

Erythritol: A Review of Biological and Toxicological Studies

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INTRODUCTION

Erythritol is a four-carbon sugar alcohol (polyol) that has a sweetness 60 to 80% that of sucrose (Sugita and Yamazaki, 1988; Goossens and Röper, 1994) and is intended for use in food principally as a low-calorie sweetener. Its structure is shown in Fig. 1. It is produced from wheat or corn starch by enzymatic hydrolysis yielding glucose which is fermented by safe and suitable food-grade osmophilic yeasts, such as *Moniliella pollinis* (Goossens and Röper, 1994) or *Trichosporonoides spp.* Once erythritol is separated from the fermentation broth, it is purified by processes typical for carbohydrate sweeteners and sugar alcohols (i.e., carbon filtration and resin treatment). The final crystalline product is more than 99% pure.

Erythritol occurs widely in nature and has been found to occur naturally in several foods including wine, sake, beer, mushroom, watermelon, pear, grape, and soy sauce at levels up to 0.13% (w/v) (Onishi and Saito, 1959, 1960; Yoshida *et al.*, 1984; Shindou *et al.*, 1988, 1989; Sponholz and Dittrich, 1985; Sponholz *et al.*, 1986; Dubernet *et al.*, 1974). Per capita consumption of erythritol in the United States from its natural occurrence in foods (mostly cheese and wine) has been estimated to be 80 mg/person/day or approximately 1.3 mg/kg body wt/day (Modderman, 1996a,b).

Evidence indicates that erythritol exists endogenously in the tissue and body fluids of humans and animals (Spencer, 1967; Horning *et al.*, 1974; Oku and Noda, 1990a,b; Goossens and Röper, 1994; Noda *et al.*, 1994). It has been identified in human plasma at levels of approximately 1.2 mg/liter (Niwa *et al.*, 1993) as well as in fetal blood of animals (Britton, 1967; Roberts *et al.*, 1976). Erythritol also occurs normally in human urine (Goossens and Röper, 1994). Urinary concentrations have been reported to range from 10 to 100 mg/liter (Pitkänen and Pitkänen, 1964) or 42 to 65 mg/g creatinine (Pfaffenberger *et al.*, 1976).

Uses in Food

Erythritol has been used since 1990 in Japan as a component of candies, sugar substitutes, chocolates, soft drinks, chewing gum, jellies, jams, and yogurt (Mitsubishi and Nikken, 1996). These uses amount to a per capita consumption in Japan of approximately 46 mg erythritol/day (Mitsubishi and Nikken, 1996) or approximately 0.7 mg/kg body wt/day for a 60-kg individual.

In the United States, erythritol is intended for use as a flavor enhancer, formulation aid, humectant, nutritive sweetener, stabilizer and thickener, sequestrant, and texturizer at maximum levels of 100% in sugar substitutes; 50% in hard candies; 40% in soft candies (mints and chocolates only); 1.5% in reduced- and low-calorie beverages; 60% in fat-based cream for use in cookies, cakes, and pastries; 7% in dietetic cookies and wafers; and 60% in chewing gum.

Erythritol is intended to be used in the same manner as existing polyol food ingredients. Because erythritol in most applications will substitute for these polyols, its actual per capita intake will not exceed that reported for total polyols.

Estimating total polyol intake from dietary surveys of motivated groups, such as persons with diabetes, led to average daily intakes of 4 g polyol/day based on a 7-day UK survey (Ministry of Agriculture, Fisheries and Food, 1990) and 5 g polyol/day based on a 2-day Finnish survey (Virtanen *et al.*, 1988). Considering the technical properties and expected market of erythritol, projected at no more than 20% of total polyols, its actual long-term intake is reasonably expected to be approximately 1 g erythritol/day (17 mg/kg body wt/day) and 4 g erythritol/day (67 mg/kg body wt/day) for mean and 90th percentile users, respectively.

Based on a recent 3-day food intake survey conducted by the U.S. Department of Agriculture and on an independent chewing gum survey, and assuming that erythritol will be used in all intended applications with no other polyols, a "maximum possible" erythritol in-

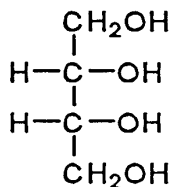


FIG. 1. Chemical structure of erythritol.

take was also estimated (Fleming, 1995). Erythritol intakes by "eaters only" of the total U.S. population for all food categories, excluding chewing gum, were estimated to be 7 g/day (115 mg/kg body wt/day) and 16 g/day (264 mg/kg body wt/day) for mean and 90th percentile users, respectively. Erythritol intakes by eaters only of the total U.S. population for chewing gum use only were estimated to be 4 g/day (67 mg/kg body wt/day) and 8 g/day (133 mg/kg body wt/day) for mean and 90th percentile users, respectively. When considering these data together with the assumption that erythritol will be used in foods at levels no greater than 20% of total polyols, as previously discussed, the resulting intake values are very similar to those derived from the UK and Finnish dietary surveys.

Based on the available survey data, it can be concluded that the 90th percentile user of erythritol would be expected to have a daily erythritol intake of no more than 4 g/day (67 mg/kg body wt) with a more likely intake estimate of approximately 1 g/day (17 mg/kg body wt/day) for mean users.

BIOCHEMICAL STUDIES

In humans, most (60 to 90%) ingested erythritol is rapidly absorbed via the small intestine (Höber and Höber 1937; Lauwers *et al.*, 1985; Winne *et al.*, 1985, 1987; Oku and Noda, 1990a; Bornet *et al.*, 1992, 1996a,b; Hiele *et al.*, 1993; Noda *et al.*, 1994; Tetzloff *et al.*, 1996). Studies with rodents and dogs have shown similar absorption rates (Noda and Oku, 1990; Oku and Noda, 1990a,b; Dean *et al.*, 1996; Lina *et al.*, 1996; Noda *et al.*, 1996; Til *et al.*, 1996; Van Ommen *et al.*, 1996). Unabsorbed erythritol undergoes microbial fermentation in the colon to volatile fatty acids (Noda and Oku, 1990, 1992).

In vitro studies and studies in rodents (Beck *et al.*, 1938; McCorkindale and Edson, 1954; Batt *et al.*, 1960; Noda and Oku, 1990, 1992; Noda *et al.*, 1996; Van Ommen *et al.*, 1996) and humans (Bornet *et al.*, 1992; Hiele *et al.*, 1993; Noda *et al.*, 1994) demonstrate that erythritol is not metabolized systemically; however, it may be involved to a minor extent in some reversible metabolic reactions such as dehydrogenation to D- or L-erythrulose by NDA-dependent cytoplasmatic polyol dehydrogenase or phosphorylation by glycerol kinase to erythritol-1-phosphate followed by dehydrogenation

to D-erythrulose-1-phosphate via α -glycerophosphate dehydrogenase (Chü and Ballou, 1961; Maret and Ault, 1988).

Following absorption, erythritol is rapidly distributed throughout the body and has been reported to occur in hepatocytes, pancreatic cells, and vascular smooth muscle cells (Johansson, 1969; Jonsson, 1971; de Pont *et al.*, 1978; Dewhurst *et al.*, 1978; Lake *et al.*, 1985; Alpini *et al.*, 1986). Bile concentrations of erythritol are proportional to plasma erythritol concentrations (Westendorf and Czok, 1983). Erythritol also has been reported to transfer across the human placenta (Schneider *et al.*, 1985; Jansson *et al.*, 1993) and has been reported to pass slowly from the plasma into the brain and cerebrospinal fluid of sheep (Dziegielewska *et al.*, 1979).

In humans, plasma erythritol levels were reported to reach a maximum of about 3 to 25 mmol/liter (366 to 3050 mg/liter) within 30 to 120 min following ingestion of 0.3 to 1 g erythritol/kg body wt (Noda *et al.*, 1994; Bornet *et al.*, 1996a,b). Absorption of erythritol appears to be protracted when taken with food rather than in aqueous solution on an empty stomach, possibly due to delayed gastric emptying.

Absorbed erythritol is rapidly excreted unchanged in the urine (Oku and Noda, 1990a; Bornet *et al.*, 1992, 1996a,b; Hiele *et al.*, 1993; Noda *et al.*, 1994; Tetzloff *et al.*, 1996). As indicated earlier, the unabsorbed fraction may undergo colonic fermentation or be excreted in the feces. In dogs, less than 2% of ingested erythritol is excreted unchanged via the feces (Dean *et al.*, 1996; Noda *et al.*, 1996) and in rats, similar results have been reported (Oku and Noda, 1990a,b; Noda and Oku, 1990; Lina *et al.*, 1996; Noda *et al.*, 1996; Til *et al.*, 1996; Van Ommen *et al.*, 1996). The biliary excretion of erythritol has been estimated at 1% using bile-cannulated dogs (Lewis *et al.*, 1982).

TOXICOLOGICAL STUDIES

Numerous toxicological studies have been conducted to evaluate the safety of erythritol. The following is a summary of the pivotal published studies demonstrating the safety of erythritol for use in foods.

Acute Studies

No effects in rats, other than diuresis, have been reported following single gavage doses as high as 18 g erythritol/kg body wt (Beck *et al.*, 1936, 1938).

Subchronic Studies

Several published subchronic studies in experimental animals have demonstrated the safety of erythritol for food use (Oku and Noda, 1990a; Dean *et al.*, 1996; Til and Modderman, 1996; Til *et al.*, 1996). The key subchronic studies are summarized in Table 1 and most

TABLE 1
Subchronic Dietary Studies with Erythritol Using Experimental Animals

| Species | Study duration | Dose administered (g/kg body wt/day) [concentration in diet (%)] | | Reference |
|---------|----------------|---|---|---------------------------|
| | | Male | Female | |
| Rat | 28 days | 0, 4.6, 9.2 ^a [0, 5, 10] | 0, 5.1, 10 ^a [0, 5, 10] | Til and Modderman (1996) |
| Rat | 28 days | 0, 4.6, 9.2 ^a [0, 5, 10] | Not studied | Oku and Noda (1990b) |
| Rat | 13 weeks | 0, 3.0, 6.0, 12 ^b [0, 5, 10, 20] | Not studied | Til <i>et al.</i> (1996) |
| Mouse | 13 weeks | 0, 11, 22, 44 ^b [0, 5, 10, 20] | 0, 11, 23, 45 ^b [0, 5, 10, 20] | Til <i>et al.</i> (1996) |
| Dog | 53 weeks | 0, 0.73, 1.8, 3.5 ^b [0, 2, 5, 10] | 0, 0.73, 1.8, 3.6 ^b [0, 2, 5, 10] | Dean <i>et al.</i> (1996) |

^a Approximate doses calculated from standard food consumption and body weight data compiled by EPA (1988).

^b Approximate doses estimated from data provided by study authors.

of these studies are discussed in detail elsewhere in this journal issue. Rats fed 5 or 10% erythritol in the diet (approximately 5 or 10 g/kg body wt/day) for 28 days showed no effects on food consumption, weight gain, organ weights, hematological parameters, or organs following histological examination. However, polydipsia, diuresis, slight increases in cecal weight, and an initial transient diarrhea, mostly in the 10% group, were reported (Oku and Noda, 1990b; Til and Modderman, 1996). These effects are known to occur commonly in rodents fed polyols (Bär, 1985). In a study in which rats and mice were fed erythritol for 13 weeks at dietary concentrations of 0, 5, 10, or 20% (approximately 0, 3, 6, or 12 and 0, 11, 23, or 45 g erythritol/kg body wt/day for rats and mice, respectively), no signs of overt toxicity were evident nor were there any effects on hematological and clinicochemical parameters (Til *et al.*, 1996). One rat group also was given a restricted diet (food access for 6 hr/day) containing 20% erythritol. Transient diarrhea similar to the 28-day studies was observed in some rats receiving 20% erythritol. In both species, urine output increased with increasing erythritol dose particularly at the two highest dose levels (i.e., 10 and 20%) indicating a diuretic effect of erythritol. In mice, the urinary excretion of creatinine-normalized protein, γ -glutamyl transferase (GGT), and electrolytes was significantly increased in the high-dose group, whereas urinary *N*-acetylglucosaminidase (NAG) was not affected. In the 10% dose group, urinary protein also was increased and GGT activity showed slight, but significant, increases in males only. GGT activity also was increased in female mice fed 5% erythritol but not in the 10% dose group. Rats showed no treatment-related changes in these urinary parameters, except that, in the 20% dose groups, urinary calcium and NAG levels were significantly increased. Urinary potassium was significantly increased only in the

ad libitum fed 20% dose group. Although dose-related increases in cecal weight and absolute and relative kidney weights were reported in rats and mice, these were not accompanied by histopathological changes.

In further support of the safety of erythritol, a 1-year dietary study in dogs showed no adverse effects when erythritol was fed at 0, 2, 5, or 10% in the diet (approximately 0, 0.7, 1.8, or 3.5 g/kg body wt/day) (Dean *et al.*, 1996). As with the shorter term rodent studies, there were no clinically relevant changes in hematological or clinicochemical parameters and no histopathological abnormalities. Urinary enzymes remained within normal limits in the dog study.

Chronic Studies

The results of a chronic rat study [described in detail elsewhere in this journal issue (Lina *et al.*, 1996)] have shown that doses of erythritol up to 5.4 g/kg body wt/day for 2 years showed no evidence of toxicity and were not carcinogenic. Groups of male and female Wistar rats were fed 0, 2, 5, or 10% erythritol in the diet (approximately 0, 0.86, 2.2, or 4.6 and 0, 1.0, 2.6, or 5.4 g/kg body wt/day for male and female rats, respectively) for 105 to 107 weeks. A positive control group was fed 10% mannitol in the diet. There were no effects on the general condition or behavior of treated animals. Urine volume was significantly increased in the 10% erythritol group except at Week 102. This was accompanied by a significant increase in NAG. There also were slight increases in urinary excretion of low-molecular-weight protein, total protein, and electrolytes at the 10% erythritol level. The urinary concentration of the renal brush-border enzyme GGT was significantly increased in the first year of the study (Week 50) in the 5 and 10% erythritol groups. Increased GGT continued to Week 78 in the 10% group only but was similar to controls at

Week 102 indicating that this effect was not progressive. Food and water consumption also were increased, but body weights were significantly reduced only in the high-dose animals. As in the other published dietary studies, cecal weights (full and empty) were significantly increased in the high-dose rats and occasionally in the mid-dose rats. Although relative kidney weights also tended to be increased in rats in the 10% erythritol group (relative kidney weights were significantly increased in males at Weeks 52 and 78, but not Week 104 and in females at Week 104), histopathological examination of all organs was unremarkable except for a statistically significant increase in the incidence of pelvic nephrocalcinosis in females of all erythritol groups and in both male and female rats in the 10% mannitol group.

Reproductive Toxicity Studies

To further examine the safety of erythritol in foods, a two-generation reproduction study was conducted using rats. This study (Waalkens-Berendsen *et al.*, 1996) is described in detail elsewhere in this journal issue. Groups of 24 male and 24 female rats were fed erythritol at dietary concentrations of 0, 2.5, 5, or 10% (approximately 0, 1.4 to 3.8, 2.8 to 7.5, or 6.5 to 16 g/kg body wt/day, respectively, depending on the stage of the pregnancy) for approximately 10 weeks prior to mating and during gestation. Twenty-four offspring of each sex and dose group formed the second generation and were treated similarly as the parental generation. For each generation, one litter was reared to 21 days. Erythritol did not affect the reproductive performance or fertility of the parental rats. Also, there were no effects on the development of the offspring. As with all the published animal feeding studies on erythritol, histopathological examination revealed no abnormalities.

Teratology Studies

Dietary administration of high concentrations of erythritol (i.e., up to 10% of the diet) to pregnant rats did not result in any abnormal effects on the fetus (Smits-van Prooije *et al.*, 1996). Groups of 32 pregnant Wistar rats were fed 0, 2.5, 5, or 10% erythritol in the diet (approximately 0, 1.7, 3.3, or 6.6 g erythritol/kg body wt/day) during Gestation Days 0 to 21. No mortality occurred and weight gain during gestation, food consumption, food efficiency, and reproductive performance were similar in all groups with the exception of reduced weight gain in the animals of the high-dose group during the second week of gestation. Examination of the fetuses for external, visceral, and skeletal abnormalities revealed no fetotoxic, embryotoxic, or teratogenic effects. Even when administered intravenously to rabbits at similar doses, no teratogenic potential has been reported (Shimizu *et al.*, 1996). Rabbits were injected intravenously with 1.0, 2.2, or 5.0 g eryth-

ritol/kg body wt/day during Days 6 to 18 of gestation (Shimizu *et al.*, 1996). Although transient maternal effects (i.e., polyuria, auricular edema, and bradypragia), likely related to osmotic load, were observed at the highest dose tested, no effects on fetal development were found. There were no differences in body weight or food consumption of treated maternal animals when compared with control animals. No abnormalities related to treatment were found in the histopathological examination of the maternal animals. Skeletal and visceral examinations of the fetuses revealed no treatment-related effects. This study is discussed in detail elsewhere in this journal issue.

Mutagenicity

Erythritol at concentrations of up to 30 mg/plate has shown no mutagenic activity when tested in five *Salmonella typhimurium* strains (TA1535, TA1537, TA1538, TA98, and TA100) using the Ames assay with or without metabolic activation with liver S9 from Aroclor-induced rats (Blijleven, 1990). Similar results have been reported in another study using *S. typhimurium* strains TA98, TA100, TA1535, and TA1537 as well as in *Escherichia coli* strain WP2 *uvrA* (Kawamura *et al.*, 1996). In the same study, erythritol at concentrations of up to 10 mM also tested negative in chromosome aberration tests using the Chinese hamster fibroblast cell line CHL/IU. These uniformly negative results indicate that erythritol is not mutagenic.

CLINICAL STUDIES

In addition to the numerous safety studies conducted in animals, several clinical studies with erythritol have been published (Bornet *et al.*, 1996a,b; Ishikawa *et al.*, 1996; Oku and Okazaki, 1996; Tetzloff *et al.*, 1996). Four of these studies (Bornet *et al.*, 1996a,b; Ishikawa *et al.*, 1996; Tetzloff *et al.*, 1996) are discussed in detail elsewhere in this journal issue. In most of the studies, erythritol was administered in either an aqueous solution or as part of a meal to healthy male and female subjects for periods of 1 to 14 days. Overall, single or repeated oral doses of about 1 g erythritol/kg body wt/day caused no adverse effects in humans. In these studies, urine output, water intake, hematology, and gastrointestinal side-effects were examined. In two of the studies, urinary enzymes also were analyzed (Bornet *et al.*, 1996b; Tetzloff *et al.*, 1996). No clinically significant effects on these parameters were evident in the studies, although, as expected on the basis of the diuretic effect of erythritol, some increases in urinary volume with increased electrolyte excretion and water intake were observed, as were slight elevations of urinary NAG, albumin, and β_2 - μ -globulin. The enzyme and protein values were within the normal physiological range (Tetzloff *et al.*, 1996). Although urinary GGT also was

analyzed in two of the clinical studies (Bornet *et al.*, 1996b; Tetzloff *et al.*, 1996), it has been shown that GGT is unstable under the storage conditions used and that erythritol enhances the stability of the enzyme (Loeb and Das, 1996) making any comparison with controls uninterpretable. For these reasons, the GGT data were not further evaluated.

Clinical studies also have been conducted in persons with diabetes. Five subjects (three males and two females) given a single 20-g dose of erythritol in aqueous solution had blood and urine samples taken at various intervals prior to and after erythritol ingestion (Ishikawa *et al.*, 1996). Blood samples were analyzed for glucose, insulin, free fatty acids, 3-hydroxybutyric acid, and erythritol. Urine samples were analyzed for erythritol. Consumption of 20 g of erythritol did not affect any of the parameters tested. Similarly, in the same study, when 20 g erythritol was administered daily for 14 days, no significant effects on the above and following parameters were observed. In this longer term study, additional analyses were conducted including measurement of body weight, fasting blood sugar, hemoglobin Alc, blood urea nitrogen, creatinine, β_2 - μ -globulin, and urinary proteins.

DISCUSSION

In the published literature, there is a considerable body of evidence supporting the safety of erythritol for its use as a sweetener in foods. Erythritol is well absorbed (~60 to 90%), with only small amounts available to undergo colonic fermentation, and, therefore, limited gastrointestinal side-effects occur. In the clinical studies, no significant gastrointestinal effects were found at doses up to 1000 mg/kg body wt/day. These doses far exceed the estimated daily intake of approximately 4200 mg/day (approximately 70 mg/kg body wt/day for a 60-kg individual). These findings are well supported by toxicological studies in which experimental animals received high oral doses of erythritol (i.e., up to 45 g/kg body wt/day) for 13 weeks without any significant gastrointestinal effects.

Since erythritol is not systemically metabolized and is rapidly excreted unchanged in the urine, several studies have focused on urinary parameters and potential renal effects of erythritol. Various urinalyses including urinary output, electrolyte excretion, urinary enzyme excretion (e.g., NAG and GGT), and protein excretion have been conducted in many of these animal studies, and no consistent effects have been noted other than those associated with diuresis. These occasional increases in urinary enzymes and electrolytes in some animal species fed high doses of erythritol may be attributable, in part, to the diuretic effect of the compound. Diuresis frequently is accompanied by a rise in urinary enzymes (Obatomi and Plummer, 1993; Mon-

dorf *et al.*, 1994) as well as electrolytes (Guyton, 1987). In dogs given erythritol, urinary enzymes remained within normal limits. In all of the animal-feeding studies conducted, no evidence of kidney damage was observed histopathologically.

In the 13-week study (Til *et al.*, 1996), a statistically significant increase in the relative kidney weights was reported at the highest dose in male rats and mice of both sexes. Likewise in the 2-year rat study (Lina *et al.*, 1996), the relative kidney weights were significantly increased at the end of the study in high-dose females and at the interim necropsy (Week 78) in high-dose males. In both studies, these increases were not accompanied by histopathological changes, except for pelvic nephrocalcinosis in the female rats fed erythritol for 2 years. Pelvic nephrocalcinosis also was observed in rats administered 10% mannitol over 2 years. This histopathological finding is a common occurrence in rodents fed polyols or slowly digestible carbohydrates (Gongwer *et al.*, 1978; Sinkeldam *et al.*, 1983, 1992; Bär, 1984, 1985, 1986; Roe and Bär, 1985; FASEB, 1986; Woutersen, 1987; Conz and Fumero, 1989; Dills, 1989; Conz and Maraschin, 1992).

The large body of published data supports the conclusion that the intake of erythritol would not be expected to cause adverse effects in humans under the conditions of its intended use in food. The available metabolic studies demonstrate that erythritol is readily absorbed, not systemically metabolized and rapidly excreted unchanged in the urine. Moreover, erythritol occurs endogenously and naturally in the diet. Both animal toxicological studies and clinical studies have consistently demonstrated the safety of erythritol even when consumed at levels well in excess of the expected daily intake. Based on the food safety data available in the published literature, the authors conclude that other qualified food safety experts would agree that erythritol is generally recognized as safe (GRAS) under the conditions of its intended use in food.

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