inadequate tablet shear strength, is thought to be the principal cause of capping and lamination, although there is some disagreement on this point (7). In support of this view (4), tablet formulations found to consistently laminate or cap were satisfactorily made with a press utilizing flexible die walls which retreat from the tablet prior to ejection.

In any case, it is apparent that the ejection of the tablet from the die subjects it to significant shear stresses. It is likely, therefore, that some internal strutural changes occur even in tablets that survive ejection and appear intact. For this reason, viscoelastic microconstants, when considered together with die wall stress, indicate the mechanical properties of the tablet within the die cavity and reflect the ability of the tablet to withstand ejection. In many, if not all, cases these parameters will not apply to the ejected tablet even though it has escaped gross fracture.

Because tablets were allowed to remain in the die for an extended period (several minutes in many cases) before being ejected manually by prying up the lower punch, the ejection event was atypical and did not reproduce production conditions. Studies utilizing an instrumented ejection cam to produce normal ejections are in progress to investigate this and other aspects of tablet viscoelasticity.

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Inhibition of Oral Lead Absorption in Rats by Phosphate-Containing Products

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Abstract □ Recent studies indicate that elevated blood lead levels in children are largely a result of exposure to this metal *via* the oral route. A logical approach to decrease or prevent lead intoxication would be to reduce its absorption as soon as lead ingestion is known or suspected. Presently, however, there are no readily available products recommended to accomplish this goal. It was found that a phosphate-buffered, saline laxative reduced lead absorption over 50% in rats administered a single oral lead acetate dose, presumably by promoting the formation of less soluble lead salts. A popular phosphate-containing carbonated beverage also decreased lead absorption ~30% after oral lead acetate or lead-based paint doses, possibly by decreasing solubility, dissolution rate and/or GI motility. It is possible that these household products, and those with similar ingredients, may be safely used to reduce lead absorption in humans.

Keyphrases □ Lead absorption—reduction *in vivo* in rats by administration of phosphate-containing products □ Phosphate—lowering of blood lead levels in rats after oral administration of lead acetate or lead-based paint.

Ingested lead is the major source of the body burden of lead for most people (1). Children are exposed to lead from household dust (2), paint (3), and hand-to-mouth activity (4). Because they absorb a greater percentage of ingested lead than do adults (5), children have a higher risk of lead intoxication. Children with pica may be prone to chronic and repeated lead intoxication (6). Therapeutic intervention is not initiated, however, until blood-lead concentrations become elevated or symptoms of lead toxicity appear. It is recognized that subtle effects of lead on behavior and intelligence may occur in children at levels of exposure which do not produce elevated blood-lead concentrations or symptoms of lead intoxication (7). Prevention of lead exposure is therefore extremely important. Reduction of environmental lead and maintenance of sufficient dietary mineral intake partially achieve this objective. Presently there are no methods recommended to prevent or reduce the absorption of ingested lead.

A logical biopharmaceutical approach to reduce the extent of intestinal lead absorption, and thereby lead intoxication, is to decrease its solubility and dissolution rate in the GI tract. For some compounds, the extent of oral absorption is directly related to the absorption rate (8), which in turn may be limited by the rate of dissolution of the solid compound in the gut fluids (9). Dissolution rate is proportional to solubility, among other factors (10). Since the solubility products of lead phosphate and hydroxide are very low (Ksp $Pb_3(PO_4)_2 = 8 \times 10^{-43}$, Ksp of $Pb(OH)_2 = 1.2 \times 10^{-15}$) (11), it is possible that products containing phosphate or hydroxide ions might significantly reduce the extent of lead absorption by promoting the formation of insoluble lead phosphate and hydroxide salts in the GI tract. Since several household products contain

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Table I—Precipitation of Lead *In Vitro*

Test Product[a]	Phosphate–Lead Molar Ratio	Lead Remaining in Solution, %	Supernatant pH
Water	—	100	4.5[b]
Carbonated beverage	0.5	29 ± 2[c]	3.8
Phosphoric acid	0.5	14 ± 6	3.1
Laxative (1:10 dilution)	4.4	0.17 ± 0.04	5.6
Laxative (1:250 dilution)	1.8	0.19 ± 0.01	4.0
Antacid	—	4.7 ± 0.3	7.4

[a] See Footnotes 1–3 for names of test products. [b] Samples were pooled for pH determination. [c] Data represent mean ± *SE* of three determinations and are expressed as percentage of control.

high contents of phosphate or hydroxide, the feasibility of lead absorption inhibition with these products was tested.

EXPERIMENTAL

Precipitation of Lead *In Vitro*—The effects of several household products on lead solubility were examined in preliminary *in vitro* experiments. The test products included a carbonated beverage[1], a phosphoric acid solution with the same phosphate content (0.56 *M*) and pH (2.4) as the carbonated beverage, a phosphate-buffered, saline laxative[2] diluted 10-fold and 250-fold, and an antacid containing magnesium and aluminum hydroxides[3]. The carbonated beverage was stored in an open container prior to use to allow liberation of carbon dioxide. In a glass tube, 0.25 ml of a lead acetate solution (10 mg of Pb/ml, pH 4.5) was mixed with 1 ml of the test product. The pH and the amount of lead remaining in the 1000×*g* supernatant solution were measured. Lead analyses were performed using atomic absorption spectrophotometry[4].

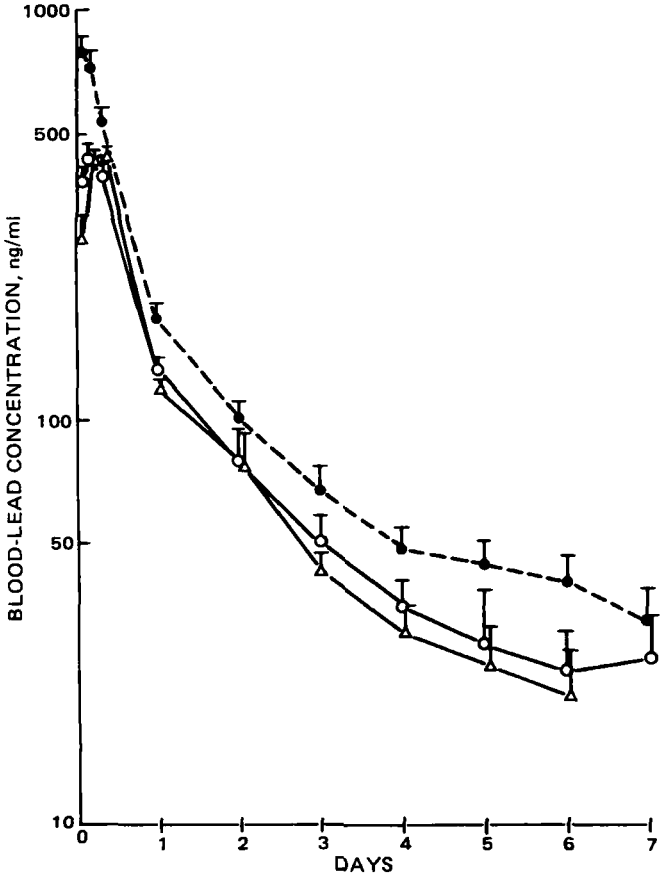

Figure 1—*Effects of a carbonated beverage (○) and a phosphoric acid solution (△) on absorption of lead after oral administration of a lead acetate solution, compared with control (●). Values represent mean* + SE.

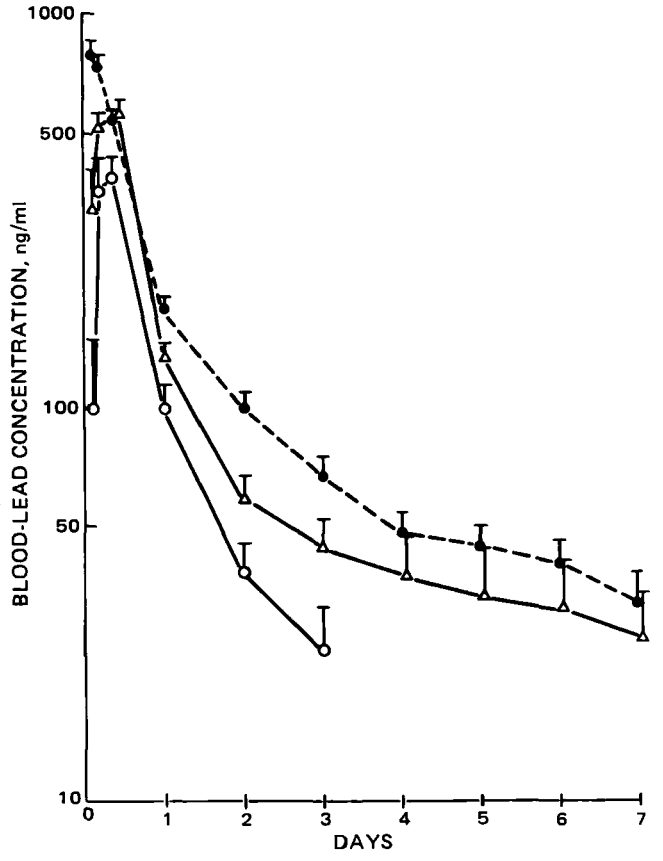

Figure 2—*Blood-lead concentrations in rats administered a 10 mg/kg oral lead dose followed by water (●), or a phosphate-buffered saline laxative diluted 1:10 (○) or 1:250 (△). Values are mean* + SE.

***In Vivo* Studies—**After an overnight fast, male Sprague-Dawley rats[5] (200–300 g) were administered, by gastric intubation, a single lead dose followed immediately by 1 ml of a test product or control treatment. Lead was administered as lead acetate (10 mg of Pb/ml, pH 4.5) or as powdered lead-based paint[6] suspended in 2% methylcellulose. The doses were 10 mg of Pb/kg, when administering lead acetate, and 50 mg of Pb/kg, when administering the lead-based paint. The amounts of lead and test product administered were similar to those used in the *in vitro* experiment. The control groups were administered 1 ml of distilled water following the lead dose. There were 5–9 rats in each group. Blood samples were collected in heparinized glass tubes by tail clipping and milking at 2, 4, and 8 hr, and every day for 7 days postdose, and were frozen immediately. Whole blood lead concentrations were determined using a previously described atomic absorption spectrophotometric method (12). During the course of the experiments the animals were housed in stainless steel cages with wire mesh floors.

Data Analysis—The area under the blood-lead concentration *versus* time curve (AUC) from 0 to 7 days was calculated for each rat. This parameter has been shown to be a good indicator of the extent of lead absorption (13). Systemic lead clearance was assumed to be unaffected by these oral treatments. Differences between any two groups were tested for significance using the Student's *t* test. All data are expressed as mean ± *SE*.

RESULTS AND DISCUSSION

Precipitation of Lead *In Vitro*—The effects of each test product on the solubility of a lead solution typical of a lead dose are shown in Table I. All test products precipitated lead from the solution, with greater precipitation at higher phosphate–lead ratios, as expected. At equal

[1] Coca-Cola.
[2] Phospho-Soda buffered saline laxative, C.B. Fleet Co., Lynchburg, Va.
[3] Maalox, W. H. Rorer, Fort Washington, Pa.
[4] Perkin-Elmer 603 with HGA 2000 Controller.
[5] Blue Spruce, Altamont, N.Y.
[6] National Bureau of Standards Reference No. 1579, 11.87 ± 0.04% Pb.

Table II—Inhibition of Lead Absorption *In Vivo*

Lead Dose	Test Product[a]	N	C_{max}, ng/ml	p	AUC, ng days/ml	p	Lead Absorption Relative to Control, %
10 mg Pb/kg Lead Acetate	Water	9	843 ± 64[b]		807 ± 71[b]		100
	Carbonated beverage	8	482 ± 36	<0.001	581 ± 57	<0.05	72
	Phosphoric acid	6	478 ± 19	<0.001	533 ± 39	<0.01	66
	Laxative (1:10)	6	433 ± 47	<0.001	359 ± 64	<0.001	44
	Laxative (1:250)	6	601 ± 42	<0.02	616 ± 79	NS	76
	Antacid	5	685 ± 77	<0.05	809 ± 115	NS	100
50 mg Pb/kg Lead-Based Paint	Water	9	871 ± 52		1095 ± 98		100
	Carbonated beverage	9	613 ± 30	<0.001	769 ± 62	<0.02	70

[a] See Footnotes 1–3 for names of test products. [b] Data are mean ± *SE* and were evaluated for statistical difference from the appropriate group administered water.

phosphate content, the carbonated beverage was not as effective as phosphoric acid in precipitating lead. The presence of other ingredients in the carbonated beverage might have altered the solubility product of lead phosphate.

Effects on Oral Lead Absorption—Decreased lead solubility *in vitro* was associated with an apparently decreased rate of *in vivo* absorption. The blood-lead concentration *versus* time profiles for those groups administered lead acetate and control, carbonated beverage, or phosphoric acid treatments are shown in Fig. 1. Similar results were observed following the administration of the phosphate laxative (Fig. 2). Although absorption rates were not calculated, the time to reach the maximum blood-lead concentration (C_{max}) was longer in each of these treatment groups than in the control group. The majority of rats administered phosphate, in either the carbonated beverage, phosphoric acid, or laxative, reached C_{max} at either 4 or 8 hr; whereas in the control group five rats reached C_{max} at 2 hr, four rats at 4 hr, and none at 8 hr. In addition to delaying absorption, each of these treatments resulted in a lower value of C_{max}, as compared with the control (Table II). The AUC, a direct index of the bioavailability of an oral lead dose, was significantly reduced when either the carbonated beverage, phosphoric acid solution, or laxative diluted 10-fold was administered after lead ingestion. The 250-fold diluted laxative also appeared to decrease the AUC, but not significantly.

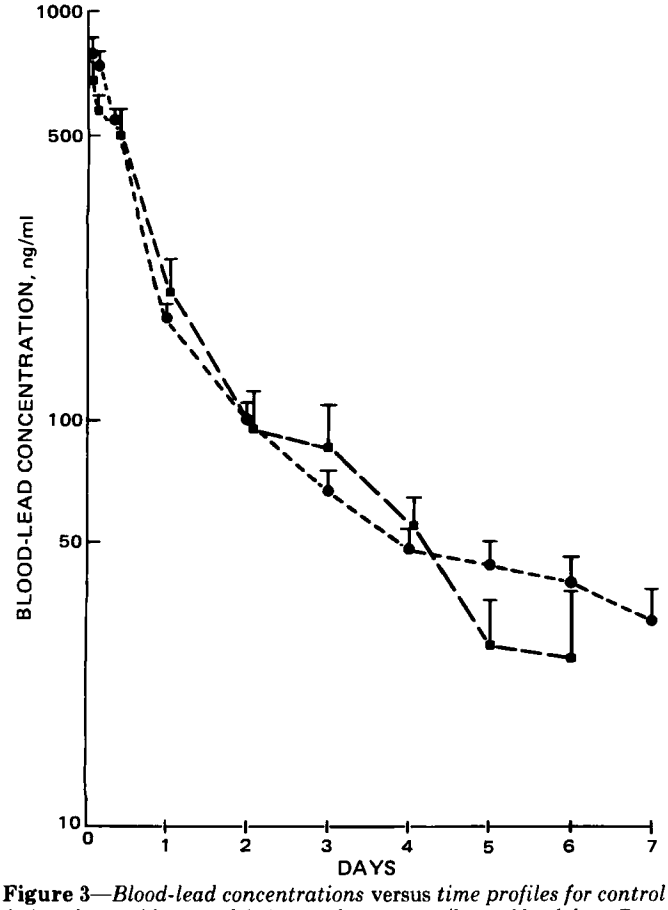

Figure 3—*Blood-lead concentrations* versus *time profiles for control (●) and antacid-treated (■) rats after a 10 mg/kg oral lead dose. Data represent mean* + SE.

Administration of the antacid after the lead dose had no apparent effect on either the blood-lead concentration *versus* time profile (Fig. 3), C_{max}, or AUC (Table II). Although the antacid caused significant precipitation of lead *in vitro*, it was ineffective in inhibiting *in vivo* lead absorption. The reasons for this lack of effect are unclear at present[7].

The effect of the carbonated beverage on lead absorption from a lead-based paint was also examined. As shown in Fig. 4, blood-lead concentrations were reduced by treatment with the carbonated beverage. The carbonated beverage again apparently decreased the rate of lead absorption, as indicated in the delay in the time C_{max} was observed (8 hr). The value of C_{max} was reduced as well (Table II). The AUC was significantly less than that observed in control rats, which were administered water after the paint dose.

The efficacies of the various treatments in reducing lead absorption were not predictable based on the amount of phosphate administered, and other effects of these treatments must be considered. Changes in gastric emptying rate, GI motility, solid particle size, and volume of fluid

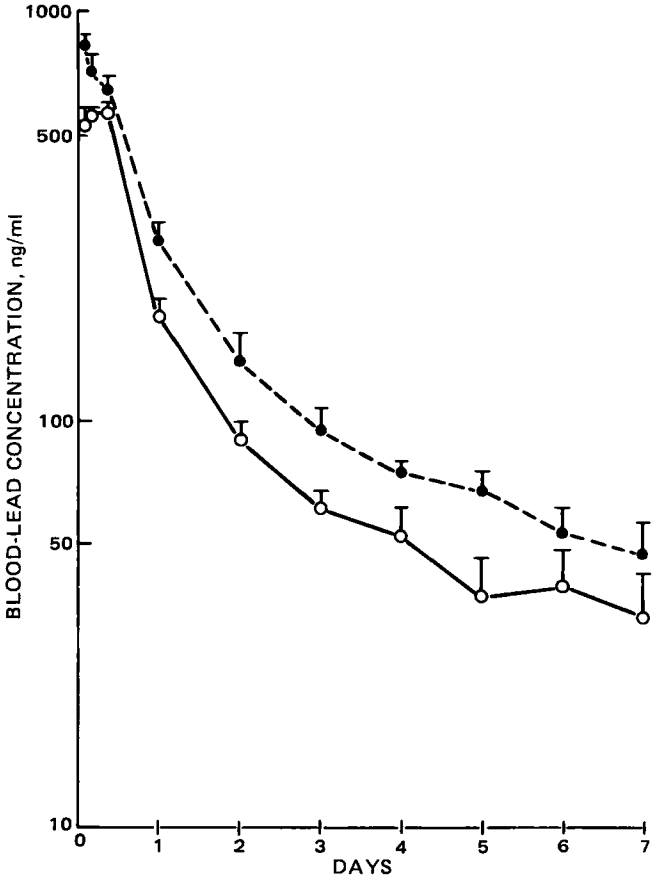

Figure 4—*Blood-level concentrations (mean* + SE*) in rats administered 50 mg of Pb/kg as a lead-based paint. Rats were also administered water (●) or a carbonated beverage (○).*

[7] In a follow-up experiment, stomach acidity was measured in three rats 20 min after dosing with the lead solution and antacid. The stomach pH in these animals was elevated to 4.5, 6.0, and 7.0, respectively, compared with control values of 2.5–3.0 in animals not treated with antacid. It appears possible that the pH effect on lead solubility might have been compensated by other effects of the antacid, *e.g.*, gastric emptying and GI motility, on lead absorption.

in the gut might also have been important. Houston and Levy reported that by inhibiting gastric emptying and GI motility, the same carbonated beverage used in this study altered the absorption rates of riboflavin and salicylamide (14). These effects were due to the phosphoric acid and carbohydrate in the carbonated beverage. In another study (15) the authors showed that propantheline bromide, an inhibitor of gastric emptying and GI motility, decreased the rate and extent of lead absorption by ~50%, suggesting that lead absorption is modified by the degree of agitation of the gut contents, among other factors. The phosphate-buffered, saline laxative functions as such by retaining water in the gut, and indirectly increases GI motility (16). Both of these actions could have counteracted the effect of decreased solubility on lead absorption.

Although abolition of lead absorption was not achieved by these products, the inhibitory effects are comparable to those shown for excess calcium and iron; administration of lead with 250-fold and 1000-fold molar excesses of calcium decreased lead absorption 46 and 43%, respectively, in rats (17, 18). Iron, at amounts 100-fold and 1000-fold greater than lead, decreased lead absorption in rats 20 and 80%, respectively (19).

Since the consequences of lead intoxication are severe (20), especially in children, prevention of undue lead exposure is very important. The household products identified here have been shown to significantly reduce lead absorption in rats when administered acutely. These agents might, therefore, also be useful in decreasing lead exposure after lead ingestion in humans. Their relatively nontoxic nature and easy accessibility make them attractive candidates for such use, particularly for children with a history of pica. Of course, the potential for use of these products is suggested only as an adjunct or supportive measure, and is not intended to replace therapeutic intervention for relief of the symptoms of lead toxicity.

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Zn(II)–Theophylline–Ethylenediamine: Structure and pH Stability

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Received November 27, 1981, from the *Department of Pharmaceutics, School of Pharmacy, State University of New York at Buffalo, Amherst, NY 14260.* Accepted for publication February 19, 1982.

Abstract □ A zinc-containing salt of theophylline, Zn(II)-aminophylline, was synthesized and its structure determined by X-ray diffraction techniques. The zinc ion is coordinated to two theophylline anions and a molecule of ethylenediamine in a tetrahedral arrangement. The solubility of the compound in water at 30° (0.047 mg/ml) is 180-fold lower than that of theophylline (8.40 mg/ml). The complex is relatively stable in the alkaline pH range, but it hydrolyzes, releasing theophylline in acidic environments. The rate of theophylline release is pH dependent. These properties are useful in formulating chewable tablets and liquid suspension dosage forms that overcome the characteristic bitter taste of theophylline, yet provide for efficacious treatment of diseases involving the respiratory tract.

Keyphrases □ Zn(II)–Aminophylline—structure determination by X-ray diffraction, release rate of theophylline, potential for use in oral preparation □ X-ray diffraction—Zn(II)–aminophylline, release rate of theophylline, potential for use in oral preparations □ Theophylline release rate—Zn(II)–aminophylline complex, X-ray diffraction, potential for use in oral preparations

Theophylline, a naturally occurring xanthine alkaloid derivative, possesses potent bronchodilating properties. Consequently, for nearly half a century both it and its ethylenediamine salt, aminophylline, have been used extensively in the treatment of diseases involving the respiratory tract (1). In particular, they have been shown to be efficacious in the treatment of asthma (2), exercise-induced bronchospasm (3), Cheyne-Stokes respiration (4), and chronic bronchitis/emphysema (5).

Although the pharmacologic properties of this drug are beneficial for such disorders, some of its physicochemical properties hinder totally effective therapy. First, the

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