Proposed maximum levels for the addition of biotin to foods including food supplements

The accompanying main opinion "**Updated recommended maximum levels for the addition of vitamins and minerals to food supplements and conventional foods**" can be found here: https://www.bfr.bund.de/cm/349/updated-recommended-maximum-levels-for-the-addition-of-vitamins-and-minerals-to-food-supplements-and-conventional-foods.pdf

1 Results

No Tolerable Upper Intake Level[1] (UL) has been derived for biotin, and no adverse health effects have been observed even when amounts far above the intake reference value were consumed. From the point of view of the German Federal Institute for Risk Assessment (BfR), it is therefore not necessary, on the basis of the current state of knowledge, to set maximum levels for biotin for use in food supplements and conventional foods.

In view of the cases of falsification of laboratory diagnostic tests by biotin that have become known in recent years, the BfR recommends that, as a matter of principle, a note should be affixed to food supplements containing biotin, indicating that persons who have to undergo a laboratory test should inform their doctor or the laboratory staff that they are taking or have recently taken biotin.

2 Rationale

2.1 Tolerable Upper Intake Level (UL) and intake reference value

In 2001, the former Scientific Committee on Food (SCF) of the European Commission, when evaluating biotin to derive a UL, had noted that no systematic dose-response studies had been conducted with biotin in humans and therefore no data were available for a quantitative risk assessment. In view of this, no UL could be derived for biotin. Based on the limited data available from observational studies, it was concluded that at the levels commonly ingested from these sources (at that time in the 97.5th intake percentiles of adults up to approximately 100 micrograms (µg) per day), the risk of adverse health effects from biotin from foods and supplements to the general population was low. However, there were insufficient data to draw conclusions for the safety of high-dose food supplements (SCF, 2001).

The D-A-CH Societies[2] have derived estimated values for adequate intakes of biotin, ranging from 25 to 35 µg per day for children aged four years and older, and of 40 µg per day for adolescents from 15 years of age and adult (D-A-CH, 2020; Table 1).

The European Food Safety Authority (EFSA) has set *Adequate* Intake (AI) values of 25 µg per day for children aged four to ten years, 35 µg per day for adolescents aged 15 to 17 years and 40 µg per day for adults based on observed intakes of biotin in Europe and given that no signs of undersupply were noticed (EFSA, 2014; Table 1).

[1] Tolerable Upper Intake Level = Maximum level of total chronic daily intake of a nutrient (from all sources) considered to be unlikely to pose a risk of adverse health effects to humans.

[2] German-Austrian-Swiss Nutrition Societies

2.2 Exposure

Data on the intake of biotin were determined in the second National Food Consumption Survey (NFCS) II on the basis of two 24-hour recalls by applying the *Multiple Source Method* (MSM). According to this, the median intakes of male and female 15- to 18-year-olds in Germany are at 45 and 36 µg per day, respectively, and those of adult men and women are between 43 and 48 µg per day and between 39 and 42 µg per day, respectively, depending on age (DGE, 2012).

According to the EsKiMo study (nutrition module in KiGGS[3]), children aged six to eleven years consumed a median of between 37.6 and 39.4 µg per day (boys) and between 33.5 and 37.0 µg per day (girls) of biotin. In the 95th percentiles of intake, these children achieved between 112 and 133 µg per day (boys) and between 89.3 and 141.2 µg per day (girls). For 12- to 17-year-old boys and girls, median intakes ranged from 56.4 to 67.2 µg per day and from 49.0 to 52.2 µg per day, respectively; 95th percentiles of intake ranged from 204.6 to 284.2 µg per day and from 230.0 to 288.3 µg per day, respectively, in boys and girls of these age groups (Mensink et al., 2007).

Table 1: Dietary reference values

Age groups	**Estimated values for adequate intake (D-A-CH, 2020)**	**Adequate intake (EFSA, 2014)**
	µg/day	
4 to < 7 years	25	25 (4 to < 11 years)
7 to < 10 years	25	
10 to < 13 years	35	35 (10 to < 18 years)
13 to < 15 years	35	
15 to < 19 years	40	
Adults	40	40 (≥ 18 years)
Pregnant women	40	40
Lactating women	45	45

2.3 Maximum levels for biotin in food supplements and conventional foods

No UL was set for biotin, and no adverse health effects had been observed for amounts commonly ingested from foods and supplements. Based on this state of knowledge, the BfR has supported since 2016 to refrain from setting maximum levels for biotin in food supplements and for fortification of conventional foods.

However, an increased number of case reports of incorrect laboratory values[4] as a result of prior or parallel biotin intake have been reported in recent years, leading to a signal management process in the Pharmacovigilance Risk Assessment Committee (PRAC) of the Euro-

[3] German Health Interview and Examination Survey for Children and Adolescents

[4] Adulteration (false high/positive or false low/negative) may occur in clinical immunoassays based on the principle of streptavidin-biotin interaction and used for the determination of a variety of biomarkers, such as hormones, cardiac, tumor or infection markers, and drug concentrations.

pean Medicines Agency (EMA). The assessment of the available data provided sufficient evidence for possible interactions of oral biotin intakes of 150 µg per day and above (and parenteral intakes of ≥ 60 µg per day) with clinical laboratory testing (EMA, 2019). For doses below 150 µg per day, the risk could not be conclusively assessed due to insufficient data.

Since biotin is predominantly excreted in the urine, patients with renal insufficiency can be expected to have higher biotin concentrations in the blood, longer half-lives and thus an increased risk of clinically significant interactions. The Federal Institute for Drugs and Medical Devices (BfArM) therefore pointed out that special attention is required in the case of high-dose biotin therapy (in the milligram range), in patients with renal insufficiency, as well as in neonates, children and pregnant women (Katić and Bick, BfArM and PEI, 2018).

Based on the PRAC assessment, it was recommended to the EU member states to add a note on observed interactions to the product information of medicinal products (for oral use) containing ≥ 150 µg biotin per dose unit and to include a corresponding warning in the package leaflets of such medicinal products (EMA, 2019). In Germany, the Summary of Product Characteristics for oral medicinal products containing ≥ 150 µg biotin per dose unit (and for parenteral medicinal products containing ≥ 60 µg biotin per dose unit) and the package leaflets of such medicinal products were subsequently updated accordingly[5,6]. Furthermore, recommendations for action have been issued for medical and pharmaceutical personnel and laboratory staff, according to which pharmacists *[should] inform patients about the risk of falsified laboratory values when dispensing products containing biotin, taking into account the diverse areas of application of biotin as medicinal products and food supplements* (Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), May 2019).

Food supplements currently contain daily doses that are sometimes far above 150 µg biotin. Interfering effects on laboratory tests may therefore also be triggered by biotin-containing food supplements. As food supplements are foodstuffs, the obligatory information for biotin-containing preparations in the field of pharmaceuticals does not automatically apply to food supplements. Also, food supplements are sold over-the-counter and are therefore not necessarily dispensed by pharmacies and are usually not taken under medical supervision.

[5] The following text has been added to the **summary of product characteristics**:

4.4. Special warnings and precautions for use

Interference with clinical laboratory tests

Biotin may interfere with laboratory tests that are based on a biotin/streptavidin interaction, leading to either falsely decreased or falsely increased test results, depending on the assay. The risk of interference is higher in children and patients with renal impairment and increases with higher doses. When interpreting results of laboratory tests, possible biotin interference has to be taken into consideration, especially if a lack of coherence with the clinical presentation is observed (e.g. thyroid test results mimicking Graves' disease in asymptomatic patients taking biotin or false negative troponin test results in patients with myocardial infarction taking biotin). Alternative tests not susceptible to biotin interference should be used, if available, in cases where interference is suspected. The laboratory personnel should be consulted when ordering laboratory tests in patients taking biotin.

[6] *[Product name] contains <quantity> biotin per <dose unit>. If you are about to undergo laboratory testing you must tell your doctor or the laboratory personnel that you are taking or have recently taken [Product name], because biotin may affect results of such tests. Depending on the test, the results may be falsely elevated or falsely low due to biotin. Your doctor may ask you to stop taking [Product name] before performing laboratory tests. You should also be aware that other products that you may take, such as multivitamins or supplements for hair, skin, and nails could also contain biotin and affect the results of laboratory tests. Please inform your doctor or the laboratory personnel, if you are taking such products.*

Against this background, the BfR recommends that, in order to reduce the risk of falsification of laboratory values by biotin, a notice should always be affixed to biotin-containing food supplements indicating that persons who have to undergo a laboratory test should inform their doctor or the laboratory staff that they are taking or have recently taken biotin.

Further information on the BfR website on the subject of biotin

Communication on biotin in food supplements: https://www.bfr.bund.de/cm/349/biotin-in-food-supplements-can-influence-laboratory-test-results.pdf

Topic page on the assessment of vitamins and minerals in foods: https://www.bfr.bund.de/en/vitamins_and_minerals-54417.html

"Opinions-App" of the BfR

3 References

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About the BfR

The German Federal Institute for Risk Assessment (BfR) is a scientifically independent institution within the portfolio of the Federal Ministry of Food and Agriculture (BMEL) in Germany. It advises the German federal government and German federal states ("Laender") on questions of food, chemical and product safety. The BfR conducts its own research on topics that are closely linked to its assessment tasks.

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