Assessing Detergent Safety: A Comparison of a Nonphosphate Laundry Detergent with Phosphate Detergents[1]

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ABSTRACT

The potential hazard of a carbonate-based, phosphate-free detergent was compared with that of a variety of granular and liquid phosphate detergents. Evaluations were made using methods prescribed by the Federal Hazardous Substances Act (FHSA) and others designed to more closely approximate exposure in actual use. Some phosphate products produced esophageal and gastric mucosal irritation similar to that produced by the nonphosphate detergent, while others caused varying, lesser degrees of injury. The nonphosphate detergent, as well as several phosphate products, was seriously irritating to the unwashed eye at required FHSA test levels. Under more realistic conditions, eye irritation was reduced significantly. Skin irritation by the nonphosphate product was comparable to that by phosphate detergents, and in some cases was lower. In skin irritation tests with human subjects, results with the carbonate detergent were equal to or lower than those obtained with phosphate detergents. The carbonate detergent was found not to be phototoxic, nor a contact- nor photo-sensitizer. Total alkalinity was shown not to correlate with the severity of tissue injury in either test animals or in man.

INTRODUCTION

The indictment of phosphorus-containing detergents in the pollution of streams and lakes and the demand that they be eliminated have stimulated considerable argument. Three central questions that have been raised are: whether controlling phosphates in detergents will control eutrophication, whether phosphate-free detergents are effective cleansing agents; and whether these newer products are safe. It is the purpose of this paper to deal with the last question by comparing the relative safety of a phosphate-free laundry detergent with several phosphate-containing products that have been marketed in recent years.

Of the practical builders considered for nonphosphate formulas, the more important have been trisodium nitrilotriacetate (NTA) and sodium carbonate. A report from the National Institute of Environmental Health Sciences (1), which raised questions as to the effect of NTA on human health, resulted in the Surgeon General's request that it be taken off the market. More recently, new doubt of the safety of this material has arisen (2).

Many phosphate-free detergents now on the market use sodium carbonate in combination with a silicate as the builder. Although some of these products contain sodium metasilicate, most employ a liquid sodium silicate with a SiO_2/Na_2O ratio of 2:1 or greater.

We differentiate between nonphosphate detergents based upon the type of silicate used. A type 1 formulation is basically the same as standard phosphate detergents, except that sodium carbonate is substituted for sodium tripolyphosphate; both contain liquid silicate. In a type 2 product carbonate is also substituted for phosphate, but the silicate is present as metasilicate.

In this study the potential hazard of a phosphate-free type 1 detergent was compared with that of typical phosphate detergents purchased in local grocery stores. A type composition of the detergents tested is presented in Table I; product 1 is the nonphosphate detergent, products 6 and 7 are liquid detergents, and products 9 and 10 are dishwashing detergents. None of the phosphate-containing products carried cautionary labeling.

[1]Presented at the AOCS Short Course, "Update on Detergents and Raw Materials," Lake Placid, New York, June 1971.

TABLE I

Type Composition of Detergents Examined

Component	Product[a]														
	1[b]	2	3	4	5	6[c]	7[c]	8	9[d]	10[d]	11	12	13	14	15
Anionic surfactant	—	+	+	+	+	+	—	—	—	—	+	+	+	+	+
Nonionic surfactant	+	—	—	—	—	—	+	+	+	+	+	—	—	—	+
Tripolyphosphate	—	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Carbonate	+	—	—	—	—	—	—	+	—	—	—	—	—	—	—
Silicate	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+
Sulfate	—	+	+	+	+	+	—	+	—	—	+	+	+	+	+
Enzyme	—	+	—	+	—	—	—	—	—	—	+	—	—	—	—
Carboxymethylcellulose	+	+	+	+	+	+	+	+	+	—	+	+	+	+	+
Adjuncts[e]	+	+	+	+	+	+	+	+	+	+	+	+	+	+	+

[a]+ = Present; — = not present.
[b]Nonphosphate laundry detergent.
[c]Liquid detergent.
[d]Dishwashing detergent.
[e]Brighteners, foam booster, perfume.

TABLE II

Acute Oral LD_{50}'s of Detergents[a]

Product	LD_{50}, g/kg		
	Test 1[b,c]	Test 2[c]	Test 3
1	2.6-3.4	1.9-3.5	>5
2	4.1-5.1	4.3-6.2	>5
3	—	—	>5
4	4.1-5.1	—	>5
5	4.1-5.1	—	>5
6	—	5.0-6.8	>5
8	5.6-6.8	—	>5
9	3.1-3.7	3.0-3.9	—
11	4.8-6.2	—	—

[a]Reference 7.
[b]Four animals were used per dose level.
[c]95% confidence limits.

EXPERIMENTAL PROCEDURES

Acute Oral Toxicity (3-5)

Groups of rats, five males and five females, except where noted, were fasted for 16 hr prior to dosing. A 25% aqueous suspension of test material was administered by stomach tube; doses ranged from 1.4 to 10.2 g/kg body wt. The animals were observed for 14 days for occurrence of reactions and death, after which survivors were sacrificed and examined.

Intragastric Irritation – Rabbits

Two groups of six albino rabbits were dosed by placing either 0.5 g or 1.0 ml of material on the base of the tongue and holding the mouth shut until the animal swallowed. The tongue, pharynx, esophagus and stomach were examined for gross and microscopic changes.

Intragastric Irritation – Dogs

Test material was placed on the base of the tongue of a Beagle dog and the mouth held shut until swallowing occurred. Three groups of animals, four per group, were used: those fasted for 24 hr and receiving a one teaspoon dose; those fed 2 hr prior to receiving a one teaspoon dose; and those fasted for 24 hr and receiving a 1 g/kg dose. Twenty-four hours after dosing, two dogs per group were sacrificed and examined for pathologic alteration. Ninety-six hours following dosing, the remaining animals in each group were sacrificed and examined.

Skin Irritation – FHSA Method (6)

Either 0.5 g powder or 0.5 ml liquid was placed in contact with the shaved intact or abraded skin of six albino rabbits and occluded by an impervious plastic sheeting. After 24 hr of exposure, the materials were removed and erythema and edema graded according to the method of Draize (7). Readings were made again at 72 hr.

Skin Irritation – Modified Method

For an evaluation of the irritative properties of detergents under conditions closer to those of probable exposure, 0.5 g moistened detergent was applied to the shaved abdomens of albino rabbits and left uncovered for periods of 5, 30 or 60 min, then rinsed off. Irritation was scored according to Draize (7).

Eye Irritation – FHSA Method (6)

Either 100 mg powdered or 0.1 ml liquid detergent was instilled into the right eye of each of six albino rabbits and the lids held together for one second. Examinations were made at 24, 48 and 72 hr, the times specified in the FHSA method. In addition, examinations were made at 1 hr, 7 and 14 days. After the 24 hr examination a physiologic solution of sodium chloride was used to rinse the eyes. The degree of irritation of cornea, iris and palpebral conjunctivae was graded at each examination according to Draize (7).

Eye Irritation – Modified Methods

In each of five albino rabbits, 0.2 ml of a 0.3% aqueous solution of detergent or 0.01 ml powdered detergent was instilled into the right conjunctival sac. After 4 sec, half the eyes receiving the solution and all those given the powder were rinsed freely with water. The left eye was used as a control. At 1 min, 1, 24 and 72 hr, and 7 days, irritation of the cornea, iris and conjunctiva were graded (7).

Using six albino rabbits per group, 0.01 ml powdered detergent was instilled into the eye with rinsing following 1 and 24 hr contact periods, and irritation graded as above. Similarly 100 mg detergent was instilled into the eye with rinsing following a 1 min contact. Irritation was graded at 1, 24 and 72 hr, and at 7 and 14 days.

Eye Irritation in Monkeys

Into the right conjunctival sac of each of three Rhesus monkeys 100 mg powdered detergent was instilled and the eye rinsed with 100 ml tap water after 1 min. After 1, 24 and 72 hr, and 7 and 14 days, irritation was scored by the criteria of Draize (7). Using Cynomolgus monkeys, 0.01 ml detergent was instilled into the eye with irrigation after 5 min of contact. Irritation was graded as above at 1, 24 and 72 hr, and 7 days.

Irritation of Human Skin – 21 Day Cumulative Irritancy Assay (8)

One per cent solutions of test detergents were applied daily to 1 $in.^2$ webril pads and held in place on the skin with supporting tapes. Pads were removed daily for observation and solutions were reapplied to test sites each day for 21 days. Reactions were graded daily on a scale in which the numeral 1 represents erythema; 2, erythema plus induration; 3, erythema plus vesicles; and 4, bullae.

Irritation of Human Skin – Modified Killian and March (9) Immersion Test

This test employs three tanks, the two outside tanks containing a solution of one material and the center one a solution of a second test material. All are kept at 38 C.

Subjects were placed between the center tank and either of the outer ones, so that they could immerse one hand and forearm in each of the two solutions. Solutions were prepared fresh daily. For three 10 min periods of each day of the test, they alternately immersed each arm for 1 min and exposed it to air for 30 sec. Immersion periods were three hr apart. At the end of each period the hands and arms were rinsed with tap water and patted dry. The test continued for 5 days. Hands and arms were examined before the first and third immersions of each day and signs of irritation scored and recorded. This procedure is slightly different from the Killian and Marsh technique in that arms are dipped up to the elbow in tanks of the solutions rather than just up to the wrist in pans, and solutions are maintained at 38 C rather than 42-45 C.

Contact Sensitization of Human Skin – Draize (7) Procedure

This test employed 200 individuals. A 2% detergent solution was patched on the back (0.5 ml per application). After 24 hr, the patch was removed and erythema and edema were graded. Fresh patches were reapplied to the same sites and graded three times weekly, at 48 hr intervals during the week and at 72 hr intervals over the weekend, for a total of 10 applications. A challenge dose at a different site was similarly given and read for each subject ten days following the last application.

TABLE III

Detergent Ingestion Study in Albino Rabbits:
Gross and Histologic Observations (1 ml dose)

Product[a]	Animal[b] no.	Tissue	Gross	Grade[c]	Histopathology	Grade
1	1	Gastric mucosa	Inflammation	2	Negative	0
			Sloughing	2	Negative	0
		Tongue	Chemical burn	2	Focal ulceration of mucosa	1
					Acute inflammation of underlying muscle	1
		Pharyngeal structure	Inflammation	1	Negative	0
	2	Esophagus	Petechiae	2	Negative	0
		Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	1	Negative	0
		Tongue	Chemical burn	2	Focal ulceration of mucosa	1
					Acute inflammation of underlying muscle	1
		Pharyngeal structure	Inflammation	2	Negative	0
	3	Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	1	Negative	
		Tongue	Hemorrhages	2	Negative	0
			Chemical burn	2	Negative	
		Pharyngeal structure	Inflammation	1	Negative	0
	4	Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	1	Negative	
		Pharyngeal structure	Inflammation	1	Negative	0
	5	Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	2	Negative	
		Tongue	Negative	0	Focal acute inflammation of muscle	1
		Pharyngeal structure	Inflammation	1	Negative	0
	6	Esophagus	Inflammation	1	Negative	0
		Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	1	Negative	0
		Pharyngeal structure	Inflammation	2	Negative	0
2	1	Gastric mucosa	Sloughing	2	Negative	0
		Pharyngeal structure	Inflammation	2	Negative	0
	2	Gastric mucosa	Sloughing	1	Negative	0
		Pharyngeal structure	Inflammation	1	Negative	0
	3	No irritation observed	Negative	0	Negative	0
	4,5,6	Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	1	Negative	
3	1,2	Gastric mucosa	Sloughing	1	Negative	0
	3	Gastric mucosa	Sloughing	1	Negative	0
		Pharyngeal structure	Inflammation	2	Negative	0
	4	Gastric mucosa	Sloughing	1	Negative	0
	5,6	Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	1	Negative	0
4	1	Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	1	Negative	0
	2,3	Gastric mucosa	Sloughing	1	Negative	0
	4	Gastric mucosa	Sloughing	1	Negative	0
	5	Esophagus	Inflammation	1	Negative	0
		Gastric mucosa	Sloughing	1	Negative	0
	6	Gastric mucosa	Sloughing	1	Negative	0
5	1,3	Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	1	Negative	1
	2	Gastric mucosa	Inflammation	2	Negative	0
			Sloughing	1	Negative	
	4,5,6	Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	1	Negative	
6	1	Esophagus	Petechiae	2	Negative	0
			Edema	2		
		Gastric mucosa	Hemorrhages	4	Focal acute inflammation	1
					Focal hemorrhages of mucosa	1
		Pharyngeal structure	Inflammation	1	Negative	0
	2	Esophagus	Petechiae	2	Negative	0
			Edema	3		
		Gastric mucosa	Hemorrhages	3	Negative	0
		Pharyngeal structure	Inflammation	1	Negative	0
	3	Gastric mucosa	Petechia	2	Negative	0
		Pharyngeal structure	Inflammation	2	Negative	0
	4	Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	1		
		Pharyngeal structure	Inflammation	2	Negative	0
	5	Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	2		
		Pharyngeal structure	Inflammation	1	Negative	0
	6	Gastric mucosa	Inflammation	2	Negative	0
			Sloughing	2		
		Pharyngeal structure	Inflammation	2	Negative	0

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TABLE III (Continued from previous page)

Detergent Ingestion Study in Albino Rabbits:
Gross and Histologic Observation (1 ml dose)

Product[a]	Animal[b] no.	Tissue	Gross	Grade[c]	Histopathology	Grade
7	1	Gastric mucosa	Edema	3	Erosion	5
			Sloughing	2		
			Subdermal hemorrhage	2		
	2	Gastric mucosa	E dema	3	Erosion	4
			Sloughing	2		
			Subdermal hemorrhage	2		
	3	Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	2		
		Pharyngeal structure	Inflammation	1	Negative	0
	4	Gastric	Inflammation	1	Negative	0
			Sloughing	1		
		Pharyngeal structure	Inflammation	1	Negative	0
	5	Gastric mucosa	Inflammation	2	Negative	0
			Sloughing			
		Pharyngeal structure	Inflammation	1	Negative	0
	6	Gastric mucosa	Inflammation	2	Negative	0
			Sloughing	2		
8	1,2	No irritation observed	Negative	0	Negative	0
	3	Esophagus	Hemorrhages	2	Negative	0
	4,5,6	No irritation observed	Negative	0	Negative	0
13	1	Gastric mucosa	Sloughing	1	Negative	0
	2	Gastric mucosa	Sloughing	2	Negative	0
	3	Gastric mucosa	Sloughing	2	Negative	0
		Pharyngeal structure	Inflammation	1	Negative	0
	4	Gastric mucosa	Sloughing	2	Negative	0
	5	Gastric mucosa	Inflammation	2	Negative	0
			Sloughing	1	Negative	
		Pharyngeal structure	Inflammation	1	Negative	0
	6	Gastric mucosa	Inflammation	2	Negative	0
			Sloughing	1		
14	1,3	Gastric mucosa	Sloughing	2	Negative	0
	2	Gastric mucosa	Sloughing	3	Negative	0
		Tongue	Hematoma	3	Negative	0
			Pinpoint corrosion	5		
	4	Gastric mucosa	Inflammation	2	Negative	0
			Sloughing	2		
	5	Gastric mucosa	Inflammation	2	Negative	0
			Sloughing	2		
		Pharyngeal structure	Inflammation	1	Negative	0
	6	Gastric mucosa	Inflammation	3	Negative	0
			Sloughing	2		
		Pharyngeal structure	Inflammation	1	Negative	0
15	1,3	Gastric mucosa	Sloughing	1	Negative	0
	2	Gastric mucosa	Inflammation	1	Negative	0
			Sloughing	2		
		Pharyngeal structure	Inflammation	1	Negative	0
	4	Gastric mucosa	Inflammation	4	Negative	0
			Sloughing	2		
		Pharyngeal structure	Inflammation	1	Negative	0
	5	Gastric mucosa	Inflammation	3	Negative	0
			Sloughing	2		

[a]Reaction to lye (positive control): five out of six animals died overnight.
[b]Animal numbers 1 to 3 in each group were sacrificed at 24 hr; animal numbers 4 to 6 were sacrificed at 96 hr.
[c]Grading system: 0 = normal; 0.5 = minimal; 1 = slight; 2 = mild; 3 = moderate; 4 = severe; and 5 = extreme.

Phototoxicity – Human (10)

Five subjects were used. The volar surface of each forearm was stripped to glistening with cellophane tape; four sites approximately 1.5 cm in diameter were delineated on each. On three sites, 0.5 ml of a 1% detergent solution was applied. To the fourth site, 0.1 ml oil of bergamot was applied as a positive control. Five minutes after the application of the material, the sites on the forearm were irradiated for 45 min using a Hanovia Inspectolamp at a distance of 6 in.; the other forearm served as a control and was not irradiated. The reactions were read 48 hr later.

Photosensitization – Human (7)

Fifty subjects were used in this test. A 2% solution of detergent was prepared for each application. Then 0.5 ml was applied to an occlusive type bandage and placed on the volar surface of the forearm of each volunteer. The patch remained in place for 48 hr during the week and for 72 hr over the weekend. Upon removal of each patch, the site was exposed to three minimal erythemal doses (MED's) of UV light from a Kromayer lamp. This sequence was repeated for a total of 10 applications, employing fresh patches on the same site. Following a 14 day rest period, a final elicitation patch was applied to a different site. After 24 hr the patch was removed and the site irradiated with ca. 10 MED's of UV light from a Kromayer light filtered through window glass to remove those rays producing ordinary erythema.

RESULTS

Acute Oral Toxicity

The acute oral toxicity of these detergents was determined at two laboratories; data are presented in Table II.

Tests 1 and 2 were performed by the same laboratory, and in each case the LD_{50} was lower for all products tested than in the other laboratory (test 3). Gastroenteric hemorrhage was observed in test 1 in surviving animals dosed with products 5 and 8; in animals dosed with the remaining products, which included the phosphate-free detergent, no gross pathological alterations were noted in survivors. In test 2, gastrointestinal hemorrhage was observed in all surviving animals with all products tested. In Test 3, no unusual findings were noted at autopsy in any of the test animals.

In evaluating these results, five detergents, products 1, 2, 4, 5, and 9, could be classified as toxic ($LD_{50} < 5$g/kg) based upon results in tests 1 and 2, and none as toxic (of those tested), based upon the results in test 3. The significance of these discrepancies is considered in the Discussion section.

Intragastric Irritation – Rabbits

At a dose of 0.5 g, none of the detergents tested caused irritation of the tongue except in one animal dosed with products 1 and 2. All except product 2 caused slight irritation to the pharyngeal structures in one or more animals. Product 6 also produced esophageal edema. Some inflammation and sloughing of the gastric mucosa was observed in animals dosed with all products, but the most severe resulted from products 6 and 7, which caused hemorrhaging. These two phosphate products tested could be rated as corrosive (causing necrotic lesions).

When 1.0 ml detergent was administered, because of differences in bulk density the phosphate detergent dose in some cases was actually less than 0.5 g. Slight to moderate irritation of the gastric mucosa was observed in animals dosed with all except product 8. With product 7, severe to extreme erosion of the gastric mucosa was observed microscopically. In two animals dosed with product 6 and sacrificed at 24 hr, moderate hemorrhaging of the gastric mucosa was observed. Mild to moderate irritation of the esophagus was noted in at least one animal dosed with products 1, 4, 6 or 8. Three animals dosed with product 1 and one animal dosed with product 14 showed mild chemical burn to the tongue. With lye as a positive control, five out of six animals died overnight. These data are presented in Table III.

Intragastric Irritation – Dogs

Because the rabbit has no regurgitation reflex, it is a useful animal for studying irritation under conditions in which material cannot be expelled by emesis. Unlike the rabbit, the dog is able to vomit.

In our dog ingestion studies, dosing was on a volume basis of one teaspoon per animal. Because of differences in product densities, these doses ranged from ca. 1.7 g for a low bulk density phosphate detergent to 4.8 g for the carbonate detergent. Of 11 different detergent products tested, only one did not produce some injury. In most cases this consisted of irritation to the epithelial mucosa. In initial tests animals were not fed for 24 hr prior to dosing.

Immediate emesis was observed in animals dosed with products 1, 9 and 10. Hyperemia and tissue consolidation were observed in the trachea and lungs of one animal dosed with product 1. This may have been a result of inhalation of regurgitated test material. Scarring was also observed in the fundic region of one animal and slight blanching below the stomach mucosal surface in one animal. In the remaining animal there was no injury observed. With product 9, stomach and intestinal injury was noted in one animal, epithelial sloughing in a second animal, and focal hyperemia in a third animal. Bloody vomitus was observed in all four test animals dosed with product 10. At sacrifice after 24 hr, one animal dosed with this product showed severe inflammation, tissue sloughing and hyperemia of the stomach; animals sacrificed at 96 hr did not show any gross pathologic alteration.

Of the remaining detergents, products 13 and 14 did not induce an emetic response in the animals dosed. Focal hyperemia of the duodenum was observed in one animal dosed with product 13 sacrificed at 24 hr, and in both animals sacrificed at 96 hr. With product 14, hyperemia and edema were observed in one animal sacrificed at 24 hr.

Emesis was delayed for ca. 1 hr in some or all of the animals dosed with products 4, 6 or 7. Hyperemia of the duodenum was observed in two of the animals dosed with product 4. In one animal dosed with product 6, hyperemia and focal inflammation of the stomach developed; hyperemia of the pharynx and colon was observed in a second animal, ulcerations and edema of the cardiac and fundic regions in a third animal, and hyperemia of the duodenum in a fourth animal. Focal inflammation in several areas of the stomach developed in one animal dosed with product 7. These observations, with histopathologic findings included, are presented in Table IV.

When dogs were dosed at a level of 1 g/kg with the phosphate-free detergent, a dose approximately twice that of animals fed one teaspoonful, no gross injury was observed in one of the four animals. All animals ate well following dosing, and at no time required supportive treatment. Esophageal irritation was not present. In one of these animals, areas of ulceration developed in the pyloric and cardiac regions; hemorrhage and focal inflammation also were noted. In the remaining two animals, partially healed ulcerations in the pyloric and cardiac regions were observed. Data are shown in Table V.

Although animals often are fasted prior to dosing to provide additional experimental control, fasting does not afford a representative experimental model for accidental product ingestion, especially when accidents involve primarily children less than 5 years old. When animals were fed 2 hr prior to dosing, the resulting injury was much less than with fasted animals, probably because the food and increased gastric secretion served as diluent and neutralizer (Table VI). Animals dosed with one teaspoonful of the nonphosphate detergent showed mild edema and hyperemia at 24 hr, and animals held for 96 hr were normal. Animals dosed with a liquid phosphate detergent (product 6) showed moderate injury at both 24 and 96 hr; injury was not as extensive as in fasted animals (See Table IV).

Skin Irritation – FHSA Method (6)

Under the extreme conditions required for testing skin irritation by the Federal Hazardous Substances Act, all of seven detergents tested produced some degree of irritation. Five of the seven, including the phosphate-free product, rated as corrosive. As defined in the Act, a corrosive substance is one that causes visible destruction or irreversible alteration in tissue at the site of contact in 24 hr or less. Scores for erythema and edema varied from 1.9 for one phosphate detergent to 8.0 (the maximum possible) for two others. The phosphate-free detergent was less irritating than three phosphate products and more irritating than three others, with a total score of 6.7.

We also examined these detergents for skin irritation using 0.5 ml material. The difference in dose is as important here as in the ingestion studies, since on a volume basis less material by weight is used when testing a low density phosphate detergent. Even though less material was used for some of these detergents than in the former study, the irritation also was severe for several products. All detergents produced chemical burns. These results are presented in Table VII.

Skin Irritation – Modified Method

Rowe and Olson (11) pointed out the deficiencies of the closed patch testing method prescribed by the Federal Hazardous Substances Act in the evaluation of household

TABLE IV

Detergent Ingestion Study in Dogs: Gross and Histologic Observations of Dogs Fasted 24 Hours Prior to Dosing (1 teaspoon dose)

Product	Animal no.	Reaction	Organ	Gross	Grade[a]	Histopathology	Grade
1	9[b]	Immediate emesis for 2-3 min	Esophagus	Hyperemia	1	Negative	0
			Lungs	Hyperemia	4	Acute bronchopneumonia	3
				Tissue consolidation	2	Negative	0
			Laryngeal-pharynx	Focal edema	4	Negative	0
			Trachea	Focal hyperemia	2	Negative	0
			Stomach	Focal inflammation with hyperemia in fundic region	3	Negative	0
	10[b]	Immediate emesis for 2-3 min	Negative	Negative	0	Negative	0
	11[c]	Immediate emesis for 2-3 min	Stomach	Yellow blanching just below mucosal surface	1	Negative	0
	12[c]	Immediate emesis for 2-3 min	Stomach	Scarring of former ulcerations in fundic region	2	Chronic gastritis with healing ulcerations Loss of glands but covered by epithelium Proliferation of connective tissue in mucosa Chronic gastritis in adjacent areas	4
3	19[b]	No reaction	Negative	Negative	0	Negative	0
	20[b]	Delayed emesis after 5-8 min	Negative	Negative	0	Negative	0
	21[c]	Immediate emesis for 2-3 min	Negative	Negative	0	Negative	0
4	31[c]	Delayed emesis after 1 hr	Small intestine	Submucosal hyperemia in duodenum	2	Hyperemia	1
	32[b]	Delayed emesis after 1 hr	Negative	Negative	0	Negative	0
	33[c]	No reaction	Small intestine	Hyperemia in duodenum	2	Hyperemia	1
	34[c]	No reaction	Negative	Negative	0	Negative	0
6	35[b]	Delayed emesis after 1 hr	Stomach	Several areas of focal inflammation	3	Hyperemia	1
				Hyperemia in fundic region	3	Negative	0
	36[b]	Immediate emesis for 2-3 min	Colon	Hyperemia	2	Negative	0
			Laryngeal-pharynx	Focal hyperemia	1	Acute inflammation Loss of epithelium - focal	3 2
	37[c]	Delayed emesis after 1 hr	Stomach	Multiple ulcerations in cardiac region	3	Negative	0
				Epithelial edema in fundic region	2	Negative	0
	38[c]	Delayed emesis after 1 hr	Small intestine	Hyperemia in duodenum	2	Negative	0
7	28[b]	Delayed emesis after 1 hr	Stomach	Several areas of focal inflammation in cardiac region	2	Negative	0
	29[b]	Delayed emesis after 1 hr	Stomach	Several areas of focal inflammation throughout	2	Focal ulcerations of the mucosa appear old	2
	30[c]	Delayed emesis after 1 hr	Negative	Negative	0	Negative	0
9	51[b]	Immediate emesis for 2-3 min	Stomach	Epithelial sloughing	3	Focal necrosis of epithelium only	4
				Yellow blanching just below mucosal surface	2		
	52[b]	Immediate emesis for 2-3 min	Small intestine	Hyperemia in duodenum	1	Negative	0
			Stomach	Focal inflammation in the cardiac and fundic regions	2	Edema of the mucosa Negative	1 0
				Edema of epithelium	3	Negative	0

	53[c]	Immediate emesis for 2-3 min	Stomach	Focal hyperemia in cardiac region	1	Negative	0
	54[c]	Immediate emesis for 2-3 min	Negative	Negative	0	Negative	0
10	47[b]	Immediate emesis followed by bloody emesis 1 hr later	Stomach	Edema	4	Coagulation, necrosis involving entire mucosa but most advanced in upper two-thirds	4
				Inflammation	4		
				Tissue sloughing	4		
				Hyperemia	4	Edema of submucosa	4
	48[b]	Immediate emesis followed by bloody emesis 1 hr later	Stomach	Petechiae in pyloric region	2	Negative	0
	49[c]	Immediate emesis followed by bloody emesis 1 hr later	Negative	Negative	0	Negative	0
	50[c]	Immediate emesis followed by bloody emesis 1 hr later	Negative	Negative	0	Negative	0
13	39[b]	No reaction	Small intestine	Focal hyperemia in duodenum	0.5	Negative	0
			Stomach	Focal hyperemia in fundic region	0.5	Negative	0
	40[b]	No reaction	Stomach	Yellow blanching just below mucosal surface	1	Negative	0
	41[c]	No reaction	Small intestine	Hyperemia in duodenum	2	Negative	0
			Stomach	Negative	0	Edema of the mucosa	0.5
	42[c]	No reaction	Small intestine	Hyperemia in duodenum and jejunum	2	Negative	0
14	59[b]	No reaction	Negative	Negative	0	Negative	0
	60[b]	No reaction	Small intestine	Hyperemia	2	Negative	0
				Edema of the duodenum	2	Negative	0
	61[c]	No reaction	Negative	Negative	0	Negative	0
	62[c]	No reaction	Stomach	Focal inflammation	2	Chronic focal gastritis and lymphoid proliferation	1
				Hyperemia in cardiac region	2	Negative	0
Soda Ash	55[b]	Immediate bloody emesis	Small intestine	Submucosal hyperemia in duodenum	3	Necrosis of epithelium and mucosa complete with subcutaneous edema and hemorrhage, necrosis and acute gastritis	4
			Stomach	Focal inflammation	3		
				Ulceration	3		
				Edema	4		
				Hyperemia	4		
			Trachea	Hyperemia	2	Negative	0
	56[b]	Immediate emesis	Small intestine	Pronounced Peyer's patches	4	Hyperplasia of lymphoid tissue	2
				Tissue sloughing	3	Negative	0
				Hyperemia	3	Negative	0
				Focal inflammation of jejunum	3	Negative	0
	57[c]	Immediate bloody emesis	Small intestine	Hyperemia of duodenum	2	Negative	0
				Pronounced Peyer's patches	3	Negative	0
				Tissue sloughing	3	Negative	0
				Edema	3	Negative	0
				Hyperemia of jeunum	3	Negative	0
			Stomach	Hyperemia	4	Negative	0
				Edema and tissue sloughing of the fundic region	4	Negative	0
	58[c]	Immediate bloody emesis	Stomach	Healing ulcerations	3	Acute gastritis and complete necrosis of epithelium	4
				Hyperemia of pyloric region	3	Edema and hemorrhage of submucosa	3
				Edema of cardiac region	2		

[a]Grade: 0 = normal; 0.5 = minimal; 1 = slight; 2 = mild; 3 = moderate; 4 = severe; and 5 = extreme.
[b]Sacrificed at 24 hours.
[c]Sacrificed at 96 hours.

TABLE V

Detergent Ingestion Study in Dogs: Gross and Histologic Observations of Dogs Fasted 24 Hours Prior to Dosing[a] (1 g/kg dose)

Product	Animal no.	Reaction	Organ	Gross	Grade[b]	Histopathology	Grade
1	1	Immediate emesis followed by bloody emesis 0.5 hr later	Small intestine	Negative	0	Hyperemia in the duodenum	1
	2	No emesis	Stomach	Two partially healed ulcerations in the pyloric region, one partially healed ulceration in the fundic region	1	Negative	0
	3	Immediate emesis followed by bloody emesis 0.5 hr later	Stomach	Three partially healed ulcerations in cardiac region, two hemorrhagic	3	Small healed ulcerations well repaired but with atrophic glandular area	2
	4	Immediate emesis followed by bloody emesis 0.5 hr later	Stomach	Several areas of ulceration in pyloric and cardiac regions	4	Necrosis of mucosa	4
				Hemorrhage	4	Inflammation of submucosa	3
				Focal inflammation	3	Edema, hemorrhage of submucosa	3

[a]Sacrificed at 96 hours.
[b]Grade: 0 = normal; 0.5 = minimal; 1 = slight; 2 = mild; 3 = moderate; 4 = severe; and 5 = extreme.

substances that are not designed for prolonged exposure under an impermeable dressing. They stated that a method useful for testing insect repellents and other substances designed for repeated use on large areas of skin may be misleading when evaluating products not meant to be used in prolonged contact with skin. For example, when substances are held under an occlusive dressing in contact with skin for 24 hr, no distinction may be possible among substances that will burn in seconds, minutes or hours. Carter and Griffith (12) have pointed out that virtually every material has primary irritant potential and that an appropriate frame of reference is essential for valid assessments of safety.

When 0.5 g of two phosphate detergents and the nonphosphate detergent moistened with water were applied without occlusive dressings for 5, 30 and 60 min, all three produced slight erythema, which was of the same degree for one phosphate detergent and the nonphosphate detergent and somewhat less for the other phosphate detergent. None produced edema, as shown in Table VIII.

TABLE VI

Detergent Ingestion Study in Dogs: Gross and Histologic Observations of Dogs Fed 2 Hours Prior to Dosing (1 teaspoon dose)

Product	Animal no.	Reaction	Organ	Gross	Grade[a]	Histopathology	Grade
1	63[b]	Immediate emesis for 2-3 min	Stomach	Edema	2	Edema	1
	64[b]	Immediate emesis for 2-3 min	Stomach	Edema	1	Edema	1
			Laryngeal-pharynx	Focal hyperemia	3	Acute inflammation	2
				Edema	1	Edema	2
						Hemorrhage	2
						Focal loss of epithelium	1
	65[c]	Immediate emesis for 2-3 min	Negative	Negative	0	Negative	0
	66[c]	Immediate emesis for 2-3 min	Negative	Negative	0	Negative	0
4	67[b]	No reaction	Laryngeal-pharynx	One mm area of hyperemia	0.5	Negative	0
	68[b]	No reaction	Negative	Negative	0	Negative	0
	69[c]	No reaction	Negative	Negative	0	Negative	0
	70[c]	Delayed emesis after 5 min	Negative	Negative	0	Negative	0
6	71[b]	Delayed emesis after 5 min	Stomach	Petechiae in fundic and cardiac regions	2	Negative	0
				Focal hyperemia in pyloric region	1	Negative	0
	72[b]	Delayed emesis after 5 min	Stomach	Several areas of focal inflammation	3	Negative	0
				Hyperemia in fundic region	3	Negative	0
	73[c]	Delayed emesis after 5 min	Stomach	Petechiae in cardiac region	1	Negative	0
	74[c]	Delayed emesis after 5 min	Stomach	Focal hyperemia in pyloric region	2	Negative	0

[a]Grade: 0 = normal; 0.5 = minimal; 1 = slight; 2 = mild; 3 = moderate; 4 = severe; and 5 = extreme.
[b]Sacrificed at 24 hr.
[c]Sacrificed at 96 hr.

TABLE VII

Primary Skin Irritation of Occluded Detergents[a,b]

Product	Results	Irritation score[c]
1	Chemical burn (2/6)[d] Subdermal hemorrhage (2/6)	5.9
2	Chemical burn (5/6) Subdermal hemorrhage (2/6)	7.5
3	Chemical burn (6/6) Subdermal hemorrhage (5/6)	8.0
4	Chemical burn (6/6) Subdermal hemorrhage (4/6)	8.0
5	Chemical burn (6/6) Subdermal hemorrhage (4/6)	8.0
6	Chemical burn (6/6) Subdermal hemorrhage (5/6)	8.0
8	Chemical burn (3/6)	4.6

[a]21 CFR 191.11.
[b]0.5 ml used.
[c]Based on a 0-8 scale, the higher the value the greater the irritation.
[d]Number of animals showing injury per number of animals tested.

Eye Irritation – FHSA Method

As with the FHSA method for testing skin irritation, the severe conditions of the FHSA test for eye irritation showed that when either a phosphate or a nonphosphate detergent is placed in the eye without rinsing until 24 hr later, severe injury may occur. Injury observed at 1 hr was generally the most severe, although in some cases the injury became progressively worse; most of this injury was confined to the cornea. Corneal corrosion was noted in one of six animals dosed with three products, one of which was the phosphate-free detergent, and chemical burn or vascularization, or both, occurred in one or more animals dosed with all other products. Nine products produced conjunctival burn or hemorrhage, or both. These detergents produced a degree of irritation at 24 hr that would require a warning on the label if the Federal Hazardous Substances Act were applied literally. Six of the detergents, including the phosphate-free detergent, could be rated as extremely irritating. Irritation persisted through 14 days in the animals receiving these detergents. Data up to 72 hr are shown in Table IX.

Eye Irritation – Modified Method

Because of the deficiencies in the method prescribed by the FHSA for testing eye irritation, Battista and McSweeney (13) have suggested several modifications, including rinsing of the eye after an interval approximating the probably time for rinsing after accidental exposure.

When 100 mg of the nonphosphate detergent was rinsed from the eye following a contact period of 1 min, the resulting irritation score was considerably lower. These results can be seen in Table X. As a 0.3% solution (higher than the conventional use concentration of 0.2%) instilled into the eye without washing, the nonphosphate detergent and the two phosphate detergents tested were all nonirritating.

We have conducted studies using lesser, more realistic amounts of powdered material. Results of these studies, in which 0.01 ml of the powdered nonphosphate detergent was instilled for a 1 or 24 hr period of contact, are shown in Table XI. Under these conditions, the injury was primarily confined to the conjunctiva and not to the cornea. The test animals recovered almost completely 1 week after dosing.

Eye Irritation in Monkeys

When different animal species are used, the resulting eye irritation scores for detergent products also may differ. It is likely that monkeys may give more representative results of what can be expected in man than rabbits, since the degree and type of irritation in man is more closely approximated by that produced in the monkey (12). Two products, the nonphosphate and a phosphate detergent, were tested in Rhesus monkeys. One hundred milligrams detergent was instilled into the eye for a contact period of 1 min. In no case did any damage of the iris result. After 7 days all corneal irritation had cleared in both sets of animals; in 14 days all irritation had cleared. Data are presented in Table XII.

When a lesser amount of nonphosphate detergent (.01 ml) was allowed to remain in the eye of Cynomolgus monkeys for 5 min before rinsing, the resulting irritation was similar to that observed in the 1 min contact period. These data are shown in Table XIII.

TABLE VIII

Nonoccluded Skin Irritation Test[a,b]

	5 Min.		30 Min.		60 Min.	
Product	Er.	Ed.	Er.	Ed.	Er.	Ed.
1	1	0	1	0	2	0
11	1	0	1	0	2	0
12	0	0	1	0	1	0

[a]Highest possible score: (erythema [Er.] + edema [Ed.]) = 8.
[b]See Reference 7 for scoring procedure.

Irritation of Human Skin – 21 Day Cumulative Irritancy Assay (8)

The effect of the nonphosphate detergent was compared with that of seven phosphate detergents in a test for cumulative irritancy potential. The data developed from that test can be seen in Table XIV. No subject experienced any reaction to the nonphosphate detergent. All phosphate detergents, on the other hand, produced some irritation. Cumulative irritation for the seven phosphate products tested ranged from 9.5 to 111. For comparative purposes a maximum extreme cumulative score for one person over 3 weeks would be a score of 4 (bullae) times 20 daily scores, or 80.

Irritation of Human Skin – Immersion Test of Killian and Marsh (9)

We have also examined the irritation potential of the nonphosphate detergent and two phosphate detergents, products 2 and 8, using the slightly modified Killian-Marsh technique. Under these exaggerated conditions, and using detergent solutions of 0.2%, slight to mild irritation was noted in all 10 subjects. Low grade papular dermatitis occurred in two cases after 11 of the 14 immersions, one with the nonphosphate detergent and one with product 2. The three detergents were essentially equal with respect to skin irritating properties.

As a 0.5% solution, each of these detergents caused dryness, itchiness and tenderness of the skin, culminating in severe irritation and low grade papular dermatitis. The number of exposures to reach this degree of irritation was six for the nonphosphate, seven for product 8 and eight for product 2.

Contact Sensitization, Phototoxicity and Photosensitization – Human Subjects

These tests were employed to determine the potential of the nonphosphate detergent to induce skin reactions other than simple irritation. In the Draize (7) sensitization test, a 2% concentration of the phosphate-free product produced no allergic responses in any of the 200 subjects tested. This represents 10 periods of 24 hr contact under occlusion plus

TABLE IX

Eye Irritation of Powdered Detergents in Albino Rabbits[a]
(100 mg powdered or 0.1 ml liquid detergent)

Product	Time after instillation, hr	Irritation score		
		Cornea[b]	Iris[c]	Conjunctiva[d]
1[e]	1	46.7	10.0	18.0
	24	40.0	10.0	16.0
	72	40.0	10.0	16.0
2[f]	1	40.0	10.0	14.0
	24	35.0	10.0	14.0
	72	14.1	6.7	5.7
3[g]	1	18.3	10.0	14.3
	24	28.3	10.0	10.3
	72	9.2	1.7	3.7
4[h]	1	33.3	10.0	16.3
	24	17.5	10.0	13.7
	72	2.5	4.2	3.3
5	1	30.0	9.2	14.0
	24	23.3	9.2	12.0
	72	19.2	4.2	6.7
6[i]	1	40.0	10.0	16.0
	24	40.0	10.0	18.0
	72	40.0	10.0	17.7
7[j]	1	20.0	10.0	14.0
	24	26.0	10.0	14.7
	72	26.7	7.5	12.0
8[k]	1	0.0	10.0	13.0
	24	10.8	8.3	11.0
	72	5.0	4.2	4.3
9[l]	1	40.0	10.0	18.0
	24	31.7	10.0	15.6
	72	28.3	9.2	10.7
13[m]	1	20.0	10.0	14.0
	24	22.5	10.0	13.0
	72	18.3	6.7	6.3
14[n]	1	20.0	10.0	14.0
	24	25.8	10.0	14.3
	72	28.3	7.5	13.7
15[o]	1	20.0	9.2	16.0
	24	36.7	10.0	18.0
	72	35.0	8.3	16.3

[a]21 CFR 191.12.
[b]Out of a possible total of 80.
[c]Out of a possible total of 10.
[d]Out of a possible total of 20.
[e]Chemical burns of conjunctiva (5/6 animals), corneal vascularization (3/6), and corneal corrosion (1/6) at 14 days.
[f]Conjunctival hemorrhage (5/6) at 24 hr; corneal vascularization (1/6) at 7 days.
[g]Conjunctival hemorrhage (1/6) and epithelial slough of iris (1/6) at 24 hr; chemical burn of conjunctiva (1/6) at 7 days.
[h]Conjunctival hemorrhage (1/6) and chemical burn of conjunctiva (5/6) at 24 hr; corneal vascularization (1/6) at 7 days.
[i]Chemical burn of conjunctiva (6/6) and corneal vascularization (5/6) at 14 days.
[j]Corneal vascularization (2/6) and conjunctival burn (4/6) at 7 days.
[k]Chemical burn of conjunctiva (6/6) at 24 hr, (1/6) at 72 hr.
[l]Conjunctival hemorrhage (3/6), corneal vascularization (3/6), and conjunctival burn (2/6) at 7 days.
[m]Ulceration and vascularization of cornea (1/6) at 7 days.
[n]Corneal vascularization (4/6), corneal corrosion (3/6), and conjunctival burn (4/6) at 7 days.
[o]Corneal vascularization (3/6), conjunctival burn (3/6) and conjunctival hemorrage (3/6) at 7 days; corneal corrosion (1/6) at 14 days.

a challenge 2 weeks after the last application.

Similarly a negative response was obtained in testing for phototoxicity using a 1% solution of the phosphate-free detergent. There was no skin damage observed upon irradiation in any of the five subjects except where oil of bergamot, used as a positive control, was applied. Finally, as a 2% solution, the nonphosphate detergent elicited no allergic response in any of the 50 subjects when applied using an occlusive patch and exposure to UV light. There were no differences between treated (irradiated) sites and control (nonirradiated) sites.

DISCUSSION

As Weil and Scala (14) have pointed out, the reproducibility of results of toxicological tests is subject to the variability inherent among and within laboratories due to operator differences. This finding has important implications for many toxicological studies, not the least significant of which is that evaluation of hazard is best made on the basis of a variety of tests and procedures. An example of laboratory variability was noted in the acute oral toxicity data presented in Table II. While internal consistency is indicated for one laboratory (tests 1 and 2) certain interlaboratory variation is evident. Clearly results must be evaluated with due consideration for variations which may occur.

The conditions for testing skin and eye irritation potential as provided by FHSA regulations do not permit a

TABLE X

Eye Irritation of Product 1 in Albino Rabbits Following a 1 Minute Residence Before Irrigation (100 mg Detergent)

Time	Irritation Score[a]		
	Cornea[b]	Iris[c]	Conjunctiva[d]
1 hr	18.3	7.5	15.7
24 hr	22.5	8.3	14.0
72 hr	16.7	4.2	9.7
7 days	5.0	0.0	5.3
14 days	1.7	0.0	0.7

[a]See Reference 7 for scoring procedure.
[b]Out of a possible total of 80.
[c]Out of a possible total of 10.
[d]Out of a possible total of 20.

TABLE XIII

Eye Irritation in Cynomolgus Monkeys Following a 5 Minute Residence Before Irrigation (0.01 ml Detergent)

Product	Time after instillation	Irritation scores[a]		
		Cornea[b]	Iris[c]	Conjunctiva[d]
1	1 hr	5.0	0.0	16.0
	24 hr	8.0	0.0	16.7
	72 hr	10.0	0.0	16.0
	7 days	6.0	0.0	11.3

[a]See Reference 7 for scoring procedure.
[b]Out of a possible total of 80.
[c]Out of a possible total of 10.
[d]Out of a possible total of 20.

TABLE XI

Eye Irritation of Product 1–Albino Rabbits (7.7 mg [0.01 ml])

Contact time, hr	Time after instillation	Irritation score[a]			
		Cornea[b]	Iris[c]	Conjunctiva[d]	Total
1	1 min	0.0	5.0	8.0	13.0
	1 hr	1.7	8.3	15.3	25.3
	24 hr	6.7	5.0	8.7	20.4
	7 days	0.0	0.0	6.0	6.0
24	1 hr	10.0	10.0	16.0	36.0
	24 hr	17.0	8.0	9.6	34.6
	72 hr	5.8	2.5	7.0	15.3
	7 days	0.0	1.6	5.0	6.6

[a]See Reference 7 for scoring procedure.
[b]Out of a possible total of 80.
[c]Out of a possible total of 10.
[d]Out of a possible total of 20.

realistic assessment of hazard for detergent products. The animal species, the amounts of material used, the length of contact and method of application as described in the Draize procedures, were originally intended to be used in the appraisal of the toxicology of foods, drugs and cosmetics. With the passage of the Federal Hazardous Substances Act, possibly for lack of better methods of evaluation, these procedures were adopted for assessing the hazard potential of household products. To the extent that FHSA regulations do not provide suitable procedures for studying hazard as opposed to toxicity, they are deficient. In this paper we have attempted to develop experimental models that yield a measure of the potential hazard of detergents. For example, under occlusion for 24 hr, most detergents examined produced severe to extreme irritation. Detergents are not designed to be in contact with the skin for extended periods of time, and for this reason the data are misleading as regards probable conditions of misuse. Similarly, in evaluating eye irritation potential, severe damage to the eye occurred when 100 mg quantities were instilled without subsequent rinsing. Such a test may be realistic for a cosmetic, but not for heavy duty detergents. Use of smaller, more reasonable amounts of material, or rinsing following within a reasonable amount of time, gives more accurate models of what can be expected realistically. This also is applicable to the animal species used; a species whose eyes produce watery tears, as will the monkey's, provides a better assessment of potential hazard to humans. This principle also should be applied in evaluating the intragastric irritation potential of detergents, i.e., the test procedure should be realistic. As we have shown, animals fed prior to dosing are less subject to irritation than animals fasted for 24 hr. This is a more practical way for assessing what can happen in a real life situation involving very young children.

TABLE XII

Eye Irritation in Rhesus Monkeys Following a 1 Minute Residence before Irrigation (100 mg Detergent)

Product	Time after instillation	Irritation score[a]		
		Cornea[b]	Iris[c]	Conjunctiva[d]
1	1 hr	36.7	0.0	12.0
	24 hr	40.0	0.0	16.7
	72 hr	20.0	0.0	16.7
	7 days	0.0	0.0	8.0
	14 days	0.0	0.0	0.0
2	1 hr	23.3	0.0	11.3
	24 hr	16.7	0.0	10.7
	72 hr	6.7	0.0	10.0
	7 days	0.0	0.0	6.0
	14 days	0.0	0.0	0.0

[a]See Reference 7 for scoring procedure.
[b]Out of a possible total of 80.
[c]Out of a possible total of 10.
[d]Out of a possible total of 20.

We turn our attention now to the confusing subject of alkalinity or causticity.

A study prepared for the National Commission on Product Safety (15) contains the conclusion that the greater the alkalinity of an automatic dishwashing detergent, the greater the hazard upon ingestion. Based on this work, some have suggested (16) that alkalinity be used as a simple indicator of the hazard of heavy duty laundry detergents. However, when the total alkalinity, pH and toxicological properties of several detergents were charted a very different picture emerged (Table XIV), undoubtedly due to the fact that the surfactant contributes to toxicity. Contrary to the affirmations of producers of some phos-

TABLE XIV

21 Day Cumulative Human Skin Irritation Study[a]
(1% solution of Detergent)

Subject	Product 1	2	3	4	5	6	8	9
1	0	9.0	15.5	54.0	17.5	5.0	0	0
2	0	6.0	69.0	10.0	7.0	10.0	13.0	0
3	0	0	0	2.0	0	0	0	0
4	0	0	3.0	13.0	48.0	3.5	2.0	1.5
5	0	0	1.5	11.5	9.5	6.5	0	0
6	0	0	0	0	.0	2.5	0	0
7	0	0	9.5	8.0	9.5	5.0	0	0
8	0	3.0	4.5	12.5	12.0	16.0	8.0	8.0
Cumulative totals	0	18.0	103.0	111.0	103.5	48.5	23.0	9.5

[a]Reference 8.

phate detergents, there is no correlation between alkalinity and hazard for heavy duty laundry detergents: product 6, the total alkalinity of which is the lowest of those measured, has biological properties similar to those of product 1, with the highest total alkalinity. Nor is there a correlation between total alkalinity and hazard among the phosphate detergents. Product 8, for example, has a higher total alkalinity than product 3 or product 5; yet it is less damaging. Similarly there is no correlation between total alkalinity and pH, and no clear correlation between pH and hazard. These data are shown in Table XV. This conclusion is true not only for animals but also for man, as evidenced in the 21 day cumulative irritancy test.

What emerges from these considerations is that it is inappropriate to consider the individual ingredients of a laundry detergent when considering its probable hazard. Rather it is necessary to determine the hazard empirically on the completely formulated product.

In evaluating hazard, one must carefully consider the usefulness of the test method and the variability inherent in it. In our judgment the modified test procedures described in this paper, including those in which additional animal species were used, provide more realistic models for the assessment of detergent hazard than do present methods prescribed by FHSA regulation.

The powdered detergents tested ranged in severity of irritation from mild to severe and were not consistently irritating or nonirritating in all types of tests used. Some were severely irritating in eye tests and only mildly or moderately irritating to skin. Other powdered detergents tested caused severe irritation to the skin and mild to moderate intragastric irritation. No correlation was found to exist between alkalinity of the detergents and their potential for damaging tissue.

Under realistic conditions of misuse, marked differences in hazard potential between the phosphate-free detergent and several of the phosphate detergents tested were not shown. One may conclude that differences would not be observed in actual human experience.

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TABLE XV

pH, Alkalinity and Tissue Damage of Selected Detergents

Product	pH[a]	Total[b] alkalinity	Tissue damage Eye[c,d]	Tissue damage Skin[d]	Upon ingestion[c,e]
1	11.2	42	Extreme irritant Extreme irritant	Severe irritant	Possibly corrosive[f] Irritant plus
2	9.3	10.4	Moderate irritant Extreme irritant	Extreme irritant	Irritant plus Corrosive
3	10.1	5.7	Severe irritant Extreme irritant	Extreme irritant	Irritant plus Corrosive
4	9.5	10.7	Moderate irritant Severe irritant	Extreme irritant	Irritant plus Corrosive
5	9.5	5.2	Moderate irritant Severe irritant	E xtreme irritant	Irritant plus Corrosive
6	11.9	3.9	Extreme irritant Extreme irritant	Extreme irritant	Irritant plus to corrosive Corrosive
7	12.4	8.9	Severe irritant	Severe irritant	Corrosive
8	9.1	6.6	Moderate irritant Severe irritant	Moderate irritant	Irritant Irritant plus
13	9.1	6.3	Moderate irritant	Moderate irritant	Irritant plus
14	10.2	7.7	Severe irritant	Mild irritant	Irritant plus
15	9.1	10	Extreme irritant	Moderate irritant	Irritant plus

[a]pH of undiluted liquid detergent (products 6 and 7) and 0.2% solutions of powdered detergent.
[b]Calculated as milligram sodium oxide per gram product.
[c]Results of two studies where shown.
[d]FHSA test procedure in rabbits.
[e]Provisional corrosion test (FDA) except that the dosage corresponding to the first rating was 1.0 ml instead of 0.5 g.
[f]Corrosive to tongue on animals observed at 24 hr; normal on those observed at 96 hr.

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