

# PEDIATRICS®

OFFICIAL JOURNAL OF THE AMERICAN ACADEMY OF PEDIATRICS

## "Inactive" Ingredients in Pharmaceutical Products: Update (Subject Review)

Committee on Drugs

*Pediatrics* 1997;99:268-278

DOI: 10.1542/peds.99.2.268

**This information is current as of May 1, 2007**

The online version of this article, along with updated information and services, is located on the World Wide Web at:

<http://www.pediatrics.org/cgi/content/full/99/2/268>

PEDIATRICS is the official journal of the American Academy of Pediatrics. A monthly publication, it has been published continuously since 1948. PEDIATRICS is owned, published, and trademarked by the American Academy of Pediatrics, 141 Northwest Point Boulevard, Elk Grove Village, Illinois, 60007. Copyright © 1997 by the American Academy of Pediatrics. All rights reserved. Print ISSN: 0031-4005. Online ISSN: 1098-4275.

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™



# AMERICAN ACADEMY OF PEDIATRICS

Committee on Drugs

## “Inactive” Ingredients in Pharmaceutical Products: Update (Subject Review)

**ABSTRACT.** Because of an increasing number of reports of adverse reactions associated with pharmaceutical excipients, in 1985 the Committee on Drugs issued a position statement<sup>1</sup> recommending that the Food and Drug Administration mandate labeling of over-the-counter and prescription formulations to include a qualitative list of inactive ingredients. However, labeling of inactive ingredients remains voluntary. Adverse reactions continue to be reported, although some are no longer considered clinically significant, and other new reactions have emerged. The original statement, therefore, has been updated and its information expanded.

---

ABBREVIATIONS. FDA, Food and Drug Administration; MDIs, metered-dose inhalers

---

Pharmaceutical products often contain agents that have a variety of purposes, including improvement of the appearance, bioavailability, stability, and palatability of the product. Excipients (substances added to confer a suitable consistency or form to a drug, such as the vehicle, preservatives, or stabilizers) frequently make up the majority of the mass or volume of oral and parenteral drug products. These pharmaceutical adjuvants are usually considered to be inert and do not add to or affect the intended action of the therapeutically active ingredients.

Some 773 chemical agents have been approved by the Food and Drug Administration (FDA) for use as inactive ingredients in drug products.<sup>2</sup> Inasmuch as these compounds are classified as “inactive,” no regulatory statutes require listing on product labeling. Pharmacopeial guidelines, enforceable under the Food, Drug, and Cosmetic Act, do require labeling of inactive ingredients for topical, ophthalmic, and parenteral preparations; orally administered products are currently exempt. Because of pressure from professional and consumer organizations asking the FDA to require complete disclosure of all ingredients, voluntary labeling was adopted by the two major pharmaceutical industry trade associations. These voluntary guidelines contain an exemption for “trade secret” components and do not require complete disclosure of all fragrance and flavoring ingredients.

Current problems encountered with “inactive” ingredients include benzalkonium chloride-induced

bronchospasm from antiasthmatic drugs, aspartame-induced headache and seizures, saccharin-induced cross-sensitivity reactions in children with sulfonamide allergy, benzyl alcohol toxicity in neonates receiving high-dose continuous infusion with preserved medications, dye-related cross-reactions in children with aspirin intolerance, lactose-induced diarrhea, and propylene glycol-induced hyperosmolality and lactic acidosis. Although many other excipients have been implicated in causing adverse reactions, these are the most significant in the pediatric population.

### ANTIASTHMATIC MEDICATIONS

It is readily appreciated that some percentage of asthmatic children will develop a “paradoxical” bronchospasm after they inhale their medication. Because many of these reactions were attributed to sulfite, which had been highly publicized as a causative agent, it was often first suspected. During the past 10 years, however, the active ingredient in sulfite-containing preparations, the nonselective  $\beta_2$ -agonists isoproterenol, isoetharine, and metaproterenol, have been replaced as drugs of choice by more selective agents, primarily albuterol, that do not contain sulfites. Paradoxical reactions continue to be reported, in some cases resulting in product reformulation because of excessive adverse reactions. Inactive ingredients that have been implicated in causing these reactions include benzalkonium chloride, oleic acid, chlorofluorocarbons, soya lecithin, and sorbitan trioleate.

### Sulfites

Sulfiting agents are widely used as antioxidants. Six sulfite compounds (sulfur dioxide, sodium sulfite, sodium bisulfite, potassium bisulfite, sodium metabisulfite, and potassium metabisulfite) have been categorized as “Generally Recognized as Safe” for use in foods and drugs. This status was revoked for raw fruits and vegetables (excluding potatoes) in 1986 after the FDA received reports of more than 250 cases of adverse reactions, including six deaths associated with the ingestion of sulfites in foods.<sup>3,4</sup> Although primary exposure in children is through foods, serious reactions have also occurred after oral, inhalational, parenteral, and ophthalmic administration of sulfite-containing drugs.

Signs and symptoms most frequently reported include wheezing, dyspnea, and chest tightness in patients with known reactive airway disease.<sup>5-9</sup> Nonimmunologic anaphylactoid reactions have also

---

The recommendations in this statement do not indicate an exclusive course of treatment or serve as a standard of medical care. Variations, taking into account individual circumstances, may be appropriate.

PEDIATRICS (ISSN 0031 4005). Copyright © 1997 by the American Academy of Pediatrics.

occurred.<sup>7,8,10,11</sup> Reactions to sulfites rarely occur in patients without reactive airway disease.<sup>12</sup> Metabisulfite hypersensitivity was demonstrated in 19 (66%) of 29 children with a history of chronic moderately severe asthma.<sup>13</sup> The incidence of sulfite sensitivity increases with age in severely asthmatic children (31% of children up to 10 years of age and 71% of older children).<sup>14</sup>

The presence of sulfites in antiasthmatic medications has been a concern, but many of these medications have been reformulated or replaced in clinical practice by more  $\beta$ -selective agents, which do not contain sulfites. Metered-dose aerosol bronchodilators do not contain sulfites. Nonsulfite-containing products used to treat asthma are presented in Table 1. Parenteral drugs, such as corticosteroids, aminoglycosides, and epinephrine, may contain sulfites (Table 2) but rarely produce reactions because of the small amounts present. Patients who react to oral challenges with small amounts (5 to 10 mg) are at risk for similar reactions from these parenteral agents.<sup>15</sup> Local dermal reactions accompanied by eo-

**TABLE 1.** Some Medications Used by Asthmatics That Do Not Contain Sulfites

Brand Name*	Manufacturer
Aerobid inhaler	Forest
Airet solution	Adams
Alupent aerosol	Boehringer Ingelheim
Alupent solution 5%*	Boehringer Ingelheim
Alupent solution Unit-dose 0.4, 0.6%	Boehringer Ingelheim
Alupent syrup	Boehringer Ingelheim
Alupent tablets	Boehringer Ingelheim
Atrovent aerosol	Boehringer Ingelheim
Azmacort	Rhone-Poulenc Rorer
Beclivent inhaler	Glaxo
Brethine injection	Ciba-Geigy
Brethine tablets	Ciba-Geigy
Bricanyl injection	Marion Merrell Dow
Bronkaid Mist aerosol	Sterling-Winthrop
Bronkometer aerosol	Sterling-Winthrop
Celestone injection*	Schering
Decadron respihaler	Merck
Duo-Medihaler aerosol	3M
Elixophyllin elixir	Forest
Intal capsules, solution, inhaler	Fisons
Isoetharine solution	Astra
Isoetharine solution	Dey
Isuprel Mistometer	Winthrop-Breon
Maxair autohaler	3M
Medihaler-Epi aerosol	3M
Medihaler-Iso aerosol	3M
Metaprel aerosol	Sandoz
Metaprel solution 5%*	Sandoz
Primatene Mist suspension aerosol	Whitehall
Primatene Mist solution aerosol	Whitehall
Proventil aerosol	Schering
Proventil solution 0.5%*	Schering
Quibron tablet, capsule	Bristol-Myers Squibb
Sus-Phrine injection	Forest
Theo-Dur sprinkle, tablets	Key
Tilade inhaler	Fisons
Tornalate inhaler	Sterling Winthrop
Tornalate solution	Sterling Winthrop
Vanceril inhaler	Schering
Ventolin aerosol	Glaxo
Ventolin nebulas solution 0.083%	Glaxo
Ventolin solution 0.5%*	Glaxo
Ventolin rotacaps, syrup, tablets	Glaxo

\* Contains benzalkonium chloride.

**TABLE 2.** Some Sulfite-containing Medications Used by Asthmatics

Brand Name	Manufacturer
Adrenalin Chloride 1:100	Parke-Davis
Adrenalin injection 1:1000	Parke-Davis
Amikin injection	Apothecon
Arm-a-Med isoetharine solution	Armour
AsthmaNefrin	Menley & James
Beta 2 isoetharine solution	Nephron
Bronkosol solution	Sanofi-Winthrop
Dey-dose epinephrine	Dey
Dey-dose isoetharine solution	Dey
Dispos-a-Med isoetharine	Parke-Davis
Epipen/Epipen Jr	Center
Garamycin injection (all but intravenous piggyback and intrathecal)	Schering
Isoetharine hydrochloride	Roxane
Isuprel injection	Sanofi-Winthrop
Isuprel solution	Sanofi-Winthrop
MicroNefrin	Bird
Minocin syrup	Lederle
Nebcin injection	Lilly
Netromycin injection	Schering

sinophilia have been reported after continuous infusion with dobutamine.<sup>16</sup> Sulfite-preserved amino acids contained in most mixtures of total parenteral nutrition are a less commonly appreciated source. Nevertheless, life-threatening situations requiring the administration of epinephrine should be treated with sulfite-preserved epinephrine if no preservative-free product is available, even in very sensitive patients. The diagnosis of sulfite sensitivity is made by history and through challenge testing.<sup>7</sup> Avoidance of foods containing sulfites through careful reading of packaged food labels and inquiry at restaurants as to the use of agents that contain sulfites may prevent reactions. A commercial sulfite-detection strip was found to be unreliable, especially when used on acidic foods or foods removed from their original containers.<sup>17</sup> Drug manufacturers must disclose the presence of sulfites in product labeling.

### Benzalkonium Chloride

Benzalkonium chloride is a commonly used bactericidal preservative in albuterol and metaproterenol nebulizer solutions in the United States and in beclomethasone and ipratropium bromide nebulizer solutions in other countries. Inhalation of pure benzalkonium chloride causes reproducible, dose-related, cumulative bronchoconstriction, with a rapid onset and prolonged duration compared with sulfites. It is frequently accompanied by a cough and burning sensation and, occasionally, by facial flushing and pruritus. Bronchoconstriction is inhibited by concurrent treatment or pretreatment with  $\beta_2$ -agonists and cromolyn sodium and partially by histamine<sub>1</sub> antagonists.<sup>18-20</sup> The mechanism appears to be non-IgE-mediated release of mast cell mediators, with atopic patients being more susceptible.<sup>21</sup>

Because the reaction is dose-related and cumulative and may be masked by the active agent in many patients, few clear-cut cases of paradoxical bronchoconstriction have been attributed to benzalkonium, primarily in patients using more than one agent containing this excipient or in those receiving frequent

dosing.<sup>22-26</sup> Unit-dose vials deliver five times as much benzalkonium as the same dose given from a multiple-dose vial, which resulted in one case of bronchoconstriction.<sup>26</sup> Other potential sources of benzalkonium in children with asthma and concurrent sinusitis include nasal saline, nasal corticosteroid, and nasal decongestant solutions.

In several studies of adult asthmatics, the lowest dose of pure benzalkonium chloride that produced a 20% decrease in forced expiratory volume in 1 second ranged from 124 to 159  $\mu\text{g}$ . Albuterol (from a multidose vial) contains 50  $\mu\text{g}$  per 0.5 mL of solution<sup>18,19</sup>; thus, a single dose is unlikely to cause a reaction. Even in patients without overt deterioration after the use of benzalkonium-preserved antiasthmatic agents, some evidence exists that benzalkonium-free solutions may have improved efficacy.<sup>21,27</sup> Thus, although the presence of benzalkonium probably has a minimal effect in most patients using single, infrequent doses of a preserved bronchodilator, development of a unit-dose, nonpreserved preparation may significantly benefit the severely ill, hospitalized patient in whom disease-related deterioration in pulmonary function may be difficult to distinguish from preservative toxicity.

#### Metered-dose Inhalers (MDIs)

Paradoxical bronchoconstriction has been reported in up to 6.9% of asthmatic patients after inhalation of pure MDI vehicle.<sup>28</sup> When combined with an active ingredient, this incidence decreases to approximately 1.5% to 4%.<sup>29</sup> Most studies of MDI-related bronchoconstriction have been confounded by the lack of testing of individual vehicle components, inherent irritability of some active ingredients (corticosteroids), or concurrent use of potent active ingredients (bronchodilators). Inactive ingredients that have been implicated in the deterioration of pulmonary function attributable to hypersensitivity or irritant effects include chlorofluorocarbons,<sup>30-33</sup> sorbitan trioleate,<sup>30,34</sup> oleic acid,<sup>28,35</sup> and soya lecithin (H. G. Wilms, written communication, October 27, 1989).<sup>28,36</sup> One metaproterenol product, reformulated to contain soya lecithin, was withdrawn from the market after 1 month because of escalating reports of coughing, gagging, and asthma exacerbation (H. G. Wilms, written communication, October 27, 1989).

### ARTIFICIAL SWEETENERS

#### Aspartame

Aspartame, a dipeptide of aspartic acid and a methyl ester of phenylalanine, is approved for use in pharmaceutical products and is being used increasingly in chewable tablet and sugar-free formulations. Labels for both prescription and nonprescription products must include the phenylalanine content. The major consideration in the use of aspartame in children is in patients with autosomal recessive phenylketonuria. Although heterozygotes do not appear to have clinically significant increases in phenylalanine after ingestion of even large amounts (equivalent to 24 12-oz cans of diet beverages), homozygotes with strict dietary restrictions should avoid aspar-

tame. Children without dietary restrictions could safely ingest 10 mg/kg/d.<sup>37-40</sup> Dietary consumption of aspartame is typically less than 5 mg/kg/d<sup>41</sup>; young children, however, could ingest considerably more. For example, a 2-year-old child weighing 12 kg consumes 17 mg/kg from drinking one 12-oz can of diet soda and one serving of a sweetened product (eg, cereal, pudding, gelatin, or frozen dessert).<sup>42</sup>

Headache is the most common adverse effect attributed to aspartame but is seldom confirmed by single-dose double-blind challenge. Up to 11% of patients with chronic migraine headaches reported headaches triggered by aspartame<sup>43</sup>; however, a double-blind challenge with three doses of 10 mg/kg given every 2 hours triggered no more headaches than did placebos in patients with vascular headaches believed to be exacerbated by aspartame.<sup>44</sup> A small, double-blind 4-week trial showed an increase in frequency of headaches after ingestion of 1200 mg/d, indicating that a longer challenge period may be necessary.<sup>45</sup>

In anecdotal reports, aspartame has been linked to various neuropsychiatric disorders, including panic attacks, mood changes, visual hallucinations, manic episodes, and isolated dizziness.<sup>46-49</sup> A small, double-blind crossover study of patients with major depression revealed a higher incidence of reactions in these patients compared with nondepressed volunteers after administration of 30 mg/kg for 7 days; symptoms included headache, nervousness, dizziness, memory impairment, nausea, temper outbursts, and depression.<sup>50</sup> None of these conditions has been rigorously proven to be caused by aspartame, but carefully conducted double-blind challenges may be indicated in patients with histories that suggest aspartame as a cause. Patients with underlying mitral valve prolapse or affective disorders may be at increased risk for neuropsychiatric effects<sup>51</sup>; several studies have shown that individuals without psychiatric or seizure disorders do not demonstrate these effects.<sup>50,52</sup>

Seizures have been reported via passive surveillance data collected by the FDA and in a few case reports.<sup>47,48,53</sup> A recent analysis of FDA reports showed 41 cases of rechallenge with a temporal relationship to aspartame consumption. Most seizures occurred in patients who had an acceptable dietary intake, except for a 16-year-old who ingested up to 57 mg/kg of aspartame.<sup>54</sup> Aspartame is generally considered safe for children with epilepsy. One study found increased spike-wave discharges in children with untreated absence seizures after a high dose of aspartame and suggested that children with poorly controlled absence seizures avoid aspartame.<sup>55</sup>

Several studies have shown no relationship between aspartame and aggressive or hyperactive behaviors or cognitive function in children; thus, children with attention deficit disorder, with or without hyperactivity,<sup>56,57</sup> do not need to avoid this sweetener.

Isolated confirmed hypersensitivity reactions resulting from ingestion of aspartame have been reported, including two patients who developed sub-

**TABLE 3.** Parenteral Medications That Contain Benzyl Alcohol

Drug	Benzyl Alcohol Content, %	Estimated Average Daily Intake of Benzyl Alcohol in Infants
Aminophylline	2.0	2–4 mg/kg
Aquamephyton neonatal injection	0.9	4.5 mg
Ativan injection	2.0	0.4–1 mg/kg
Bacteriostatic saline	1.5	99–234 mg/kg
Bacteriostatic water	1.5	99–234 mg/kg
Dexamethasone injection	1.0	2.5 mg
Dopram	0.9	21.6–32.4 mg/kg
Folate sodium	1.5	0.6–0.9 mg
Heparin injection (1000 U/mL)	1.0	1.2 mg
Multivitamin infusion	0.9	45 mg
Netromycin injection*	1.0	0.4–0.65 mg/kg
Norcuron with supplied diluent	0.9	0.4 mg/kg
Pavulon injection	1.0	2–3 mg/kg
Tracrium multidose vial	0.9	3.6 mg/kg
Vasotec injection	0.9	0.1–0.5 mg/kg

\* Netromycin neonatal injection does not contain benzyl alcohol.

cutaneous nodules or granulomas resembling erythema nodosum.<sup>58,59</sup> Other reported reactions include orofacial granulomatosis, erythema, pruritus, urticaria, and angioedema.<sup>60–62</sup> A meticulous workup with double-blind challenge usually fails to confirm the purported reaction; hypersensitivity reactions appear to be rare.<sup>63,64</sup> These reactions may be related to breakdown products formed during the storage of liquid products, such as diketopiperazine derivatives, especially after exposures to higher temperatures.<sup>62</sup> If so, rechallenge with fresh encapsulated powder could produce a false-negative reaction.

### Saccharin

Many oral drugs, including both solid and liquid dosage forms, contain saccharin as a sweetening agent. Saccharin is not included in drug labeling. The most frequent use of saccharin is in foods and beverages, accounting for 70% of the total consumption. A British survey found that conventional soft drinks were the predominant source of saccharin in children aged 2 to 9 years, replaced by diet soft drinks in adolescents. The median intake of saccharin was 0.2 to 0.9 mg/kg/d in the general population and 0.6 to 2.3 mg/kg/d in diabetics.<sup>65</sup> Foods containing saccharin must carry a label stating that the “use of this product may be hazardous to your health . . . contains saccharin which has been determined to cause cancer in laboratory animals.”

Saccharin may be present in drugs in substantial amounts. Ingestion of the recommended daily dosage of chewable aspirin or acetaminophen tablets in a school-age child would provide approximately the same amount of saccharin contained in one can of a diet soft drink. This amount, relative to the body weight of a child younger than 9 or 10 years, ingested for prolonged periods would be considered as “heavy use,” as defined in a major large-scale FDA/National Cancer Institute epidemiologic study.<sup>66</sup> In this study, heavy use of artificial sweeteners was associated with a significantly increased risk for the development of bladder cancer. An independent review of this study concluded that there was no association.<sup>67</sup> An investigation of saccharin performed by the American Medical Association in 1985 con-

cluded that bladder changes were species-specific, were confined to the second generation of male rats, and occurred in association with large doses (equivalent to several hundred cans of diet soft drink per day). The no-effect level was equivalent to 500 mg/kg/d.<sup>68,69</sup> Saccharin is not genotoxic; the presumed mechanism of toxicity is the binding of saccharin to urinary proteins (not normally found in humans), creating a nidus for the formation of silicate crystals, which are cytotoxic to bladder epithelium.<sup>70</sup>

Saccharin is an o-toluene sulfonamide derivative and causes similar dermatologic reactions. Cross-sensitivity with sulfonamides has been demonstrated; therefore, children with “sulfa” allergy should also avoid saccharin. Hypersensitivity can usually be confirmed by a radioallergosorbent test for saccharin.<sup>71</sup> In a series of 42 patients with adverse effects resulting from consumption of saccharin in pharmaceutical agents, pruritus and urticaria were the most common reactions, followed by eczema, photosensitivity, and prurigo.<sup>72</sup> Other reactions include wheezing, nausea, diarrhea, tongue blisters, tachycardia, fixed eruptions, headache, diuresis, and sensory neuropathy.<sup>73–77</sup>

Ingestion of saccharin-adulterated milk formula by infants was associated with irritability, hypertonia, insomnia, opisthotonos, and strabismus, which resolved within 36 hours after ingestion. Two anecdotal reports of an accidental overdose in an adult and a child discussed reactions of generalized edema, oliguria, and persistent albuminuria.<sup>75</sup> Because of the paucity of data on the toxicity of saccharin in children, the American Medical Association has recommended limiting the intake of saccharin in young children and pregnant women.<sup>68</sup>

### BENZYL ALCOHOL

Benzyl alcohol is commonly used as a preservative in many injectable drugs and solutions. A number of neonatal deaths and severe respiratory and metabolic complications in low-birth-weight premature infants have been associated with use of this agent in bacteriostatic saline intravascular flush and endotracheal tube lavage solutions.<sup>78–80</sup> In a controlled study, intraventricular hemorrhage, metabolic acidosis, and

**TABLE 4.** Examples of Dye-free Orally Administered Liquid Medications

Classification and Product (Manufacturer)	Active Ingredients (per 5 mL Unless Otherwise Indicated)
<b>Analgesics</b>	
Demerol (Sanofi Winthrop)	Meperidine 50 mg
Indomethacin (Roxane)	Indomethacin 25 mg
Meperidine* (Roxane)	Meperidine 50 mg
Methadone Intensol* (Roxane)	Methadone 50 mg
Opium tincture (Lilly)	Morphine 50 mg
Rescudose* (Roxane)	Morphine sulfate 20 mg
Roxanol* (Roxane)	Morphine sulfate 100 mg
Roxanol* (Roxane)	Morphine sulfate 20 mg
Roxicodone Intensol* (Roxane)	Oxycodone 100 mg
<b>Antibiotics/anti-infective</b>	
Furoxone (Roberts)	Furazolidone 50 mg
Gantrisin syrup (Roche)	Sulfisoxazole 500 mg
Gantrisin pediatric suspension (Roche)	Sulfisoxazole 500 mg
Mandelamine 250 (Parke-Davis)	Methenamine mandelate 250 mg
Minocin (Lederle)	Minocycline 50 mg
Mintezol (Merck Sharp & Dohme)	Thiazabendazole 500 mg
Nystatin (Roxane)	Nystatin 500,000 units
Pediazole (Ross)	Erythromycin 200 mg, sulfisoxazole 600 mg
Suprax (Lederle)	Cefixime 100 mg
Vancocin** (Lilly)	Vancomycin 250 or 417 mg
Vantin (Upjohn)	Cefpodoxime axetil 50 mg
<b>Antihistamine/decongestant/antitussive</b>	
Atarax syrup (Roerig)	Hydroxyzine 10 mg
Chlorafed (Hauck)	Chlorpheniramine 2 mg, pseudoephedrine 30 mg
Codclear DH (Central)	Hydrocodone 5 mg, guaifenesin 100 mg
Deconamine syrup (Berlex)	Chlorpheniramine 2 mg, pseudoephedrine 30 mg
Entuss-D (Hauck)	Hydrocodone 5 mg, pseudoephedrine 30 mg, guaifenesin 300 mg
Iodinated glycerol (Roxane)	Iodinated glycerol 60 mg
Iodinated glycerol/Dextromethorphan (Roxane)	Iodinated glycerol 30 mg, dextromethorphan 10 mg
Isoclor (Fisons)	Chlorpheniramine 2 mg, pseudoephedrine 30 mg
Tuss-Ornade (SmithKline Beecham)	Phenylpropanolamine 12.5 mg, caramiphen 6.7 mg
<b>Cardiovascular agents</b>	
Aldomet (Merck Sharp & Dohme)	Methyldopa 250 mg
Colestid** (Upjohn)	Colestipol 5 g per packet
Digoxin elixir (Roxane)	Digoxin 0.25 mg
Hydrochlorothiazide (Roxane)	Hydrochlorothiazide 50 mg
Propranolol oral solution (Roxane)	Propranolol 20 or 40 mg
Propranolol Intensol (Roxane)	Propranolol 400 mg
<b>Gastrointestinal</b>	
AlternaGEL (Johnson & Johnson-Merck)	Aluminum hydroxide 600 mg
Aluminum hydroxide gel (Roxane)	Aluminum hydroxide 450 mg
Aluminum hydroxide concentrated (Roxane)	Aluminum hydroxide 675 mg
Aromatic cascara fluid extract (Roxane)	Cascara sagrada extract equivalent to 1 g/mL
Castor oil** (Roxane)	Castor oil
Citrocarbonate+ (Upjohn)	Sodium citrate 1.82 g, sodium bicarbonate 0.78 g
Doxinate (Hoechst-Roussel)	Docusate 50 mg
Effersyllium+ (Johnson & Johnson-Merck)	Psyllium hydrocolloid 3 g
Gaviscon ESRF (Marion Merrell Dow)	Aluminum hydroxide 254 mg, magnesium carbonate 237.5 mg
Ipecac syrup (Roxane)	Ipecac alkaloids 20 mg/15 mL
Kaolin pectin (Roxane)	Kaolin, pectin
Kaopectate regular flavor (Upjohn)	Attapulgit 200 mg
Loperamide (Roxane)	Loperamide 1 mg
Maalox plus, extra strength (Rhone-Poulenc Rorer)	Aluminum hydroxide 500 mg, magnesium hydroxide 450 mg, simethicone 40 mg
Milk of Magnesia* (Roxane)	Magnesium hydroxide 400 mg
Milk of Magnesia concentrated (Roxane)	Magnesium hydroxide 1200 mg
Mylanta double strength (Johnson & Johnson-Merck)	Aluminum hydroxide 400 mg, magnesium hydroxide 400 mg, simethicone 40 mg
Parapectolin (Rhone-Poulenc Rorer)	Attapulgit 200 mg
Perdiem+ (Rhone-Poulenc Rorer)	Psyllium (82% w/v), senna (18% w/v)
<b>Hormonal agents</b>	
Dexamethasone solution (Roxane)	Dexamethasone 0.5 mg
Dexamethasone Intensol* (Roxane)	Dexamethasone 5 mg
Prednisone solution (Roxane)	Prednisone 5 mg
Prednisone Intensol* (Roxane)	Prednisone 25 mg
Proglycem (Baker Cummins)	Diazoxide 250 mg

TABLE 4. Continued

Classification and Product (Manufacturer)	Active Ingredients (per 5 mL Unless Otherwise Indicated)
Psychotropics	
Chlorpromazine Intensol (Roxane)	Chlorpromazine 150, 500 mg
Cibalith-S (Ciba-Geigy)	Lithium 8 mEq
Haldol* (McNeil)	Haloperidol 10 mg
Haloperidol Intensol* (Roxane)	Haloperidol 10 mg
Lithium citrate (Roxane)	Lithium 8 mEq
Navane (Roerig)	Thiothixene 25 mg
Prozac (Lilly)	Fluoxetine 20 mg
Sinequan (Roerig)	Doxepin 50 mg
Thioridazine solution (Roxane)	Thioridazine 80 mg/15 mL
Thioridazine Intensol (Roxane)	Thioridazine 150, 500 mg
Thiothixene Intensol* (Roxane)	Thiothixene 25 mg
Thorazine (SmithKline Beecham)	Chlorpromazine 10 mg
Trilafon (Schering)	Perphenazine 16 mg
Sedatives/hypnotics	
Chloral hydrate syrup (Roxane)	Chloral hydrate 250, 500 mg
Lorazepam Intensol* <sup>+</sup> (Roxane)	Lorazepam 10 mg
Spasmolytics/bronchodilators	
Aquaphylline (Ferndale)	Theophylline 5.33 mg
Elixophyllin GG (Forest)	Theophylline 100 mg, guaifenesin 100 mg,
Marax DF (Roerig)	Ephedrine 6.25 mg, theophylline 32.5 mg, hydroxyzine 2.5 mg
Slo-Phyllin GG (Rhône-Poulenc Rorer)	Theophylline 50 mg, guaifenesin 30 mg
Somophyllin DF (Fisons)	Theophylline 90 mg
Theoclear-80 (Central)	Theophylline 26.66 mg
Theolair liquid (3M Riker)	Theophylline 26.66 mg
Theophylline solution (Roxane)	Theophylline 26.66 mg
Theostat 80 syrup (Laser)	Theophylline 26.66 mg
Vitamins	
DHT intensol (Roxane)	Dihydrotachysterol 1 mg
Drisdol (Sanofi Winthrop)	Ergocalciferol 8000 U/mL
Theragran liquid (Apothecon)	Multivitamins
Miscellaneous	
Antiminth (Roerig)	Pyrantel pamoate 250 mg
Glyoxide (Marion Merrell Dow)	Carbamide peroxide 100 mg/mL, anhydrous glycerol
Klorvess (Sandoz)	Potassium chloride 10%

\* Flavoring free.

<sup>+</sup> Preservative free.

increased mortality were positively correlated with substantial benzoic acid and benzyl alcohol levels in neonates.<sup>81</sup> The incidence of premature infant mortality, kernicterus, and intraventricular hemorrhage decreased markedly after discontinuation of preserved flush solutions.<sup>82-84</sup> In surviving infants, exposure to benzyl alcohol was also found to be associated with morbidity, including cerebral palsy and developmental delay.<sup>83</sup>

Most therapeutic agents, other than large-volume fluids, contain amounts of benzyl alcohol smaller than those associated with neonatal death. The effects of lower amounts, however, have not been adequately studied (Table 3). Toxicity has been described in one infant weighing 3350 g who received 32 to 105 mg/kg/d.<sup>80</sup> Continuous infusions of high doses of some medications containing benzyl alcohol, such as doxapram, may reach the range of benzyl alcohol dosage associated with toxicity in this case report. Premature infants receiving low doses in medications were found to have peak benzoic acid levels 10 times higher than those in term infants but without evidence of toxicity.<sup>85</sup> Two studies noting the striking decrease in kernicterus after removal of benzyl alcohol did not reveal a dose-response relationship and could not exclude the possibility that other advances in therapy were responsible.<sup>84,86</sup>

The US Pharmacopeia requires labeling of bacteriostatic water and saline for injection with the phrase, "Not for use in newborns." The FDA declined similar labeling for multidose parenteral medications, because serious toxic effects from benzyl alcohol had virtually disappeared.<sup>87</sup> The toxic effects in newborns relate primarily to the use of preservative-containing flush solutions, which clearly are to be avoided in newborns. At low doses, such as those present when medications preserved with benzyl alcohol are administered, benzyl alcohol is safe for newborns.

Bacteriostatic saline solution containing benzyl alcohol was associated with severe bronchitis and hemoptysis when used to dilute albuterol for nebulization in an adult man.<sup>88</sup> Nonpreserved saline solution should be used in children to dilute nebulized bronchodilators.

Benzyl alcohol may also rarely cause hypersensitivity reactions. Contact dermatitis,<sup>89</sup> as well as more generalized allergic symptoms including nausea, fatigue, fever, maculopapular rash, or angioedema, may occur after parenteral administration of products containing benzyl alcohol as a preservative.<sup>90-92</sup>

#### COLORING AGENTS

Numerous dyes are used in pharmaceutical manufacturing. These dyes give products a distinctive,

identifiable appearance, and they impart a uniform and attractive color to products that might otherwise be drab and unappealing or exhibit color variation among batches.

Several groups of dyes have been associated with serious adverse effects. The azo dye tartrazine (FD&C Yellow No. 5) is known to be potentially dangerous in aspirin-intolerant individuals. Approximately 2% to 20% of asthmatics are sensitive to aspirin. The incidence of cross-reaction to tartrazine was previously believed to be as high as 10%,<sup>93,94</sup> but more recent carefully blinded studies have shown the incidence to be less than 2.4%.<sup>95-98</sup> Unlike aspirin, tartrazine does not alter prostaglandin synthesis and does not, therefore, exert anti-inflammatory actions. Nonetheless, reactions to tartrazine are similar to those produced by aspirin, occur in patients both with and without a history of aspirin intolerance, and include acute bronchospasm, nonimmunologic urticaria, eosinophilia, and angioedema.<sup>94,99-107</sup> Rarely, nonimmunologic anaphylactoid reactions occur.<sup>108,109</sup> The most likely mechanism for these reactions is dose-related histamine release from mast cells.<sup>110,111</sup> Patients with recurrent allergic vascular purpura may experience exacerbations after exposure to azo dyes, such as tartrazine, sunset yellow, and new cocine.<sup>112-114</sup> Because of both the seriousness of these reactions and the widespread use of tartrazine in foods and over-the-counter and prescription drugs, since 1980 the FDA has required that all products containing tartrazine be labeled so that these substances can be avoided.<sup>115</sup>

Patients with the classic aspirin triad reaction (asthma, urticaria, and rhinitis) or anaphylactoid reactions may also develop similar reactions from dyes other than tartrazine, including amaranth,<sup>116-118</sup> erythrosine,<sup>118,119</sup> indigo carmine (FD&C Blue No. 2),<sup>103</sup> ponceau,<sup>106,116,118</sup> new cocine,<sup>113,117</sup> sunset yellow,<sup>103,106,108,113,117,118</sup> Brilliant Blue (FD&C Blue No. 1),<sup>106,118</sup> methyl blue,<sup>120</sup> quinolone yellow,<sup>121</sup> and FD&C Red No. 40.<sup>122</sup>

Gastrointestinal intolerance, with abdominal pain, vomiting, and indigestion, has been associated with sunset yellow; in one case, eosinophilia and hives were also present.<sup>123,124</sup> Other dermatologic reactions, including photosensitivity, erythroderma, and desquamation,<sup>125</sup> have been attributed to erythrosine, an iodine-containing dye. By mandate, erythrosine has been removed from topical products and is being voluntarily removed from many oral drug products because of concerns about carcinogenicity.

Contact dermatitis has been associated with neutral red,<sup>126,127</sup> D&C Yellow No. 11,<sup>128,129</sup> indigo carmine (FD&C Blue No. 2),<sup>130</sup> quinoline yellow,<sup>129</sup> and gentian violet (CI Basic Violet No. 3).<sup>131,132</sup>

Dyes and other food additives have also been suggested as a cause or aggravating factor in some cases of hyperactivity in children<sup>116</sup>; carefully controlled trials<sup>133-136</sup> and current opinion<sup>137-139</sup> generally refute a possible association.

Because carefully controlled double-blind challenges often fail to confirm suspected reactions in children with atopic eczema,<sup>140</sup> a controlled challenge is recommended before dyes are eliminated

from the diet. Hypersensitive individuals should avoid dyes; liquid medications and nutritional supplements that do not contain dyes are listed in Table 4. These listings were originally compiled from voluntary responses to personal communications received from 56 US drug manufacturers and updated with a repeat mailing in December 1992. Until complete ingredient labeling is mandated, these lists will provide a tool to prevent reactions through avoidance in sensitive children using liquid dosage forms. Because inactive ingredients may change without changes in labeling, information in these tables should be verified.

## LACTOSE

Lactose (milk sugar) is widely used as a filler or diluent in tablets and capsules and to give bulk to powders. Lactase deficiency, occurring either as a rare congenital disorder or more commonly as an acquired lack of intestinal brush border disaccharidase, may lead to diarrhea, abdominal cramping, bloating, and flatulence after ingestion of milk products or lactose. These effects are produced either by lactic acid formed in the intestine by bacteria from undigested lactose or by a high intestinal osmotic load caused by unabsorbed carbohydrate with production of carbon dioxide and hydrogen gas by bacterial fermentation.<sup>141</sup> Lactose intolerance in infants and young children may be associated with severe, prolonged diarrhea complicated by bacterial proliferation in the small bowel, dehydration, and metabolic acidosis.<sup>142</sup> Lactose may be detrimental to the galactose-intolerant infant.

Late-onset lactase deficiency (adult hypolactasia) is a common disorder. Approximately 90% of adult American blacks and 60% to 80% of Mexican-Americans, Native Americans, Asians, and most Middle Eastern and Mediterranean populations have abnormal findings on lactose tolerance tests.<sup>143-148</sup> Approximately 10% of the white population with Scandinavian or European ancestry is affected.<sup>148</sup> Lactase deficiency may develop sporadically in otherwise tolerant individuals while they are suffering from an intestinal disease, such as tropical sprue or acute gastroenteritis.<sup>149</sup>

Sensitivity to lactose varies widely in severity, although some individuals (adults and children) may experience diarrhea, gaseousness, or cramping after ingestion of as little as 3 g or less of lactose.<sup>150,151</sup> Such symptoms can occur in sensitive individuals after ingestion of drugs containing lactose.<sup>152-154</sup> Two adult asthmatics who developed bronchospasm from lactose-containing medications had positive double-blind challenges with 300 and 500 mg of lactose.<sup>155,156</sup>

## PROPYLENE GLYCOL

Propylene glycol is commonly used as a drug solubilizer in topical, oral, and injectable medications.

Absorption of the agent from creams applied to burns<sup>157,158</sup> and injection of multivitamin products or enoximone (a phosphodiesterase inhibitor) in infants has resulted in serum hyperosmolality,<sup>159,160</sup> which was associated with cardiorespiratory arrest in one case.<sup>160</sup> Neonates have a longer propylene glycol

half-life (16.9 hours) compared with adults (5 hours).<sup>158,159</sup> Although the use of a multivitamin containing propylene glycol correlated strongly with serum osmolality in very low-birth-weight premature infants,<sup>161</sup> propylene glycol from phenobarbital injection contributed an insignificant amount to the osmolar gap in another study.<sup>162</sup> The higher amount of propylene glycol contained in an intravenous multivitamin product delivering 3 g/d was associated with a higher incidence of seizures in these infants compared with those receiving lower doses from an alternative product delivering 300 mg/d.<sup>163</sup> Hyperosmolality related to topical propylene glycol occurred in 9 of 262 hospitalized burn patients.<sup>164</sup>

Because propylene glycol is metabolized to lactic acid, lactic acidosis may occur.<sup>165</sup> Hemolysis, central nervous system depression, hyperosmolality, and lactic acidosis have been reported after intravenous administration.<sup>165-168</sup> Hyperlactemia is associated with high propylene glycol levels, usually in patients with renal insufficiency, and is generally of minor clinical importance.<sup>169</sup> Rapid infusion of concentrated propylene glycol-containing drugs has also been associated with respiratory depression, arrhythmias, hypotension, and seizures.<sup>170</sup> Inadvertent administration of a highly concentrated solution can occur during manual push infusions; a piggyback infusion is preferred.<sup>171</sup> Seizures and respiratory depression have also occurred in children who have ingested oral liquid medications containing propylene glycol.<sup>172,173</sup>

Several cases of localized contact dermatitis from the application of propylene glycol as a vehicle to skin or mucous membranes have been reported.<sup>174-180</sup> In a series of 487 patients with eczematous contact dermatitis, 4.5% were found to be sensitive to propylene glycol.<sup>181</sup> Oral or parenteral administration may exacerbate dermatitis in sensitized patients.<sup>182,183</sup> The high concentration of propylene glycol contained in certain drug products, such as phenytoin, diazepam, digoxin, and etomidate, may induce thrombophlebitis when administered intravenously.<sup>184,185</sup> In one study, 22% of patients experienced venous reactions to etomidate in propylene glycol, with no reactions to etomidate lipid emulsion.<sup>186</sup>

### RECOMMENDATIONS

In a previous review of inactive ingredients, the American Academy of Pediatrics recommended mandatory labeling of inactive ingredients for all prescription and over-the-counter products. Since voluntary labeling was adopted, the legislative push for mandatory labeling has been abandoned, other than for nutritional supplements. A recently published survey of labeling on 102 chewable and liquid pediatric preparations found that only 90% labeled sweeteners, 80% labeled dyes and coloring agents, and 65% labeled preservatives. Although 90% of the preparations labeled flavorings, few provided the specific ingredient, in accordance with the voluntary guidelines.<sup>187</sup> Therefore, the voluntary system is clearly inadequate. Again, the American Academy of Pediatrics recommends mandatory labeling for all prescription and over-the-counter drugs.

### COMMITTEE ON DRUGS, 1995 TO 1996

Cheston M. Berlin, Jr, MD, Chair  
D. Gail McCarver, MD  
Daniel A. Notterman, MD  
Robert M. Ward, MD  
Douglas N. Weismann, MD  
Geraldine S. Wilson, MD  
John T. Wilson, MD

### LIAISON REPRESENTATIVES

Donald R. Bennett MD, PhD  
American Medical Association/United States Pharmacopeia  
Joseph Mulinare, MD, MSPH  
Centers for Disease Control and Prevention  
Iffath Abbasi Hoskins, MD  
American College of Obstetricians and Gynecologists  
Paul Kaufman, MD  
Pharmaceutical Research and Manufacturers of America  
Michael J. Rieder, MD  
Canadian Paediatric Society  
Gloria Troendle, MD  
Food and Drug Administration  
Sumner J. Yaffe, MD  
National Institutes of Health

### AAP SECTION LIAISON

Charles J. Coté, MD  
Section on Anesthesiology  
Stanley J. Szeffler, MD  
Section on Allergy and Immunology

### CONSULTANT

Susan C. Smolinske, PharmD

### REFERENCES

1. American Academy of Pediatrics, Committee on Drugs. "Inactive" ingredients in pharmaceutical products. *Pediatrics*. 1985;76:635-643
2. Brown JL. Incomplete labeling of pharmaceuticals: a list of "inactive" ingredients. *N Engl J Med*. 1983;309:439-441
3. Food and Drug Administration. Sulfite update. *FDA Drug Bull*. 1984; 14:24
4. Food and Drug Administration. Sulfiting agents: revocation of GRAS status for use on fruits and vegetables intended to be served or sold raw to consumers: final rule. *Fed Reg*. 1986;51:25021-25026
5. Freedman BJ. Asthma induced by sulphur dioxide, benzoate and tartrazine contained in orange drinks. *Clin Allergy*. 1977;7:407-415
6. Baker GJ, Collett P, Allen DH. Bronchospasm induced by metabisulfite-containing foods and drugs. *Med J Aust*. 1981;2:614-617
7. Schwartz HJ. Sensitivity to ingested metabisulfite: variations in clinical presentations. *J Allergy Clin Immunol*. 1983;71:487-489
8. Stevenson DD, Simon RA. Sensitivity to ingested metabisulfites in asthmatic subjects. *J Allergy Clin Immunol*. 1981;68:26-32
9. Koepke JW, Christopher KL, Chai H, Selner JC. Dose-dependent bronchospasm from sulfites in isoetharine. *JAMA*. 1984;251:2982-2983
10. Prenner BM, Stevens JJ. Anaphylaxis after ingestion of sodium bisulfite. *Ann Allergy*. 1976;37:180-182
11. Twarog FJ, Leung DY. Anaphylaxis to a component of isoetharine (sodium bisulfite). *JAMA*. 1982;248:2030-2031
12. Schwartz HJ, Sher TH. Metabisulfite sensitivity in a patient without hyperactive airways disease. *Immunol Allergy Pract*. 1986;8:308-311
13. Towns SJ, Mellis CM. Role of acetyl salicylic acid and sodium metabisulfite in chronic childhood asthma. *Pediatrics*. 1984;73:631-637
14. Vandenbossche LE, Hop WC, de Jonste JC. Bronchial responsiveness to inhaled metabisulfite in asthmatic children increases with age. *Pediatr Pulmonol*. 1993;16:236-242
15. Smolinske SC. Review of parenteral sulfite reactions. *J Toxicol Clin Toxicol*. 1992;30:597-606
16. Wu CC, Chen WJ, Cheng JJ, Hsieh YY, Lien WP. Local dermal hypersensitivity from dobutamine hydrochloride (Dobutrex solution) injection. *Chest*. 1991;99:1547-1548
17. Wanderer AA, Solomons C. Detection characteristics of a commercially available sulfite detection test (SULFITEST): problems with de-

- creased sensitivity and false negative reactions. *Ann Allergy*. 1987;58:41–44
18. Beasley CR, Rafferty P, Holgate ST. Bronchoconstrictor properties of preservatives in ipratropium bromide (Atrovent) nebuliser solution. *BMJ*. 1987;294:1197–1198
  19. Zhang YG, Wright WJ, Tam WK, Nguyen-Dang TH, Salome CM, Woolcock AJ. Effect of inhaled preservatives on asthmatic subjects. II. Benzalkonium chloride. *Am Rev Respir Dis*. 1990;141:1405–1408
  20. Miszkiel KA, Beasley R, Rafferty P, Holgate ST. The contribution of histamine release to bronchoconstriction provoked by inhaled benzalkonium chloride in asthma. *Br J Clin Pharmacol*. 1988;25:157–163
  21. Rafferty P, Beasley R, Holgate ST. Comparison of the efficacy of preservative free ipratropium bromide and Atrovent nebuliser solution. *Thorax*. 1988;43:446–450
  22. Menendez R, Lowe RS, Kersey J. Benzalkonium chloride and bronchoconstriction. *J Allergy Clin Immunol*. 1989;84:272–274
  23. Boucher M, Roy MT, Henderson J. Possible association of benzalkonium chloride in nebulizer solutions with respiratory arrest. *Ann Pharmacother*. 1992;26:772–774
  24. Finnerty JP, Howarth PH. Paradoxical bronchoconstriction with nebulized albuterol but not with terbutaline. *Am Rev Respir Dis*. 1993;148:512–513
  25. Clark RJ. Exacerbation of asthma after nebulised beclomethasone dipropionate. *Lancet*. 1986;2:574–575
  26. Ponder RD, Wray BB. A case report: sensitivity to benzalkonium chloride. *J Asthma*. 1993;30:229–231
  27. O'Driscoll BR, Taylor RJ, Horsley MG, Chambers DK, Bernstein A. Nebulised salbutamol with and without ipratropium bromide in acute airflow obstruction. *Lancet*. 1989;1:1418–1420
  28. Yarbrough J, Mansfield LE, Ting S. Metered dose inhaler induced bronchospasm in asthmatic patients. *Ann Allergy*. 1985;55:25–27
  29. Yarbrough J, Mansfield LE, Ting S. Immediate bronchoconstrictive response to metered dose albuterol (MD-A). Presented at the 39th Annual Congress of the American College of Allergy; January 1983; New Orleans, LA
  30. Brooks SM, Mintz S, Weiss E. Changes occurring after freon inhalation. *Am Rev Respir Dis*. 1972;105:640–643
  31. Graff-Lonnevig V. Diurnal expiratory flow after inhalation of freons and fenoterol in childhood asthma. *J Allergy Clin Immunol*. 1979;64:534–538
  32. Witek TJ, Schachter EN, Zuskin E. Paradoxical bronchoconstriction following inhalation of isoetharine aerosol: a case report. *Respir Care*. 1987;32:29–31
  33. Sterling GM, Batten JC. Effect of aerosol propellants and surfactants on airway resistance. *Thorax*. 1969;24:228–231
  34. Malish DM. Possible allergic reactions to inert ingredient in Alupent metered dose inhaler, sorbitan trioleate. *Immunol Allergy Pract*. 1985;7:467–469
  35. Shim C, Williams MH. Cough and wheezing from beclomethasone aerosol. *Chest*. 1987;91:207–209
  36. Fine SR. Possible reactions to soya lecithin in aerosols. *J Allergy Clin Immunol*. 1991;87:600
  37. Guttler F, Lou H. Aspartame may imperil dietary control of phenylketonuria. *Lancet*. 1985;1:525–526
  38. Koch R, Schaeffler G, Shaw NF. Results of loading doses of aspartame by two phenylketonuric (PKU) children compared with two normal children. *J Toxicol Environ Health*. 1976;2:459–469
  39. Caballero B, Mahon BE, Rohr FJ, Levy HL, Wurtman RJ. Plasma amino acid levels after single-dose aspartame consumption in phenylketonuria, mild hyperphenylalaninemia, and heterozygous state for phenylketonuria. *J Pediatr*. 1986;109:668–671
  40. Stegink LD, Filer LJ, Bell EF, Ziegler EE, Tephly TR, Krause WL. Repeated ingestion of aspartame-sweetened beverages: further observations in individuals heterozygous for phenylketonuria. *Metabolism*. 1990;39:1076–1081
  41. Enders J, Stenzel TE, Butchko HH. Aspartame: ensuring safe intake levels in children. *J Am Diet Assoc*. 1990;90:360, 362, 364
  42. Thomas-Dobersen D. Calculation of aspartame intake in children. *J Am Diet Assoc*. 1989;89:831–833
  43. Lipton RB, Newman LC, Cohen JS, Soloman S. Aspartame as a dietary trigger of headache. *Headache*. 1989;29:90–92
  44. Schiffman SS, Buckley CE, Sampson HA, et al. Aspartame and susceptibility to headache. *N Engl J Med*. 1987;317:1181–1185
  45. Koehler SM, Glaros A. The effect of aspartame on migraine headache. *Headache*. 1988;28:10–14
  46. Drake ME. Panic attacks and excessive aspartame ingestion. *Lancet*. 1986;2:631
  47. Wurtman RJ. Aspartame: possible effect on seizure susceptibility. *Lancet*. 1985;2:1060
  48. Walton RG. Seizure and mania after high intake of aspartame. *Psychosomatics*. 1986;27:218, 220
  49. Gulya AJ, Sessions RB, Troost TR. Aspartame and dizziness: preliminary results of a prospective, nonblinded, prevalence and attempted cross-over study. *Am J Otol*. 1992;13:438–442
  50. Walton RG, Hudak R, Green-Waite RJ. Adverse reactions to aspartame: double-blind challenge in patients from a vulnerable population. *Biol Psychiatry*. 1993;34:13–17
  51. Watts RS. Aspartame, headaches and beta blockers. *Headache*. 1991;31:181–182
  52. Lapiere KA, Greenblatt DJ, Goddard JE, Harmatz JS, Shader RI. The neuropsychiatric effects of aspartame in normal volunteers. *J Clin Pharmacol*. 1990;30:454–460
  53. Eshel Y, Sarova-Pinhas I. Aspartame and seizures. *Neurology*. 1993;43:2154–2155
  54. Tollefson L, Barnard RJ. An analysis of FDA passive surveillance reports of seizures associated with consumption of aspartame. *J Am Diet Assoc*. 1992;92:598–601
  55. Camfield PR, Camfield CS, Dooley JM, Gordon K, Jollymore S, Weaver DF. Aspartame exacerbates EEG spike-wave discharge in children with generalized absence epilepsy: a double-blind controlled study. *Neurology*. 1992;42:1000–1003
  56. Kruesi MJ, Rapoport JL, Cummings EM, et al. Effects of sugar and aspartame on aggression and activity in children. *Am J Psychiatry*. 1987;144:1487–1490
  57. Shaywitz BA, Sullivan CM, Anderson GM, Gillespie SM, Sullivan B, Shaywitz SE. Aspartame, behavior, and cognitive function in children with attention deficit disorder. *Pediatrics*. 1994;93:70–75
  58. Novick NL. Aspartame-induced granulomatous panniculitis. *Ann Intern Med*. 1985;102:206–207
  59. McCauliffe DP, Poitras K. Aspartame-induced lobular panniculitis. *J Am Acad Dermatol*. 1991;24:298–300
  60. Reed BE, Barrett AP, Katelaris C, Bilous M. Orofacial sensitivity reactions and the role of dietary components: case reports. *Aust Dent J*. 1993;38:287–291
  61. Bradstock MK, Serdula MK, Marks JS, et al. Evaluation of reactions to food additives: the aspartame experience. *Am J Clin Nutr*. 1986;43:464–469
  62. Kulczycki A Jr. Aspartame-induced urticaria. *Ann Intern Med*. 1986;104:207–208
  63. Garriga MM, Berkebile C, Metcalfe DD. A combined single-blind, double-blind, placebo-controlled study to determine the reproducibility of hypersensitivity reactions to aspartame. *J Allergy Clin Immunol*. 1991;87:821–827
  64. Geha R, Buckley CE, Greenberger P, et al. Aspartame is no more likely than placebo to cause urticaria/angioedema: results of a multicenter, randomized, double-blind, placebo-controlled, crossover study. *J Allergy Clin Immunol*. 1993;92:513–520
  65. Sweetener intakes. *Food Chem Toxicol*. 1991;29:71–72
  66. Hoover RN, Strasser PH. Artificial sweeteners and human bladder cancer: preliminary results. *Lancet*. 1980;1:837–840
  67. Walker AM, Dreyer NA, Friedlander E, Laughlin J, Rothman KJ, Kohn HI. An independent analysis of the National Cancer Institute study on non-nutritive sweeteners and bladder cancer. *Am J Public Health*. 1982;72:376–381
  68. Council on Scientific Affairs. Saccharin: review of safety issues. *JAMA*. 1985;254:2622–2624
  69. Cohen SM. Saccharin: past, present, and future. *J Am Diet Assoc*. 1986;86:929–931
  70. Cohen SM, Cano M, Earl RA, Carson SD, Garland EM. A proposed role for silicates and protein in the proliferative effects of saccharin on the male rat urothelium. *Carcinogenesis*. 1991;12:1551–1555
  71. Gordon HH. Photosensitivity to saccharin. *J Am Acad Dermatol*. 1983;8:565
  72. Birbeck J. Saccharin-induced skin rashes. *N Z Med J*. 1989;102:24
  73. Miller R, White LW, Schwartz HJ. A case of episodic urticaria due to saccharin ingestion. *J Allergy Clin Immunol*. 1974;53:240–242
  74. Gordon HH. Episodic urticaria due to saccharin ingestion. *J Allergy Clin Immunol*. 1975;56:78–79
  75. Gordon HH. Untoward reactions to saccharin. *Cutis*. 1972;10:77–81
  76. Dordonkos AN, Arnold HL, Odom RB. *Andrews' Diseases of the Skin: Clinical Dermatology*. 7th ed. Philadelphia, PA: WB Saunders; 1982
  77. Fishman HC. Notalgia paresthetica. *J Am Acad Dermatol*. 1986;15:1304–1305
  78. Gershanik JJ, Boecler B, George W, Sola A, Leitner M, Kapadia C. The

- gasping syndrome: benzyl alcohol (BA) poisoning? *Clin Res.* 1981;29:895A. Abstract
79. Brown WJ, Buist NR, Gipson HT, Huston RK, Kennaway NG. Fatal benzyl alcohol poisoning in a neonatal intensive care unit. *Lancet.* 1982;1:1250
  80. Anderson CW, Ng KJ, Andresen B, Cordera L. Benzyl alcohol poisoning in a premature newborn infant. *Am J Obstet Gynecol.* 1984;148:344-346
  81. Menon PA, Thach BT, Smith CH, et al. Benzyl alcohol toxicity in a neonatal intensive care unit: incidence, symptomatology, and mortality. *Am J Perinatol.* 1984;1:288-292
  82. Hiller JL, Benda GI, Rahatzad M, et al. Benzyl alcohol toxicity: impact on mortality and intraventricular hemorrhage among very low birth weight infants. *Pediatrics.* 1986;77:500-506
  83. Benda GI, Hiller JL, Reynolds JW. Benzyl alcohol toxicity: impact on neurologic handicaps among surviving very low birth weight infants. *Pediatrics.* 1986;77:507-512
  84. Jardine DS, Rogers K. Relationship of benzyl alcohol to kernicterus, intraventricular hemorrhage, and mortality in preterm infants. *Pediatrics.* 1989;83:153-160
  85. LeBel M, Ferron L, Masson M, Pichette J, Carrier C. Benzyl alcohol metabolism and elimination in neonates. *Dev Pharmacol Ther.* 1988;11:347-356
  86. Cronin CM, Brown DR, Ahdab-Barmada M. Risk factors associated with kernicterus in the newborn infant: importance of benzyl alcohol exposure. *Am J Perinatol.* 1991;8:80-85
  87. Food and Drug Administration. Parenteral drug products containing benzyl or other antimicrobial preservatives: withdrawal of notice of intent. *Fed Reg.* 1989;54:49772
  88. Reynolds RD. Nebulizer bronchitis induced by bacteriostatic saline. *JAMA.* 1990;264:35
  89. Fisher AA. Allergic paraben and benzyl alcohol hypersensitivity relationship of the "delayed" and "immediate" varieties. *Contact Dermatitis.* 1975;1:281-284
  90. Lagerholm B, Lodin A, Gentele H. Hypersensitivity to phenylcarbinol preservative in vitamin B12 for injection. *Acta Allergologica.* 1958;12:295-298
  91. Grant JA, Bilodeau PA, Guernsey BG, Gardner FH. Unsuspected benzyl alcohol hypersensitivity. *N Engl J Med.* 1982;306:108
  92. Wilson JP, Solimando DA, Edwards MS. Parenteral benzyl alcohol-induced hypersensitivity reaction. *Drug Intell Clin Pharm.* 1986;20:689-691
  93. Szczeklik A, Gryglewski RJ. Asthma and anti-inflammatory drugs: mechanisms and clinical patterns. *Drugs.* 1983;25:533-543
  94. Settignano GA. Adverse reactions of aspirin and related drugs. *Arch Intern Med.* 1981;141:328-332
  95. Simon RA. Adverse reactions to drug additives. *J Allergy Clin Immunol.* 1984;74:623-630
  96. Virchow C, Szczeklik A, Bianco S, et al. Intolerance to tartrazine in aspirin-induced asthma: results of a multicenter study. *Respiration.* 1988;53:20-23
  97. Morales MC, Basomba A, Pelaez A, Garcia Villalmanzo I, Campos A. Challenge tests with tartrazine in patients with asthma associated with intolerance to analgesics (ASA-triad): a comparative study with placebo. *Clin Allergy.* 1985;15:55-59
  98. Stevenson DD, Simon RA, Lumry WR, Mathison DA. Adverse reactions to tartrazine. *J Allergy Clin Immunol.* 1986;78:182-191
  99. Spector SL, Wangaard CH, Farr RS. Aspirin and concomitant idiosyncrasies in adult asthmatic patients. *J Allergy Clin Immunol.* 1979;64:500-506
  100. Juhlin L, Michaelsson G, Zetterstrom O. Urticaria and asthma induced by food-and-drug additives in patients with aspirin hypersensitivity. *J Allergy Clin Immunol.* 1972;50:92-98
  101. Settignano GA, Pudupakkam RK. Aspirin intolerance. III. Subtypes, familial occurrence, and cross-reactivity with tartrazine. *J Allergy Clin Immunol.* 1975;56:215-221
  102. Hariparsad D, Wilson N, Dixon C, Silverman M. Oral tartrazine challenge in childhood asthma: effect on bronchial reactivity. *Clin Allergy.* 1984;14:81-85
  103. Supramaniam G, Warner JO. Artificial food additive intolerance in patients with angio-oedema and urticaria. *Lancet.* 1986;2:907-909
  104. Baungardner DJ. Persistent urticaria caused by a common coloring agent. *Postgrad Med.* 1989;85:265-266
  105. Bell RT, Fishman S. Eosinophilia from food dye added to enteral feeding. *N Engl J Med.* 1990;322:1822
  106. Chafee FH, Settignano GA. Asthma caused by FD&C approved dyes. *J Allergy.* 1967;40:65-72
  107. Pohl R, Balon R, Berchou R, Yeragani VK. Allergy to tartrazine in antidepressants. *Am J Psychiatry.* 1987;144:237-238
  108. Desmond RE, Trautlein JJ. Tartrazine (FD&C Yellow #5) anaphylaxis: a case report. *Ann Allergy.* 1981;46:81-82
  109. Trautlein JJ, Mann WJ. Anaphylactic shock caused by yellow dye (FD&C No 5 and FD&C No 6) in an enema (case report). *Ann Allergy.* 1978;41:28-29
  110. Murdoch RD, Pollock I, Naeem S. Tartrazine induced histamine release in vivo in normal subjects. *J R Coll Physicians Lond.* 1987;21:257-261
  111. Schaubsluger WW, Zabel P, Schlaak M. Tartrazine-induced histamine release from gastric mucosa. *Lancet.* 1987;2:800-801
  112. Criepp LH. Allergic vascular purpura. *J Allergy.* 1971;48:7-12
  113. Michaelsson G, Pettersson L, Juhlin L. Purpura caused by food and drug additives. *Arch Dermatol.* 1974 109:49-52
  114. Parodi G, Parodi A, Rebora A. Purpuric vasculitis due to tartrazine. *Dermatologica.* 1985;171:62-63
  115. Food and Drug Administration. Yellow No. 5 (tartrazine) labeling on drugs to be required. *FDA Drug Bull.* 1979;9:18
  116. Lockey SD Sr. Hypersensitivity to tartrazine (FD&C Yellow No. 5) and other dyes and additives present in foods and pharmaceutical products. *Ann Allergy.* 1977;38:206-210
  117. Michaelsson G, Juhlin L. Urticaria induced by preservatives and dye additives in food and drugs. *Br J Dermatol.* 1973;88:525-532
  118. Weber RW, Hoffman M, Raine DA Jr, Nelson HS. Incidence of bronchoconstriction due to aspirin, azo dyes, non-azo dyes, and preservatives in a population of perennial asthmatics. *J Allergy Clin Immunol.* 1979;64:32-37
  119. Fisherman EW, Cohen GN. Aspirin and other cross-reacting small chemicals in known aspirin intolerant patients. *Ann Allergy.* 1973;31:476-484
  120. Rodenstein D, Stanescu DC. Bronchial asthma following exposure to ECG ink. *Ann Allergy.* 1982;48:351-352
  121. Bell T. Colourants and drug reactions. *Lancet.* 1991;338:55-56
  122. Koppel BS, Harden CL, Daras M. Tegretol excipient-induced allergy. *Arch Neurol.* 1991;48:789
  123. Jenkins P, Michaelsson R, Emerson PA. Adverse drug reaction to sunset-yellow in rifampicin isoniazid tablet. *Lancet.* 1982;2:385
  124. Gross PA, Lance K, Whitlock RJ, Blume RS. Additive allergy: allergic gastroenteritis due to Yellow Dye #6. *Ann Intern Med.* 1989;111:87-88
  125. Castelain PY, Piriou A. Photosensitization eczema with positive erythrosine test. *Contact Dermatitis.* 1978;4:305
  126. Goldenberg RL, Nelson K. Dermatitis from neutral red therapy of herpes genitalis. *Obstet Gynecol.* 1975;46:359-360
  127. Conant M, Maibach HI. Allergic contact dermatitis due to neutral red. *Arch Dermatol.* 1974;109:735
  128. Larsen WG. Cosmetic dermatitis due to a dye (D&C Yellow #11). *Contact Dermatitis.* 1975;1:61
  129. Bjorkner B, Magnusson B. Patch test sensitization to D & C Yellow No. 11 and simultaneous reaction to quinoline yellow. *Contact Dermatitis.* 1981;7:1-4
  130. Mancuso G, Staffa M, Errani A, Berdondini RM, Fabbri P. Occupational dermatitis in animal feed mill workers. *Contact Dermatitis.* 1990;22:37-41
  131. Goldenstein MB. Sensitivity to gentian violet (methylosaniline). *Arch Dermatol.* 1940;41:122
  132. Bielicky T, Novak M. Contact-group sensitization to triphenylmethane dyes: gentian violet, brilliant green, and malachite green. *Arch Dermatol.* 1969;100:540-543
  133. Adams W. Lack of behavioral effects from Feingold diet violations. *Percept Mot Skills.* 1981;52:307-313
  134. Mattes JA, Gittelman R. Effects of artificial food colorings in children with hyperactive symptoms: a critical review and results of a controlled study. *Arch Gen Psychiatry.* 1981;38:714-718
  135. David TJ. Reactions to dietary tartrazine. *Arch Dis Child.* 1987;62:119-122
  136. Thorley G. Pilot study to assess behavioural and cognitive effects of artificial food colours in a group of retarded children. *Dev Med Child Neurol.* 1984;26:56-61
  137. Kavale KA, Forness SR. Hyperactivity and diet treatment: a meta-analysis of the Feingold hypothesis. *J Learn Disabil.* 1983;16:324-330
  138. Ribon A, Joshi S. Is there any relationship between food additives and hyperkinesia? *Ann Allergy.* 1982;48:275-278
  139. Mattes JA. The Feingold diet: a current reappraisal. *J Learn Disabil.* 1983;16:319-323
  140. Devlin J, David TJ. Tartrazine in atopic eczema. *Arch Dis Child.* 1992;67:709-711
  141. Leenthal E. Small intestinal disaccharidase deficiencies. *Pediatr Clin North Am.* 1975;22:757-766

142. Lifshitz F. Carbohydrate problems in paediatric gastroenterology. *Clin Gastroenterol.* 1977;6:415–429
143. Simoons FJ. Progress report: new light on ethnic differences in adult lactose intolerance. *Am J Digest Dis.* 1973;18:595–611
144. Dill JE, Levy M, Wells RF, Weser E. Lactase deficiency in Mexican-American males. *Am J Clin Nutr.* 1972;25:869–870
145. Newcomer AD, Thomas PJ, McGill DB, Hofmann AF. Lactase deficiency: a common genetic trait of the American Indian. *Gastroenterology.* 1977;72:234–237
146. Leichter J. Lactose tolerance in a Jewish population. *Am J Digest Dis.* 1971;16:1123–1126
147. Gilat T, Malachi EG, Shochet SB. Lactose tolerance in an Arab population. *Am J Digest Dis.* 1971;16:203–206
148. Bayless TM, Rothfeld B, Massa C, Wise L, Paige D, Bedine MS. Lactose and milk intolerance: clinical implications. *N Engl J Med.* 1975;292:1156–1159
149. Alpers DH, Seetharam B. Pathophysiology of diseases involving intestinal brush-border proteins. *N Engl J Med.* 1977;296:1047–1050
150. Paige DM, Leonardo E, Nakasima J, Adrianzen B, Graham GG. Response of lactose-intolerant children to different lactose levels. *Am J Clin Nutr.* 1972;25:467–469
151. Bedine MS, Bayless TM. Intolerance of small amounts of lactose by individuals with low lactase levels. *Gastroenterology.* 1973;65:735–743
152. Lieb J, Kazienko DJ. Lactose filler as a cause of “drug-induced” diarrhea. *N Engl J Med.* 1978;299:314
153. Brandstetter RD, Conetta R, Glazer B. Lactose intolerance associated with Intal capsules. *N Engl J Med.* 1986;315:1613–1614
154. Malen DG. Parnate formulation change. *J Clin Psychiatry.* 1992;53:328–329
155. Zeiss CR, Lockey RF. Refractory period to aspirin in a patient with aspirin-induced asthma. *J Allergy Clin Immunol.* 1976;57:440–448
156. Van Assendelft AH. Bronchospasm induced by vanillin and lactose. *Eur J Respir Dis.* 1984;65:468–472
157. Bekeris L, Baker C, Fenton J, Kimball D, Bermes E. Propylene glycol as a cause of an elevated serum osmolality. *Am J Clin Pathol.* 1979;72:633–636
158. Fligner CL, Jack R, Twiggs GA, Raisys VA. Hyperosmolality induced by propylene glycol: a complication of silver sulfadiazine therapy. *JAMA.* 1985;253:1606–1609
159. Glasgow AM, Boeckx RL, Miller MK, MacDonald MG, August GP, Goodman SI. Hyperosmolality in small infants due to propylene glycol. *Pediatrics.* 1983;72:353–355
160. Huggon I, James I, Macrae D. Hyperosmolality related to propylene glycol in an infant treated with enoximone infusion. *BMJ.* 1990;301:19–20
161. MacDonald MG, Fletcher AB, Johnson EL, Boeckx RL, Getson PR, Miller MK. The potential toxicity to neonates of multivitamin preparations used in parenteral nutrition. *J Parenter Enteral Nutr.* 1987;11:169–171
162. Giacoia GP, Miranda R, West KI. Measured vs calculated plasma osmolality in infants with very low birth weights. *AJDC.* 1992;146:712–717
163. MacDonald MG, Getson PR, Glasgow AM, Miller MK, Boeckx RL, Johnson EL. Propylene glycol: increased incidence of seizures in low birth weight infants. *Pediatrics.* 1987;79:622–625
164. Kulick MI, Lewis NS, Bansal V, Warpeha R. Hyperosmolality in the burn patient: analysis of an osmolal discrepancy. *J Trauma.* 1980;20:223–228
165. Cate JC IV, Hedrick R. Propylene glycol intoxication and lactic acidosis. *N Engl J Med.* 1980;303:1237
166. Demey H, Daelemans R, DeBroe ME, Bassaert L. Propylene glycol intoxication due to intravenous nitroglycerin. *Lancet.* 1984;1:1360
167. Kelner MJ, Bailey DN. Propylene glycol as a cause of lactic acidosis. *J Anal Toxicol.* 1985;9:40–42
168. Bedichek E, Kirschbaum B. A case of propylene glycol toxic reaction associated with etomidate infusion. *Arch Intern Med.* 1991;151:2297–2298
169. Demey HE, Daelemans RA, Verpooten GA, et al. Propylene glycol-induced side effects during intravenous nitroglycerin therapy. *Intensive Care Med.* 1988;14:221–226
170. Louis S, Kutt H, McDowell F. The cardiocirculatory changes caused by intravenous Dilantin and its solvent. *Am Heart J.* 1967;74:523–529
171. York RC, Coleridge ST. Cardiopulmonary arrest following intravenous phenytoin loading. *Am J Emerg Med.* 1988;6:255–259
172. Martin G, Finberg L. Propylene glycol: a potentially toxic vehicle in liquid dosage form. *J Pediatr.* 1970;77:877–878
173. Arulanantham K, Genel M. Central nervous system toxicity associated with ingestion of propylene glycol. *J Pediatr.* 1978;93:515–516
174. Fisher AA, Pascher F, Kanof NB. Allergic contact dermatitis due to ingredients of vehicles: a “vehicle tray” for patch testing. *Arch Dermatol.* 1971;104:286–290
175. Cochran RJ, Rosen T. Contact dermatitis caused by ECG electrode paste. *South Med J.* 1980;73:1667–1668
176. Fisher AA, Brancaccio RR. Allergic contact sensitivity to propylene glycol in a lubricant jelly. *Arch Dermatol.* 1979;115:1451
177. Fisher AA. Reactions to popular cosmetic humectants. III. Glycerin, propylene glycol, and butylene glycol. *Cutis.* 1980;26:243–244
178. Eun HC, Kim YC. Propylene glycol allergy from ketoconazole cream. *Contact Dermatitis.* 1989;21:274–275
179. Degreef H, Dooms-Goossens A. Patch testing with silver sulfadiazine cream. *Contact Dermatitis.* 1985;12:33–37
180. Oleffe JA, Blondeel A, deConinck A. Allergy to chlorocresol and propylene glycol in a steroid cream. *Contact Dermatitis.* 1979;5:53–54
181. Eiermann HJ, Larsen W, Maibach HI, Taylor JS. Prospective study of cosmetic reactions: 1977–1980. North American Contact Dermatitis Group. *J Am Acad Dermatol.* 1982;6:909–917
182. Hannuksela M, Forstrom L. Reactions to peroral propylene glycol. *Contact Dermatitis.* 1978;4:41–45
183. Fisher AA. Contact dermatitis from topical medicaments. *Semin Dermatol.* 1982;1:49–57
184. Mattila MA, Ruoppi M, Korhonen M, Larni HM, Valtonen L, Heikkinen H. Prevention of diazepam-induced thrombophlebitis with cremophor as a solvent. *Br J Anaesth.* 1979;51:891–894
185. Zacharias M, Clarke RS, Dundee JW, Johnston SB. Venous sequelae following etomidate. *Br J Anaesth.* 1979;51:779–783
186. Doenicke A, Kugler A, Vollmann N. Venous tolerance to etomidate in lipid emulsion or propylene glycol (hypnomidate). *Can J Anaesth.* 1990;37:823–824
187. Kumar A, Rawlings RD, Beaman DC. The mystery ingredients: sweeteners, flavorings, dyes, and preservatives in analgesic/antipyretic, antihistamine/decongestant, cough and cold, antidiarrheal, and liquid theophylline preparations. *Pediatrics.* 1993;91:927–933

## "Inactive" Ingredients in Pharmaceutical Products: Update (Subject Review)

Committee on Drugs  
*Pediatrics* 1997;99:268-278  
DOI: 10.1542/peds.99.2.268

**This information is current as of May 1, 2007**

<b>Updated Information &amp; Services</b>	including high-resolution figures, can be found at: <a href="http://www.pediatrics.org/cgi/content/full/99/2/268">http://www.pediatrics.org/cgi/content/full/99/2/268</a>
<b>References</b>	This article cites 164 articles, 34 of which you can access for free at: <a href="http://www.pediatrics.org/cgi/content/full/99/2/268#BIBL">http://www.pediatrics.org/cgi/content/full/99/2/268#BIBL</a>
<b>Citations</b>	This article has been cited by 1 HighWire-hosted articles: <a href="http://www.pediatrics.org/cgi/content/full/99/2/268#otherarticles">http://www.pediatrics.org/cgi/content/full/99/2/268#otherarticles</a>
<b>Subspecialty Collections</b>	This article, along with others on similar topics, appears in the following collection(s): <b>Therapeutics &amp; Toxicology</b> <a href="http://www.pediatrics.org/cgi/collection/therapeutics_and_toxicology">http://www.pediatrics.org/cgi/collection/therapeutics_and_toxicology</a>
<b>Permissions &amp; Licensing</b>	Information about reproducing this article in parts (figures, tables) or in its entirety can be found online at: <a href="http://www.pediatrics.org/misc/Permissions.shtml">http://www.pediatrics.org/misc/Permissions.shtml</a>
<b>Reprints</b>	Information about ordering reprints can be found online: <a href="http://www.pediatrics.org/misc/reprints.shtml">http://www.pediatrics.org/misc/reprints.shtml</a>

American Academy of Pediatrics

DEDICATED TO THE HEALTH OF ALL CHILDREN™

