PROBLEM DEFINITION STUDY
LEAD β-RESORCYLATE

FINAL REPORT

R. S. Wentsel
W. E. Jones, III
W. H. Fitzpatrick
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February, 1979

Sponsored by:

U. S. ARMY MEDICAL RESEARCH AND DEVELOPMENT COMMAND
Fort Detrick, Frederick, Maryland 21701

Contract No. DAMD17-77-C-7057

COTR: Clarence Wade, Ph. D.

ATLANTIC RESEARCH CORPORATION
Alexandria, Virginia 22314

SECURITY CLASSIFICATION OF THIS PAGE (When Data Entered)

REPORT DOCUMENTATION PAGE

READ INSTRUCTIONS BEFORE COMPLETING FORM

1. REPORT NUMBER	2. GOVT ACCESSION NO. / 3. RECIPIENT'S CATALOG NUMBER
4. TITLE (and Subtitle) Problem Definition Study Lead β-resorcylate	5. TYPE OF REPORT & PERIOD COVERED Final Report July, 1978 - February, 1979 6. PERFORMING ORG. REPORT NUMBER 49-5730-07
7. AUTHOR(s) R.S. Wentsel; W.E. Jones, III; W.H. Fitzpatrick; J.F. Kitchens	8. CONTRACT OR GRANT NUMBER(s) DAMD17-77-C-7057
9. PERFORMING ORGANIZATION NAME AND ADDRESS Atlantic Research Corporation 5390 Cherokee Avenue Alexandria, Virginia 22314	10. PROGRAM ELEMENT, PROJECT, TASK AREA & WORK UNIT NUMBERS 62620A 3E762720 A835.00.003
11. CONTROLLING OFFICE NAME AND ADDRESS U.S. Army Medical Research and Development Command Ft. Detrick, Frederick, Maryland 21701	12. REPORT DATE February, 1979 13. NUMBER OF PAGES 54
14. MONITORING AGENCY NAME & ADDRESS(if different from Controlling Office)	15. SECURITY CLASS. (of this report) Unclassified 15a. DECLASSIFICATION DOWNGRADING SCHEDULE

16. DISTRIBUTION STATEMENT (of this Report)

Approved for public release

Distribution Unlimited

17. DISTRIBUTION STATEMENT (of the abstract entered in Block 20, if different from Report)

18. SUPPLEMENTARY NOTES

19. KEY WORDS (Continue on reverse side if necessary and identify by block number)

lead β-resorcylate
toxicology
biology
aquatic toxicity
environmental fate
chemistry
propellant production
literature review

20. ABSTRACT (Continue on reverse side if necessary and identify by block number)

This report presents the results of a literature search and evaluation of potential health and environmental hazards associated with lead β-resorcylate. Only limited information is available on this compound and its toxicological and environmental hazards must be inferred from data on other compounds. Preliminary acute aquatic toxicity studies with fish and invertebrates indicate that lead β-resorcylate is relatively non-toxic to fish and moderately toxic to invertebrates.

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SUMMARY

Lead β-resorcylate is used as a burning rate modifier in solid propellant formulations. The Army is the main user of this chemical in the United States. Radford AAP effluents are probably the main source of pollution of this salt. The environmental fate of lead β-resorcylate has not been determined. By analogy to other lead complexes, it is probably hydrolyzed to inorganic lead and precipated as the carbonate or sulfate.

The toxicity of lead β-resorcylate to mammals is unknown. In acute doses, lead β-resorcylate is expected to show low toxicity if comparison with lead salicylate is valid. However, chronic toxic effects could be a problem.

The aquatic toxicity of lead β-resorcylate is variable with fish being relatively insensitive and invertebrates moderately sensitive to this salt.

Five studies are recommended in order to fill in the information gaps on lead β-resorcylate:

1. Further enumeration of the composition, chemistry, and analysis methods for salts

2. Sampling and analysis at Radford AAP to determine amounts of lead β-resorcylate in the effluent and accumulation in the New River sediment and biota

3. Acute mammalian toxicity study

4. Chronic mammalian toxicity study

5. Determine the effectiveness of proposed treatment facilities to remove lead β-resorcylate from Radford's AAP effluents.

FOREWORD

A. Study Goals

This report presents the results of an evaluation of the available information on the toxicological and environmental hazards of lead β-resorcylate. Lead β-resorcylate is used by the Army as a burning rate moderator in solvent and solventless double base propellants. This salt enters the environment in the wastewater generated during the blending of propellant ingredients at the Army Ammunition plants. The wastewater generated at the Army propellant manufacturing facilities is a major source of entry of lead β-resorcylate into the environment. The evaluation of toxicological and environmental hazards of lead β-resorcylate was undertaken in order to aid the Army in identification of research needs and in recommendation of effluent standards for this compound.

B. Study Methodology

The methodology utilized to gather information for this report included a detailed search of the literature and numerous personal contacts. During the literature search, the following sources were reviewed for pertinent information on lead β-resorcylate.

- Chemical Abstracts	1940 - present
- Biological Abstracts	1950 - present
- Excerpta Media	1950 - present
- TOXLINE	1965 - present
- National Technical Information Services	1964 - present
- Defense Documentation Center	1958 - present
- COMPENDEX	1970 - present

Personal contacts were made with U.S. and foreign manufacturers, Army Ammunition Plant personnel and Army and civilian researchers.

1. Contacts with U.S. Manufacturers

Mr. Don Hurley, NL Industries, Sept. 27, 1978. Mr. Hurley said that since lead β-resorcylate was never used in medicines or pharmaceutical preparations, no toxicological studies were ever done. NL Industries uses the same precautions that are applicable to other toxic lead compounds.

Mr. Ted E. Potter, Environmental Manager, The Shepherd Chemical Co., Sept. 22, 1978. Mr. Potter supplied an oral LD50 for lead salicylate of 4.3 gm/kg in the rat. No information was available for lead β-resorcylate.

2. Foreign Contacts

Nine foreign companies listed in the 1978 Directory of Chemical Producers in Western Europe were contacted by Telex in October 1978.

FRANCE
Melle-Bezons SA
Rhone-Poulenc Industries SA

FED. REP. OF GERMANY
Akzo Chemie GmbH
Chemische Werke Munchen Otto
Barlocher GmbH
Metallgesellschaft AG

ITALY
Stabilital SpA

Spain
Industrias Quimicas de Parets. SA

UNITED KINGDOM
Akzo Chemie UK Ltd.
Hopkin & Williams

Four companies responded, none of them had any toxicological information.

3. Radford AAP Personnel

The following Radford AAP personnel were contacted Sept. 28, 1978:

Mr. Jon Horvath
Mr. Tom Grady
Mr. Ted Topper

Mr. Horvath had no information. Mr. Grady suggested calling Dr. Emil Christifano of Hercules Inc. or NL Industries since they produce the compound. Mr. Topper searched for toxicological information but found none.

4. Other Sources

Dr. Jay Abercrombie of the U.S. Army Chemical Systems Laboratory, Aberdeen Proving Ground, Md., was contacted Sept. 12, 1978. He reported no information of the lead compounds.

Mr. J. Gareth Pearson of AMRDC, Fort Detrick, Md., was visited Sept. 1978. Data on the aquatic toxicity of lead β-resorcylate was provided.

Dr. Emil Christifano and Mr. Tom Butler of Hercules, Inc., were contacted on October 2, 1978, for toxicological information on lead β-resor-

cylate. They had no specific data.

The Department of Transportation was contacted in October 1978, for any toxicological information on lead β-resorcylate. However, they had no specific information.

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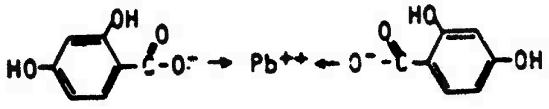
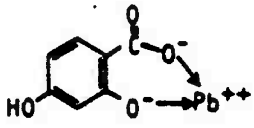
1. INTRODUCTION

Lead β-resorcylate is the divalent lead salt of resorcyclic acid. It is produced by the reaction of lead oxide with resorcylic acid and is available commercially from N. L. Industries and Shepherd Chemical Company. Commercial lead β-resorcylate is apparently a mixture of dibasic lead β-resorcylate, monobasic lead β-resorcylate and possibly a third variety.



dibasic lead β-resorcylate



monobasic lead β-resorcylate

Analysis of this third salt indicates that it has a 7:4 lead to resorcylate ratio (Satriana, 1971a).

The pertinent alternate names for lead β-resorcylate are listed below:

Mixture

CAS Registry No.:	20936-32-7
CA Name (9CI):	Benzoic acid, 2,4-dihydroxy, lead salt
CA Name (8CI):	beta-resorcylic acid, lead salt
Synonyms:	Lead beta-resorcylate; Lead 2,4-dihydroxybenzoate

Monobasic

CAS Registry No.:	41453-51-4
Molecular Formula:	$C_7H_4O_4Pb$
CA Name (9CI):	Benzoic acid, 2,4-dihydroxy, lead(2+) salt(1:1)
Synonyms:	2,4-dihydroxybenzoatolead(II)

Dibasic

CAS Registry No.:	41453-50-3
Molecular Formula:	$C_7H_5O_4 \cdot 1/2\ Pb$
CA Name (9CI):	Benzoic acid, 2,4-dihydroxy, lead(2+) salt(2:1)
Synonyms:	Bis(2,4-dihydroxybenzoate)lead(II)

II. PHYSICAL AND CHEMICAL PROPERTIES

A. Physical Properties

Only limited information was found on the physical properties of lead β-resorcylate. Satriana (1971a) reported solubility data, infrared spectra, X-ray diffraction patterns, thermograms and thermogravimetric data for monobasic and dibasic lead β-resorcylate and the third variety mentioned above (designated sample 62-1 by Satriana).

Solubility data for the three lead β-resorcylate salts are presented in Table I. As indicated in Table I, the dibasic salt is soluble in most polar solvents and even slightly soluble in benzene. The monobasic salt and sample 62-1 were insoluble in all solvents tested. The infrared spectra and X-ray diffraction patterns shown in Figures 1 and 2 indicate that the three salts are different in composition and structure.

B. Chemical Properties

1. General Chemistry

The only literature references to the chemistry of lead β-resorcylate are those of Satriana (1971a; 1971b) who investigated the synthesis of the lead β-resorcylates and the adsorption of water by dibasic lead β-resorcylate. Pure monobasic lead β-resorcylate was obtained in good yield when lead oxide and resorcylic acid were mixed in a 1:2 ratio in an alcoholic solution. Good yields of the pure dibasic salt were obtained when the resorcylate concentration was increased to three times that of the lead oxide. When water was the solvent in the synthesis, an unknown salt resulted.

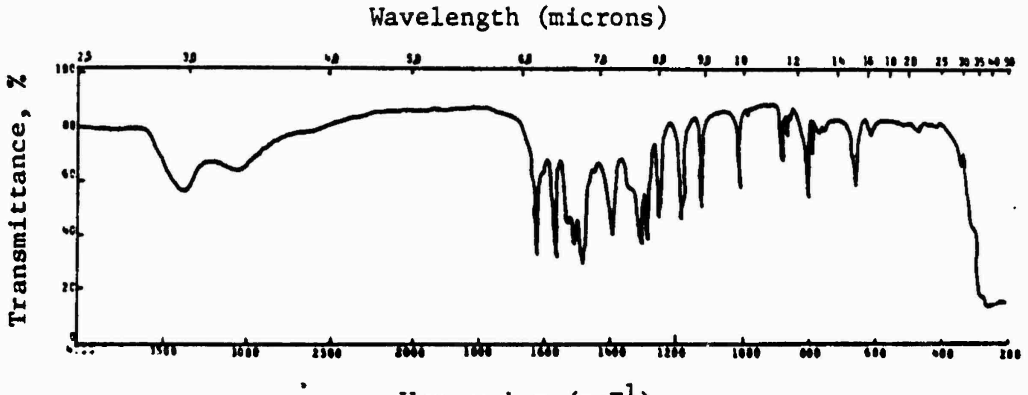
Differential thermal analysis (DTA) and thermogravimetric analysis (TGA) curves of lead β-resorcylate are shown in Figures 3 and 4. The DTA and TGA curves of the dibasic salt suggest the reversible loss of a water molecule at approximately 100-150°C. All three salts showed larger weight losses consistent with loss of the resorcylate anions at higher temperatures. Propellants containing lead β-resorcylate have been shown to ooze resorcylic acid on aging. This loss is due either to hydrolysis or expulsion of the anhydride (Satriana, 1971b).

2. Environmental Reactions

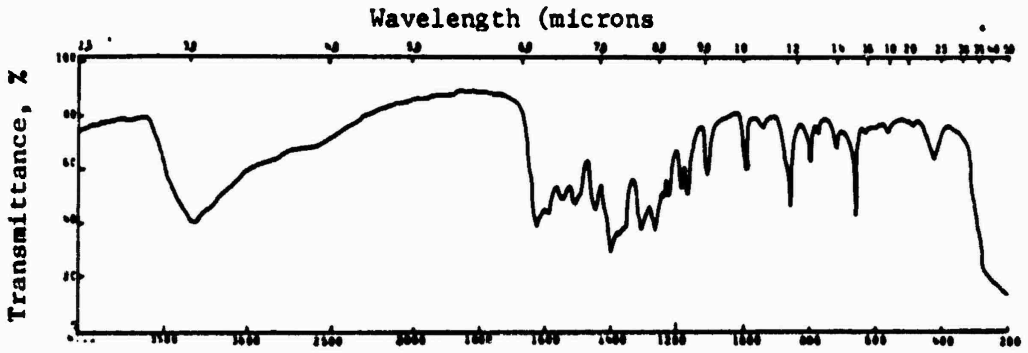
No data on the environmental fate of lead resorcylate was found in the literature search. One would expect the initial formation of lead oxide and resorcylic acid either via direct hydrolysis

Table I. Solubility Properties of Lead β-Resorcylate Salts. (Satriana, 1971a)

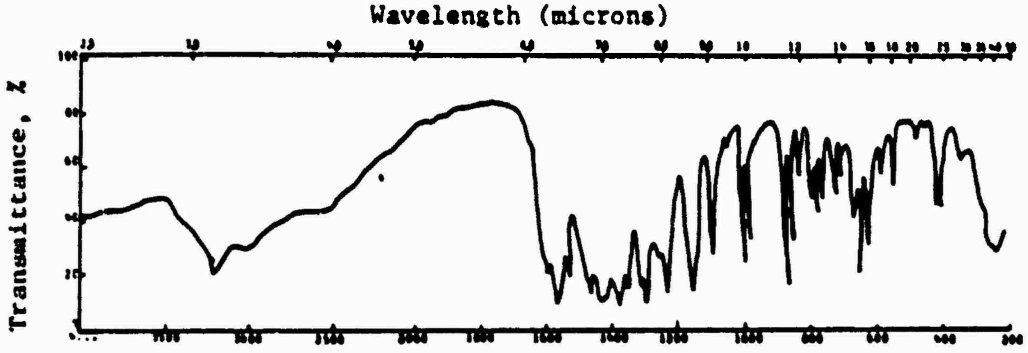
Solvent	Dibasic Salt	Monobasic Salt	Sample 62-1
Water	Slightly soluble	Insoluble	Insoluble
95% Ethanol	Soluble	Insoluble	Insoluble
Dimethylformamide	Soluble	Insoluble	Insoluble
Acetone	Soluble	Insoluble	Insoluble
Tetrahydrofuran	Soluble	Insoluble	Insoluble
Dimethylsulfoxide	Soluble	Insoluble	Insoluble
Benzene	Slightly soluble	Insoluble	Insoluble



Dibasic Lead β-Resorcylate



Monobasic Lead β-Resorcylate



Unidentified Lead β-Resorcylate Salt (Sample 62-1)

Figure 1. IR Spectra of Three Lead β-Resorcylate Salts (Satriana, 1971a)

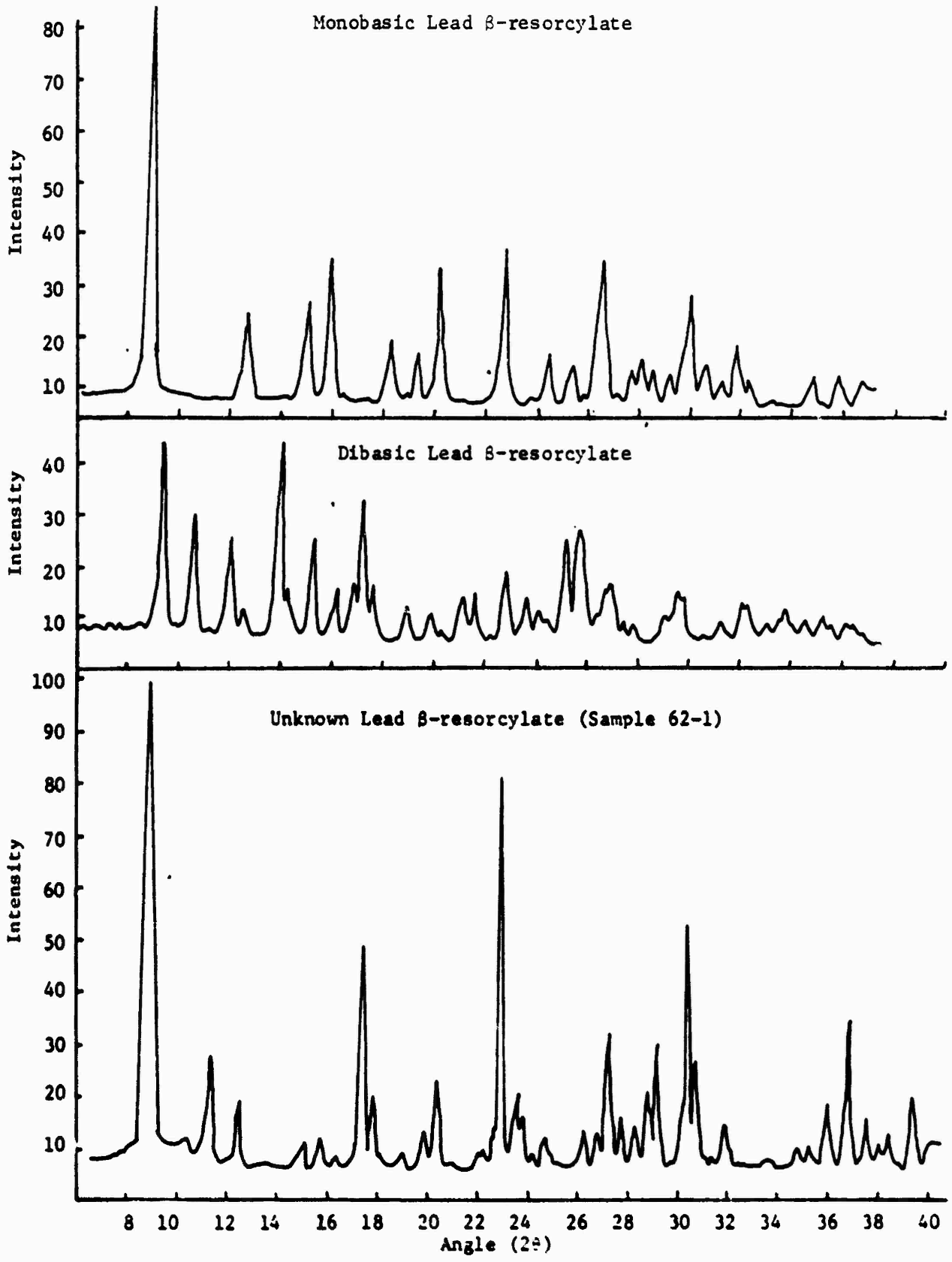
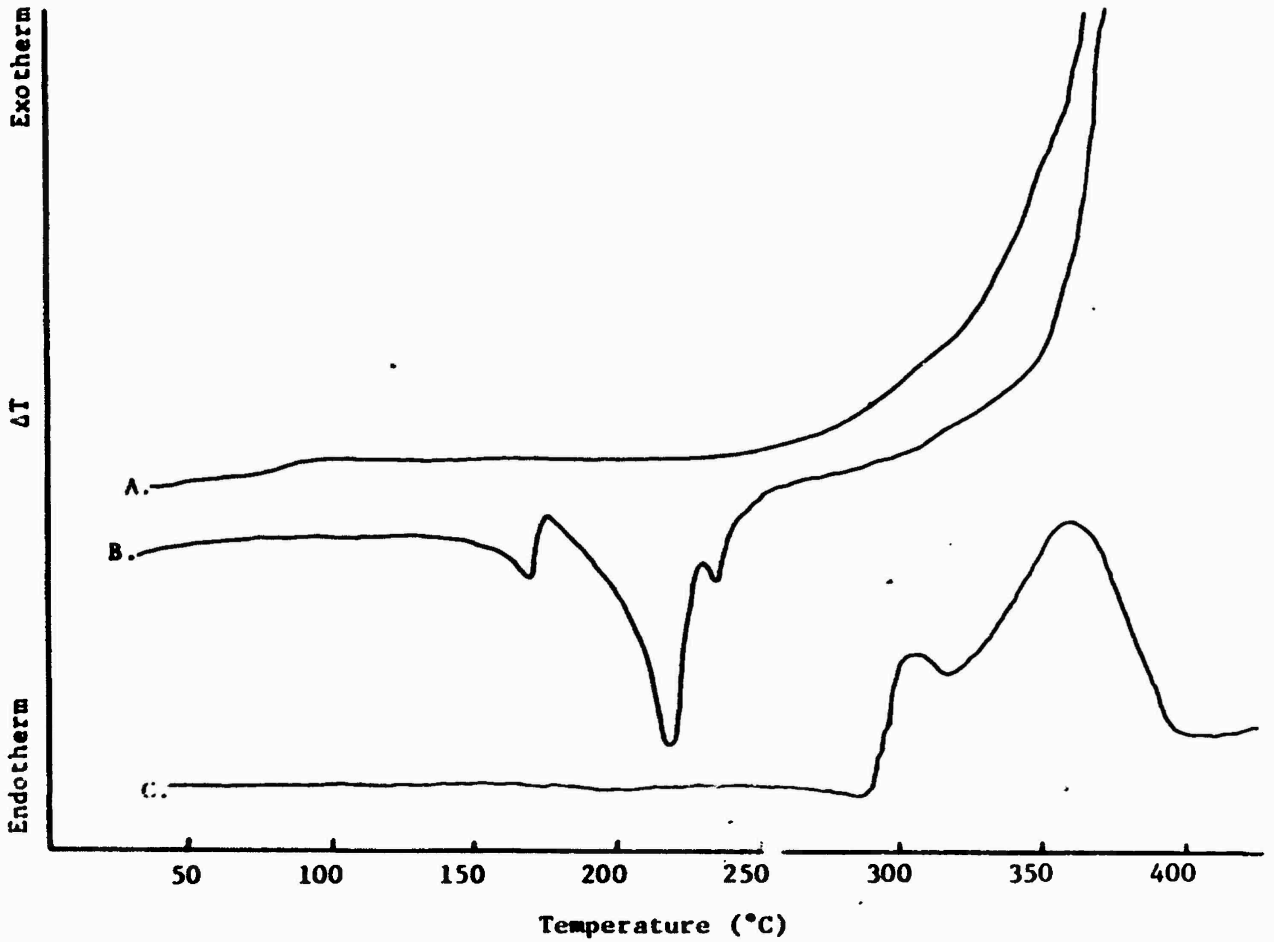
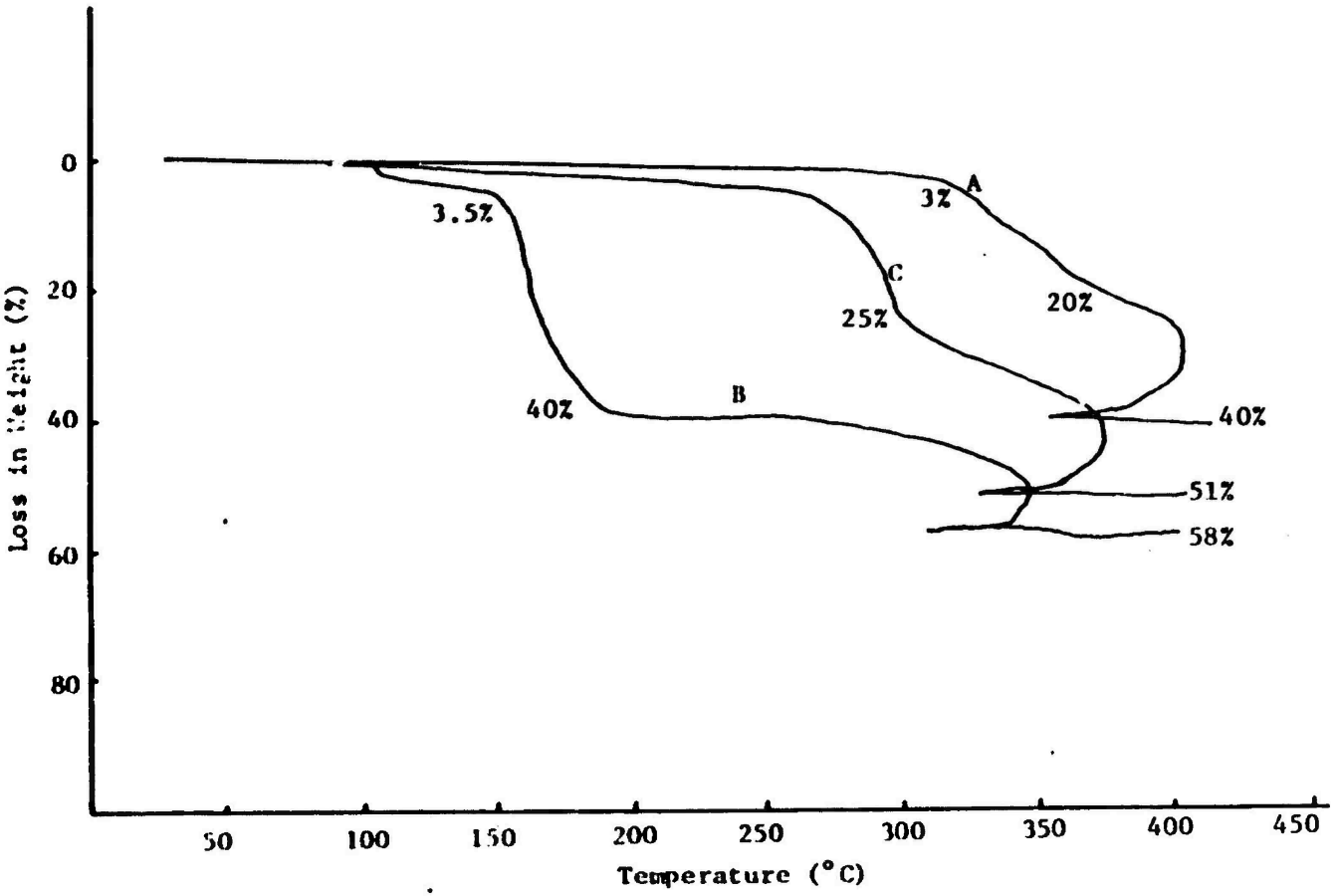


Figure 2. X-ray Diffraction Patterns of Three Lead β-resorcylate Salts. (Satriana, 1971a)



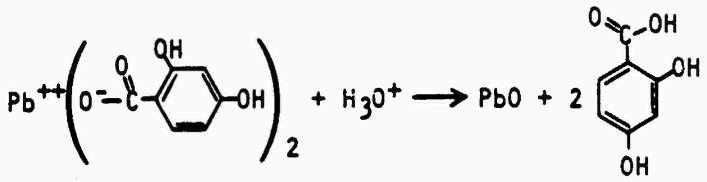
A. monobasic lead β-resorcylate
B. dibasic lead β-resorcylate
C. sample 62-1

Figure 3. Thermograms of Three Lead β-Resorcylate Salts. (Satriana, 1971a; Satriana, 1971b)

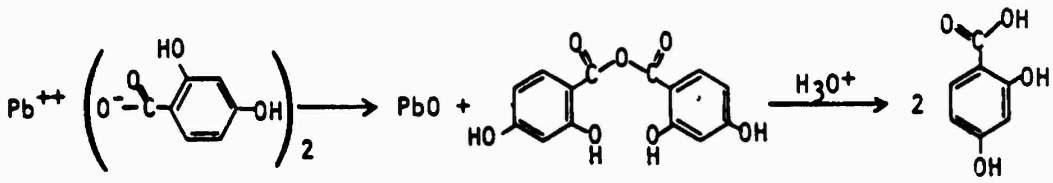


A. Monobasic lead β-resorcylate
B. Dibasic lead β-resorcylate
C. Sample 62-1

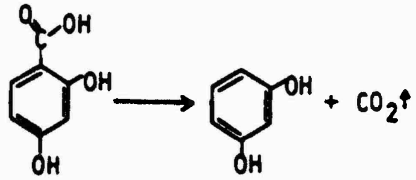
Figure 4. Thermogravimetric Trace of Three Lead β-resorcylate Salts. (Satriana, 1971a; Satriana, 1971b)



or by the initial fragmentation into lead oxide and resorcylic anhydride followed by hydrolysis.



The resorcylic acid would in all probability decarboxylate yielding resorcinol.



III. MONITORING AND ANALYSIS

A. Analytical Methods

Quantitative analysis for lead β-resorcylate may be accomplished by oxidation to lead oxide. The lead can then be determined by atomic absorption. Conversion to lead dithiocyanate allows quantitative determination of the lead content by absorption of 520 nm (Franson, 1975). Thin layer chromatography has been employed for analysis of lead β-resorcylate in solid propellant mixtures containing keranvic, stearic and salicylic acid salts of copper and lead (Habermann, 1971). Quantitative determination of the resorcylate in propellants has also been accomplished by gas chromatography. The propellant mixtures were first treated with a 1:1 mixture of trimethylsilylchloride and bis(trimethylsilyl) acetamide to convert the resorcylate to its trimethylsilyl ester. The products were then chromatographed at 70-190°C on a 3% UCW-98/Gas-Chrom Q column (Alley and Dykes, 1973).

B. Monitoring

No reference to existing environmental or industrial monitoring data on lead β-resorcylate was found in the literature.

IV. HEALTH EFFECTS

A. Biology

Studies on the biological interactions of lead β-resorcylate have not been reported in the literature. Therefore, the effects of these compounds on and their interactions with the mammalian body must be inferred from studies on other lead compounds. Lead acetate is the only lead compound similar to lead β-resorcylate for which toxicological studies have been performed. Therefore, much of the data presented herein is for lead acetate and the effects of lead β-resorcylate have been inferred from these data.

1. Absorption

Several studies have been conducted in order to determine the factors that influence lead absorption through the gastrointestinal tract in man. Under normal conditions, only 8-12% of the lead ingested by man is absorbed into the body. The main absorption site is the small intestines. The colon also absorbs some lead but none is absorbed in the stomach (Harvey, 1970). The main factor controlling lead absorption appears to be the motor activity of the bowel. In his studies with human subjects, Kehoe (1942) found no effect of dietary changes in calcium or phosphorus on lead absorption. Barltrop and Meek (1975) observed no definite differences between the absorption of inorganic and organic lead compounds in the gastrointestinal tract of rats. However, they did find that an increase in the dietary fat increased the amount of lead absorbed. The lead content, from lead acetate, of rat kidney was increased from 11.4 to 20 mg when 7.5% corn oil was added to the diet.

In contrast to the low percentage of ingested lead compounds absorbed through the gastrointestinal tract, absorption of lead and lead compounds by the respiratory tract is more rapid and more complete. Estimates of percentage of lead absorbed by the respiratory tract are 37% (Belilles, 1975). Absorption occurs in all portions of the respiratory tract and is dependent on three processes: deposition, mucociliary clearance and alveolar clearance. The deposition of lead containing particles in the respiratory tract is controlled mainly by the size of the particles, inhalation route, respiration rate and tidal volume. Large particles are generally trapped in the nasopharyngeal system. For smaller particles, deposition in the tracheobronchial system and lungs occurs. Once deposition has taken place, lead particles can be removed from the respiratory system by mucociliary clearance and alveolar clearance (Task Group on Metal Accumulation, 1973). Mucociliary clearance occurs as a result of mucous flow and ciliary activity in the nasopharyngeal and tracheobronchial systems. This clearance results in expectoration of the particles or translocation to the gastrointestinal tract. Alveolar clearance is the result of three processes (Task Group on Metal Accumulation, 1973).

- The particles can be transported from the alveoli to a region where mucociliary action will remove the material from the respiratory tract.

- The lead particles can pass through membrane into pulmonary tissues.

- The lead particles can pass through the pulmonary tissue into the blood or lymph system.

No absorption of inorganic lead occurs through the skin. However, organolead compounds such as tetraethyllead are known to rapidly penetrate the skin. Rostogi and Clausen (1976) showed that lead acetate and lead naphthenate was absorbed into the body of rats when a solution of this compound was coated on their skins. Based on the absorption data for other lead compounds, it is expected that lead β-resorcylate can be absorbed into the body via the respiratory and gastrointestinal tracts and through the skin. The respiratory tract will probably be the main absorption site, especially in occupational exposures. However, skin absorption may also be significant.

2. Transport

After absorption, lead is initially distributed to the soft tissues. While in the blood, inorganic lead is associated with the erythrocytes. The kidneys and liver are the main target organs for initial lead deposition. The biological half-life of lead in tissues is estimated at a few weeks (Clarkson, 1978).

Studies by Baxter *et al.* (1977) were carried out on 85-day old $B6CF_1$ Argonne bred female mice to determine differences in early retention of lead acetate and lead citrate at intervals up to 14 days. Tissues examined were liver, spleen, kidney, femur, lung, brain and blood. Ultrafilterable lead acetate or lead citrate containing labeled lead was intravenously injected at a level of 1 mg/kg (pH 5.1). After 1 hour the distributions of lead acetate and lead citrate were as follows (reported as percentage injected dose per g of tissue, % ID/g):

Organ	Lead Acetate % ID/g	Lead Citrate % ID/g
liver	51.1	17.6
spleen	18.5	3.6
kidney	35.3	63.4
femur	11.3	22.5

In animals given lead acetate, there was a tendency to accumulate more lead in the lungs and less in the brain and blood in one hour than in animals given lead citrate. During days 1-14, animals given lead acetate showed a

greater loss of lead from the liver and spleen, whereas animals given lead citrate showed a greater loss from the kidneys. Evidence from this study suggests that lead acetate undergoes hydrolysis in blood and is more rapidly converted to the inorganic lead than is lead administered as the citrate, which is a more stable complex.

Lead can also penetrate the placental and the blood-brain barrier. Organo-lead compounds such as tetraethyllead penetrate this barrier more rapidly than inorganic lead compounds. This penetration is often by a partially metabolized compound (Task Group on Metal Accumulation, 1973). Penetration of the blood-brain barrier by organic lead salts such as lead β-resorcylate has not been studied.

Lead compounds initially deposited in the soft tissue are gradually redistributed and the lead deposited in the bones, teeth and hair (Harvey, 1970). Deposition of lead in the bones resembles calcium deposition. High phosphate intake is necessary for bone deposition of lead, as the lead is deposited in the form of tertiary lead phosphate (Harvey, 1970). Vitamin D aides in lead deposition in the bones. However, bone lead content is highly dynamic. Low phosphate and/or high calcium intake, acidosis, and the presence of iodides and bicarbonate favor removal of lead from the bones. The biological half-life of lead in bone is ~10 years unless body conditions favor its removal (Clarkson, 1978).

3. Metabolism

In the body, organo-lead compounds can be slowly biotransformed. If this transformation is carried to completion, inorganic lead will result. In studies by Baxter *et al.* (1977), evidence of *in vivo* hydrolysis of lead acetate and lead citrate was observed. The rate and degrees of hydrolysis is dependent on the stability of the lead complex. Thus, *in vivo* hydrolysis of lead β-resorcylate could be expected to occur slowly.

4. Elimination

Lead is eliminated from the body through the feces and urine. The fecal lead content is mainly that lead which was not absorbed by the body, although there is some evidence that absorbed lead is excreted in the bile. Klaassen and Shoeman (1974) conducted a study of the biliary excretion of lead and concluded that the liver may have an active transport mechanism for lead excretion. However, Kehoe (1961) found that inhaled lead did not reach the feces of human subjects and the major portion of absorbed lead is excreted in the urine. This excretion route is favored by those mechanisms which tend to mobilize lead from bone and soft tissue and by the presence of chelating agents such as dimercaprol, calcium disodium edetate (ethylenediamine tetraacetic acid) and penicillamine.

5. Pharmacology

Lead preferentially binds with sulfur and sulfur containing organics forming compounds and complexes of greater stability with this element than with oxygen or nitrogen containing organics. Thus, lead is expected to exert a major influence on SH-dependent enzymes by combining with the sulhydryl group. Lead also binds with oxygen and nitrogen functional groups of proteins, enzymes, etc. Literature evidences suggests that administration of lead complexes such as lead acetate results in these types of interferences.

Lead interferes with *in vivo* biosynthesis of heme, globin synthesis in the erythrocytes and with the utilization of iron. A schematic showing the various points of lead interference is presented in Figure 5. Lead inhibits the synthesis of porphobilinogen (Step #2) by interfering with the SH-containing enzyme, δ-aminolevulinic acid dehydratase (ALAD). The interference with heme synthetase (Step #6) is also well documented as a characteristic of human lead poisoning. Lead inhibition of the enzyme δ-aminolevulinic acid synthetase (ALAS) (Step #1) is based on experimental evidence. Other interference mechanisms have not been clearly established.

Other effects of biochemical interactions of lead have been documented. For example, Ono *et al.* (1973) showed that intraperitoneal injection in mice of 0.3 ml of a 0.9% saline solution containing 1 mM lead acetate caused an increase in SH groups in the kidney over that in controls. Thus, the amount of SH in mouse kidney may be an indication of the degree of disturbance caused by lead or other heavy metals.

Hrdina *et al.* (1976) examined the effect of heavy metals on brain biogenic amines in the rat. In part of the study, rats were chronically fed lead acetate at levels of 0.2 and 1.0 mg/kg/day for 45 days. This treatment caused an increase in cerebrocortical acetylcholine and a decrease in brain stem norepinephrine. The changes in the regional levels of these biogenic amines occur before outward toxic effects become manifest. Thus, these changes may be early signs of adverse effects of lead on the central nervous system.

Cornell and Filkins (1974) administered 5 mg lead acetate intravenously to male rats. Gluconeogenesis was determined *in vivo* by measuring conversion of labeled alanine into glucose and *in vivo* by using isolated hepatocytes. Results showed that lead treated rats sustained a depression in the conversion of labeled alanine into blood glucose. In isolated hepatocytes, gluconeogenesis from alanine, lactate or pyruvate was reduced 40-60%. It was suggested that there is a locus of lead action in the mitochondria and that defects in the regulation of glucose by the liver may exert some effect in the toxicity of acute lead poisoning.

Studies on the effect of experimental lead poisoning on the permeability of the lysomal membrane of the rat were carried out by Apostolov *et al.* (1977). Results showed that as early as the third day of a daily feeding of 20 mg of lead acetate/kg body weight, two lysosomal enzymes, alpha-manno-

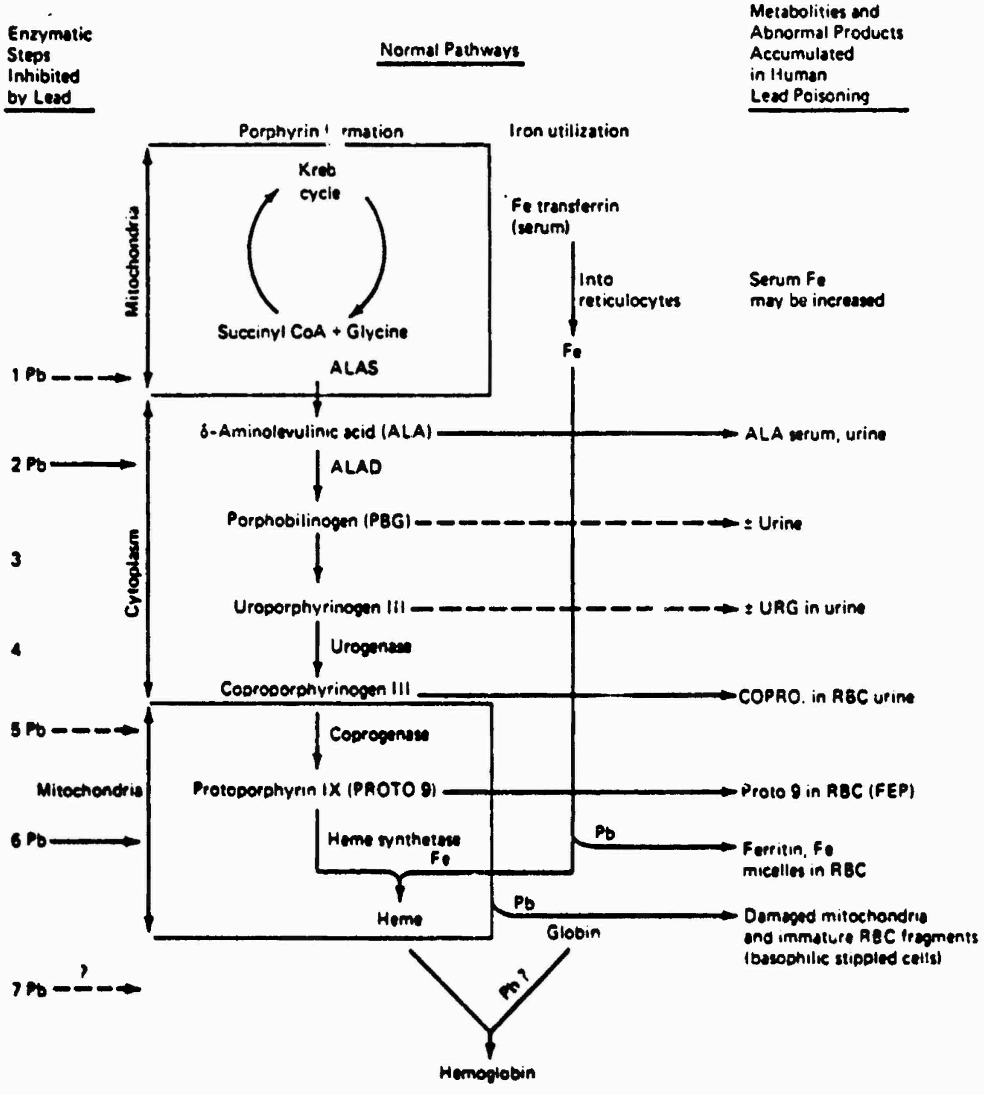


Figure 5. Biosynthesis of Heme Showing Points of Lead Interference (Beliles, 1975)

sidase and beta-acetylglucosaminidase, were found to have been activated in the blood serum. Thus, in the pathogenesis of lead poisoning, damage to the lysosomal membrane may play an important role.

B. Effects of Human Exposure

1. Epidemiology

No information was found on the epidemiology of lead β-resorcylate. However, chronic lead poisoning in man is well documented. The effects of lead poisoning observed in man are listed in Table II.

2. Occupational Exposure Studies

Occupational exposure studies on lead β-resorcylate have not been conducted. However, several studies with lead acetate have been performed. Cytogenetic studies were carried out on 11 male volunteers (20-30 years) who ingested lead acetate for 49 days. The concentration of lead in the blood was maintained at 400 ppb from the third week. At the end of the study, the lymphocytes showed increased mitotic activity but no increase in chromosome abberations (Bijlsma and De France, 1976).

In a review of the effects of lead on the female and reproduction, Rom (1976) points out that there is biologic evidence that women may be more susceptible to the toxic effects of lead. In animal studies, lead exerts a markedly deterious effect on pregnancy and fetal development. A still unresolved question is whether lead is responsible for chromosomal aberrations. It was hypothesized that there may be no threshold limit at which the adverse effects of lead could not occur during the course of the development of the human fetus.

In ulnar motor nerve conduction studies on 11 male volunteers fed lead acetate for 49 days, Verberk (1976) showed that there was a 13% reduction in conduction velocity in fast conducting fibers and 15% reduction in slow conducting fibers.

C. Effects on Experimental Animals

1. Acute Toxicity

No mammalian toxicological data exists for lead β-resorcylate. A similar lead compound, lead salicylate, was found to have a low oral acute toxicity to rats of 4.3 g/kg (Potter, 1978).

2. Subacute Toxicity

No specific information exists on the subacute or chronic toxicity of lead β-resorcylate. However, information on other organo-lead(+2) compounds may give an indication of the toxicity of lead β-resorcylate. Lead acetate concentrations of 20 mg/kg/day to calves induced neurologic altera-

Table II. Effects of Lead Poisoning (Beliles, 1975)

Central Nervous System

- Encephalopathy
- Fatigue
- Headache
- Tremor
- Hallucinations
- Intellectual deterioration
- Cortical atrophy
- Hydrocephalus
- Blindness
- Convulsions

Gastrointestinal

- Colic
- Loss of appetite
- Nausea
- Vomiting
- Constipation

Hematologic

- Anemia, hypochromic normocytic
- Basophilic stippling erythroblasts
- Binucleated erythroblasts
- Increased serum iron

Renal

- Hyperuricemia
- Nephritis
- Glycosuria
- Hyperaminoaciduria

Other

- Gum lead line (black or purplish line of gum margin)
- Skin pallor (ashen gray)
- Loss of weight
- Weakness, extensor muscles (wrist or foot drop)

tions (Wells *et al.*, 1976). Hoffman *et al.* (1974) found that sublethal doses of lead acetate caused ultrastructural changes in rat livers.

3. Chronic Toxicity

Numerous studies have been conducted on the effects of chronic exposure of experimental animals to lead acetate and other lead compounds. Many of these studies were aimed at behavioral effects, pharmacology, carcinogenicity, etc. of lead acetate and are reported in other sections of this report. However, Eyden *et al.* (1978) have conducted a long-term, well controlled lead acetate feeding study to determine the effects of this compound on survival and body weight in Balb/c^+ mice. These animals were fed lead acetate ranging from 0 to 4.0% of their diet. The mean survival time of the controls and mice receiving 0.5 to 4.0% dietary lead acetate are shown in Table III. Inspection of the table indicates a dramatic relationship between dose and survival time. Longer survival rates were observed for the 0.1% dietary level with 57% still living at the end of 541 days. The body weights of the mice receiving the 1.0% dietary level of lead acetate began to decrease significantly at 4 weeks after start of treatment as compared to the controls. At 11 weeks, these mice weighed approximately half that of the controls. Similar survivals were noted by Van Esch and Kroes (1969) for Swiss mice in their study of tumor induction by lead acetate.

4. Teratogenicty and Mutagenicity

Several studies have been conducted on the teratogenicity of lead acetate. Jacquet *et al.* (1975) administered a diet containing 0, 0.125, 0.250 and 0.500% lead acetate to female mice after mating. The mice were dissected 18 days later. The administration of lead was found to reduce markedly the incidence of pregnancies, to increase postimplantation loss, and to decrease the weight of the surviving embryos. However, no gross abnormalities were observed in the lead treated embryos. Zegorska *et al.* (1974) demonstrated that a single injection of 2.5 g lead acetate/100 g of body weight on the 9th day of pregnancy caused a 75% fetal mortality and a 20% incidence of developmnental defects in the head of the rat fetuses. This study would indicate that, under these conditions of acute administration, lead acetate was teratogenic in the rat. Kennedy *et al.* (1975) treated pregnant rats and mice by gavage with doses up to 714 mg lead acetate/kg or 10 mg of tetraethyl lead/kg. These lead compounds were administered daily during the period of rapid organogenesis. There were no signs of teratogenicity resulting from use of either lead compound.

Gilani (1974) studied ultrastructural changes during cardiogenesis in thick embryos administered 0.015 mg lead acetate/egg at day 2 of incubation. Abnormalities observed in the endocardial cushion were swollen mitochondria, mitochondria with abnormal cristae and matrix, and disrupted nuclear membrane. The mitochondria seemed to be the organelle most frequently affected. Thus, it was shown that lead poisoning can induce ultrastructural changes in developing heart.

Table III. Relation Between Dietary Lead Acetate Dose and Mean Survival Time (Eyden *et al.*, 1978)

Lead Acetate (%)	Mean Survival Time (days)	Sex of Animal	Number of Animals
4.0	11.3 ± 1.6	F	10
3.0	18.3 ± 3.6	F	10
2.0	43.2 ± 8.25	F	10
1.0	98.7 ± 1.6	F	21
1.0	99.9 ± 1.9	M	21
0.5	115.1 ± 1.6	F	10
0	745 ± 17.2	M	150

By comparison with lead acetate, it is expected that lead β-resorcylate will exhibit teratogenic effects when administered to pregnant animals in either an acute or chronic exposure.

5. Carcinogenicity

The ability of lead acetate and basic lead acetate to induce renal tumors in experimental animals has been reported by several authors (Van Esch *et al.*, 1962; Van Esch and Kroes, 1969; Waszynski, 1977). In their initial experiments with Wistar rats, Van Esch *et al.* (1962) found renal neoplasms in 13 of 24 rats fed a diet containing 1.0% lead acetate. Even at the 0.1% level 11 of the 32 rats had renal tumors. In later experiments Swiss mice were fed diets containing 0, 0.1% and 1.0% (reduced to 0.5% on the 92(M) or 115th (F) day) basic lead acetate for 2 years. Sick or dead animals were autopsied as were all animals living at the end of 2 years. Of the 1.0% group, 7 of 50 animals had renal tumors (1 renal adenoma in a female, and 2 renal adenomas and 4 renal carcinomas in males). Only 1 mouse in the 1.0 (0.5)% group had a renal tumor. However, most of these animals died early in the experiment due to basic lead acetate poisoning. In this study, hamsters were also fed basic lead acetate, however, they also died early in the experiment from toxic effects.

A more recent study by Waszynski (1977) confirms the earlier results on the carcinogenicity of lead acetate. This author also found the rat to be more susceptible to renal tumors as the result of lead acetate intoxication than the mouse.

6. Behavior - Symptomology

Several studies have been conducted to determine the effects of lead acetate on behavior. Behavioral responses of experimental animals are much the same as those observed in human infants. Lead β-resorcylate absorption should result in the same general behavioral symptoms.

Sabotka and Cook (1974) examined the postnatal exposure of rats to lead acetate and its possible relationship to minimal brain dysfunction. In this study, rats were fed 0, 9, 27 or 81 mg lead acetate/kg body weight for 3 weeks. As weanlings, the rats displayed behavioral characteristics similar to those seen in minimally brain dysfunctional children. Thus, it would appear that exposure of rats to lead during the perinatal period may bear a etiological relationship to some of the variants of minimal brain dysfunction.

Golter and Michaelson (1975) studied the growth, behavior, and brain catecholamines in lead exposed neonatal rats. Results showed that daily oral administration of lead to newborn rats exerted no adverse effect on their body weight. They were, however, more active than age matched controls. Levels of brain dopamine were unchanged, whereas norepinephrine levels were increased. These findings would suggest a possible relationship between lead exposure during early development, increased motor activity, and brain epinephrine, and not dopamine, as had earlier been postulated.

It was pointed out (Michaelson and Saverhoff, 1974) that the older method of studying lead encephalopathy produced in suckling rats when lead is added to the mother's diet, showed only growth retardation, and paraplegia and lesions of the cerebellum which developed during the 4th week of life. The authors, therefore, devised a new model for studying lead induced brain dysfunction in the suckling rat. In this model, they changed the mother's diet on the 16th day from one containing 5% lead acetate to one containing 25 ppm of lead and allowing the neonates free access to the same solid diet as the mother. Results showed that the sucklings had retarded body growth but did not develop paraplegia or damage of the cerebellum. However, during the 4th week, these animals did develop hyperactivity, tremors and sterotyped behavior. The authors suggested that the severe paraplegia and histopathologic lesions reported by workers using the older model obscures the signs of minimal brain dysfunction. Accordingly, they suggest use be made of this procedure as a model for studying the subtle effects of lead intoxication on the central nervous system.

Allen *et al.* (1974) showed that when infant rhesus monkeys were exposed to lead by addition of 0.5-9 mg lead acetate/kg body weight, they developed symptoms of lead poisoning within 6 weeks. The predominant changes noted were seizures, muscular tremors, and altered social behavior. In some of the more severely affected animals, visual impairment was also noted. Although visual impairment was reduced and the seizures subsided following removal of lead from the diet, the altered social behavior persisted in the infant monkey. However, in adolescent and adult monkeys, no obvious behavioral adnormalities were observed. Thus non-human primates are similar to humans in their reactions to lead in that the infant is more susceptible to lead poisoning than the adults.

Morrison *et al.* (1975) carried out a study in which mice suckled by mothers given tap water and by mothers given a 5 mg/ml of lead acetate solution during lactation were given a choice between tap water and a lead acetate solution after lactation. Results showed that all offspring demonstrated an immediate aversion to the lead acetate solution. Further, the lead acetate offspring drank a greater quantity of total fluid (tap water plus lead acetate) after weaning than the controls. This would indicate changes in both learned and unlearned motivation for fluid after ingestion of lead via the mother's milk in infancy.

V. ENVIRONMENTAL EFFECTS

A. Entry into the Environment

Lead β-resorcylate is manufactured in the United States for use as a burning rate modifier in solid propellant formulations. Under current operations, this lead compound is used sporadically by Radford AAP with an average use rate of 670 lb/month. At full mobilization Radford AAP would require 3,000 lb/month of lead β-resorcylate. Badger and Sunflower AAPs also use this compound when they are operational. At full mobilization use rates of lead β-resorcylate, ~45 to 150 lb/month of this compound are estimated to be lost to the New River (Kitchens *et al.*, 1978). This source of lead β-resorcylate is probably the major point of entry of this compound into the environment.

B. Behavior in Soil and Water

1. Transport, Accumulation and Degradation

Losses of lead β-resorcylate to the environment will occur primarily in the Radford AAP effluent to the New River. The river concentrations which would occur at different flow rates and mixing are shown in Table IV.

Table IV. Lead β-Resorcylate Levels (ppm) in the New River at Full Mobilization

Degree of Mixing	Low Flow (620 mgd)	Average Flow (2380 mgd)
1%	.10	.03
10%	.01	.003
100%	.001	.0003

The table assumes the lead β-resorcylate is initially in the water. Weitzel *et al.* (1976) found lead levels at Radford AAP in the New River ranged from 1-2 ppb. However, sediment levels were greater than 100 ppm. These data indicate that lead and lead β-resorcylate accumulated in the sediment of the New River.

Once in the sediment, it is probable that the lead β-resorcylate is slowly degraded either biologically or through complexation by the sediment. This complexation should be similar to that observed with other organo-lead compounds in soil. A pathway for complexation of organo-lead compounds

in soil is shown in Figure 6. The end result of this pathway is generally immobilization of the lead as insoluble carbonate or phosphate salts. Lead β-resorcylate is expected to undergo this type of reaction. The controlling factors for lead fixation in soils appears to be soil pH and cation-exchange capacity (Zimdahl and Skogerboe, 1977).

2. Background Concentrations

Although natural lead β-resorcylate concentrations in the environment are non-existant, lead background concentrations have been studied. Swaine (1955) estimated typical levels of lead in soil ranged from 1-200 ppm with a mean of 15 ppm. Kopp and Kroner (1967) sampled 1500 streams and found lead levels greater than 10 ppb in 20% of the samples. Livingstone (1963) estimated natural lead levels in water to be between 1-10 ppb.

C. Effects on Animals

1. Mammals

The effects of compounds related to lead β-resorcylate on experimental mammals were discussed in Section IV C. No information on the effects of environmental exposure to lead β-resorcylate or related compounds on mammals was found.

2. Birds

No information on the effects of lead β-resorcylate or related compounds on birds was found.

3. Fish

In a study by Warner *et al.* (1978), fathead minnows (*Pimephales promelus*) were exposed to 4096 ppm of lead β-resorcylate in hard water (192 ppm as $CaCO_3$). No deaths were observed. As shown in Table V, the toxicity of lead compounds is reduced 20-70 fold as the hardness of the water is increased 18 fold. By analogy, the toxicity of lead β-resorcylate in soft water (20 ppm $CaCO_3$) should be ~450 ppm. Therefore, if it is not degraded to a soluble lead compound, lead β-resorcylate should have a low acute toxicity to fish. However, this compound may prove to be a chronic toxic hazard if it bioaccumulates in fish. Although no specific information is available on bioaccumulation of lead β-resorcylate, the solubility characteristics of the dibasic salt indicate a potential for bioaccumulation.

4. Amphibians

No information was found on the effects of lead β-resorcylate or related compounds on amphibians.

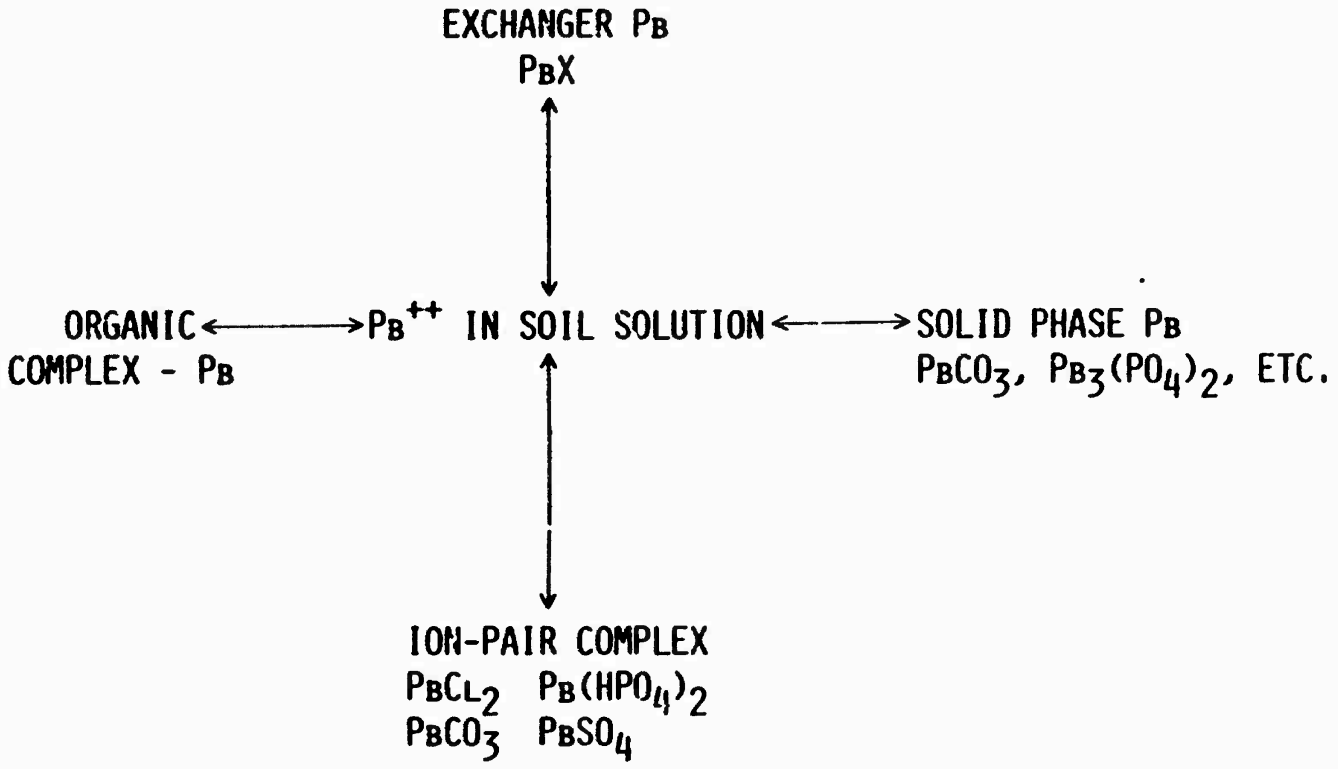


Figure 6. Complexation of Organo-lead Compounds in Soil (Jurinak and Santillan-Medrano, 1974)

Table V. Effects of Lead Compounds on Fish.

Organism	Compound	96 Hr. LC50 (ppm as Pb)	Hardness (ppm as $CaCO_3$)	Reference
Fathead minnow (*Pimephales promelas*)	$PbCl_2$	5.6-7.3	20	Pickering and Henderson, 1965
"	$PbCl_2$	482	360	"
"	$Pb(C_2H_3O_2)_2 \cdot H_2O$	7.5	20	"
Bluegills (*Lepomis macrochirus*)	$PbCl_2$	23.8	20	"
"	$PbCl_2$	442	360	"

5. Invertebrates

Warner *et al.* (1978) estimated the EC50 toxicity of lead β-resorcylate to *Daphnia magna* to be between 10 and 50 ppm in hard water (192 ppm as $CaCO_3$). If the toxicity of lead β-resorcylate is projected to increase 10-50 times in soft water (~20 ppm as $CaCO_3$), then the EC50 range to *Daphnia magna* would be 0.2-5 ppm. These estimates would indicate that lead β-resorcylate has a moderate toxicity to aquatic invertebrates.

Bringmann and Kuhn (1977) determined the LC50 of lead acetate to *Daphnia magna* to be 2.5 ppm in soft water. Lead β-resorcylate and lead acetate would thus appear to have a similar toxicity to aquatic invertebrates.

6. Microorganisms

No information was found on the toxicity or degradation of lead β-resorcylate or related compounds on microorganisms.

D. Effects on Plants

No information was found on the interaction of lead β-resorcylate or related compounds with plants.

VI. REGULATIONS AND STANDARDS

A. Air and Water Standards

There are no air and water standards specific for lead β-resorcylate. However, criteria have been set for lead in potable water and effluents (EPA, 1976). For potable water the lead content can be no greater than 50 µg/l. Due to the variability of lead solubility and toxicity in different waters, the following criterion has been set for effluents (using the receiving water as a diluent):

- 0.01 times the 96-hour LC50 value expressed as dissolved lead for the most sensitive species.

This criterion requires that 96-hour LC50 test be performed with the actual water samples and the most sensitive species in the local ecosystem.

B. Human Exposure Standards

No specific standards for lead β-resorcylate have been set for occupational exposure to this chemical. However, a criteria document has recommended an air standard of 150 µg(Pb)/m^3 for lead stearate (NIOSH, 1977). A similar TLV for lead β-resorcylate should afford workers adequate protection.

VII. EVALUATION AND COMMENTS

Very little is known concerning the chemistry, and toxicological and environmental hazards of lead β-resorcylate. No information on the acute and chronic mammalian toxicology of this salt is available. The biological interactions of lead β-resorcylate can only be inferred from studies on lead acetate. Aquatic toxicity information on lead β-resorcylate is limited to two preliminary studies. These studies indicate a low acute toxicity of this compound to fish and a moderate toxicity to invertebrates.

No information is available on the environmental fate of lead β-resorcylate. Hydrolysis of this salt to inorganic lead and bioaccumulation are both possible.

In view of the very limited data available on lead β-resorcylate, the following studies are recommended to fill in the information gaps.

1. Further chemical analysis to identify the specific lead compounds and their percentage composition in lead β-resorcylate used in propellants. This work should include further enumeration of the chemistry of lead β-resorcylate and development of a scheme to qualitatively identify and quantitate lead β-resorcylate and breakdown products in the environment.

2. Sampling and analysis of lead β-resorcylate concentrations entering the New River in Radford AAP effluents and correlation of these results with production. The concentrations of these salts and breakdown products in the sediments and biota of the New River should also be determined.

3. The LD50 of lead β-resorcylate to rats should be determined.

4. A chronic feeding study using rats should be undertaken to determine the long term effects and carcinogenic potential of lead β-resorcylate.

5. Effectiveness of the proposed treatment facilities at Radford AAP in removing this salt from the effluent should be evaluated.

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LIST OF ABBREVIATIONS

°C	- Degrees in Centegrade
CA	- Chemical Abstracts
$CaCO_3$	- Calcium Carbonate
CAS	- Chemical Abstracts Service
CI	- Collective Index
CO_2	- Carbon Dioxide
DTA	- Differential Thermal Analysis
EC50	- Concentration Required to Affect 50% of the Exposed Population
F	- Female
g	- Gram
gpd	- Gallons per Day
H_3O^+	- Hydronium Ion
%ID/g	- Percentage Injected Dose per Gram of Tissue
kg	- Kilogram
LC50	- Concentration Required to Kill 50% of the Exposed Population
LD50	- Dose Required to Kill 50% of the Exposed Population
M	- Male
m^3	- Cubic Meter
mg	- Milligram
µg	- Microgram
ml	- Milliliter
mM	- Millimolar
nm	- Nanometer
No.	- Number
%	- Percent
Pb	- Lead
PbO	- Lead Monoxide
pH	- Negative Log of the Hydrogen Ion Concentration
ppb	- Parts Per Billion
ppm	- Parts Per Million
SH	- Sulfhydryl Group
ΔT	- Temperature Change
TGA	- Thermogravimetric Analysis
TLV	- Threshold Limit Value

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