</sub> > 2.0 g/kg (rat)	LD <sub>50</sub> > 2.0 g/kg (rabbit)
68457-79-4	LD <sub>50</sub> > 2.0 g/kg (rat)	LD <sub>50</sub> > 20.0 g/kg (rabbit)
68784-31-6	LD <sub>50</sub> > 2.0 g/kg (rat)	LD <sub>50</sub> > 5.0 g/kg (rabbit)
113706-15-3	Bridging	No testing needed <sup>2</sup>
26566-95-0	Bridging	No testing needed <sup>2</sup>
68988-46-5	Bridging	LD <sub>50</sub> > 2.0 g/kg (rabbit)
2215-35-2	LD <sub>50</sub> > 2.0 g/kg (rat)	No testing needed <sup>2</sup>
4259-15-8	LD <sub>50</sub> > 2.0 g/kg (rat)	LD <sub>50</sub> > 5.0 g/kg (rabbit)
28629-66-5	Bridging	No testing needed <sup>2</sup>
25103-54-2	Bridging	LD <sub>50</sub> > 8.0 g/kg (rabbit)
54261-67-5	Bridging	No testing needed <sup>2</sup>
11059-65-7	Bridging	No testing needed <sup>2</sup>

<sup>1</sup>Toxicity endpoints are expressed as median lethal dose (LD<sub>50</sub>) for acute oral and dermal toxicity.

<sup>2</sup> Acute toxicity end point satisfied by acute oral toxicity results

#### 5.1.1 Acute Oral Toxicity

Commercial oil-based samples of eight of the twelve substances in the zinc dialkyldithiophosphate category have been tested for acute oral toxicity. The acute oral LD<sub>50</sub> for these studies in rats ranged from 2000-3500 mg/kg. Clinical signs observed following treatment included diarrhea, lethargy, reduced food consumption and staining about the nose and eye. Ptosis, piloerection, ataxia and salivation were occasionally observed. The incidence and severity of these symptoms were proportional to the dose. In many cases the effects were found to be reversible during observation week 2. Necropsy findings were few in number. Lung congestion, gastrointestinal irritation and a reduction in body fat were observed in some animals. Significant necropsy findings in survivors were uncommon. Overall, the acute oral LD<sub>50</sub> for these substances ranged from 2000 –3500 mg/kg indicative of a relatively low order of lethal toxicity.

### 5.1.2 Acute Dermal Toxicity

Commercial oil-based samples for nine of the twelve substances in the zinc dialkyldithiophosphate category have been tested for acute dermal toxicity. The acute dermal LD<sub>50</sub> for these studies in rabbits were greater than 2000 mg/kg (limit tests). No treatment-related mortality was observed at doses ranging from 2000-8000 mg/kg. Dermal application of the test materials to abraded skin for 24 hours typically produced moderate-to-severe erythema and edema, which in some cases persisted through the 14-day observation period. Clinical signs included varying degrees of reduced food consumption, weight loss, diarrhea, lethargy, ataxia, ptosis, motor incoordination and/or loss of righting reflex. There were no remarkable gross necropsy observations. Overall, the acute dermal LD<sub>50</sub> for these substances were greater than 2000 mg/kg indicative of a relatively low order of lethal toxicity.

### 5.1.3 Data Assessment for Acute Mammalian Toxicity

In total, seventeen adequate acute toxicity studies have been conducted with commercial samples of the zinc dialkyldithiophosphate in highly refined lubricating base oil. These studies involved two species of laboratory animals (rats or rabbits); two routes of exposure (oral and dermal); and evaluated the toxicity of ten of the twelve members of the category. The substances tested ranged from those with the shortest (C<sub>3</sub>-C<sub>6</sub>) alkyl side chains (mixed isobutyl and pentyl derivative; and mixed isopropyl and 1,3-dimethylbutyl derivative) to the derivative containing diisodecyl (C<sub>10</sub>) esters. The data consistently demonstrate a low order of acute toxicity regardless of the length of the alkyl side chain. Bridging will be used to fill the acute toxicity data gaps for the remaining four category members.

- Acute toxicity data for the mixed isopropyl and 1,3-dimethylbutyl derivative, mixed isobutyl and pentyl derivative, mixed sec-butyl and 1,3-dimethylbutyl derivative, mixed isobutyl and 2-ethylhexyl derivative will be bridged to the 1) mixed sec-butyl and isooctyl derivative and 2) mixed isobutyl, pentyl, and isooctyl derivatives. This bridging is justifiable based on the increasing length of the alkyl side chains in this range of the category (from mixed C<sub>3</sub>-C<sub>6</sub> to mixed C<sub>4</sub>-C<sub>8</sub>) and the lack of an increasing trend in acute toxicity across the entire category.
- Acute toxicity data for the 1,3-dimethylbutyl derivative, 2-ethylhexyl derivative, isooctyl derivative will be bridged to the diisodecyl derivative. This bridging is also justifiable based on the increasing length of the alkyl side chains in this range of the category (from C<sub>6</sub> to C<sub>8</sub>) and the lack of an increasing trend in acute toxicity across the entire category.
- Acute toxicity data for the tetrapropenyl derivative will be bridged to dodecylphenol derivative since both members of the category are characterized by C<sub>12</sub> alkyl side chains on an aromatic ring.

By bridging these data to the four untested substances, the acute toxicity of the category has been evaluated with respect to all acute toxicity endpoints, and the dataset is complete.

## 5.2 Genotoxicity

A summary of the mutagenicity information for commercial samples of zinc dialkyldithiophosphates in highly refined lubricating base oil category is presented in Table 5B. *In vitro* bacterial gene mutation assays, *in vitro* mammalian gene mutation assays, or *in vivo* chromosomal aberration assays have been conducted for seven of the twelve members of the category. Frequencies of reverse mutations in bacteria were not significantly changed after exposure to the zinc dialkyldithiophosphates. *In vitro* mutation studies in mammalian cells indicate that the zinc dialkyldithiophosphates do not consistently display mutagenic activity in the absence of metabolic activation, however, upon biotransformation, these materials showed mutagenic activity. The findings in bacterial and mammalian cells did not vary in proportion to the alkyl chain length or any other physicochemical parameter.

**Table 5B. Genotoxicity Data**

CAS Number	GENE MUTATION ASSAY	CHROMOSOMAL ABERRATION ASSAY
84605-29-8	<ul style="list-style-type: none"> <li>Bacterial Reverse Mutation Assay – Not mutagenic</li> <li><i>In vitro</i> Point Mutation Assay in Mouse Embryo Cells- Not mutagenic in the absence of metabolic activation</li> <li><i>In vitro</i> Point Mutation Assay in Mouse Embryo Cells- Mutagenic in the presence of metabolic activation</li> </ul>	Mouse Micronucleus Assay – Not clastogenic
68457-79-4	<ul style="list-style-type: none"> <li><i>In vitro</i> Point Mutation Assay in Mouse Embryo Cells- Mutagenic in the absence of metabolic activation</li> <li><i>In vitro</i> Mouse Lymphoma Mutagenicity Assay – Not mutagenic in the absence of metabolic activation</li> </ul>	Bridging
68784-31-6	<ul style="list-style-type: none"> <li>Bacterial Reverse Mutation Assay – Not mutagenic</li> </ul>	Mouse Micronucleus Assay – Not clastogenic
113706-15-3	<ul style="list-style-type: none"> <li><i>In vitro</i> Point Mutation Assay in Mouse Embryo Cells- Mutagenic in the absence of metabolic activation (only at extremely high toxic doses)</li> <li><i>In vitro</i> Mouse Lymphoma Mutagenicity Assay – Not mutagenic in the absence of metabolic activation</li> <li><i>In vitro</i> Mouse Lymphoma Mutagenicity Assay – Mutagenic in the presence of metabolic activation</li> </ul>	Bridging

CAS Number	GENE MUTATION ASSAY	CHROMOSOMAL ABERRATION ASSAY
26566-95-0	<ul style="list-style-type: none"> <li>Bacterial Reverse Mutation Assay – Not mutagenic</li> <li><i>In vitro</i> Point Mutation Assay in Mouse Embryo Cells- Mutagenic in the absence of metabolic activation</li> <li><i>In vitro</i> Point Mutation Assay in Mouse Embryo Cells- Mutagenic in the presence of metabolic activation</li> <li><i>In vitro</i> Mouse Lymphoma Mutagenicity Assay – Not mutagenic in the absence of metabolic activation</li> <li><i>In vitro</i> Mouse Lymphoma Mutagenicity Assay – Equivocal mutagenic response in the presence of metabolic activation</li> </ul>	Mouse Micronucleus Assay – Not clastogenic
68988-46-5	<ul style="list-style-type: none"> <li><i>In vitro</i> Point Mutation Assay in Mouse Embryo Cells- Not mutagenic in the absence of metabolic activation</li> <li><i>In vitro</i> Mouse Lymphoma Mutagenicity Assay – Not mutagenic in the absence of metabolic activation</li> <li><i>In vitro</i> Mouse Lymphoma Mutagenicity Assay – Mutagenic in the presence of metabolic activation</li> </ul>	Bridging
2215-35-2	Bridging	Bridging
4259-15-8	<ul style="list-style-type: none"> <li>Bacterial Reverse Mutation Assay – Not mutagenic</li> <li><i>In vitro</i> Point Mutation Assay in Mouse Embryo Cells- Not mutagenic in the absence of metabolic activation</li> <li><i>In vitro</i> Point Mutation Assay in Mouse Embryo Cells- Mutagenic in the presence of metabolic activation</li> <li><i>In vitro</i> Mouse Lymphoma Mutagenicity Assay – Not mutagenic in the absence of metabolic activation</li> <li><i>In vitro</i> Mouse Lymphoma Mutagenicity Assay – Equivocal mutagenic response in the presence of metabolic activation</li> </ul>	Mouse Micronucleus Assay – Not clastogenic
28629-66-5	Bridging	Bridging
25103-54-2	Bridging	Bridging
54261-67-5	Bridging	Bridging
11059-65-7	Bridging	Bridging

### 5.2.1 Bacterial Gene Mutation Assay

Commercial oil-based samples of four of the twelve substances in this category have been tested in a bacterial reverse mutation test (OECD Guidelines 471 and/or 472). All tested substances were negative for mutagenic activity, with and without metabolic activation.

*Mammalian Gene Mutation Assay in Non-transformed Cells:* Commercial oil-based samples of six of the twelve substances in this category were tested in an *in vitro* point mutation assay in mouse embryo cells (Schechtman and Kouri, 1977<sup>5</sup>). The results of the studies performed in the absence of hepatic microsome activation were inconsistent, but in general indicating that zinc dialkyldithiophosphates have mutagenic potential (3 studies negative, 3 studies positive in the absence of metabolic activation). However, the weight of evidence (2 studies positive, 1 study negative) indicates that metabolic activation of zinc dialkyldithiophosphates by induced hepatic microsomal enzymes results in a significant increase in the mutagenic potential of this class of chemical substances.

*Mammalian Gene Mutation Assay in Transformed Cells:* Commercial oil-based samples of five of the twelve substances in this category were tested in an *in vitro* mouse lymphoma cell mutagenicity assay (Guideline 476, *In vitro Mammalian Cell Gene Mutation Test*). The results of these studies indicate that, in the absence of hepatic microsome activation, zinc dialkyldithiophosphates are not mutagenic. However, the weight of evidence indicates that metabolic activation of zinc dialkyldithiophosphates by induced hepatic microsomal enzymes results in a significant increase in the mutagenic potential of this class of chemical substances.

### 5.2.2 In vivo Chromosomal Aberration Assays

Commercial oil-based samples of four of the twelve substances in this category were tested in an *in vivo* chromosomal aberration assay (OECD Guideline 474, *Mammalian Erythrocyte Micronucleus Test*). All test substances were negative for clastogenicity.

### 5.2.3 Data Assessment for Mutagenicity

Commercial samples for seven of the twelve zinc dialkyldithiophosphates in highly refined lubricating base oil category have been evaluated for genotoxic potential in tests for gene mutations and chromosomal aberrations. The assays included point mutations in bacteria, two types of cultured mammalian cells and *in vivo* chromosomal aberrations in mice. The findings from the bacterial reverse mutation assay and *in vivo* mouse micronucleus tests were negative for mutagenic potential for all of the tested materials with alkyl side chains that ranged from mixed C<sub>3</sub>-C<sub>6</sub> to C<sub>8</sub>. The results from the *in vitro* mammalian cell gene mutation test gave inconsistent results for four members of the category with alkyl side chains that ranged from mixed C<sub>4</sub>-C<sub>8</sub>. The results from the *in vitro* BALB/3T3 point mutation (ouabain locus) and cell transformation assays indicate that zinc dialkyldithiophosphates may have genotoxic potential. Despite the high cytotoxicity, variability and mixed test results, the overall data indicated that microsome-

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<sup>5</sup> Schechtman LM and Kouri RE. (1977) Control of benzo(a)pyrene-induced mammalian cell cytotoxicity, mutagenicity and transformation by exogenous enzyme fractions. In: Progress in Genetic Toxicology, D. Scott, B.A. Bridges and F.J. Sobels, eds. Elsevier/North-Holland Biomedical Press, New York, pp. 307-316.

activated zinc dialkyldithiophosphates were mutagenic. However, zinc ion has been shown to cause cytotoxicity and mutagenicity in similar cultured mammalian cell systems (Amaker et al., 1979<sup>6</sup>). Therefore, as a follow-up to this report, two materials containing zinc (zinc chloride and zinc oleate) were tested in the BALB 3T3 point mutation and cell transformation assays. These two zinc salts were found to be mutagenic in these systems. Further, no mutagenic activity was attributed to a calcium analog of a zinc dialkyldithiophosphate that had previously shown activity in these *in vitro* mammalian cell assays. These findings point to zinc ion as the causative subcomponent in the *in vitro* mammalian cell studies. However, genotoxicity studies conducted in a variety of test systems have failed to provide unequivocal evidence for mutagenicity of zinc (ATSDR, 1992<sup>7</sup>). Furthermore, the US Food and Drug Administration (1982<sup>8</sup>) concluded that zinc ion is not carcinogenic. Dermal carcinogenicity tests conducted in mice revealed that new motor oils containing between 1% and 3% zinc dialkyldithiophosphate were found to be non-carcinogenic (American Petroleum Institute). In summary, the weight of evidence supports the conclusion that zinc dialkyldithiophosphates have a low potential genotoxicity, and that these substances do not present a significant risk for mutagenicity or carcinogenicity in humans. Bridging will be used to fill the genetic toxicity data gaps for the remaining twelve substances.

- Bacterial gene mutation and *in vivo* chromosomal aberration data for commercial samples of the mixed isopropyl and 1,3-dimethylbutyl derivative in highly refined lubricating base oil will be bridged to mixed isobutyl and pentyl derivative.
- Bacterial gene mutation and *in vivo* chromosomal aberration data for commercial oil-based samples of the mixed sec-butyl and 1,3-dimethylbutyl derivative and the mixed isobutyl and 2-ethylhexyl derivative will be bridged to 1) mixed sec-butyl and isooctyl derivative and 2) mixed isobutyl, pentyl, and isooctyl derivative.
- Bacterial gene mutation and *in vivo* chromosomal aberration data for a commercial sample of the 2-ethylhexyl derivative in highly refined lubricating base oil will be bridged the remaining members of the category with longest alkyl chain lengths- 1) isooctyl derivative; 2) diisodecyl derivative; and 3) dodecyl phenol derivative and 4) tetrapropenyl phenol derivative.

By bridging these data to those substances which lack bacterial gene mutation and *in vivo* chromosomal aberration data, the genetic toxicity of the category has been evaluated with respect to all mutagenic and clastogenic endpoints.

### 5.3 Repeated Dose Toxicity

A summary of the results from the repeated-dose studies for commercial samples of zinc dialkyldithiophosphates in highly refined lubricating base oil is presented in Table 5C. Repeated-dose toxicity tests have been performed on six members of the zinc dialkyldithiophosphate category by two routes of administration and in two species of laboratory animals.

<sup>6</sup> Amacher et al. Mammalian Cell Mutagenesis: Maturation of Test Systems. Banbury Report 2, 277-293, 1977

<sup>7</sup> Toxicological Profile for Zinc. Prepared by Syracuse Research Corporation and Clement International Corporation for the United States Department of Health and Human Service, Public Health Service, Agency for Toxic Substances and Disease Registry, October 1992

<sup>8</sup> 47 FR 47441 October 1982, corrected 48 FR 3381 January 1983

Table 5C: Repeated-Dose Toxicity

CAS Number	REPEATED-DOSE TOXICITY	REPRODUCTIVE/ DEVELOPMENTAL TOXICITY
84605-29-8	Bridging	Bridging
68457-79-4	Bridging	Bridging
68784-31-6	Bridging	Bridging
113706-15-3	<p><u>25%</u></p> <ul style="list-style-type: none"> <li>• Four deaths or moribund sacrifices</li> <li>• Body weight loss</li> <li>• Erythema, edema, atonia, desquamation, eschar formation and exfoliation</li> <li>• Reduction in hemoglobin, hematocrit and erythrocyte counts</li> <li>• Platelet count elevation</li> <li>• Increased serum cholesterol</li> <li>• Decreased serum albumin</li> <li>• Reduction in plasma, erythrocyte and brain cholinesterase levels</li> <li>• Testes and epididymal weight reduction</li> <li>• Adrenal and kidney weight elevation</li> <li>• Morphological abnormalities in the seminiferous tubules characterized by aspermatogenesis, diffuse tubular hypoplasia and reduced mitotic activity</li> </ul> <p><u>5%</u></p> <ul style="list-style-type: none"> <li>• One death</li> <li>• Body weight loss</li> <li>• Erythema, edema, atonia, desquamation, fissuring, eschar formation and exfoliation</li> <li>• Increased serum cholesterol</li> <li>• Reduction in plasma, erythrocyte and brain cholinesterase levels</li> <li>• Kidney weight elevation</li> </ul> <p><u>Vehicle control</u></p> <ul style="list-style-type: none"> <li>• Dermal irritation (lesser degree than in treatment groups)</li> </ul>	Bridging
26566-95-0	<p>21-day repeated-dose dermal study in rabbits NOAEL not established (adverse effects at all doses)</p> <p><u>860 mg/kg/day</u></p> <ul style="list-style-type: none"> <li>• One death (male)</li> <li>• Decedent clinical signs included severe dermal reactions, loss of body weight, anorexia, adipsia, diarrhea, lethargy</li> <li>• Survivor clinical signs included moderate-</li> </ul>	Bridging

CAS Number	REPEATED-DOSE TOXICITY	REPRODUCTIVE/ DEVELOPMENTAL TOXICITY
	<p>severe dermal reactions, weight loss, nasal and ocular discharge, gastrointestinal distress, occasional lethargy and ptosis, suppression of sperm formation (aspermia)</p> <p style="text-align: center;"><u>430 mg/kg/day</u></p> <ul style="list-style-type: none"> <li>• Two deaths (male and female)</li> <li>• Decedent clinical signs included severe dermal reactions, loss of body weight, anorexia, adipsia, diarrhea, lethargy</li> <li>• Survivor clinical signs included moderate-severe dermal reactions, weight loss, nasal and ocular discharge, gastrointestinal distress, occasional lethargy and ptosis, suppression of sperm formation</li> </ul> <p style="text-align: center;"><u>210 mg/kg/day</u></p> <ul style="list-style-type: none"> <li>• No deaths</li> <li>• Survivor clinical signs included moderate-severe dermal reactions, weight loss, nasal and ocular discharge, gastrointestinal distress, occasional lethargy and ptosis</li> </ul> <p style="text-align: center;"><u>Control</u></p> <ul style="list-style-type: none"> <li>• Various signs of distress including nasal and ocular discharge, gastrointestinal distress, occasional lethargy and ptosis,</li> <li>• One animal with severely reduced spermatogenesis</li> </ul>	
68988-46-5	<p>21-day repeated-dose dermal study in rabbits NOAEL not established (adverse effects at all doses)</p> <p><u>100%</u></p> <ul style="list-style-type: none"> <li>• All animals in group died (18)</li> <li>• Moderate-severe dermal reactions in proportion to dose</li> <li>• Hyperirritability, diarrhea, decrease motor activity, ataxia, loss of righting reflex, ocular discharge</li> <li>• Severe body weight losses</li> <li>• Reductions in hematology parameters</li> </ul> <p><u>25%</u></p> <ul style="list-style-type: none"> <li>• 15/18 animals died</li> <li>• Moderate-severe dermal reactions in proportion to dose</li> <li>• Hyperirritability, diarrhea, decrease motor activity, ataxia, loss of righting reflex, ocular discharge</li> <li>• Severe body weight losses</li> </ul>	Bridging

CAS Number	REPEATED-DOSE TOXICITY	REPRODUCTIVE/ DEVELOPMENTAL TOXICITY
68988-46-5 (continued)	<ul style="list-style-type: none"> <li>• Reductions in hematology parameters</li> </ul> <p><u>5%</u></p> <ul style="list-style-type: none"> <li>• One death</li> <li>• Moderate-severe dermal reactions in proportion to dose</li> <li>• Hyperirritability, diarrhea, decrease motor activity, ataxia, loss of righting reflex, ocular discharge</li> <li>• Body weight losses</li> <li>• Reductions in hematology parameters</li> </ul> <p><u>3%</u></p> <ul style="list-style-type: none"> <li>• No deaths</li> <li>• Moderate-severe dermal reactions in proportion to dose</li> <li>• Hyperirritability, diarrhea, decrease motor activity, ataxia, loss of righting reflex, ocular discharge</li> <li>• Body weight losses</li> <li>• Reductions in hematology parameters</li> </ul> <p><u>Vehicle control</u></p> <ul style="list-style-type: none"> <li>• One death</li> <li>• Moderate-severe dermal reactions in proportion to dose</li> <li>• Body weight losses</li> </ul> <p><u>Sham control</u></p> <p>No deaths</p>	
2215-35-2	<p>21-day repeated-dose dermal study in rabbits NOAEL not established (adverse effects at all doses)</p> <p><u>1.6 ml/kg/day</u></p> <ul style="list-style-type: none"> <li>• Three animals sacrificed moribund</li> <li>• Severe erythema and edema at the site of application</li> <li>• Body weight loss</li> <li>• White blood cell count reductions</li> <li>• Increased serum triglyceride, uric acid, SGOT, LDH and GGT</li> <li>• Reductions in testes, liver, heart and ovary weights</li> <li>• Decreased spermatogenesis</li> </ul> <p><u>0.8 ml/kg/day</u></p> <ul style="list-style-type: none"> <li>• One death</li> <li>• Severe erythema and edema at the site of application</li> <li>• Progressive weight loss over the course of study</li> </ul>	Bridging



CAS Number	REPEATED-DOSE TOXICITY	REPRODUCTIVE/ DEVELOPMENTAL TOXICITY
28629-66-5	28-day repeated-dose dermal study in rabbits NOEAL not established (adverse effects at all doses) <u>25%</u> <ul style="list-style-type: none"> <li>• 4/20 animals died</li> <li>• Moderate-to-severe dermal reactions (proportional to dose)</li> <li>• Body weight losses</li> <li>•</li> <li>• Alterations in hematology and clinical chemistry parameters</li> <li>• Testicular hypotrophy and aspermatogenesis</li> </ul> <u>5%</u> <ul style="list-style-type: none"> <li>• No deaths</li> <li>• Moderate-to-severe dermal reactions (proportional to dose)</li> <li>• Body weight losses</li> <li>• Alterations in hematology and clinical chemistry parameters</li> <li>• Testicular hypotrophy and aspermatogenesis</li> </ul> <u>Vehicle control</u> No deaths	<ul style="list-style-type: none"> <li>• One incident of total litter loss</li> <li>• Increased pup mortality during post-natal period <u>100 mg/kg/day</u></li> <li>• Two incidents of total litter loss</li> <li>• Increased pup mortality during post-natal period <u>30 mg/kg/day</u></li> <li>• No significant adverse effects Bridging</li> </ul>
25103-54-2	Bridging	Bridging
54261-67-5	Bridging	Bridging
11059-65-7	Bridging	Bridging

### 5.3.1 Systemic Toxicity

Six of the twelve substances in the zinc dialkyldithiophosphate category have been tested for subchronic toxicity. Commercial oil-based samples of 1,3-dimethyl butyl derivative (CAS # 2215-35-2), mixed sec-butyl and isooctyl derivative (CAS # 113706-15-3), mixed isobutyl and 2-ethylhexyl derivative (CAS # 26566-95-0), mixed isobutyl, pentyl and isooctyl derivative (CAS # 68988-46-5), and 2-ethylhexyl derivative (CAS # 4295-15-8) were each evaluated in

separate 21-28 day repeated-dose dermal toxicity studies in rabbits (methodologies consistent with OECD Guideline 410, *Repeated Dose Dermal Toxicity: 21/28 Day*). The concentration of test articles applied to the skin in these studies ranged from 3-100%. Deaths were common at the higher concentrations but the incidence decreased in proportion to a reduction in dose. The clinical signs throughout the treated groups included ano-genital staining, nasal and ocular bloody discharge, lacrimation, diarrhea, lethargy, anorexia, adipsia, loss of body weight, emaciation, and behavioral distress. Moderate-to-severe dermatitis (erythema, edema, atonia, desquamation, fissuring, eschar formation and exfoliation) at the site of topical application was observed in all the treated animals and to a lesser degree in control animals exposed to vehicle. The incidence and severity was proportional to the concentration and duration of exposure to the test material. Significant reductions in hemoglobin, hematocrit and erythrocyte counts were noted in test material treated groups. In addition, several clinical chemistry parameters (alkaline phosphatase, BUN, bilirubin, albumin and cholesterol) were affected by treatment with the test material. Testes and epididymal weights were markedly reduced in the high dose groups and to a lesser degree after lower doses. Adrenal and kidney weights were elevated in some higher dose groups. Microscopic examination of the testes revealed aspermatogenesis, diffuse tubular hypoplasia and reduced mitotic activity. In no dermal study was a NOAEL for systemic toxicity established.

The 2-ethylhexyl derivative (CAS # 4295-15-8) in highly refined lubricating base oil was evaluated in a 28-day repeated dose oral toxicity study in rats (OECD Guideline 407, *Repeated Dose 28-Day Oral Toxicity Study in Rodents*). The test material was administered to rats by oral gavage at 10, 50, 125, 250 and 500 mg/kg/day for 28 consecutive days. Three animals of each sex died at the high dose. One female died at 125 mg/kg/day. Clinically significant findings related to the test material included rales, salivation, and reductions in body weight gain. Necropsy findings included thickened mucosa of the non-glandular mucosa of the stomach in the mid and high dose animals accompanied by microscopic evidence of submucosal edema and suppurative inflammation. Adrenal weights were increased in the high dose animals without evidence of histopathologic abnormalities. The NOAEL was established at 10 mg/kg/day.

### **5.3.2 Reproductive and Developmental Toxicity**

The 2-ethylhexyl derivative (CAS # 4295-15-8) in highly refined lubricating base oil was tested for reproduction and developmental toxicity (OECD Guideline 421 *Reproduction/Developmental Screening Test*). The test material was administered to rats by oral gavage at doses of 30, 100 and 200 mg/kg/day. Male and female rats in each dose group received daily treatment for 14 days prior to, and during, the mating period. In addition, the females were treated during gestation and through day 4 of lactation. Control animals received corn oil. **Results.** Treatment-related deaths (2/12 males, 3/12 females) were recorded in the high dose group. Clinical signs in the decedents included respiratory distress, salivation, hunched posture and mucoid diarrhea. At necropsy, gastric irritation was also observed in the decedents. Mean body weight gain was found to be significantly reduced in the high dose group only. Apart from the gastric observations in the high dose decedents, there was no significant organ weight or microscopic changes because of treatment. There were no significant treatment related effects on reproductive indices or microscopic anatomy of the reproductive organs in the parents of any group. Pup viability in the mid and high dose groups was reduced at parturition and in the post-natal period. No treatment related effects were observed upon necropsy of the pups found dead

or at the scheduled termination. The NOAEL was determined to be 30 mg/kg/day for the parental animals (mortality, clinical signs) and 30 mg/kg/day for the F1 offspring (neonatal mortality).

### 5.3.3 Data Assessment for Repeated Dose Toxicity

Adequate data for repeated-dose toxicity exist for commercial oil-based samples of six of the twelve substances in the zinc dialkyldithiophosphate category. The results of these studies indicate that in repeated dermal exposure to these materials in rabbits can cause moderate-to-severe dermatitis, significant loss of body weight, behavioral distress, reductions in hematology parameters, loss of normal testicular function, and even death at the higher doses. These effects were observed across several members of the category with carbon chain lengths ranging from C<sub>4</sub>-C<sub>8</sub>. There was no evidence that the incremental increase in carbon chain length or molecular weight could be correlated with significant changes in toxicity parameters.

Repeated oral administration of commercial samples of zinc dialkyldithiophosphates in highly refined lubricating base oil resulted in evidence of severe gastrointestinal irritation with submucosal edema and suppurative inflammation, mucoid diarrhea, significant body weight loss, distress, and death at the higher doses. However, no significant adverse effects were noted on the testes or male accessory reproductive organs.

The totality of the repeated dose toxicity data indicates that the reproductive organ effects observed in male rabbits are attributed to the stress associated with the severe dermal responses to the test material, rather than direct a systemic response to the test materials. Changes in male reproductive organs in the rabbit have been observed when other irritating substances are applied to the skin at dose levels that cause skin lesions.<sup>9,10</sup> Thus, dermal irritation alone, or in combination with the accompanying weight loss and stress, is thought to play a role in the reproductive organ response to repeated cutaneous application of zinc dialkyldithiophosphates.

- Data for the six zinc dialkyldithiophosphates in highly refined lubricating base oil with carbon chain lengths ranging from C<sub>4</sub>-C<sub>8</sub> indicate similar effects, largely attributable to profound dermal irritation at the site of test material application. There was no evidence of increasing toxicity that could be correlated with an increase or decrease in carbon chain length or molecular weight. Consequently, available repeated dose data on the six intermediate carbon chain length zinc dialkyldithiophosphates in highly refined lubricating base oil will be used as read across to the following category members of similar or higher carbon chain length (molecular weight):
  - Mixed isobutyl and pentyl derivative (CAS # 68457-79-4),
  - Mixed sec-butyl and 1,3-dimethylbutyl derivative (CAS # 68784-31-6),
  - Diisodecyl derivative (CAS # 25103-54-2),
  - Dodecylphenol derivative (CAS # 54261-67-5), and
  - Tetrapropenylphenol derivative (CAS # 11059-65-7)

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<sup>9</sup>Wong, Z. A., VonBurg, R., Spangler, W. L., and MacGregor, J. A. (1982) Testicular Damage in the Rabbit Resulting from Simple Chemical Cutaneous Irritation. *The Toxicologist* 2: 41.

<sup>10</sup>McKee, R. H., Kapp, Jr., R. W., and Ward, D. P. (1985) Evaluation of the Systemic Toxicity of Coal Liquefaction-Derived Materials Following Repeated Dermal Exposure in the Rabbit. *J. App. Toxicol.* 5: 345-351.

- Reproduction/developmental toxicity data is available for a commercial sample of the 2-ethylhexyl derivative in highly refined lubricating base oil. Although the repeated dose dermal toxicity studies indicated that exposure to zinc dialkyldithiophosphates can have adverse effects on testicular function, it is believed that these effects are secondary to profound dermal irritation, body weight loss and stress. This is evidenced by the lack of reproductive organ effects in the oral reproduction/developmental toxicity assay observed with the 2-ethylhexyl derivative and supportive literature linking dermal irritation and testicular function in experimental animals. Furthermore, epidemiological studies support the lack reproductive findings in experimental analyses. In 1980, National Institute for Occupational Safety and Health investigators conducted a survey to obtain process and toxicology research information, and to conduct employee interviews at a zinc dialkyldithiophosphate production plant<sup>11</sup>. The plant produced zinc dialkyldithiophosphates of various chain lengths ranging from C<sub>3</sub>-C<sub>8</sub>. Review of medical histories showed no significant difference between the “exposed” and “controls” zinc dialkyldithiophosphate manufacturing plant workers with regard to birth defects in offspring, infertility, or miscarriages and stillbirths experienced by wives or partners. Physical examination showed no gross abnormalities in secondary sexual characteristics for exposed and controls. Semen analysis showed no azoospermia or oligospermia in the exposed group. Other parameters of the semen analysis showed no significant difference between exposed and controls. The conclusion of the report was that workers exposed to zinc dialkyldithiophosphates in an occupational setting did not exhibit untoward effects on reproductive health when compared to workers not exposed to such compounds.

Given this information, it is reasonable that the results on the epidemiological study on workers in a zinc dialkyldithiophosphate (C<sub>3</sub>-C<sub>8</sub>) manufacturing plant in combination with reproduction/developmental toxicity study results on the 2-ethylhexyl derivative (CAS # 4295-15-8) be used as read-across to the following members of the category:

- Mixed isopropyl and 1,3-dimethylbutyl derivative (CAS # 84605-29-8)
- Mixed isobutyl and pentyl derivative (CAS # 68457-79-4)
- Mixed sec-butyl and 1,3-dimethylbutyl derivative (CAS # 68784-31-6)
- Mixed sec-butyl and isooctyl derivative (CAS # 113706-15-3)
- Mixed isobutyl and 2-ethylhexyl derivative (CAS # 26566-95-0)
- 1,3-dimethylbutyl derivative (CAS # 2215-35-2)
- Mixed isobutyl, pentyl and isooctyl derivative (CAS # 68988-46-5)
- Isooctyl derivative (CAS # 28629-66-5)
- Diisodecyl derivative (CAS # 25103-54-2),
- Dodecylphenol derivative (CAS # 54261-67-5)
- Tetrapropenylphenol derivative (CAS # 11059-65-7).

The process of analyzing the existing zinc dialkyldithiophosphate data was performed in a thoughtful and qualitative manner. HERTG concludes that given the relatively minor structural variation between adjacent members of the category, in combination with the totality of human experience and experimental evidence that the reproduction/

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<sup>11</sup> NIOSH Health Hazard Evaluation Report HETA 80-228-1241, 1980.

developmental hazard profile is sufficiently described for the entire category. Therefore, no additional repeated dose toxicity testing is proposed based on the following considerations.

- 1) Through the collaborative efforts of the lubricant additive manufacturers, zinc dialkyldithiophosphates are perhaps the most extensively reviewed and tested additive component from a health and safety perspective. The industry has several decades of zinc dialkyldithiophosphate use in automotive crankcases without any evidence of repeated dose or cumulative effects on humans.
- 2) As discussed above, there is no evidence of direct effects of repeated doses of zinc dialkyldithiophosphates on reproduction systems or indices. Neonatal mortality in rodents following repeated dosing was observed only in the presence of material toxicity, and thus was considered to be of equivocal toxicological significance. Additional animal testing would not significantly contribute to the understanding of the effect of repeated dose exposure to humans, and is unlikely to demonstrate any additional risk to those in the workplace or to the general public.
- 3) The low potential for repeated dose toxicology in humans is due, in part, to the physical-chemical characteristics of these materials. Zinc dialkyldithiophosphates are high molecular weight components (average > 500 gm/mol), which generally accepted that the molecular weight limit for passive transport across biological membranes. Thus, upon exposure it is unlikely that significant amounts of these components will be absorbed for systemic distribution. In addition, these materials have a low water solubility that further inhibits absorption and distribution in the mammalian system. A Japanese MITI publication<sup>12</sup> cited a bioaccumulation factor of less than 100 for a C<sub>4</sub>-C<sub>5</sub> ester zinc dithiophosphate indicating a low potential for bioconcentration or cumulative effects. Finally, the negligible vapor pressure and high viscosity at ambient temperature indicates that these materials are unlikely to represent an inhalation exposure under conditions of use.

The exposure profile of zinc dialkyldithiophosphates also demonstrates that there is minimal risk for repeated dose toxicity. Zinc dialkyldithio-phosphates have a singular use in automotive crankcase lubricant additive. Apart from the filling operation, zinc dialkyldithiophosphates are retained in a closed system (i.e., the crankcase), and their use does not result in wide distribution of this component. Furthermore, these materials are designed to undergo thermal decomposition in the crankcase, resulting in the production of a lubricant film on critical engine parts to minimize engine wear and oxidation. Three populations that are most likely to have exposure to zinc dialkyldithiophosphate include manufacture, blending, original equipment manufacturer and downstream automobile service operations. The manufacture of zinc dialkyldithiophosphates is conducted in closed reaction vessels and transfers are performed in closed pipes. The exposure profile to production workers is very low

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<sup>12</sup> Handbook of Existing and New Chemical Substances. Fifth Edition. Edited by the Chemical Products Safety Division, Basic Industries Bureau, Ministry of International Trade and Industry. Published by Japan Chemical Industry Ecology-Toxicology & Information Center. The Chemical Daily Co. 1992.

due to process, engineering and personal protection equipment controls. The only practical exposure of concentrated component would be acute and only occur in the rare case of an accidental spill. The dermal route would be the principal means of exposure. Oral or inhalation exposure is expected to be rare.

As mentioned previously, epidemiological studies on workers in zinc dialkyldithiophosphate manufacturing plants did not reveal evidence of cumulative toxicity. Transportation of zinc dialkyldithiophosphates occurs in bulk and transfer to blending operation occurs in closed pipes and vessels. Again, the exposure profile during blending is very low. Zinc dialkyldithiophosphates are then mixed with other lubricant additives, in the presence of high molecular weight, highly refined mineral oil for use as motor oils. The typical concentration of zinc dialkyldithiophosphate in passenger car motor oil is low (e.g., 1-3%). Although OEM factory fill is largely automated and does not result in human contact, dermal exposure to low levels of zinc dialkyldithiophosphate in fresh motor oil is possible for workers in services stations and with do-it-yourself motor oil changers. However, even this small amount of exposure to the general public is falling due to extended drain intervals and the ever increasing fee-for-service lubrication operations staffed by service personnel trained in good occupational hygiene.

- 4) In addition to the arguments outlined above, HERTG believes that additional testing of zinc dialkyldithiophosphates would have caused unnecessary distress to experimental animals.

Zinc dialkyldithiophosphates are prepared from strong acids that are subsequently neutralized with zinc oxide. Extensive experimental studies demonstrate that zinc dialkyldithiophosphates are skin, eye and mucosal irritants. These hazards are clearly communicated on supplier material safety data sheets (MSDS) and product shipping labels. Animals used in the subchronic dermal toxicity studies were clearly in distress resulting from the severe local skin damage caused by repeated topical administrations of zinc dialkyldithiophosphates. The clinical signs/symptoms along with the supporting gross and microscopic pathology indicate that the experimental animals in the dermal studies experienced distress and suffering. Observations to support this assertion include, but are not limited to, changes in the physical appearance (e.g., blood around eyes and nose as well as ano-genital staining suggestive of a stress- or pain-related condition resulting in secretions not being removed by grooming), and changes in body weight and emaciation (often related changes in food and water consumption due to stress). Furthermore, it is clear that oral administration of zinc dialkyldithiophosphates caused gastrointestinal distress. This conclusion is based on the clinical observations which include salivation and hunched posture following dosing, reductions in body weight, mucoid diarrhea, nasal ocular and ano-genital staining as well as pathological indication of severe gastrointestinal irritation with gastric mucosal edema and suppurative inflammation. It is well accepted that strong mucosal irritants can cause pain, suffering and distress resulting from ulceration and cell death in the stomach lining when administered by the oral route. It is important to remember that the principal hazard of zinc dialkyldithiophosphates is their strong irritant property. HERTG shares EPA's

commitment to reduce the number of animals needed for testing and to reduce pain and suffering of test animals to the extent that it is practical and scientifically justifiable. Based on a thoughtful scientific review, HERTG concluded that it would be unable to conduct additional repeated dose testing of zinc dialkyldithiophosphates without imparting unnecessary and substantial distress and suffering to the experimental animal.

## 6.0 FINAL REPORT SUMMARY

This report summarizes existing publicly available and company data for the zinc dialkyldithiophosphate category in conjunction with scientific judgment and analysis to characterize the SIDS endpoints for physicochemical properties, environmental fate and toxicity and mammalian toxicity. The category consists of structurally similar chemicals and grouping these together in a single category is scientifically valid and provides a rational framework for evaluating SIDS data needs for these chemicals. As discussed in this report, the physicochemical, environmental toxicity and fate, and toxicological properties of the zinc dialkyldithiophosphate category members in highly refined lubricant base oils are similar and follow a regular, predictable pattern. This report presents a comprehensive evaluation of the physicochemical, environmental fate and toxicity and health hazard of the members of this category. The SIDS data needs for all category members are covered by collecting additional test data on representative members and by bridging data to make read-across assessments as summarized in the table 6.0.

Table 6.0 Summary Table

CAS Number	Environmental Fate					Ecotoxicity			Human Health Effects				
	Phys-hem	Photodeg.	Hydrolysis	Fugacity	Biodeg.	Acute Fish Toxicity	Acute Invertebrate Toxicity	Algal Toxicity	Acute Toxicity	Point Mutations	Chron. Effects	Sub-chronic	Repro/Develop
84605-29-8	T <sup>1</sup>	T <sup>2</sup>	D	C	A	T	T	T	A	A	A	B	B
68457-79-4	D	B	D	C	B	B	B	B	A	A	B	B	B
68784-31-6	D	B	D	C	B	B	B	B	A	A	A	B	B
113706-15-3	D	B	D	C	B	B	B	B	B	A	B	A	B
26566-95-0	D	B	D	C	B	B	B	B	B	A	A	A	B
68988-46-5	D	B	D	C	B	B	B	B	A	A	B	A	B
2215-35-2	D	B	D	C	B	B	B	B	A	B	B	A	B
4259-15-8	T <sup>1</sup>	B	D	C	B	T	T	T	A	A	A	A	A
28629-66-5	D	B	D	C	B	B	B	B	B	B	B	A	B
25103-54-2	D	B	D	C	B	B	B	B	A	B	B	B	B
54261-67-5	D	B	D	C	A	B	B	B	B	B	B	B	B
11059-65-7	T <sup>1</sup>	B	D	C	B	T	T	T	B	B	B	B	B

A Adequate data available

C Computer modeling

B Bridging

D Technical discussion

T Test

T<sup>1</sup> Solubility TestingT<sup>2</sup> UV absorption