Risk Assessment — Biotin

General Information

Chemistry

D-Biotin (biotin, coenzyme R, vitamin H) is a water-soluble vitamin. It has a bicyclic ring structure. One ring contains a ureido group and the other contains a heterocyclic sulphur atom and a valeric acid side-group.

Natural occurrence

Biotin is derived from *de novo* synthesis by bacteria, primitive eukaryotic organisms including yeasts, moulds and algae, and some plant species.

Occurrence in food, food supplements and medicines

Biotin is widely distributed in natural foodstuffs but at very low levels compared to other water-soluble vitamins. Foods relatively rich in biotin include egg yolk, liver, kidney, muscle and organ meats, and some vegetables. Liver contains approximately 1 mg/kg biotin, whereas fruits and most other meats contain approximately 0.01 mg/kg biotin. Biotin, usually either in the form of crystalline D-biotin or brewer's yeast, is included in many dietary supplements, infant milk formulas and baby foods, as well as various dietetic products. The maximum dose in supplements sold in the UK is 2 mg. Several medicines containing biotin, which are available only from pharmacies, are licensed for the prevention and treatment of nutrient deficiency, supplementation of special diets and malabsorption. The maximum daily dose of biotin in licensed medicines is 0.50 mg.

Recommended amounts

Due to insufficient data, COMA was unable to set Dietary Reference Values for biotin, but considered that intakes between 0.010 and 0.20 mg/day are both safe and adequate (COMA, 1991).

Analysis of tissue levels and biotin status

Measurement of biotin in plasma is not a reliable indicator of status. Changes in urinary excretion of biotin, or its metabolites bisnorbiotin, 3-hydroxyisovaleric acid and 3-methylcrotonylglycine, are good indicators of biotin status.

Brief overview of non-nutritional beneficial effects

Biotin has been claimed to be beneficial in the treatment of brittle nails, hyperinsulinaemia and impaired glucose tolerance and in sternocostoclavicular hyperostosis. Biotin supplements are also indicated in the management of inborn biotin-associated enzyme abnormalities such as deficiency of biotinidase, holocarboxylase synthetase and the individual carboxylase enzymes.

Function

Biotin acts as an essential cofactor for the acetyl-CoA, propionyl-CoA, ß-methylcrotonyl-CoA and pyruvate carboxylase enzymes, which are important in the synthesis of fatty acids, the catabolism of branched-chain amino acids and the gluconeogenic pathway. Biotin may also have a role in the regulation of gene expression arising from its interaction with nuclear histone proteins.

Deficiency

Biotin deficiency has been observed in individuals maintained on total parenteral nutrition, people who consume large amounts of uncooked egg white, sufferers from inherent or acquired biotin malabsorption, haemodialysis patients, and individuals receiving some forms of long-term anticonvulsant therapy. Pregnancy may be associated with marginal biotin deficiency. Signs of biotin deficiency include a fine scaly desquamating dermatitis and characteristic skin rash frequently observed around the eyes, nose and mouth, hair loss, conjunctivitis and ataxia. Biotin deficient infants show signs of hypotonia, lethargy, developmental delay and withdrawn behaviour, all of which are characteristic of a biotin deficiency-related neurological disorder. 'Egg white injury' may be associated with glossitis, anorexia, nausea, hallucinations, depression and somnolence. Inherited deficiencies in biotinidase and holocarboxylase synthetase result in multiple carboxylase deficiency. These deficiencies and those of specific carboxylase enzymes may produce the same or similar disorders and manifestations of biotin deficiency. Clinical manifestations of biotin deficiency are generally thought to result, directly or indirectly, from deficient activities of the carboxylase enzymes. Biotin deficiency has been shown to cause abnormal foetal development in animals.

Interactions

Some anticonvulsant drugs and alcohol may inhibit intestinal carrier-mediated transport of biotin. Steroid hormones and some anticonvulsant drugs may accelerate the catabolism of biotin in the tissues. Peroxisome proliferators have been shown to accelerate biotin catabolism in rats. However, the human relevance of this finding is questionable. Pantothenic acid and biotin may share common carrier-mediated uptake mechanisms in some tissues but at present there are no known clinical implications of this interaction.

Absorption and bioavailability

Biotin uptake from the small intestine occurs by a carrier-mediated process that operates with a high carrier affinity and also by slow passive diffusion. The carrier is driven by an electron-neutral sodium (Na^+) gradient, has a high structural specificity and is regulated by the availability of biotin, with up-regulation of the number of transporter molecules when biotin is deficient. The colon is also capable of absorbing biotin via a similar transport mechanism. Approximately 80% of biotin in plasma is in the free form and the remainder is either reversibly or covalently bound to plasma proteins. The existence of a specific biotin carrier protein in plasma is a subject of debate.

Factors determining the bioavailability of biotin present in the diet are uncertain. The bioavailability of biotin that is covalently bound to protein is reduced in individuals suffering from biotinidase deficiency. There are few data concerning the bioavailability of crystalline biotin supplements, but a recent study has suggested that doses as high as 22 mg may be completely absorbed. The nutritional significance of biotin synthesis by bacteria present in the lower gut is a subject of controversy.

Distribution and metabolism

Uptake into tissues occurs by specific transport mechanisms dependent upon Na^+ gradients. Transplacental transport is thought to involve the active accumulation of biotin within the placenta followed by its passive release into the foetal compartment. Biotin is metabolically trapped within the tissues by its incorporation into carboxylase enzymes. In the normal turnover of cellular proteins, carboxylase enzymes are broken down to biocytin or oligopeptides containing lysyl-linked biotin. Biotin may be released for recycling by the hydrolytic action of biotinidase. Liberated biotin may be reclaimed in the kidney against a concentration gradient. Biotin not incorporated into carboxylase enzymes may be metabolised oxidatively at the sulphur present in the heterocyclic ring and/or at the valeric acid side chain.

Excretion

Biotin metabolites are not active as vitamins and are excreted in the urine. Very little biotin is thought to undergo biliary excretion and the substantial amounts of biotin that appear in the faeces are derived from colonic bacteria.

Toxicity

Human data

Anecdotal reports suggest that typical daily doses of 10 mg are without adverse effects and toxicity has not been reported in individuals receiving as much as 200 mg per day. Clinical data are limited but studies have reported no biotin-related adverse effects following the administration of 9 mg/day for up to 4 years, 10 mg/day for 15 days, 4 mg/day for 3 weeks or 2.5 mg/day for 6-15 months.

Animal data

The database on the toxicity of biotin in laboratory animals is limited. Acute toxicity in mice and rats after intravenous or oral dosage appears to be low. There is controversy as to whether high doses of biotin given sub-cutaneously cause adverse effects to the reproductive system in laboratory animals. Biotin-related disturbances in oestrus cycle, atrophic changes in ovaries, inhibition of foetal and placental growth and the increased resorption of foetuses were reported following administration of biotin (50 mg/kg) by injection to female Holzman rats, up to 3 weeks prior to mating. These effects were not observed in a similar study conducted in Ibm:RORO$_f$ rats or ICR mice. These studies were not appropriate for risk assessment of oral doses.

Carcinogenicity and genotoxicity

No carcinogenicity data are available for biotin. It has been shown to be negative in the Ames test. However, further data on the mutagenicity testing of biotin are not available.

Genetic variations

No relevant genetic variations have been identified.

Mechanism of toxicity

No relevant data are available.

Dose-response characterisation

No relevant data are available.

Vulnerable groups

No potential vulnerable groups have been identified.

Studies of particular importance in the risk assessment:

(For full review see http://www.food.gov.uk/science/ouradvisors/vitandmin/evmpapers or the enclosed CD)

Human data

Maebashi et al., 1993

Biotin (9 mg, in combination with 3 g of an anti-microbial drug, Miya-BM) was administered daily, by the oral route (in three divided doses), for up to 4 years, to 20 patients (sex and age unspecified) suffering from non-insulin dependent diabetes. The number of patients followed up after 24, 30, 36 and 48 months was 15, 15, 10 and 5, respectively. There was no control group included in the study. Fasting blood glucose levels decreased to normal within 2 months and remained normal thereafter with continuing treatment. Serum insulin levels were not significantly changed. The authors reported that there were no observed clinical aggravations or undesirable side effects. This study cannot be used for risk assessment because of the unusual design and the small number of subjects.

Velazquez et al., 1995

In a double blind placebo controlled study, protein deficient children (n=22) were administered 10 mg biotin/day for fifteen days. Plasma biotin concentrations and lymphocyte carboxylase enzymes were measured. The authors reported no adverse effects. This study cannot be used to define the safety of biotin in children with a normal protein intake.

Exposure assessment

Total exposure/intake:

Food	mean: 0.033 mg/day (1986/7 NDNS) 97.5th percentile: 0.066 mg/day
Supplements	up to 2 mg/day (Annex 4)

Estimated maximum intake: 0.066 + 2 = 2.07 mg/day

No potential high intake groups were identified.

Risk assessment

There are relatively few human data available on the oral toxicity of biotin. The data available are in the form of anecdotal case reports or from clinical trials or supplementation studies designed primarily to investigate beneficial effects of biotin. The latter rarely specifically report on the presence or absence of adverse effects.

The animal toxicity database for biotin is very limited, especially when given by the oral route.

ESTABLISHMENT OF GUIDANCE LEVEL

The data from studies in humans and animals are not adequate for the establishment of a Safe Upper Level.

The numerous clinical case reports in the literature describe the outcome of oral biotin administration to patients (infants, juveniles and adults) with biotin-responsive inborn errors of metabolism and other forms of biotin deficiency. Furthermore, in cases where foetal biotin-responsive disorders have been suspected, biotin has been administered prenatally, via the mother. Typically, doses of 10 mg/day (250 x the average intake of the adult male in the UK) have been studied for therapeutic effects, without reported adverse side effects.

Supplemental doses of 9 mg/day given to human volunteers for up to 4 years have not been associated with adverse effects. The study is limited in that it was performed in diabetics, there was no control group and only a few individuals remained in the study after 4 years. The authors concluded that there were no adverse effects related to the biotin treatment, although they reported a tendency for the treatment to lower blood sugar. Due to the low number of individuals studied, and the small proportion of volunteers followed up long term, an uncertainty factor of 10 for inter-individual variation has been applied in this case to allow for inter-individual variation. Thus, for guidance purposes only, a supplemental daily intake of 0.9 mg biotin (equivalent to 0.015 mg/kg bw/day in a 60 kg adult) would not be expected to produce adverse effects, although this value may not be applicable to all life stages. Assuming a maximum intake of 0.066 mg/day from food, an estimated total intake (from all sources) of 0.97 mg/day biotin (equivalent to 0.016 mg/kg bw/day in a 60 kg adult) would not be expected to result in any adverse effects.

References

COMA (1991). Dietary Reference Values for Food Energy and Nutrients for the United Kingdom. Report of the Panel on Dietary Reference Values, Committee on Medical Aspects of Food and Nutrition Policy. HMSO, London.

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