WHAT DOCTORS DON'T TELL YOU

August 2001 Volume 12 No 5

Drug additives

The not-so-inactive ingredients

Most of the so-called inactive ingredients added to food and drugs to make them more appealing can have as many side-effects as drugs themselves.

When you use a drug, whether by mouth, by inhalation, by injection or on your skin, you're getting more than just the active ingredients. You are also getting what the pharmaceutical industry calls excipients—inactive ingredients which are added to all drug products to make them look and taste appealing, to maintain their shelf life and to help the active ingredients blend together properly.

More than 700 chemical agents are used as excipients in drug products (N Engl J Med, 1983; 309: 439–41), but only a few have been fully researched to determine their safety. Because these compounds are classified as 'inactive', there are no regulations requiring listing them on product labels. Many excipients, such as flavourings and fragrances, even fall under the heading of 'trade secrets', so manufacturers are exempt from full disclosure of these chemicals on their labels.

Adverse reactions to drugs are common. Patients reporting such reactions to drugs are often not taken seriously because doctors can find no link between the symptom and the active ingredient. Yet, some inactive ingredients have a major role to play in adverse drug reactions.

These chemicals are known to cause a number of health problems, including allergic reactions (Can Med Assoc J, 1984; 131: 1449–52; Med Toxicol, 1988; 3: 128–65; 209–40). One review went so far as to declare that "excipients should not be considered as inactive ingredients as they have been associated with a wide range of adverse reactions in some individuals" (Drug Safety, 1990; 5 [Suppl 1]: 95–100).

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WATCH OUT FOR DYES AND COLORANTS

There are currently more than 100 dyes and colouring agents approved by the Food and Drug Administration (FDA) for use in pharmaceutical preparations (Med Toxicol, 1988; 3: 128–65). Most oral liquid formulations contain between one to three different dyes.

Exposure to dyes and colorants in medications has been associated with a range of hypersensitivity reactions. These can occur in anyone, but may be particularly severe in those—for instance, the 2–20 per cent of asthmatics—who are also aspirin-intolerant.

Individuals who react to aspirin with the classic triad of symptoms—asthma, hives and rhinitis—or who experience anaphylactoid (shock) reactions may also develop bronchoconstriction, localised vascular oedema, hives, abdominal pain and vomiting, and contact dermatitis on ingestion of the following dyes and colorants:

- Amaranth
- Brilliant blue
- Erythrosine
- Indigo carmine
- Methyl blue
- New coccine
- Ponceau
- Sunset yellow*
- Quinolone yellow
- Tartrazine

Skin reactions including photosensitivity, skin rashes and peeling have been associated with erythrosine, an iodine-containing dye (Contact Dermat, 1978; 4: 305). Erythrosine has been removed from topical products and is being voluntarily removed from many oral drug products because of concerns about carcinogenicity. However, many other dyes can cause skin reactions like contact dermatitis. These include:

- D&C yellow no. 11
- Gentian violet
- Indigo carmine
- Neutral red
- Quinoline yellow

Some parents and clinicians believe there is link between dyes, and hyperactivity and aggressive behaviour in children, although this has not been borne out in controlled clinical trials (Pediatrics, 1985; 76: 635–43; Ann Allergy, 1977; 38: 206–10).

**Sunset yellow has also been associated with gastrointestinal intolerance, abdominal pain, vomiting and indigestion (Lancet, 1982; ii: 385; Ann Intern Med, 1989; 111: 87–8).*

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The more problematical excipients include certain preservatives, sweeteners, solvents and dyes known to cause a variety of symptoms—from respiratory difficulties to headache, skin rashes, gastrointestinal upsets and diarrhoea, as well as less obvious reactions such as hyperosmolality (an increased permeability of body cells and tissues allowing the exchange of otherwise separately contained fluids).

Preservatives

A variety of antimicrobials and antioxidants are added to drugs to prolong shelf life and maintain sterility. The most commonly used antimicrobials include chlorbutol, benzyl alcohol, sodium benzoate, sorbic acid, phenol, thimerosal, parabens and benzalkonium chloride. Common antioxidants include butylated hydroxytoluene and hydroxyanisole as well as propyl gallate and sulphites (Med Toxicol, 1988; 3: 128–65; 209–40).

While necessary to ensure the safety of pharmaceutical products, the inclusion of preservatives has also been associated with a range of adverse effects.

Benzyl alcohol, for example, can cause several hypersensitivity reactions. Contact dermatitis (Contact Dermat, 1975; 1: 281–4) as well as more general allergic reactions such as nausea, fatigue, fever, maculopapular rash or angioedema (localised vascular oedema) have occurred after parenteral administration of products preserved with benzyl alcohol (Acta Allergol, 1958; 12: 295–8; N Engl J Med, 1982; 306: 108).

The link between benzyl alcohol and neonatal cardiovascular collapse—dubbed 'gasping baby syndrome'—is perhaps the most widely publicised adverse reaction related to 'inactive' ingredients. The relationship was discovered in 1982 after a series of newborns died or developed a severe respiratory illness associated with gasping, metabolic acidosis (an overly acidic body pH) and blood abnormalities.

TAKING YOUR BREATH AWAY

Some individuals dependent on inhalers and other breathing aids develop 'paradoxical' bronchospasm after they inhale their medication. In the past, such reactions were attributed to the presence of sulphites. However, in the last decade or so, sulphite-containing products—for example, the non-selective β_2-agonists isoproterenol, isoetharine and metaproterenol—have been replaced primarily by albuterol, which doesn't contain sulphites. Nevertheless, paradoxical reactions continue to be reported, with some cases resulting in product reformulation because of excessive adverse reactions.

Inactive ingredients that have been implicated in causing these reactions include benzalkonium chloride (see main article), oleic acid, chlorofluorocarbons, soya lecithin and sorbitan trioleate (J Allergy Clin Immunol, 1991; 87: 600; J Allergy Clin Immunol, 1979; 64: 534–8; Respir Care, 1987; 32: 29–31; Thorax, 1969; 24: 228–31; Immunol Allergy Pract, 1985; 7: 467–9; Chest, 1987; 91: 207–9).

Eventually the cause of this syndrome was determined to be intravenous flush solutions and medications containing benzyl alcohol (N Engl J Med, 1982; 307: 1384–8; Am J Perinatol, 1984; 1: 288–92). As a result, both the US Food and Drug Administration (FDA) and American Academy of Pediatrics recommended that, whenever possible, infants should avoid products containing this chemical (MMWR, 1982; 31: 290–1; Pediatrics, 1983; 72: 356–8).

The incidence of premature infant mortality, severe neurological symptoms and intraventricular haemorrhage decreased significantly after discontinuation of the use of benzyl alcohol in intravenous drugs intended for infants (Pediatrics, 1986; 77: 500–6; Pediatrics, 1989; 83: 153–60).

While not all infants exposed to this chemical died, many of those who survived suffered from one of a range of illnesses associated with exposure, including cerebral palsy and developmental delay (Pediatrics, 1986; 77: 507–12).

But it's not just infants who react badly to benzyl alcohol. In one report, a man who was nebulised with albuterol diluted in a solution containing benzyl alcohol reacted with severe bronchitis and blood-stained sputum (J Am Med Assoc, 1990; 264: 35).

In older patients, benzyl alcohol continues to be associated with a range of hypersensitivity reactions such as contact dermatitis, nausea, bronchitis and a range of adverse neurological events (Contact Dermat, 1999; 41: 302–3; Am J Contact Dermat, 1999; 10: 228–32; J Fam Pract, 1995; 40: 35–40; Med J Aust, 2000; 173: 141–3).

Another common antimicrobial, benzalkonium chloride, has received considerable attention over the past several years as a result of its use in many nasal sprays and metered-dose inhalers (it is also found in numerous 'natural' products, most recently, grapefruit seed extract). In some asthmatic patients, benzalkonium chloride can produce significant respiratory distress.

In a study by Zhang and colleagues of 28 asthmatics, a significant decrease in lung function—which began within a minute and lasted up to 60 minutes—was observed after benzalkonium chloride administration (Am Rev Respir Dis, 1990; 141: 1405–8). The authors noted that the response was blocked by the simultaneous administration of the antihistamine cromolyn, suggesting an allergic mechanism.

In non-asthmatic patients, the use of nasal sprays with benzalkonium chloride has been associated with burning, dryness and irritation of the nasal passages (J Allergy Clin Immunol, 2000; 105: 39–44). It has also been linked to increasing nasal congestion. Inclusion of this chemical explains, in

part, the rebound congestion seen with prolonged use of such products (Clin Exp Allergy, 1994; 25: 401–5; Clin Ther, 1999; 21: 1749–55).

Flavourings

A wide variety of natural and synthetic flavourings are used in the production of pharmaceutical products. In a survey of medications for oral use, Kumar and colleagues (Pediatrics, 1993; 91: 927–33) found that more than 90 per cent of the products they evaluated contained both sweeteners and flavourings.

In this survey, 35 per cent of the products evaluated did not provide information on flavourings, making it difficult to identify the specific causes of adverse reactions or allergies. Menthol, lemon oil and oil of peppermint have all been associated with hypersensitivity reactions in children.

Few, if any, manufacturers fully disclose what goes into their flavourings, preferring to hide behind the labelling loophole of 'trade secret'. Yet, flavourings contain numerous ingredients. For example, one brand of synthetic strawberry flavouring contained more than 30 different components (Neurosci Biobehav Rev, 1993; 17: 313–45).

Sugar-free, but not risk-free

In addition to flavourings, a variety of sweeteners are used in drugs. Saccharin, sucrose, sorbitol, aspartame and fructose are the most commonly used sweeteners and, often, two or more of these are present in oral liquid preparations.

The concentration of sweeteners in oral solutions and suspensions ranges from 30 to 50 per cent of the formulation. In some antibiotic and cough/cold preparations, the sweetener content can be as high as 80 per cent (Am J Hosp Pharm, 1988; 45: 135–42).

As sucrose in oral medicines has been shown to result in an increased risk of tooth decay in children (Pediatrics, 1981; 68: 416–9; Public Health, 1994; 108: 121–30), the current trend is towards the use of artificial sweeteners, such as aspartame and saccharin.

But the use of artificial sweeteners brings its own problems. Aspartame, an excitotoxin (a central nervous system stimulator), is increasingly being used in chewable tablets and sugar-free formulations of drugs and supplements.

Headache is the most common adverse effect linked to aspartame. Up to 11 per cent of patients with chronic migraines report that their headaches are triggered by aspartame (Headache, 1989; 29: 90–2). This effect, however, has been disputed in the medical press. In one double-blind, placebo-controlled trial, for example, three doses of aspartame given every two hours to patients who believed their migraines were made worse by aspartame triggered no more headaches than did placebo (N Engl J Med, 1987; 317: 1181–5). However, a small, double-blind four-week trial showed an increase in frequency of headaches after ingestion of 1200 mg daily of aspartame, suggesting that it may take longer for adverse reactions to become apparent (Headache, 1988; 28: 10–4). Other studies have also confirmed the aspartame/headache link (Neurology, 1994; 44: 1787–93).

In anecdotal reports, aspartame has been linked to conditions such as panic attacks, mood changes, visual hallucinations, manic episodes and isolated dizziness (Lancet, 1986; *ii*: 631; Lancet, 1985; *ii*: 1060; Psychosomatics, 1986; 27: 218, 220; Am J Otol, 1992; 13: 438–42). A small double-blind, crossover study of patients with major depression found that these individuals may be more sensitive to the effects of aspartame than non-depressed subjects. Taking 30 mg/kg of aspartame for seven days resulted in a higher incidence of adverse reactions, including headache, nervousness, dizziness, impaired memory, nausea, temper outbursts and depression (Biol Psychiatry, 1993; 34: 13–7).

In the US, passive surveillance data collected by the FDA showed a link between seizures and aspartame consumption (Lancet, 1985; *ii*: 1060; Psychosomatics, 1986; 27: 218, 220; Neurology, 1993; 43: 2154–5). This finding, however, was disputed by a randomised double-blind placebo-controlled trial (Epilepsia, 1995; 36: 270–5).

Nevertheless, though 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. The authors also suggested that children with poorly controlled absence seizures should

WHAT ARE VACCINES MADE OF?

A number of excipients are used in the production of vaccines. These include:

- *Thimerosal* (thiomersal in Europe), a mercury derivative used as a preservative, is a common cause of allergic or sensitivity reactions (Contact Dermat, 1989; 20: 173–6). Animal studies have also shown that mercury can cause immune suppression (Toxicol Appl Pharmacol, 1983; 68: 218–28). Since the mid-1990s, manufacturers have been under pressure to remove this chemical from their vaccines, but progress has been frustratingly slow. A recent review suggested that some infants receiving thimerosal-preserved vaccines may be exposed to cumulative levels of mercury higher than those considered to be safe (Pediatrics, 2001; 107: 1147–54).
- *Formalin* is a dilute formaldehyde solution used to inactivate viruses and detoxify toxins. Nearly 50 studies have shown a link between formaldehyde exposure and leukaemia and cancers of the brain, colon and lymphatic tissues (Neustaedter R, *The Vaccine Guide*, Berkley, CA: North Atlantic Books, 1996).
- *Aluminium sulphate* an adjuvant used to boost the effectiveness of a vaccine. Studies show that aluminium-containing vaccines cause more reactions than others.

Also common are phenol, a disinfectant and dye; ethylene glycol, the main ingredient in antifreeze; benzethonium chloride, an antiseptic; and methylparaben, a preservative and antifungal known to have hormone-disrupting qualities.

Last year, it was revealed that vaccines contain a new danger. Many vaccines manufactured in the late 1980s and early 1990s were made using bovine products obtained from countries where bovine spongiform encephalitis (BSE) was a substantial risk.

In the US, the FDA has repeatedly asked pharmaceutical companies not to use materials from cattle raised in countries where BSE is a problem. However, according to a recent report in the New York Times (8 February 2001), five companies, including GlaxoSmithKline, Aventis and American Home Products, were still using these ingredients in 2000 to make nine widely used vaccines, including those for polio, diphtheria and tetanus.

In the UK, the Daily Express (2 May 2000) reported that seven vaccines (including those for polio, diphtheria and tetanus) given to children during 1988–1989, and manufactured by SmithKline and Wellcome, were made from potentially contaminated bovine products. Later that year, the Mirror (21 October 2000) reported that the polio vaccine made by Medeva and in current use had been recalled due to possible contamination with bovine products.

avoid the sweetener (Neurology, 1992; 42: 1000–3).

A few hypersensitivity reactions resulting from ingestion of aspartame have been reported, including two patients who developed inflamed bumpy skin resembling erythema (Ann Intern Med, 1985; 102: 206–7; J Am Acad Dermatol, 1991; 24: 298–300). Other reported reactions include orofacial granulomatosis (inflammation of the skin around the mouth), erythema, pruritus (itching), urticaria (hives) and angioedema (vascular oedema) (Am J Clin Nutr, 1986; 43: 464–9).

Such reactions are thought to be rare (J Allergy Clin Immunol, 1991; 87: 821–7; J Allergy Clin Immunol, 1993; 92: 513–20) and, some argue, may not be necessarily related to aspartame *per se*. Instead, they may be related to breakdown products such as diketopiperazine derivatives, formed during the storage of liquid products especially after exposure to higher temperatures (Ann Intern Med, 1986; 104: 207–8).

If this is the case, it may explain why challenging sensitive individuals with fresh aspartame powder sometimes produces false-negative results. Although not yet fully researched, there is a possibility that aspartame breaks down into the carcinogen formaldehyde, as suggested in some animal experiments (Life Sci, 1998; 63: 337–49).

Saccharin

Another common sweetener, saccharin can be present in substantial amounts in drugs. A sulphonamide derivative, saccharin can cause skin reactions similar to those associated with other 'sulpha' drugs. Studies have demonstrated cross-sensitivity with sulphonamides; therefore, those with a sulpha allergy should also avoid saccharin.

In 42 patients who had adverse effects due to consumption of saccharin in pharmaceutical agents, pruritus and urticaria were the most common reactions, followed by eczema, photosensitivity and prurigo (a blistering, crusting rash) (NZ Med J, 1989; 102: 24). Other reported reactions include wheezing, nausea, diarrhoea, tongue blisters, rapid heart rate, headache, diuresis (excessive urination) and sensory neuropathy (nerve pain) (J Allergy Clin Immunol, 1974; 53: 240–2; J Allergy Clin Immunol, 1975; 56: 78–9; Cutis, 1972; 10: 77–81; J Am Acad Dermatol, 1986; 15: 1304–5).

A major large-scale FDA/National Cancer Institute (NCI) epidemiological study concluded that ingestion of the recommended daily dosage of chewable aspirin or acetaminophen (paracetamol) tablets in a school-age child would provide roughly the same amount of saccharin as in a can of a diet soft drink. Prolonged periods of ingestion of this amount, given the body weight of a child aged under 9 or 10 years, is considered "heavy use" (Lancet, 1980; *i*: 837–40). In this study, heavy use of artificial sweeteners was associated with a significantly increased risk for bladder cancer.

An independent review of this study, however, refuted this finding (Am J Public Health, 1982; 72: 376–81). A later animal investigation of saccharin by the American Medical Association concluded that bladder changes were species-specific (confined to the second generation of male rats), and occurred in association with large doses (equivalent to several hundreds of cans of diet soft drink a day) (J Am Med Assoc, 1985; 254: 2622–4).

Nevertheless, many agencies, including the US Environmental Protection Agency (EPA) and National Academy of Sciences, concluded that, even though human data are lacking, saccharin should still be considered a potential human carcinogen.

Lactose

Although a sugar, lactose (milk sugar) is more widely used as a filler or diluting agent in tablets and capsules, and to give bulk to powders. Although most people can tolerate this sugar without adverse effects, some experience hypersensitivity reactions. Those who are lactose-intolerant have been reported to develop diarrhoea even with the intake of the small quantities found in tablets.

Sensitivity to lactose varies widely in severity, although some (adults and children) may experience diarrhoea, gas or cramping after ingestion of as little as 3 g or less of lactose (Am J Clin Nutr, 1972; 25: 467–9; Gastroenterology, 1973; 65: 735–43). Such symptoms have been noted in sensitive persons after taking drugs containing lactose (N Engl J Med, 1978; 299: 314; N Engl J Med, 1986; 315: 1613–4; J Clin Psychiatry, 1992; 53: 328–9). There have been two reports of adult asthmatics who developed bronchospasm from lactose-containing medications, and who tested positive in double-blind challenges with 300 mg and 500 mg of lactose (J Allergy Clin Immunol, 1976; 57: 440–8; Eur J Respir Dis, 1984; 65: 468–72).

Lactose can also cause complications in those with lactase deficiency. This condition occurs either as a rare congenital disorder or is acquired in later life. Its symptoms include diarrhoea, abdominal cramping, bloating and flatulence after ingesting milk products or lactose.

Late-onset lactase deficiency (adult hypolactasia) is surprisingly common. Around 90 per cent of adult American blacks, 60–80 per cent of Mexican Americans, Native Americans and Asians, and most Middle Eastern and Mediterranean populations have abnormal findings on lactose tolerance tests (Am J Dig Dis, 1973; 18: 595–611; Am J Clin Nutr, 1972; 25: 869–70; Gastroenterology, 1977; 72: 234–7; Am J Dig Dis, 1971; 16: 1123–6,

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GMO RISKS

Recently, concerns have been expressed that some excipients in nutriceuticals could carry extra dangers for consumers—namely, the largely unquantifiable risks from genetically modified (GM) ingredients. Most health supplements not licensed as medicines are classed as foods and are obliged to warn the consumer on the label if they contain GM ingredients. But supplements that are licensed medicines (for example, some folic acid and cod liver oil supplements) do not have this requirement.

According to the UK Genetic Food Alert (GFA), unless expressly denied by manufacturers, the following may be GM:

- Derivatives of soya, maize (corn), cotton or rapeseed, including oils, used as carriers for vitamins (A, D and E) in supplements; lecithin and vitamin E; and sweeteners such as dextrose, glucose, dextrins, maltodextrins and sorbitol;
- Microorganisms, including certain bacteria, and brewers and bakers yeast or their byproducts, such as aspartame, and enzymes used as processing aids (which may not be listed on the label) such as α-acetolactate decarboxylase, α-amylase, catalase, chymosin A or B, cyclodextrin-glucosyl transferase, β-glucanase, glucose isomerase, glucose oxidase, hemicellulase, lipase, triacylglycerol, maltogenic amylase, pectinesterase, protease and pullulanase;
- Products such as gelatine, bonemeal and albumin from animals raised on GM ingredients, or injected with GM growth hormones such as BST.

A list of guaranteed GM-free supplements can be accessed on the GFA's website (www.geneticfoodalert.supanet.com) along with other information on GM additives in supplements.

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Case Study

Drugs may have triggered lupus

In one of your issues, you cited the antibiotic Minocin as being linked to triggering autoimmune illness, namely, lupus. At around age 16, I was put on Minomycin for acne. Apart from digestive upset and allergies, it worked.

At 18, I started taking the Pill along with the Minomycin. In my early 20s, my acne resurfaced and my doctor gave me Minocin, telling me it was the same as Minomycin. Instantly, I suffered side-effects—severe digestive upsets and weight loss.

A year later, I restarted the Pill. One day, out of the blue, I had an episode of severe dizziness, followed by a migraine of such intensity and duration that I went to see my doctor. I also wanted an answer to other perplexing 'incidents'—lack of blood flow to my fingers and toes, strange purple spots on my jawline which bled beneath the skin, breathlessness and strange flu-like episodes.

The doctor told me that on no account could the Pill cause headaches, and that I needed to see a psychiatrist. I reacted by throwing out all of my acne medication and pills. Within four weeks, I felt better.

My acne, however, worsened considerably, so I reluctantly obtained more Minocin. The new packet had a leaflet saying that Minocin is thought to increase bloodflow to the capillaries, which is believed to contribute to healing acne. Horrified, I didn't take the medication as my previous bleeding beneath the skin was probably due to the drug.

At 28, I became pregnant, and everything was fine for the first six months. Then, I began to feel very tired, and the baby stopped growing. At 30 weeks, I gave birth to a stillborn baby. A doctor at the hospital told me he had seen such a case before—in a woman with lupus—and blood tests were needed. But, at the six-week check-up, the obstetrician told me I didn't have lupus antibodies, but antibodies to cardiolipin. Could this have caused the stillbirth? Years passed. I was unable to become pregnant again.

Then, a magazine article on lupus described a related problem called 'sticky blood in pregnancy'. I wrote to the lupus group cited in the article and asked them what anticardiolipin was. They sent me a photocopy of a paper stating that it was the name of the antibody they had referred to.

Eventually, I was diagnosed with an autoimmune disease like lupus.—HS, Sussex

203–6). Approximately 10 per cent of the white population of Scandinavian or European ancestry are also affected (N Engl J Med, 1975; 292: 1156–9).

Solvents

Medications that are not highly water-soluble are problematical for pharmaceutical manufacturers. To render the product soluble enough for oral, topical or intravenous use—without significantly altering its stability—a variety of solvents, such as propylene glycol and polyethylene glycol, are used (Med Toxicol, 1988; 3: 128–65).

In particular, propylene glycol—used in topical, oral and injectable medications—has been associated with cardiac arrhythmias, seizures and respiratory depression.

The high concentration of this agent in drugs such as phenytoin, phenobarbital, diazepam, digoxin and etomidate may induce thrombophlebitis (inflammation of a vein associated with a blood clot) when administered intravenously (Br J Anaesth, 1979; 51: 891–4, 779–83).

For this reason, these medications need to be administered slowly when given intravenously. Rapid infusion of concentrated propylene glycol-containing drugs has been further associated with respiratory depression, cardiac arrhythmias, hypotension and seizures (Am Heart J, 1967; 74: 523–9).

Intravenous solutions containing propylene glycol have also been associated with seizures, and liver and kidney damage (J Child Neurol, 1998; 13 [Suppl 1]: S11–4; Am J Kidney Dis, 1997; 30: 134–9) as well as haemolysis (loss of haemoglobin from red cells), central nervous system depression, hyperosmolality and lactic acidosis (Lancet, 1984; *i*: 1360; J Anal Toxicol, 1985; 9: 40–2; Arch Intern Med, 1991; 151: 2297–8). Case reports continue to show that intravenous propylene glycol can be toxic (N Engl J Med, 2000; 343: 815; Crit Care Med, 2000; 28: 1631–4; Am J Crit Care, 1999; 8: 499–506).

Several cases of localised contact dermatitis from the application of products containing propylene glycol have also been reported (Arch Dermatol, 1971; 104: 286–90; Cutis, 1980; 26: 243–4; Contact Dermat, 1989; 21: 274–5; Contact Dermat, 1985; 12: 33–7). These include propylene glycol-containing jellies such as those used in electrode placement, and steroid creams (South Med J, 1980; 73: 1667–8; Arch Dermatol, 1979; 115: 1451; Contact Dermat, 1979; 5: 53–4).

In 487 patients with eczematous contact dermatitis, 4.5 per cent were found to be sensitive to propylene glycol (J Am Acad Dermatol, 1982; 6: 909–17).

But propylene glycol doesn't have to be applied to the skin to cause skin reactions. Oral and parenteral preparations can also cause dermatitis in sensitised patients (Contact Dermat, 1978; 4: 41–5; Semin Dermatol, 1982; 1: 49–57).

Recently, GlaxoWellcome issued a warning against its anti-HIV drug, the protease inhibitor amprenavir (Agenerase), which contained a large amount of propylene glycol. The company revealed that some patients—such as infants, pregnant women, those with kidney or liver problems as well as those treated with disulfiram or metronidazole—were not able to metabolise propylene glycol adequately, leading to its accumulation in the body and a range of adverse effects (Pharmaceutical J, 2000; 264: 685).

Propylene glycol is particularly dangerous in infants. This is because newborns have a longer propylene glycol half-life (16.9 hours) compared with adults (five hours) (J Am Med Assoc, 1985; 253: 1606–9; Pediatrics, 1983; 72: 353–5).

The propylene glycol contained in an intravenous multivitamin product delivering 3 g/day was associated with a higher incidence of seizures compared with lower doses from an alternative product delivering just 300 mg/day (Pediatrics, 1987; 79: 622–5). In addition, seizures and respiratory depression were seen in children who ingested liquid medications containing propylene glycol (J Pediatr, 1970; 77: 877–8; J Pediatr, 1978; 93: 515–6).

These are just some of the adverse reactions associated with some of the most commonly used excipients. Many more excipients are used, but have never been fully investigated for safety.

Reactions to chemicals such as aspartame and propylene glycol may be even more common because our exposure to them extends beyond mere drug use to the foods we eat, herbal and nutritional supplements, and even toiletries.

Clearly, these 'inactive' ingredients can have a profound effect on health. Until manufacturers are compelled by law to list all of the ingredients in their drug preparations, such reactions will continue to be commonplace.

Pat Thomas