U.S. High Production Volume (HPV) Chemical Challenge Program

201-16427A

Final Submittal

BARIUM NONYLPHENATE

CAS Number 28987-17-9

The Metal Carboxylates Coalition

A SOCMA Affiliated Consortium

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SUMMARY

The Metal Carboxylates Coalition has sponsored 20 compounds that are metal salts of carboxylic acids. Metal Carboxylates are metal salts of carboxylic acids. These compounds readily dissociate to the corresponding metal and carboxylic acid. The HPV endpoints are fulfilled using a combination of data from the parent molecule, as well as for the dissociation products; that is, a metal salt and/or a carboxylic acid. Selected testing of the parent molecules was conducted to further fulfill HPV endpoints. Robust summaries are provided for the parent molecules as well as the dissociation products.

This submittal provides the information for Barium Nonylphenate (CAS Number 28987-17-9). This compound dissociates and barium is present only as a small proportion of the overall molecular weight (24%). Barium has a low order of toxicity; therefore, any observed toxicity of the salt would be expected to be due primarily to the nonylphenol moiety. Commercial nonylphenol is an alkylated phenol. The alkyl group is C9, and can be linear or branched. This group can also vary slightly in length and substitution patter on the ring.

The completed test plan is presented in Table 6.

1.0 BACKGROUND

This submittal provides the information for Barium Nonylphenate (CAS Number 28987-17-9). Figure 1 provides the structure of this material.

1.1 Use Patterns for Metal Carboxylates

The metal carboxylates function to deliver a metal ion into chemical reactions. The carboxylic acids (acids) are tailored for use in different products or chemical reactions.

1.2 Common Characteristics of Metal Carboxylates

This metal is a divalent compound and has two carboxylic acid moieties per molecule. The metal carboxylate salts are designed to add metals to chemical reactions; therefore, they are designed to readily dissociate into the free metal and free acid.

2.0 Dissociation Studies

One key characteristic of metal carboxylates is that they readily dissociate from an ion pair into free metal and free acid. They are found as partially dissociated products in the ambient environment (i.e., neutral pH). Dissociation is a reversible process and the portion of dissociated salt present is dependent on the pH and pKa (the dissociation constant), which is the pH at which 50% dissociation occurs. In the low pH environment of the digestive tract (e.g., pH 1.2) complete dissociation will occur for these metal carboxylates. The transport and bioavailability of the metals and acids are determined by their solubility in environmental media and biological fluids which is determined by environmental parameters such as pH.

Completion of the dissociation study with this compound was not possible due to its low water solubility, although this compound is expected to readily dissociate (Crompton Corporation, personal communication). Studies with other metal carboxylates indicate that significant dissociation will occur at approximately neutral pH (i.e., representative of aquatic and marine ecosystems), while complete dissociation will occur at physiologically relevant pH of the mammalian stomach (pH 1.2). These findings are particularly important in relating available data for the respective acids and metals to support the existing data for barium nonylphenate and in the fulfillment of critical endpoints.

Dissociation is a reversible reaction, splitting the parent compound into two or more chemical species which may be ionic, but are not necessarily so. The process can be generally represented as:

High pH Low pH

$$[RCOO^-]_x{:}[M^+]_x \leftrightarrow [RCOO^-]_x + [M^+]_x \leftrightarrow [RCOOH]_x + [MCl]_x$$

(salt) (Titrate with HCl →) free acid and free metal

The pKa and pH are equal when the metal carboxylate salt is 50% dissociated. The parent compounds, the metal carboxylate salts, are associated ionized molecules.

The dissociation constant is important for two reasons. First, it determines the proportion of any specific acid or metal that is dissociated at a given pH. The free acid and corresponding free metal are often much different than the salt (ion pair) moiety in characteristics such as solubility, adsorption, and toxicity. The proportion of dissociation influences the behavior of the substance in the environment and bioavailability of the acid and metal constituents of metal carboxylate salts.

The dissociation constants for 17 related metal carboxylate compounds tested have pKa (pKb) values (pKa1) in the neutral range (5.088 to 8.448). This indicates that in the neutral pH range, significant portions of the metal carboxylates will be dissociated. In addition, at the low pH of the mammalian stomach (pH 1.2) all of the metal carboxylates would be expected to be completely or nearly completely dissociated. This indicates that the absorption and any observed toxicity would be independent for the respective acid and metal when administered orally.

The dissociation constants show that at the pH of the stomach and at the pH of environmental media the important moieties are the ionized free acid and metal. Because of this, environmental fate, ecotoxicity, and mammalian toxicity of the free acid, or that for a simple salt (e.g., the sodium salt), can to serve as surrogate data for the acid component of the respective metal carboxylates. Similarly, under these conditions, data for the metal ion can be represented by fate and toxicity data for the free metal ion or simple metal salts (e.g., metal chlorides). Therefore, the role in any observed toxicity for acids and metals can be evaluated independently (i.e., as the free metal and/or free acid).

This compound dissociates and the metal barium is present only as a small proportion of the overall molecular weight (24%). Barium has a low order of toxicity; therefore, any observed toxicity of the salt would be expected to be due primarily to the nonylphenol moiety. Commercial nonylphenol is an alkylated phenol. The alkyl group is C9, and can be linear or branched. This group can also vary slightly in length and substitution patter on the ring.

3.0 Bioequivalency

The work described below by Stopford et al. (2002) shows that the metal chloride is similar to, or more bioavailable than, the corresponding metal carboxylate salts, which makes the chloride a conservative surrogate in estimating bioavailability and toxicity of dissociated metals. Chlorides of the various metals have been emphasized during preparation of the attached robust summaries and are the preferred surrogate data for carboxylate salts.

Recent studies conducted to evaluate the “bioequivalency” (an estimate of bioavailability) of cobalt compounds, included three cobalt carboxylates and cobalt chloride. The solubility of these compounds in synthetic biological fluids (gastric juices, intestinal juices, several interstitial fluids, and cytosol) showed that these salts were completely dissociated and dissolved at gastric pH and cytosolic pH. The dissolution of

these compounds ranged from 26.1% to 80.4 % of available cobalt at neutral pH (Table 1). The results for cobalt chloride and cobalt 2-ethyl-hexanoate were very similar at acidic and neutral pH. Cobalt neodecanoate and cobalt naphthenate showed similar levels of dissolution at acidic (gastric and cytosolic) pH, but smaller proportions of the metal component of these compounds were dissolved at neutral pH. The differences in dissolution for these metal carboxylates at neutral pH in synthetic body fluids could be related to differences in their dissociation constants.

Table 1: Results of Extraction of Cobalt from Surrogate Biological Fluids

Matrix (pH)	**Maximum Solubility (% of available metal)**			
	$CoCl_2$	Co 2-ethyl-hexanoate	Co naphthenate	Co neodecanoate
Gastric pH (1.5)	>91.6	100	>85.7	100
Intestinal pH (7.4)	>79.4	50.8*	45.4*	30.8*
Alveolar pH (7.4)	>68	>59.6	35.4*	26.1*
Interstitial pH (7.4)	78.4	>80.4	40*	43.1*
Serum	>85	>66.9	42.9*	46.6*
Intracellular pH (4.5)	>89.6	100	>79.1	>78.1

* Maximum extraction level at 72 hours
All data are taken from Stopford et al. (2002)

These data are valuable in understanding barium nonylphenate for three reasons:

1. They confirm the prediction that barium nonylphenate would be expected to be completely dissociated in the gastrointestinal tract (low pH) and a substantial proportion would be expected to be dissociated and bioavailable at neutral pH (7.4).
2. The fraction of the three cobalt carboxylates that is dissolved at acidic and neutral pH is very similar for different acid constituents with a range of molecular weights and chain lengths. This finding greatly strengthens the extrapolation of the results to barium nonylphenate.
3. The work by Stopford et al. (2002) shows that the metal chloride is similar to, or more bioavailable than, the corresponding metal carboxylate salts, which makes the chloride a conservative surrogate in estimating bioavailability and toxicity of dissociated metals. Chlorides of the various metals have been emphasized during preparation of the attached robust summaries and are the preferred surrogate data for carboxylate salts.

4.0 Supporting Data for Barium Nonylphenate and its Dissociation Products

Data for barium nonylphenate (Appendix A) and its dissociation products (barium (as barium, barium chloride and barium sulfate) and nonylphenol, Appendices B and C, respectively) are provided in robust summary format.

Consistent with discussions between the Metal Carboxylates Coalition and the EPA, data for the dissociation products (metals and acids) are recognized as being essential to understanding the environmental fate and toxicological characteristics of the respective

metal carboxylate salts. Data for nonylphenol and barium are useful in characterizing the hazards of barium nonylphenate.

In summary, the key points relative to barium nonylphenate are:

- Dissociation to barium and nonylphenol;
- Expected dissociation constants (pKa) in the circum neutral range (mean pKb values were 8.34, 6.81 and 5.62 at 20 deg C);
    - Complete or nearly complete dissociation at gastric and cytosolic pH levels;
    - A moderate to high proportion of dissociation in the neutral pH range;
- General bioequivalency for salts with the same metal cation (cobalt used as an example within this document) and different acids or the chloride salt;
- Provision of data for the parent molecule or one or both of its dissociation products

5.0 HPV Endpoint Data

The Metal Carboxylates Coalition has relied on the fact that this compound will dissociate and that the dissociation products (nonylphenol and barium) are the chemicals of interest. Dissociation was demonstrated and is expected to dissociate readily in water at neutral pH's and to be completely dissociated at the pH of the stomach (pH 1.2) as demonstrated for other metal carboxylates.

The Metal Carboxylates Coalition is relying on the data for nonylphenol and barium to support this material and to minimize unnecessary testing. The Coalition has prepared a robust summary document for barium nonylphenate, barium (as barium, barium chloride and barium sulfate) and nonylphenol, which describes the necessary endpoint data under the HPV Program (Appendixes A, B and C).

Physicochemical Properties:

Table 2 provides a summary of the estimated physical chemical data for barium nonylphenate, as well as its dissociation products. The calculated melting point and boiling point are 264 deg C and 609 deg C, respectively (EPIWIN). The vapor pressure is anticipated to be very low (modeling data indicate the vapor pressure will be approximately 1E-13 hPa). The water solubility of this material is very low (nearly insoluble).

Table 2: Summary of Physical Chemical Properties Data for Barium Nonylphenate and Dissociation Products

Compound	**Physical Chemical Properties**			
	Melting Point (deg C)	Boiling Point (deg C)	Vapor Pressure (hPa)	Water Solubility (g/L)
Barium Nonylphenate (28987-17-9)	264 (Epiwin)	609 (Epiwin)	<1E-13 (Epiwin)	~ .05 (Lezotte and Nixon, 2002

Dissociation Product: as Barium (7440-39-3)	~710(O'Neil, 2002)	~1600 (O'Neil, 2002)	*** Not relevant/ Negligible	*** Not relevant/ Negligible
Dissociation Product: as Barium sulfate (7727-43-7)	1580 (ATSDR, 1992) (decomposes)	1149 (ATSDR, 1992)	*** Not relevant/ Negligible	Insoluble** (O'Neil, 2002)
Dissociation Product: as Barium chloride (10361-37-2)	963 (O'Neil, 2002)	1560 (DHHS, 1990)	*** Not relevant/ Negligible (DHHS, 1990)	37.5 g/100 cm3 at 26 ^{o}C (Http:/en.wikipedia, 2005)
Dissociation Product: Nonylphenol (25154-52-3; 84852-15-3)	~ -8 (EU, 2001; Huels, 1994a) 2 (Dutch Institute, 1991) 24.5 (Akylphenol and Ethoxylates, 1990)	290-302 (EU, 2001; Huels, 1994a; Akylphenol and Ethoxylates, 1990; Dutch Institute, 1991; Merck, 1983)	~.0016 (EU, 2001; Huels, 1994b) .01 (Huels, 1994a) .0000455 (Akylphenol and Ethoxylates, 1990)	.011 (Huels, 1988a) .0063 (Akylphenol and Ethoxylates, 1990) ~ .003 (Huels, 1994c)

** = 1 gram in 400,000 parts
*** = not relevant for metals/metal compounds

Environmental Fate:

Table 3 provides a summary of the available environmental fate data for barium nonylphenate, as well as its dissociation products. Most tests of environmental fate (partition coefficient, stability in water and biodegradation) are not appropriate for this material due to its very low predicted water solubility. Model estimates of these parameters are presented in Table 3. Partition coefficient and biodegradation studies are available for nonylphenol, which is considered to be representative of barium nonylphenate since this compound dissociates and nonylphenol will be the moiety of interest. Nonylphenol is not readily biodegradable, and has a partition coefficient of ~4. Photodegradation and transport (fugacity) have been calculated using SAR models (e.g., EPIWIN) for barium nonylphenate.

Table 3: Summary of Environmental Fate Data for Barium Nonylphenate and Dissociation Products

Compound	**Environmental Fate**				
	Partition Coefficient	Stability in Water	Photodegr.	Level III Fugacity Model	Biodeg
Barium Nonylphenate (28987-17-9)	11.78 (Epiwin) (a)	No data*	$T_{1/2}$ = .083 days (Epiwin)	Air 0.0526 Water 3.43 Soil 28.3 Sediment 68.2 (Epiwin)	No data – read across to nonylphenol
Dissociation Product: as Barium (7440-39-3)	** 0.23 (Epiwin)	**/****	**** Not relevant	Air 37.9 Water 55.8 Soil 6.18 Sediment 0.0944 (Epiwin)	***

Dissociation Product: as Barium sulfate (7727-43-7)	** 0.63 (Epiwin)	**/****	**** Not relevant	Air 1.42e-006 Water 47.4 Soil 52.5 Sediment 0.091 (Epiwin)	***
Dissociation Product: as Barium chloride (10361-37-2)	** 0.85 (Epiwin)	**/****	**** Not relevant	Air 9.42e-006 Water 46 Soil 53.9 Sediment 0.0906 (Epiwin)	***
Dissociation Product: Nonylphenol (25154-52-3)	3.3 (Huels, 1989) 3.8-4.8 (CMA, 1991)	No data	$T_{1/2}$ = .3 days (Calc)	Air 0.53 Water 17.4 Soil 39.4 Sediment 42.7 (Epiwin)	7% in 28 days (Huels, 1990) 78% after 40 days (Huels, no date)

* = Dissociation of the test substance will occur at environmentally-relevant pH values (approximately neutral) and at physiologically-relevant pH values (~ pH 1.2) (Lezotte and Nixon, 2002)
** = Not relevant; substance readily dissociates
*** = Barium compounds are not expected to be readily biodegradable
**** = Cannot be modeled with Epiwin
(a) The partition coefficient of the test substance cannot be determined because it is not possible to make sure the equilibrium established between the aqueous and the organic phase is based upon the undissociated form of the test item as specified by the guideline (RCC Ltd., 2006).

Environmental Effects:

Table 4 provides a summary of the available environmental effects data for barium nonylphenate and its dissociation products. The 96-hour LL_{50} (lethal loading rate) for barium nonylphenate and rainbow trout (*Oncorhynchus mykiss*) based on nominal loading rates was 1.3 mg/l loading rate WAF (Water Accommodated Fractions). The No Observed Effect Loading rate was 1.0 mg/l loading rate WAF. As shown in Table 4, the acute aquatic toxicity of nonylphenol is greater than that of barium, barium sulfate or barium chloride. Thus, the toxicity of barium nonylphenate is likely to be due to nonylphenol, rather than barium. Since the results of the acute fish toxicity study show a similar toxicity between barium nonylphenate and nonylphenol, no additional studies are needed, and the toxicity of barium nonylphenate in an aquatic system is adequately described by nonylphenol.

Table 4: Summary of Environmental Effects Data for Barium Nonylphenate and Dissociation Products

	Environmental Effects		
Compound	Acute Toxicity to Fish (96 hr LC50; mg/L)	Acute Toxicity to Daphnia (48 hr LC50; mg/L)	Acute Toxicity to Algae (96 hr EC50; mg/L)
Barium Nonylphenate (28987-17-9)	LL50 = 1.3 (SafePharm Laboratories, 2006a)	No data – read across to dissociation products	No data – read across to dissociation products
Dissociation Product: as Barium (7440-39-3)	>500 (*Cyprinodon variegates*; Heitmuller, et al., 1981)	410 (*Daphnia magna*; LeBlanc, 1980; AQUIRE, 2005a)	No data

Dissociation Product: as Barium sulfate (7727-43-7)	LC0 = 59000 (*Poecillia latipinna; AQUIRE, 2005b)*	32 (*Daphnia magna*; *AQUIRE, 2005c)* 2.81 (*Daphnia magna*; Khangarot and Ray, 1989)	No data
Dissociation Product: as Barium chloride (10361-37-2)	42.7** (*Onchorhynchus mykiss*; AQUIRE, 2005d)	14.5 (*Daphnia magna*; Biesinger and Christensen, 1972; AQUIRE, 2005e)	25 (*Lemna minor*; Wang, 1986)
Dissociation Product: Nonylphenol (25154-52-3)	0.31 (*Cyprinodon variegates*; CMA, 1990) 0.135 (*Pimephales promelas*; Holcombe et al, 1984) 0.56-0.92 (*Salmo gairdneri;* Ernst et al, 1980)	0.14 (*Daphnia magna*; Huels, 1992)	ECr50= 0.41 (*Selenastrum capricornutum*; CMA, 1990) ECr50= 0.027 (*Skeletonema costatum*; CMA, 1990)

**Exposure period not specified

Human Health Effects:

Mammalian toxicity is represented by data for barium nonylphenate and its dissociation products (Table 5).

The acute oral toxicity (LD50) of nonylphenol in rats are consistently reported to be in a range between 1000 and 2000 mg/kg bw, with two exceptions, where a value of 580 mg/kg bw and a value of 2462 mg/kg bw were reported; for barium the LD50 = 118 mg/kg (as barium chloride). An acute toxicity study has not been conducted with barium nonylphenate. The acute toxicity of this material is represented by the more toxic of its dissociation products (barium, as barium chloride).

Oral administration of barium nonylphenate to rats, by gavage, at dose levels of 150, 250 and 1000 mg/kg/day for seven consecutive days resulted in deaths at 1000 and 250 mg/kg/day. Clinical signs of toxicity were observed for animals treated with 1000 and 250 mg/kg/day. An increase in liver and kidney weights was also observed for males treated with 1000 mg/kg/day. The No Observed Effect Level (NOEL) was therefore considered to be 150 mg/kg/day. Both nonylphenol and barium (as barium chloride) have been extensively tested for repeat dose, developmental toxicity and effects on fertility. The NOAEL for repeated dose toxicity for the dissociation products are similar (Table 5), with values of 200 ppm (nonylphenol) and 50 ppm (barium chloride). Neither nonylphenol nor barium (as barium chloride) has been shown to cause developmental effects (Table 5). The NOAEL for reproductive toxicity of nonylphenol has been identified in a three generation study with rats (NOAEL = 2000 ppm). No reproductive effects were observed in a one generation study with barium chloride in mice (NOAEL = 200 mg/l). Similar findings are anticipated for barium nonylphenate.

Barium nonylphenate has not been tested for genotoxicity either *in vitro* or *in vivo*. With one exception, neither dissociation product has been shown to produce mutagenic effects

in numerous test systems. Barium chloride was found to be mutagenic in the presence of metabolic activation in a mouse lymphoma assay using L5178/TK$^{+/-}$ cells, but negative in the absence of activation. The overall weight of evidence suggests a lack of mutagenic effects for barium chloride. Similar findings of a lack of genotoxicity are anticipated for barium nonylphenate.

Table 5: Summary of Mammalian Toxicity Data for Barium Nonylphenate and Dissociation Products

	Mammalian toxicity		
Compound	Acute Toxicity (LD50) (mg/kg)	Repeat Dose Toxicity (NOAEL)	Genetic Toxicity
Barium Nonylphenate (28917-17-9)	No data – read across to dissociation products	NOEL = 150 mg/kg/day (7 day, rat, gavage) (Safepharm, 2006b)	No data – read across to dissociation products
Dissociation Product: as Barium (7440-39-3)	No data	No data	No data
Dissociation Product: as Barium sulfate (7727-43-7)	No data	No data	No data
Dissociation Product: as Barium chloride (10361-37-2)	132 (rat; Tardiff et al. 1980) >2000 (rat; NTP, 1994) >692 ppm (mouse; NTP, 1994)	1000 ppm (13 week, rat, drinking water; NTP, 1994) 500 ppm (13 week, mouse, drinking water; NTP, 1994) 1000 ppm (14 d, rat, drinking water; NTP, 1994) 346 ppm (14 d, mouse, drinking water; NTP, 1994) 50 ppm (13 week, rat, drinking water; Tardiff et al. 1980)	Negative: *Salmonella typhimurium* TA 97, TA 98, TA 100, TA 1535, TA 1537 (NTP, 1994) Negative: *E. coli* $WP_s(\lambda)$ (Rossman et al., 1991) Positive: mouse lymphoma assay (NTP, 1994) Negative: in vitro chromosome aberration (NTP, 1983) Negative: in vitro SCE assay (NTP, 1983)
Dissociation Product: Nonylphenol (25154-52-3)	1900 (rat; Huels, 1986) 1537 (rat; Smyth, 1969) 580 (rat ; Texaco, 1985) 1300 (rat ; Monsanto, 1985) 1246 (rat ; Taupin, 1981) 2462 (rat ; Gaworski, 1979) 1882 (rat ; Berol Kemi, 1982) 1525 (rat ; Hoechst, 1988) 1000-2500 (male rats; ICI PLC, 1984) 1814 (female rats; ICI PLC, 1984) 1000-5000 (rat, ICI Ltd, 1979)	100 mg/kg/day (28 day, diet, rat; Huels, 1981) 650 ppm (equivalent to 50 mg/kg/day; 90 day, diet, rat; Cunny et al. 1997) 200 ppm (3-generation study, diet, rat; RTI, 2006)	Negative: *Salmonella typhimurium* TA 98, TA 100, TA 1535, TA 1537, TA 1538 (Huels, 1984a) Negative: CHO HGPRT (Huels, 1984b) Negative: Micronucleus (1988b)

Table 5 (continued): Summary of Mammalian Toxicity Data for Barium Nonylphenate and Dissociation Products

	Mammalian toxicity	
Compound	Repro. Effects (NOAEL)	Develop. Effects (NOAEL)
Barium Nonylphenate (28917-17-9)	No data – read across to dissociation products	No data – read across to dissociation products
Dissociation Product: as Barium (7440-39-3)	No data	No data
Dissociation Product: as Barium sulfate (7727-43-7)	No data	No data
Dissociation Product: as Barium chloride (10361-37-2)	4000 mg/l (rat, drinking water; WHO, 1990) 2000 mg/l (mouse, drinking water; WHO, 1990)	4000 mg/l (rat, drinking water; WHO, 1990) 2000 mg/l (mouse, drinking water; WHO, 1990)
Dissociation Product: Nonylphenol (25154-52-3)	2000 ppm (3 generation, rat; RTI, 2006)	Rat, gavage, gestation days 6-15 75 (maternal) mg/kg bw, 300 (teratogen) mg/kg bw (IBR, 1992) 2000 ppm (3 generation, rat; RTI, 2006)

6.0 TEST PLAN SUMMARY

Table 6 provides the completed test plan for barium nonylphenate. No additional testing is needed, and the assessment of barium nonylphenate is complete.

Table 6: Completed Test Plan for Barium Nonylphenate

Melting Point	**Boiling Point**	**Vapor Pressure**	**Water Solubility**
A (calc)	A (calc)	A (calc)	A

Partition Coefficient	**Dissociation Constant (pKb)**	**Stability in Water**	**Photodegradation**	**Level III Fugacity Model**	**Biodegradation**
NA/DP	8.34, 6.81 and 5.62 at 20 deg C	NA (dissociates)	A (calc)	A (calc)	DP

Acute Toxicity to Fish	**Acute Toxicity to Daphnia**	**Acute Toxicity to Algae**
A	DP	DP

Acute Toxicity	**Repeat Dose Toxicity**	**Reproductive Effects**	**Developmental Effects**	**Genetic Toxicity**
DP	A/DP	DP	DP	DP

A= Endpoint requirement fulfilled with adequate existing data
NA=Not applicable due to chemical/physical properties of the substance
NWS=Not applicable (not soluble in water)
Test= Endpoint requirements to be fulfilled with testing
DP= Endpoint requirements to be fulfilled using data for dissociation products
A/DP= Endpoint requirements to be fulfilled using data for dissociation products as well as a 7 day repeat dose bridging study with barium nonylphenate

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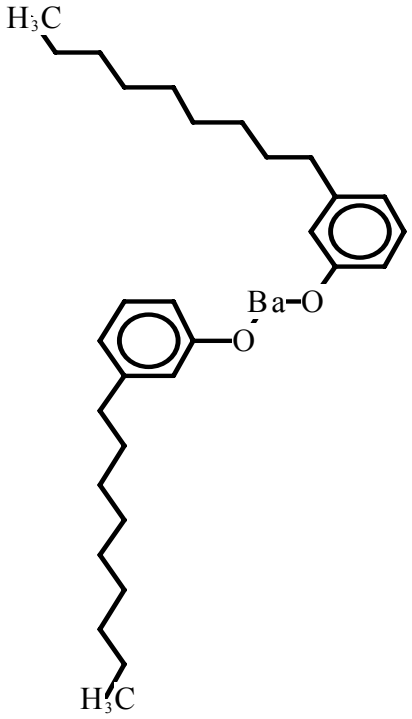
Figure 1: Structure of Barium Nonylphenate



APPENDIX A

BARIUM NONYLPHENATE ROBUST SUMMARIES

APPENDIX B
BARIUM ROBUST SUMMARIES
(Barium, Barium Chloride and Barium Sulfate)

APPENDIX C
NONYLPHENOL ROBUST SUMMARIES