

TABLE 1.—CASE REPORTS OF REYE'S SYNDROME OR SUSPECTED REYE'S SYNDROME IN PEOPLE WHO TOOK BISMUTH SUBSALICYLATE—Continued

FDA Number ¹	Age ²	Gender ³	Event (year)	Other drugs ⁴	Outcome ⁵
824683	12Y	F		U	D
830479 ¹	between 8 and 15Y	U	1978	ASA	H
830513	U	U	1989	U	U
830516 ¹	between 8 and 15Y	U	1978	ASA	H
952481	6Y	M	1991	NR	D
957562	12Y	F	1992	ASA, D	D
958922	34M	F	1992	NR	D
947149	3Y	F	1993	NR	D
1502057 ¹	14Y	M	1994	APAP, CC	H
1623073	4Y	F	1995	APAP, D	D
1855719	2Y	M	1996	NR	D

¹ Also literature report² M = months, Y = years, P = pediatric, U = unknown³ F = female, M = male, U = unknown⁴ ASA = aspirin, APAP = acetaminophen, CC = cough/cold preparation, D = diphenhydramine, NR = none reported, U = unknown⁵ D = died, H = hospitalized, U = unknown

Because of the limited information available on these cases, it is not certain that bismuth subsalicylate was the cause of Reye's syndrome. However, most of the reports identified bismuth subsalicylate use only prior to the diagnosis of Reye's syndrome. Death was reported in 60 percent of the cases.

The agency notes that a recent report by Orlowski (Ref. 9) suggested that many people originally diagnosed with Reye's syndrome may have had metabolic disorders. To test this hypothesis, Orlowski evaluated the medical records of subjects in the Australian studies (Refs. 5 and 6) that had not shown an association with aspirin or salicylate ingestion and Reye's syndrome. The medical records of 26 people who were originally diagnosed with Reye's syndrome and survived were reassessed using more precise diagnostic criteria. Eighteen (69 percent) of these were subsequently diagnosed as having other diseases (15 with inborn errors of metabolism). The most common metabolic disorder was medium-chain acyl-coenzyme-A dehydrogenase deficiency. Orlowski speculated that the disappearance of Reye's syndrome in the 1980s may be more related to the discovery of, and ability to diagnose, inborn errors of metabolism that mimic Reye's syndrome clinically, biochemically, and pathologically than to warning labels and the reduced use of aspirin. Although some people previously diagnosed with Reye's syndrome have been found to have metabolic disorders that may meet the criteria for a diagnosis of Reye's syndrome, and some people with metabolic disorders may be predisposed to developing Reye's syndrome, the agency finds there is no definitive evidence at this time that Reye's syndrome can generally be

attributed to metabolic disorders. As discussed previously, other studies (Refs. 1, 2, and 3) have shown an association with aspirin ingestion and Reye's syndrome.

The agency notes one comment's statement that the incidence of Reye's syndrome is low despite many foods with naturally occurring salicylates. Salicylates occur in many foods at low concentrations and in certain foods at relatively high concentrations. For instance, a few herbs and spices contain as much as 200 milligrams salicylate per 100 grams (Ref. 10). However, these food products are generally consumed in small amounts. The agency has no information to suggest that salicylates in food are associated with Reye's syndrome. Although salicylates are present in a wide range of foods, the amount consumed from foods is generally lower than the therapeutic doses in drugs.

The references submitted by the comment that suggested that the acetylation mechanism of aspirin may be responsible for Reye's syndrome did not provide adequate information to support this suggestion. The references included discussion of the hydrolysis of acetylsalicylic acid into acetyl and salicylic acid moieties and the further hydrolysis of the acetyl moiety to acetate, which is ultimately metabolized to carbon dioxide. Up to 50 percent of orally administered doses of acetylsalicylic acid are hydrolyzed before they reach the blood stream because of esterases located in the gut wall and the clearance of the compound by the liver (Ref. 11). Packham (Ref. 12) noted that the acetyl moiety can rapidly acetylate cyclo-oxygenase in platelets at micromolar concentration. However, it may not remain in the circulation long enough to acetylate other proteins to an

extent that alters their function. Salicylic acid is the circulating drug form which is shared by all salicylate products. It undergoes direct renal excretion and hepatic biotransformation through several enzymatic systems.

As noted in the October 1993 proposed rule (58 FR 54228 at 54229) there are some in vitro biochemical data that suggest salicylate may contribute to mitochondrial injury that is characteristic of Reye's syndrome. Based on a more recent in vitro study, Trost and Lemasters (Ref. 13) suggested that induction of the mitochondrial permeability transition (MPT) is a common pathophysiological mechanism causing mitochondrial injury in Reye's syndrome. In that study, MPT induction by aspirin required alkaline hydrolysis. Because aspirin spontaneously decomposes to salicylate, the authors said it is likely that salicylate, rather than acetylsalicylate, is the primary inducer of MPT.

While some in vitro studies (Refs. 14 and 15) suggest salicylate is responsible for mitochondrial injury that may be responsible for the pathogenesis of Reye's syndrome, the agency agrees with the comment that the evidence is not sufficient to show the salicylate moiety is responsible for Reye's syndrome. The pathogenesis of Reye's syndrome is not known. None of the submitted references link Reye's syndrome to either the salicylate or acetyl drug moiety.

Although the agency does not have definitive evidence that drugs containing nonaspirin salicylates significantly increase the risk of Reye's syndrome, a number of case reports (Ref. 8) suggest an association. Because of the serious consequences of Reye's syndrome, the agency has determined, in the interest of safe use of OTC drug