EVALUATION OF THE HEALTH ASPECTS OF BIOTIN AS A FOOD INGREDIENT

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Prepared for

Bureau of Foods
Food and Drug Administration
Department of Health, Education, and Welfare
Washington, D.C.

Contract No. FDA 223-75-2004
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Life Sciences Research Office
Federation of American Societies for Experimental Biology
9650 Rockville Pike
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NOTICE

This report is one of a series concerning the health aspects of using the Generally Recognized as Safe (GRAS) or prior sanctioned food substances as food ingredients, being made by the Federation of American Societies for Experimental Biology (FASEB) under contract no. 223-75-2004 with the Food and Drug Administration (FDA), U.S. Department of Health, Education, and Welfare. The Federation recognizes that the safety of GRAS substances is of national significance, and that its resources are particularly suited to marshalling the opinions of knowledgeable scientists to assist in these evaluations. The Life Sciences Research Office (LSRO), established by FASEB in 1962 to make scientific assessments in the biomedical sciences, is conducting these studies.

Qualified scientists were selected as consultants to review and evaluate the available information on each of the GRAS substances. These scientists, designated the Select Committee on GRAS Substances, were chosen for their experience and judgment with due consideration for balance and breadth in the appropriate professional disciplines. The Select Committee's evaluations are being made independently of FDA or any other group, governmental or non-governmental. The Select Committee accepts responsibility for the content of each report. Members of the Select Committee who have contributed to this report are named in Section VII.

Tentative reports are made available to the public for review in the Office of the Hearing Clerk, Food and Drug Administration, after announcement in the Federal Register, and opportunity is provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the substances covered by the report. The data, information, and views presented at the hearing are considered by the Select Committee in reaching its final conclusions. Reports are approved by the Select Committee and the Director of LSRO, and subsequently reviewed and approved by the LSRO Advisory Committee (which consists of representatives of each constituent society of FASEB) under authority delegated by the Executive Committee of the Federation Board. Upon completion of these review procedures the reports are approved and transmitted to FDA by the Executive Director of FASEB.

While this is a report of the Federation of American Societies for Experimental Biology, it does not necessarily reflect the opinion of all of the individual members of its constituent societies.

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I. INTRODUCTION

This report concerns the health aspects of using biotin as a food ingredient. It has been based partly on the information contained in a scientific literature review (monograph) furnished by FDA (1), which summarizes the world's scientific literature from 1920 through 1974. To assure completeness and currency as of the date of this report this information has been supplemented by searches of over 30 scientific and statistical reference sources and compendia that are generally available; use of new, relevant books and reviews and the literature citations contained in them; consideration of current literature citations obtained through computer retrieval systems of the National Library of Medicine; searches for relevant data in the files of FDA; and by the combined knowledge and experience of members of the Select Committee and the LSRO staff.

In addition, an announcement was made in the Federal Register of February 17, 1978 (43 FR 7036-7038) that opportunity would be provided for any interested person to appear before the Select Committee at a public hearing to make oral presentation of data, information, and views on the health aspects of using biotin as a food ingredient. The Select Committee received no requests for such a hearing on biotin.

As indicated in the Food, Drug, and Cosmetic Act [21 USC 321(s)], GRAS substances are exempt from the premarking clearance that is required for food additives. It is stated in the Act and in the Code of Federal Regulations (2) [21 CFR 170.3 and 170.30] that GRAS means general recognition of safety by experts qualified by scientific training and experience to evaluate the safety of substances on the basis of scientific data derived from published literature. These sections of the Code also indicate that expert judgment is to be based on the evaluation of results of credible toxicological testing or, for those substances used in food prior to January 1, 1958, on a reasoned judgment founded in experience with common food use, and is to take into account reasonably anticipated patterns of consumption, cumulative effects in the diet, and safety factors appropriate for the utilization of animal experimentation data. FDA (2) recognizes further [21 CFR 170.30] that it is impossible to provide assurance that any substance is absolutely safe for human consumption.

The Select Committee on GRAS Substances of LSRO is making its evaluations of these substances in full recognition of the foregoing provisions.

*The document (PB-234 890/2) is available from the National Technical Information Service, U.S. Department of Commerce, P.O. Box 1553, Springfield, Virginia 22161.
In reaching its conclusions on safety, the Committee, in accordance with FDA's guidelines, is relying primarily on the absence of substantive evidence of, or reasonable grounds to suspect, a significant risk to the public health. While the Committee realizes that a conclusion based on such reasoned judgment is expected even in instances where the available information is qualitatively or quantitatively limited, it recognizes that there can be instances where, in the judgment of the Committee, there are insufficient data upon which to base a conclusion. The Committee is aware that these conclusions will need to be reviewed as new or better information becomes available.

In this context, the LSRO Select Committee on GRAS Substances has reviewed the available information on biotin and submits its interpretation and assessment in this report, which is intended for the use of FDA in determining the future status of this substance under the Federal Food, Drug, and Cosmetic Act.

II. BACKGROUND INFORMATION

Biotin, one of the B-complex vitamins, is (±)-cis-hexahydro-2-keto-1H-thieno-(3,4)-imidazole-4-valeric acid. It has been variously known as a yeast growth factor, the curative factor (vitamin H) for egg white injury, the "protective factor," "factor X," or "the factor protective against egg white injury" (1). Chemical properties are described in György and Langer (3) and Goodhart (4).

Biotin is a white crystalline compound with molecular weight 244.31. It melts at 230° to 232°C with some decomposition, is soluble in hot water and dilute ethanol, sparingly soluble in cold water, and insoluble in chloroform, benzene and ether. It is destroyed by heating with strong alkalis but is heat stable in acid solution. Neutral and acidic solutions are stable for several months. Biotin contains three asymmetric carbons, making possible four diastereoisomers or eight optically active isomers, but only natural biotin, having the formula indicated above, is biologically active (3,5). According to Food Chemicals Codex specifications (5), the biologically active, food grade form, must assay at least 97.5 percent biotin, melt between 229° and 232°C, have a specific rotation [α]D 25 between +89° and +93°, and contain not more than 3 ppm of arsenic nor more than 10 ppm of heavy metals (as lead).

No chemical or physicochemical method for determining biotin concentration in foods or in body tissues or fluids is in general use. Because microbiologic assays detect free but not bound biotin, it is necessary to employ enzymatic or acid hydrolysis which introduces conditions of assay that are difficult to control. Moreover, oleic acid can partially substitute for biotin in certain microorganisms, and others may be able to utilize close homologs
of biotin that animals cannot (3, 8). On the other hand, d-biotinol, the alcohol analog of biotin, is inactive for Lactobacillus casei and Saccharomyces cerevisiae, but is converted to biotin by the rat and man and is as effective as d-biotin in curing egg white-induced biotin deficiency in the rat (7).

Biotin is listed as GRAS in the Code of Federal Regulations (2) for use as a nutrient or dietary supplement [21 CFR 182.5159].

Biotin is present in small quantities in most foods. Particularly rich sources of biotin are liver, egg yolk, yeast, certain fish (mackerel, salmon, sardines), soybeans, cauliflower and cow peas (8).

III. CONSUMER EXPOSURE DATA

A comprehensive survey conducted by a subcommittee of the National Research Council (NRC) disclosed that infant formulas are the only foods to which biotin is added (9). The Physicians' Desk Reference (10) indicates that biotin is not added to milk-based infant formulas (i.e., those fed to the great majority of U.S. infants) but is added to some soy isolate-based infant formulas and to certain other milk-free formulas prepared either for infants or for other age groups. The level of addition generally ranges from 0.05 to 0.15 mg per liter (i.e., 0.075 to 0.222 mg per 1000 kcal). Thus, a 4-month-old infant consuming 430 kcal per day (the estimated 50th percentile value for formula consumption at that age) from a formula fortified with biotin at the maximal level, would receive approximately 95 µg of added biotin per day. An adult receiving 2000 kcal of special formula fortified with 150 µg of biotin per 1000 kcal might receive 300 µg of added biotin per day.

Total usage of biotin in foods, based on reports by manufacturers (9), was recalculated to 100 percent from the survey data which the NRC subcommittee estimated to represent about 60 percent of the actual usage. On this basis, total biotin added to foods in 1970 was estimated to be 33 kg, a value 30 percent larger than that for 1960.

It is difficult to account for the use of 33 kg of biotin in infant formulas. Based on the estimates of Fomon (11) regarding the percentage of infants fed milk-free formulas and the approximately 3.5 million infant births in the United States in 1970 (12), approximately 44 million liters of milk-free formulas were fed to infants in that year. If all of these formulas had been fortified with biotin at the maximal level (0.15 mg per liter), only 6.6 kg of biotin would have been needed. Special biotin-fortified formulas fed to individuals in other age groups seem unlikely to account for 26.4 kg of biotin. Therefore, it is possible that a substantial portion of the
biotin usage reported by the manufacturers consisted of amounts used in vitamin supplements rather than in infant formulas.*

The amounts of biotin consumed in infant formulas or special formulas for older individuals may be considered in relation to the natural biotin content of certain foods. Human milk provides approximately 8 μg of biotin per liter and cow milk about 31 μg per liter (13). Milk-based formulas may be expected to provide an amount of biotin intermediate between human milk and cow milk. Thus, normal infants may receive less than 8 μg of biotin per day (a breastfed infant consuming less than 1 liter of human milk and no other foods) or more than 30 μg per day (1 liter of cow milk or less than 1 liter of cow milk plus other foods, some rich in biotin). Adult diets may range from less than 30 to more than 170 μg per day (14, 15).

IV. BIOLOGICAL STUDIES

Absorption

Urinary excretion of biotin increases as oral intake of biotin increases, and at high dietary intakes urinary excretion approaches intake, indicating that orally administered biotin is absorbed (14, 15). It is not clear whether this absorption occurs predominantly in the small intestine or whether moderate amounts of biotin may be absorbed from the large intestine.

Transport of biotin against a concentration gradient appears in studies with everted small intestinal sacs of the hamster, white mouse, gerbil, chinchilla, squirrel, and chipmunk but not in the rat, rabbit, guinea pig, ferret or carp (16).

Dietary biotin is required by germ-free rats (17). Synthesis in and absorption from the large intestine occur under normal circumstances, but the extent of absorption is uncertain (18). Fecal excretion of biotin by the human is commonly several times greater than intake (14, 15, 19, 20). Although urinary excretion has in some instances been reported to be greater than intake (19, 21), the difference between intake and urinary excretion has seldom been large. It is recognized in this respect that measuring differences in intake and excretion are difficult because microbiologic assays of foods which require hydrolysis present problems as compared to biologic assays of urine which do not. However, because large doses (0.5 to 1 mg) of biotin administered rectally to two patients resulted in increased urinary excretion (22), it seems likely that at least a small amount of endogenously synthesized biotin may be available to the human.

*A revised estimate of 7.6 kg for annual usage of biotin was received from NRC March 23, 1978, indicating that biotin was mainly used in infant formulas.
Metabolism, distribution and excretion

Biotin participates in many carboxylation, decarboxylation, carbamylation, and deamination reactions in carbohydrate, fatty acid, protein and nucleic acid metabolism in man (3, 23, 24). These reactions include the conversion of propionate to methylmalonate, pyruvate to oxaloacetate, malate to pyruvate and oxalosuccinate to α-ketoglutarate. Other reactions in which biotin is required include those involved in fatty acid synthesis and in the metabolism of aspartic acid and other amino acids. In biotin-catalyzed carboxylation reactions, an enzyme-biotin-carbon dioxide complex is formed as an intermediate with the aid of adenosine triphosphate (ATP).

Several studies in which radioactively-labeled biotin was administered parenterally to rats have provided data on the distribution and metabolism of the vitamin. When rats were injected intraperitoneally with 10 to 20 μg of biotin labeled with 14C in the ureido carbonyl group, 85 percent of the administered radioactivity was excreted in the urine in one day (25). About half of the excreted radioactive material was biologically active by a S. cerevisiae assay. No expired radioactivity was detected. These findings were subsequently confirmed and extended by Lee et al. (26, 27) using large doses of biotin (5 mg of biotin per kg body weight). After intraperitoneal injection of ureido carbonyl [14C]-labeled biotin into male rats, more than 90 percent of the intact vitamin was recovered in the urine in 12 hours. With injection of smaller quantities of labeled biotin, lesser percentages were recovered in the urine in the same time period. At the same dosage, lesser percentages of labeled biotin were recovered in the urine of biotin-deficient than in the urine of normal animals.

After injection of 100 μg of carboxyl-labeled biotin per kg of body weight to biotin-deficient rats, approximately 16 percent of the dose was incorporated into liver in 4 hours, and nearly half of this radioactivity was found in the fraction of the cell supernatant precipitated at pH 5.2 (28). Most of the biotin in various cell fractions, except in microsomes, was in the bound form.

A slight but presumably statistically significant increase in concentration of sugar in the blood of rats was observed after endoperitoneal injection of 1 mg or 2 mg (5 or 10 mg per kg body weight) of biotin but not after a control injection or injection of 0.5 mg of biotin (29). No effect of biotin administration at similar levels was demonstrated on the hypoglycemic response after administration of insulin.

Reports concerning the effect of biotin administration on concentrations of cholesterol in serum or various organs of the rat are equivocal (30, 31). Braginski et al. (32) were unable to demonstrate a statistically significant effect on serum concentration of cholesterol when biotin, 1 mg daily (about 17 μg per kg body weight), presumably by mouth, was given for
7 days to 12 healthy adults. Similar dosage for a similar period of time, given to 64 patients with mild hypercholesterolemia, was associated with a statistically significant decrease in concentration of cholesterol (from a mean of 216 to 188 mg per 100 ml). Dalton (33) found no effect on the serum cholesterol of normal and hypercholesterolemic Mongolian gerbils after oral or subcutaneous administration of 1 mg biotin per kg body weight for 3 weeks.

In fowl, deficiency manifestations can be produced with relative ease by feeding a biotin-free diet. However, in mammals it is typically necessary to include egg white or avidin in the diet, or to administer sulfasuxidine, sulfaguanidine or other poorly absorbable bacteriostatic or bactericidal agents (3, 4). Avidin, a protein of egg white, interacts with biotin and renders it inactive. The nature of the avidin-biotin complex has been discussed by several authors (3, 25, 34). The syndrome known as egg-white injury, produced when rats consume large amounts of uncooked egg white, includes dermatitis, spasticity or paralysis of the hind limbs, and circumocular loss of hair or "spectacle eye" (3, 4).

Attempts to produce biotin deficiency in rhesus monkeys by feeding diets low in biotin content with the addition of uncooked, powdered egg white or a sulfonamide seem to have been successful in at least some instances in creating manifestations of biotin deficiency (35).

Studies of human subjects have elucidated the relation between dietary intake of biotin from foods and urinary excretion of biotin. With diets providing 20 to 40 µg of biotin daily, as judged by microbiologic assays, urinary excretion was generally similar to intake; in some instances it was somewhat greater and in other instances, somewhat less (19, 21). With unrestricted diets, urinary excretion of biotin ranged from 14 to 111 µg daily (21).

Ten women of college age were studied for 10 days while receiving diets low, moderate or high in biotin (9 to 171 µg of biotin daily). Increasing the biotin content of the diet from 9 to 33 µg per day resulted in a 40 percent increase in fecal excretion of biotin but no increase in urinary excretion. With a daily intake of 171 µg of biotin, both urinary and fecal excretion were increased (14). In another study (15), 15 healthy women received diets providing 21 to 161 µg of biotin daily. At relatively low intakes of biotin, doubling the intake had little effect on urinary or fecal excretion; however, with high doses of biotin, urinary excretion was markedly increased.

Sydenstricker et al. (36, 37) fed four human volunteers a restricted diet of low biotin content and containing dehydrated egg white. Dermatitis, lassitude, neurosensory manifestations, anorexia and hematologic abnormalities that developed disappeared after injection of as little as 150 µg biotin daily. A case of possible biotin deficiency has been reported in a
66-year-old man who had subsisted for years on a diet consisting primarily of raw eggs and wine (38). Two attempts to produce biotin deficiency in patients with malignant tumors have been unsuccessful (39, 40).

Acute toxicity

Crittenden (41) reported that single intravenous injections of 1 g of dl-biotin per kg of body weight in mice weighing an average of 20 g (number not stated) did not produce signs of toxicity. The oral LD$_{10}$ in mice was reported to be greater than 10 g of biotin per kg of body weight (42). Rapid intravenous injection of two anesthetized cats with 250 µg of biotin per kg of body weight failed to elicit changes in blood pressure, heart rate or respiration (43). It has also been reported that at a skin clinic, daily doses of biotin of 60 mg orally or 100 mg intramuscularly have been given to human subjects for up to 3 weeks without side effects (42).

Short-term animal studies

Crittenden (41) has reported short-term studies of biotin administration to mice, rats, and dogs. Evidences of toxicity were not observed in 7-week-old or 14-week-old mice, 10 to 15 animals in each group, treated for 60 days with daily oral doses of 1 mg of dl-biotin (about 50 mg per kg body weight) in physiologic saline, 1 mg of d-biotin in saline, or saline alone. Administration of 50 mg (about 360 mg per kg) d-biotin daily for 10 days by stomach tube to five male rats did not influence hematologic status and no gross pathologic changes were noted at necropsy. Male rats, five per group, were given oral doses of 5 mg d-biotin (about 35 mg per kg), 5 mg dl-biotin or 1 ml of physiologic saline alone for 120 days. The animals appeared normal but mean body weight of controls at the end of the experiment averaged 46 g greater than that of animals fed dl-biotin and 35 g greater than that of animals fed d-biotin. Hemoglobin concentration, blood cell count, hepatic and renal function were unaffected. Four dogs weighing from 6 to 10.8 kg were injected intravenously with 10 mg of d-biotin (1 to 2 mg per kg) daily for 10 successive days. No changes were observed in general behavior, body weight, reflexes, heart and respiratory rate, urinalysis, hemoglobin concentration or red or white blood cell count.

Short-term human studies

Doses of biotin, administered for days, weeks, or even months, have been used to treat several diseases without observed adverse effects. Biotin has been reported by a number of authors (44, 45) to be effective in treatment of seborrheic dermatitis of infants and young preschool children, including the severe, generalized desquamating form known as Leiner's disease (erythroderma desquamativum). Results have been reported to be better with parenteral than with oral administration. Dosage has generally ranged from 2 to 10 mg daily for 14 to 30 days. No adverse effects from
these doses have been observed.

Gautier et al. (46) employed biotin in treatment of 30 infants, mostly less than 3 months of age, with dermatitis. Nine patients were treated with oral doses of 2 to 6 mg per day for 7 to 28 days. Fifteen patients were treated with intramuscular injections of 5 mg per day for 5 to 17 days. Other patients received intramuscular injections less frequently or combined oral and intramuscular dosage. No adverse reactions were noted and the dermatitis was thought to improve in the majority of cases; however, there were no control studies.

Five patients, 18 to 48 years of age with severe onychodystrophy were treated with large doses of biotin (47). After 40 days of control observation, each subject received 120 mg of biotin daily in three equal, oral doses (about 2 mg per kg per day) for 50 days. The condition of the nails improved and the rate of nail growth increased. The author states that he could detect no harmful side effects of the large doses of biotin but mentions, in passing, increased appetite and gain in weight.

Forty-six women, 17 to 51 years of age, with diffuse alopecia were studied in a double-blind design (48). Twenty-eight women received 10 mg of biotin daily (about 200 µg per kg) presumably by mouth, for 28 days and 18 received a placebo. No effect was noted on the state of the hair roots or on the quantity of sebaceous material. While the treatment was not effective, no adverse effects were apparent.

Long-term studies

No reports of studies of animals fed biotin for long periods have come to the attention of the Select Committee.

Reproductive performance

Decreased reproductive performance has been reported for Mexican fruit flies (49), house flies (50), and hidebeetles (51), receiving large intakes (0.1 to 2 percent in feed) of biotin. Paul et al. (52) studied the effect of biotin administration to colony bred, adult female rats of the Holtzman strain, approximately 3 months of age. Under standardized light-dark, temperature and feeding conditions, the normal estrous cycle was observed for three cycles. Eighteen rats were then given 50 mg of biotin per kg of body weight (estimated requirement 0.003 mg per day). The dose was dissolved in 0.2 ml of 0.1 N sodium hydroxide and given subcutaneously in two injections daily, morning and evening, at the diestrous stage of the cycle. Six control rats were given only the sodium hydroxide vehicle. Of the rats given biotin, six were sacrificed at each of the following days after injection: 7, 14, and 21. Control rats were sacrificed 7 days after injection. The sodium hydroxide-treated controls were unaffected. The biotin-treated rats demonstrated
irregularity of the estrous cycle. Leukocyte infiltration of the vaginal lumen was exaggerated and prolonged. Although formation of corpora lutea was enhanced, a large number of corpora lutea and much of the stroma demonstrated atrophic changes. In a subsequent similar experiment by the same investigators (53), 36 virgin female rats were injected with 50 mg of biotin per kg of body weight and exposed in three groups, 12 rats per group, to males of the same strain 7, 14, and 21 days after the biotin injections. Six females in each group were sacrificed on the 15th day of pregnancy and six on the 22nd day. Most of the biotin-treated rats resorbed their fetuses and only implantation sites were present at the end of 21 days. Fetal and placental weights were below normal in those few instances in which pregnancy was maintained.

Other studies

Studies of the mutagenicity and carcinogenicity of biotin have not come to the attention of the Select Committee, but two studies carried out in the 1940's are noted. Kline et al. (54) and Harris et al. (55) explored the effects of biotin and avidin on carcinogenesis and tumor growth in rats. Avidin was found to retard and biotin to accelerate the development of hepatomas in rats fed p-dimethylaminoazobenzene.

V. OPINION

Biotin, one of the B-complex vitamins, is an essential nutrient functioning as a part of the enzyme systems of the human body that are involved in carboxylation and decarboxylation reactions. It is present in many foods and usual diets of adults probably supply an average of 30 to 40 μg daily, with large variation. The difficulty of producing biotin deficiency in mammals without the use of avidin indicates that the usual intakes are in excess of those required for normal maintenance and growth.

Currently the only food use of biotin is in milk-free infant formulas and certain special formulas used in the management of older subjects. Infant formulas are likely to provide approximately 95 μg of biotin per day for a 4-month-old (about 20 μg per kg body weight) and an adult receiving 2000 kcal in the form of foods for special dietary use under medical supervision could receive up to 300 μg biotin per day (about 5 μg per kg body weight). Considerably larger doses (up to 2 mg per kg body weight) have been administered without untoward effects in attempts at treating several disease conditions.

Although adverse effects of biotin administration on reproductive performance have been reported in limited experiments in rats, the effective doses have been extremely large (about 50 mg of biotin per kg of body weight).
Such doses are orders of magnitude greater than those to which humans could conceivably be exposed by consumption of processed foods containing added biotin.

The Select Committee concludes that:

There is no evidence in the available information on biotin that demonstrates, or suggests reasonable grounds to suspect a hazard to the public when it is added to foods at levels that are now current or that might reasonably be expected in the future.
VI. REFERENCES CITED


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April 25, 1978
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