Discover Food

Review

The biological effects of deuterium present in food

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Abstract

We have evaluated the biological importance of deuterium in foods based on literature data. Deuterium is a stable isotope of hydrogen that occurs naturally in our environment and is specifically enriched in certain foods. Deuterium has specific physical and chemical properties and a high kinetic isotopic effect. Morphological and physiological changes can be observed in cells treated with deuterium, affecting fundamental processes in the body such as cell division or metabolic processes. Deuterium is naturally present in food, food products and liquids and is naturally enriched depending on the type of food. Naturally and typically, there are deuterium-poor and deuterium-rich foods. Our studies have examined the effects of this naturally occurring deuterium in the biological range on the body and concluded that deuterium ingestion is of great importance.

Keywords Food · Nutrition · Deuterium · Isotope · Mitochondria · ATP · Kinetic isotope effect

1 Introduction

Deutenomics is an emerging field of science that studies the biochemical and biophysical changes that occur in living organisms in the presence of deuterium (D). D is a stable isotope of hydrogen. Its natural abundance is ~ 1/6600 hydrogen atoms. D is a rare isotope in nature, with a natural abundance of 155.6 ppm (155.6 D per 1 million hydrogen atoms) in living ocean water. Its nucleus contains one proton and one neutron, leaving its charge unchanged but nearly doubling its mass [1]. This physical difference results in a kinetic isotope effect that affects. In an inanimate environment, the presence of D2O can alter the rate of chemical reactions, making them either faster or slower. Additionally, the magnitude of the resulting isotope effect is also influenced by the ambient temperature [2]. However, the kinetic isotope effect of D causes significant negative alterations in living plant and animal organisms [3]. It has an effect on chemical bonds, chemical reactions, and biochemical processes in the body [4–6]. The aim of our review was to investigate whether deuterium, which occurs naturally in food, has any nutritional significance. A common feature of previous studies on the effect of deuterium on living organisms is that no importance was attached to the natural presence of deuterium, heavy water was used in excess 1000–6000 times [7]. Deuterium is naturally present in food, food products and liquids and is naturally enriched depending on the type of food, due to the different types of plant metabolic pathways naturally and typically, there are deuterium-poor and deuterium-rich foods [8, 9]. The feeding protocol for farm animals also affects the deuterium content in dairy or meat products. The products of agricultural livestock appear on people's tables in various formats as food, making these foods fundamental carriers of deuterium, the amount of which depends on what

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has been described previously. The products of agricultural commodities appear on people's tables as food in various formats, so they are the basic carriers of deuterium, the amount of which depends on what has been written before [10, 11]**.** Nowadays dynamic field of research, the effects of deuterium on the organism are investigated, especially with regard to the amount of deuterium present in the environmental biological range. Investigation the deuterium intake from food and its effects on the human body is crucial for maintaining health in the short and long term, as well as for preserving or enhancing mental and physical activity.

2 Materials and methods

We conducted our research using qualitative internal document analysis based on peer-reviewed literature. The study investigated the presence of deuterium from agricultural production through food to sub-molecular biochemical changes. Literature was searched and evaluated to specifically address biological (115–155 ppm) deuterium concentrations and their impact in our biological system and from food.

3 Results

3.1 Deuterium

The deuterium discovered by Harold Clayton Urey in 1931 [12], who was awarded the Nobel Prize in Chemistry in 1934. The ^{1}H and ^{2}H (D) are hydrogen isotopes, with an occurrence of 99.985 atomic % and 0.015 atomic %, respectively [13]. We should also mention the presence of ^{3}H (tritium), whose natural occurrence is very low, so its effect is minimal and not part of the present study. D is present in a regulated way in the field of medical medicine, in April 2017 the FDA approved the use of deutetrabenazine (deutetrabenazine, 1(d6-tetrabenazine, SD809, SD-809, TEV50717) for the treatment of Huntington's disease [14], but it is also used in medicinal chemistry [15].

3.2 The physical properties

The masses of hydrogen and its stable isotopes, the constituents of the nucleus, are given in Table 1.

The data show that deuterium has almost double the mass of the hydrogen atom. The variation in the mass of the nucleus results in different physical properties, which are shown in Table 2.

D is most found as HDO or D_2O, with a natural occurrence of 0.015% of the hydrogen atoms present in the oceans [18–20]. Deuterium rotation in natural waters shown great variability. The amount of deuterium in Antarctic ice is minimal (Standard Light Antarctic Precipitation, SLAP), $\frac{\text{D SLAP}}{\text{H SLAP}} = -428.5‰$, which corresponds to a concentration of 89 ppm deuterium [21, 22]. The ice sheet in the Northern Hemisphere has higher values for deuterium concentrations. Deuterium content of Greenland ice sheet (Greenland Ice Core Projects, GISP) ice $\frac{\text{D GISP}}{\text{H GISP}} = -189.5‰$ equivalent to 124.6 ppm when converted [23]. The standard for deuterium content in waters is the Vienna Standard Average Ocean Water (VSMOW), $(\frac{\text{D VSMOW}}{\text{H VSMOW}}) = 0.00‰$, which is a deuterium concentration of 155.76 ppm [24–27]**.** The amount of deuterium present in rainwater varies between geographical location and seasons [28, 29]. The amount of deuterium in our natural waters varies, depending on the water cycle [30, 31] and as we move away from the oceans towards the mainland, the deuterium content of rainwater and tap water decreases (taking into account prevailing flow directions and topography) [32, 33]. The different deuterium content of rainwater according to season and geographical location explains the different isotopic composition of freshly squeezed vegetables and fruit juices of different geographical origin [34].

Table 1 Nuclear mass of hydrogen and its stable isotopes [16]

Naming	Marking	Mass (dalton)
Protium	${}_{1}^{1}H$	1.0078250322
Deuterium	${}_{1}^{2}H$	2.0141017782
Tritium	${}_{1}^{3}H$	3.0160492779

Table 2 Comparison of physical properties of molecular forms of hydrogen [17]

	H_2	HD	D_2
The molecular volume of the solid at the triple point (cm3)	23.25	21.84	20.48
triple point (K)	13.96	16.60	18.73
vapour pressure in triple points (mmHg)	54.0	92.8	128.6
boiling point (K)	20.39	22.13	23.67
Heat of fusion at triple point (cal/mol)	28.0	38.1	47.0
heat of vaporization (cal/mol)	216*	257**	293***

* At 20.39 K, ** At 22.54 K, *** At 23.67 K

Owning to the electron distribution of the isotopes is identical, isotopes of hydrogen can participate in identical chemical reactions. The speed of chemical bonds is influenced by the ratio of the masses of the reacting atoms. Chemical reactions that contain identical atoms, but different stable isotopes may exhibit different reaction rates, which is called kinetic isotope effects (KIE). KIE is higher when bonds are formed and broken at the site of isotopic substitution (primary effect), but they are also observed when significant rearrangements occur periphery at a site that undergoes bond change (secondary effect). Both effects of KIE reflect the nature of the energy barrier of the basic chemical reaction [35]. D will behave differently in chemical reactions due to its mass difference. The chemical properties resulting from ESL give rise to differences in biological systems. Deuterium correlates with the photosynthetic pathway. According to the differences in the photosynthesis process, plants are divided into three groups of C3, C4 and CAM types. The primary product of CO_2 fixation is based on four-carbon dicarboxylic acid, therefore this form of CO_2 reduction is called C4-dicarboxylic acid pathway and plants photosynthesizing in this way are called C4 plants. Plants whose primary product of CO2 fixation is three-carbon phosphoglyceric acid are called C3 type plants. In contrast, plants that use Crassulean Acid Metabolism (CAM) may increase the concentration of deuterium in photosynthesis products under certain conditions.

The physiological difference between C3 (for example: green peas, wheat, spinach) and C4 (for example: sugar cane, maize, sorghum crops) is summarized in Table 3.

When comparing plants of type C3 and C4 physiologically, it is necessary to highlight the relatively high intensity of photosynthesis of the latter and the point of light saturation of plants of type C3. The leaves of C3 plants do not take full advantage of the intense radiation of the midday hours of summer days, the intensity of photosynthesis increases only to about 50% of total illumination. In addition, due to increased evaporation, the stomata often close in the midday hours, due to which the supply of CO_2 decreases [37]. C3 and C4 plants differ not only in leaf tissue structure and CO_2 fixation mechanism, but also in the amount of D present in plant parts. Based on Ziegler's research, the average δD values of C3 plants are – 132 ‰ for shoots and – 117 ‰ for roots. For C4 plants, the mean δD values are – 91‰ in shoots and – 77‰ in roots. For roots and shoots of CAM plants, the δD value is – 75‰ lower than the SMOW (155 ppm) [38]. C3 plants have a lower deuterium content than C4 and CAM plants what shown in the following calculation in ppm.

The above values have been converted in ppm according to the following formula for easy comparison, then we get the following results, which are shown in Table 4.

Table 3 Comparison of some physiological indicators of C3 and C4 plants [36]

Physiological indicator	Plants	
	C3	C4
The primary CO2 fixation enzyme	RuDP- carboxylase	PEP-carboxylase
Light saturation point	Full illumination 25–50%	Practically none
CO_2-compensation point, ppm CO_2	30–70	0–10
Maximum net photosynthesis intensity, CO_2 mg · dm – 2 · h – 1	15–40	40–80
The optimum temperature for photosynthesis	15–25 °C	30–47 °C
Photorespiration	active	Unlikely
Pure photosynthesis productivity, dry matter g · dm – 2 · d – 1	0.5–2	4–5
Transspiration coefficient, g water/g dry matter	450–950	250–350
Annual dry matter production, t/10,000 m2	22.0 ± 3.3	38.6 ± 16.9

Table 4 Average content D of shoots and roots of C3, C4 and CAM plants (own edit)

Part of plant	Quantity of D (ppm)
Average content D of C3plant shoots	134.540
Average D content of C3 plant roots	136.865
Average content D of C4 plant shoots	140.895
Average D content of C4 plant roots	143.065
Average content D of CAM plant shoots	143.375
Average D content of CAM plant roots	143.375

Table 5 Average D content of food [92, 93]

Food	D (ppm)
Water from cottage cheese	151
Flour	150
Sugar	146
Cabbage	142
Potato	142
Wheat grain	142
Oat grain	141
Carrot	141
Pork	137
Beef	137
Chicken	136
Cottage cheese	136
Sunflower oil	130
Olive oil	130
Butter	125
Butter	124
Beef fat	121
Pork lard	118
Pork lard	116

$$\delta H = \left(\frac{\frac{D}{H} sample}{\frac{D}{H} s\tan dard} - 1 \right) * 10^3 \tag{1}$$

$$\frac{D}{H} sample = \left(\frac{\delta H}{10^3} + 1 \right) * \frac{D}{H} s\tan dard \tag{2}$$

It is important to point out that the above table concerned the shoots and roots of the plant, not its crop. This difference is well demonstrated by wheat. Wheat belongs to the C3 group of plants, and the meal made from its fruits still has a high deuterium content, which is shown in Table 5. The relationship between the photosynthetic system of plants and the stable isotope ratio can also be measured in the cellulose of the plant and has the same trend result as above [39]. Starch and cellulose are both glucose polymers made by plants either from glucose made by photosynthesis in the leaves or from sucrose transported from the leaves through the vascular system. However, there are differences. Cellulose made from β-D glucose and starch made from α-D glucose. The site of starch synthesis is chloroplast, and the site of cellulose synthesis is outer surface of cell membrane. The structure of starch is also different from cellulose. Starch encloses water in itself. There is type A starch and type B starch and a mixture of both. Type "A" contains 8 molecules of water, type "B" contains 36 molecules of water [40]. In addition to these differences, it should be noted that recently among animal tissues, the level of proline abnormal D has been published [41]. This fractionation process is not yet fully explored and requires further investigation but based on the data published in the reviewed literature, the authors agree that fractionation D must take place, which requires isotopic studies under in vivo conditions. Similarly, it was previously unknown what caused the difference between the sensitivity of tonoplast ATPase and plasma membrane ATPase to nitrate receptors between proton pumps in plant cells, but it getting better described nowadays [42, 43]. Wheat also contains ~ 10–12% protein and ~ 2% fat [44, 45]**.**

The feeding protocol of farm animals, the composition of their feed and the geographical origin are different. The composition of today's feed mixtures includes a mixture of C3, C4 and CAM plant derivatives and cereals [46]. As a result of the mixed composition, e.g. the use of cereal grains increases the D content of otherwise lower green fodder. The metabolic effects on cattle of the conventional feed protocol excluding D content of feeds and the lower D feeding protocol were described in detail in our previous publication [47].

3.3 Effects of deuterium on living organisms

Water present in living animal (human) tissues enters the body in two ways, through drinking and metabolism of food substrates. The nutrient entering the cells via the metabolic route is oxidized to CO_2. Its hydrogens are transferred to transfer molecules (NAD +, FAD), which are temporarily reduced, and then oxygen is reduced to water with the received hydrogen. At the expense of the energy released in this way, ADP is phosphorylated to ATP. The cleavage of ATP terminal phosphate groups serves as an energy source for various energy-intensive processes.

Primary source D is dietary intake of water produced during metabolism of food substrates, including a reduced form of nicotinamide adenine dinucleotide (NAD) in the mitochondrial respiratory chain [48–51]. If D is involved in a chemical bond instead of protium, it will split 6–10 times more slowly [52–55]. If D is integrated into the double-stranded DNA molecule, then the kinetic isotope effect affects the rate of fission, depending on which C atom it is located on. This speed is 1.67X slower in 5' position and 1.14X slower in 3' position [56]. It is important to note that if D substitutes hydrogen for the 5'-carbon of ribose on the GUA base triple, a significant 5'-deuterium kinetic isotope effect can be observed at fission on U. Ingle et al. concluded that this hydrogen bond contributes to the rigidity and stability of the structural framework [57].

The binding site of D on molecules also shows characteristic features on biologically synthesized molecules. For example, methyl linoleate isolated from peanut oil has a different distribution of deuterium at different places in the carbon chain. The deuterium concentration of the hydrogen atom bound to the 7th carbon atom is ~ 99, the 8th ~ 137, the 9th ~ 63 ppm, the 10th ~ 137 ppm, the 11th ~ 99 ppm, the 12th ~ 137 ppm, and the 13th ~ 62 ppm. Difference and regularity are also observed on capsaicin. The average value of D for the acetate derivative 6,7-dihydrocapsaicin (136.8 ppm: C3–C6: the significantly higher amount of D than the portion derived from valine (110.2 ppm: C7–C10). This is compatible with the fact that the latter is the result of a relatively long biosynthesis, during which general D impoverishment is likely [58, 59]. In fact, the variation within this section can also be interpreted in relation to the biosynthesis of valine, so that the least impoverished C8 enters at a late stage of biosynthesis, while the methyl groups C9 and C10 derived from pyruvate methyl remained unchanged [60]. This frequency shows that the concentration and occurrence of D is determined and controlled, not random.

The is difference in in the world of living beings, and prokaryotes and eukaryotes [61, 62]. Another significant difference is that deuterated hydrogen bonds are somewhat stronger than those formed with protium [63].

The formation of hydrogen bonds is of critical importance to the function, folding, and tertiary structure formation of biological macromolecules. The presence of heavy water has been observed to disrupt the function of the "spindle fibres" (mitotic spindles), which play an essential role in mitotic cell division in eukaryotic organisms. The growth of plants that are solely watered with heavy water is arrested. Seeds fail to germinate because heavy water prevents cell division in eukaryotic cells. In contrast, mitotic problems do not occur in prokaryotic organisms, such as bacteria. These organisms can grow and reproduce even in a completely deuterated environment, while their proteins and DNA fully replace their hydrogen atoms with deuterium atoms [64].

Among the processes taking place through the cell membrane, the Na + /H + pump is of great importance. The ion pump, when activated, takes a Na + atom from outside the cell while giving up an H + atom from inside the cell, so a pH shift occurs within the cell in an alkaline direction. This process can be activated by growth hormone that stimulates cell division. As the H concentration decreases, the D/H ratio within the cell also changes, because the cell removes the more easily mobilizable H + atom (half the mass), and the D/H ratio within the cell shifts towards D [65–68]. The increase in the ratio of D and H atoms is contributed by the fact that the enzyme ATPase distinguishes between isotopes, does not accept it as a substrate, and retains D in the cell [69], but cell sensitivity to D during H + transport has also been observed in aquatic plants [70]. The entry molecule of the Szent-Györgyi-Krebsz cycle in the mitochondria is acetyl-CoA, which has 2–2 C atoms and bonded hydrogen atoms. When nutrients are digested, the most important carbohydrate derivative is glucose, and fatty acids are released from lipids. In the cytosol, pyruvate formed during the breakdown of glucose—glycolysis—enters the mitochondria, and there it is converted to acetyl-CoA in a reaction catalyzed by the pyruvate dehydrogenase enzyme complex. Acetyl-CoA is also formed during fatty acid oxidation. The C atoms of the acetyl group of acetyl-CoA oxidize to CO_2 in the citrate cycle, and the hydrogens enter the electron transfer chain of terminal oxidation as NADH + , H + and $FADH_2$ and finally participate in the reduction of oxygen to water. The vast majority of amino acids produced during protein breakdown are also converted to pyruvate, acetyl-CoA, and citrate cycle intermediates. In oxidative phosphorylation coupled to terminal oxidation, ADP is phosphorylated to ATP.

During different phases of growth, a continuous decrease in the deuterium concentration of intracellular water was observed in the prokaryote *Escherichia coli*. [71]. During the steps of the Szent-Györgyi–Krebs cycle, the organism strives to keep the deuterium content of intracellular water as low, with the main source being the water produced during metabolic oxidation. The deuterium content of the water generated during metabolic oxidation depends on the deuterium content of the molecules entering the cycle [72]. The entering molecules D concertation are food dependent. Moreover, during the oxidation of glucose, metabolic water with a higher deuterium level is produced. A carbohydrate-rich diet has been observed to result in the formation of metabolic water with a deuterium concentration of approximately 155.75 parts per million (ppm). The oxidation of fats and lipids by mitochondria has been shown to result in the production of metabolic water with a deuterium concentration of 118 ppm [73].

Due to the different D concentration of foods, it follows that the molecule entering the cycle will also have different D content, and during the biochemical cycle the D content of the resulting metabolic water will also be different. Foods with high D content will produce high levels of D metabolism, so the cell cannot compensate for the higher D/H ratio associated with an increase in cell pH, which favors uncontrolled division of cancer cells [74]. The possible high deuterium content of acetyl-CoA entering causes damage to the entire citric acid cycle [75]. The importance of D is also expressed in the efficiency of the production of ATP integrated into the membrane of the mitochondria present in our cells [76, 77]. ATP synthase is capable of special selection [78], but above a certain content D, the efficiency of filtering decreases [79]. Studies on bovine heart muscle showed that mitochondrial ATP synthase was impaired by deuterium and that the degree of damage was dose dependent [80]. This damage is due to the biological effects of deuterium on mitochondrial ATP synthase [81].

Part of the hydrogen present in living organisms (hydrogen atoms linked to oxygen, sulphur, nitrogen) is rapidly exchanged for deuterium in heavy water. One consequence of this is that hydrogen bridges, which are primarily responsible for the stability of proteins, are replaced by deuterium bridges. The resulting bonds are stronger than the hydrogen bonds originally formed with protium. This may explain why proteins are more stable in heavy water and more resistant to denaturation and conformational changes. Many biological processes, including DNA replication, DNA repair, and cytochrome P450 enzymatic reactions, operate at a rapid pace that are sensitive to kinetic isotope action [82, 83]**.** Many biological processes, including DNA replication, DNA repair and cytochrome P450 enzymatic reactions, operate at a fast rate that is sensitive to kinetic isotope effects. Low deuterium content can reduce DNA damage, and the incidence of single-strand breaks associated with cancer mutations [84, 85]. Also observed are the effects of DDW on nucleic acids, including its ability to increase the intensity of mitochondrial activity and autophagy, and to alter the transcriptomic pattern of miRNA in cells in some tumors. In addition, DDW reduces the number of single-stranded DNA breaks and modifies the miRNA profile.

A detailed discussion of deuterium biology can be found in Basov et al., 2019 article [86], which we herein reiterate using a deutenomics narrative developed for translational sciences [87] as follows. The presence of D in the agricultural and food verticals is significant. The feeding of farm animals, the composition of feed (D content—C3/C4/CAM plants and their crops and grain ratio) has a major impact on the biochemical balance of the animal. Glycogen substrates used by grain-fed animals, such as cornstarch, branched-chain amino acids and odd-chain fatty acids, are inherently higher in D [88], associated with cell proliferative disorders [72, 89]. Furthermore, branched-chain amino acids (leucine, isoleucine and valine) with a higher content (> 140 ppm) D in animals fed with artificially mixed grain are present in significant quantities [90] enter the citric acid cycle via succinic acid, which triggers expression of methylmalonyl-CoA mutase genes in mitochondria. In the case of lactating cattle, when synthetic feeds and seed mixtures are used, the essential branched-chain amino acid raw materials (leucine, isoleucine and valine, methionine, threonine and thymine) and the odd-chain, longer-chain fatty acid derivatives of the fed animals will have a higher D content [47].

D content has a natural distribution in foods [91]. Typically, there are foods and drinks with lower and higher D content, which are summarized in Table 5.

Based on Table 5, with proper choice of food, it is possible to reduce the amount of D entering the body, which is directly related to the load D on the body. It is important to note that with a normal diet, the water content of the food will prevail at the D-concentration of the local environment. This is not the only factor that influences the final concentration of D in the body, since the organic molecules of nutrients also contain protium and deuterium, which appear in metabolic water after oxidation of mitochondria.

Nowadays, more and more forward-looking research has been published that has successfully used the reduction of the amount of D entering the body as a treatment for various cancers. In 1921, it was reported that acetone and beta-hydroxybutyric acid appear in normal subjects under the influence of starvation or a diet that is too low in carbohydrates and too high in fat [94]. At this time, more attention was paid to the direction of fasting than possible to cure certain diseases. Dr. Wilder at the Mayo Clinic suggested that the benefits of fasting can be achieved when ketosis in the body is produced in another way, rather than through fasting [95]. The method had positive results during the treatment of epilepsy patients and the term ketogenic diet was created, which is based on the fact that 1 g of protein per kilogram of body weight, a total of 10–15 g of carbohydrates, and the remaining amount of energy is provided from fat [96]. The ketogenic diet has been used with high efficiency as an adjunct to cancer treatment. [97, 98]. Based on the proven anticancer effect of DDW, it is hypothesized that the beneficial effect of the ketogenic diet in cancer cases is due to its deuterium-depleting effect, since mitochondria oxidize fats instead of carbohydrates to produce metabolic water with a D content of 118 ppm. In a study conducted in vivo mice, it was concluded that the anticancer effect of DDW was enhanced by consumption of a deuterium-depleted diet. Naturally low D-content lipids in the ketogenic diet have a significant effect on tumor growth by preventing cells from raising the D/H ratio in an unfavorable direction [99].

4 Conclusion

Foods (both dry matter and water content) have a well-defined and quantifiable D content, depending on the type of food, its origin and where it is grown. Dietary D affects the efficiency of ATP production through metabolic pathways, the natural synthesis of various organic substances, or the regulation of cell division. The ketogenic diet has been used successfully in the treatment of certain cancers, where the state of ketosis is induced by animal fats, which are naturally low in D (due to a longer synthesis pathway). Reducing the amount of D in foods and beverages in the diet has a beneficial effect in the treatment of some cancers.

Our research has led us to conclude that the deuterium content of foods in the diet is of significant importance for both short- and long-term health maintenance and physical performance.

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Data availability No datasets were generated or analysed during the current study.

Declarations

Competing interests The authors declare no competing interests.

References

1. Urey HC. The separation and properties of the isotopes of hydrogen. Science. 1933;78(2034):566–71.
2. Wiberg KB. The deuterium isotope effect. Chem Rev. 1955;55(4):713–43.
3. Kselíková V, Vítová M, Bišová K. Deuterium and its impact on living organisms. Folia Microbiol. 2019;64:673–81.
4. Fukuzumi S, Lee YM, Nam W. Deuterium kinetic isotope effects as redox mechanistic criterions. Bull Korean Chem Soc. 2021;42(12):1558–68.
5. Simmons EM, Hartwig JF. On the interpretation of deuterium kinetic isotope effects in C H bond functionalizations by transition-metal complexes. Angew Chem Int Ed. 2012;51(13):3066–72.
6. Westheimer FH. The magnitude of the primary kinetic isotope effect for compounds of hydrogen and deuterium. Chem Rev. 1961;61(3):265–73.
7. Somlyai G, Molnár M, Laskay G, Szabó M, Berkényi T, Guller I, Kovács A. Biological significance of naturally occurring deuterium: the antitumor effect of deuterium depletion. Orv Hetil. 2010;151:1455–60. https://doi.org/10.1556/oh.2010.28865.
8. Fleischer U, Kutzelnigg W, Limbach HH, Martin GJ, Martin ML, Schindler M. Deuterium and shift calculation (Vol. 23). Springer Science & Business Media. 2012.
9. Krumbiegel P. Large deuterium isotope effects and their use: a historical review. Isot Environ Health Stud. 2011;47(1):1–17.
10. Korchinsky N, Davis AM, Boros LG. Nutritional deuterium depletion and health: a scoping review. Metabolomics. 2024;20(6):117.
11. Wilkinson GM, Cole JJ, Pace ML. Deuterium as a food source tracer: sensitivity to environmental water, lipid content, and hydrogen exchange. Limnol Oceanogr Methods. 2015;13(5):213–23.
12. Urey HC, Brickwedde FG, Murphy GM. A hydrogen isotope of mass 2 and its concentration. Phys Rev. 1932;40:1. https://doi.org/10.1103/PhysRev.40.1.
13. West JB, Bowen GJ, Cerling TE, Ehleringer JR. Stable isotopes as one of nature's ecological recorders. Trends Ecol Evol. 2006;21:408–14. https://doi.org/10.1016/j.tree.2006.04.002.
14. FDA Reference ID: 4078379. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/208082s000lbl.pdf.
15. Pirali T, Serafini M, Cargnin S, Genazzani AA. Applications of deuterium in medicinal chemistry. J Med Chem. 2019;62:5276–97. https://doi.org/10.1021/acs.jmedchem.8b01808.
16. US National Institute of Standards and Technology (NIST) Values for Deuterium Mass 12H, Proton Rest Mass mp, and Neutron Rest Mass mn. https://physics.nist.gov/cgi-bin/Compositions/stand_alone.pl?ele=H.
17. Britannica T. "deuterium". Encyclopedia Britannica, 14 Jul. 2023, 2022. https://www.britannica.com/science/deuterium. Accessed 10 August 2023.
18. Friedman I. Deuterium content of natural waters and other substances. Geochim Cosmochim Acta. 1953;4:89–103. https://doi.org/10.1016/0016-7037(53)90066-0.
19. Schiegl WE, Vogel JC. Deuterium content of organic matter. Earth Planet Sci Lett. 1970;7:307–13. https://doi.org/10.1016/0012-821X(69)90041-7.
20. Rosman K, Taylor P. Isotopic compositions of the elements 1997 (Technical Report). Pure Appl Chem. 1998;70:217–35. https://doi.org/10.1351/pac199870010217.
21. De Wit JC, Van der Straaten CM, Mook WG. Determination of the absolute hydrogen isotopic ratio of V-SMOW and SLAP Geostand. Geoanalytical Res. 1980;4:33–6. https://doi.org/10.1111/j.1751-908X.1980.tb00270.x.
22. Genda H. Origin of Earth's oceans: an assessment of the total amount, history and supply of water. Geochem J. 2016;50:27–42. https://doi.org/10.2343/geochemj.2.0398.
23. Hut G. Consultants' group meeting on stable isotope reference samples for geochemical and hydrological investigations International Atomic Energy Agency, Vienna (Austria). 1987.
24. Magdas DA, Feher I, Dehelean A, Cristea G, Magdas TM, Puscas R, Marincaş O. Isotopic and elemental markers for geographical origin and organically grown carrots discrimination. Food Chem. 2018;267:231–9. https://doi.org/10.1016/j.foodchem.2017.10.048.
25. Bykov MI, Dzhimak SS, Basov AA, Arcybasheva OM, Shashkov D, Baryshev MG. Comparative characteristics of the isotopic D/H composition and antioxidant activity of freshly squeezed juices from fruits and vegetables grown in different geographical regions. Vopr Pitan. 2015;84:89–96.
26. Hagemann R, Nief G, Roth E. Absolute isotopic scale for deuterium analysis of natural waters. Absolute D/H ratio for SMOW. Tellus. 1970;1(22):712–5. https://doi.org/10.1111/j.2153-3490.1970.tb00540.x.
27. IAEA. Reference sheet for international measurement standards. 2009.
28. Bershaw J. Controls on deuterium excess across. Asia Geosci. 2018;8:257. https://doi.org/10.3390/geosciences8070257.
29. Ehhalt D, Knott K, Nagel JF, Vogel JC. Deuterium and oxygen 18 in rain water. J Geophys Res. 1963;68:3775–80. https://doi.org/10.1029/JZ068i013p03775.
30. Good SP, Noone D, Kurita N, Benetti M, Bowen GJ. D/H isotope ratios in the global hydrologic cycle. Geophys Res Lett. 2015;42:5042–50. https://doi.org/10.1002/2015GL064117.
31. Bowen GJ. A faster water cycle. Science. 2011;332:430–1. https://doi.org/10.1126/science.1205253.
32. Bowen GJ, Ehleringer JR, Chesson LA, Stange E, Cerling TE. Stable isotope ratios of tap water in the contiguous United States. Water Resour Res. 2007. https://doi.org/10.1029/2006WR005186.
33. Craig H. Isotopic variations in meteoric waters. Science. 1961;133:1702–3. https://doi.org/10.1126/science.133.3465.1702.
34. Magdas DA, Puscas R. Stable isotopes determination in some Romanian fruit juices. Isotopes Environ Health Stud. 2011;47:372–8. https://doi.org/10.1080/10256016.2011.600454.
35. Roth JP, Klinman JP. Kinetic isotope effects. 2004;522–527, ISBN 9780124437104.
36. Black CC Jr. Photosynthetic carbon fixation in relation to net CO2 uptake. Ann Rev Pl Phys. 1973;24:253–86. https://doi.org/10.1146/annurev.pp.24.060173.001345.
37. Pethő M. Mezőgazdasági növények élettana. Akadémiai Kiadó. 2006. https://doi.org/10.1556/9789630598316.

38. Ziegler H, Osmond CB, Stichler W, Trimborn P. Hydrogen isotope discrimination in higher plants: correlations with photosynthetic pathway and environment. Planta. 1976;128:85–92.
39. Sternberg LO, Deniro MJ, Johnson HB. Isotope ratios of cellulose from plants having different photosynthetic pathways. Plant Physiol. 1984;74:557–61. https://doi.org/10.1104/pp.74.3.557.
40. Galliard T. Starch: properties and potential. (No Title). 1987.
41. Gharibi H, Chernobrovkin AL, Eriksson G, Saei AA, Timmons Z, Kitchener AC, et al. Abnormal (hydroxy) proline deuterium content redefines hydrogen chemical mass. J Am Chem Soc. 2022;144(6):2484–7.
42. Han Y, Liu Q, Gu J, Gong J, Guan C, Lepo JE, et al. V-ATPase and V-PPase at the Tonoplast Affect NO 3− content in Brassica napus by controlling distribution of NO 3− between the cytoplasm and vacuole. J Plant Growth Regul. 2015;34:22–34.
43. Migocka M, Warzybok A, Papierniak A, Kłobus G. NO3−/H+ antiport in the tonoplast of cucumber root cells is stimulated by nitrate supply: evidence for a reversible nitrate-induced phosphorylation of vacuolar NO3−/H+ antiport. PLoS ONE. 2013;8(9): e73972.
44. Shewry PR. Wheat. J Exp Bot. 2009;60(6):1537–53.
45. Kumar P, Yadava RK, Gollen B, Kumar S, Verma RK, Yadav S. Nutritional contents and medicinal properties of wheat: a review. Life Sci Med Res. 2011;22(1):1–10.
46. Halmemies-Beauchet-Filleau A, Rinne M, Lamminen M, Mapato C, Ampapon T, Wanapat M, Vanhatalo A. Alternative and novel feeds for ruminants: nutritive value, product quality and environmental aspects. Animal. 2018;12(s2):s295–309.
47. Lech JC, Dorfsman SI, Répás Z, Krüger TP, Gyalai IM, Boros LG. What to feed or what not to feed-that is still the question. Metabolomics. 2021;17:1–6.
48. Kohn MJ. Predicting animal δ18O: accounting for diet and physiological adaptation. Geochim Cosmochim Acta. 1996;60:4811–29. https://doi.org/10.1016/S0016-7037(96)00240-2.
49. Podlesak DW, Bowen GJ, O'Grady S, Cerling TE, Ehleringer JR. δ2H and δ18O of human body water: a GIS model to distinguish residents from non-residents in the contiguous USA. Isotopes Environ Health Stud. 2012;48:259–79. https://doi.org/10.1080/10256016.2012.644283.
50. Podlesak DW, Torregrossa A, Ehleringer JR, Dearing MD, Passey BH, Cerling TE. Turnover of oxygen and hydrogen isotopes in the body water, CO2, hair, and enamel of a small mammal. Geochim Cosmochim Acta. 2008;72:19–35. https://doi.org/10.1016/j.gca.2007.10.003.
51. Li H, Yu C, Wang F, Chang SJ, Yao J, Blake RE. Probing the metabolic water contribution to intracellular water using oxygen isotope ratios of PO4. Proc Natl Acad Sci. 2016;113:5862–7. https://doi.org/10.1073/pnas.1521038113.
52. Van Hook A. Kinetic isotope effects: introduction and discussion of the theory. In: CJ Collins, NS Bowman (eds). Isotope effects in chemical reactions. 1971, pp. 20–35.
53. Rundel PW, Ehleringer JR, Nagy KA. Stable isotopes in ecological research. Springer Science & Business Media. 2012.
54. Jancsó G. Isotope effects. In: Vértes A, Nagy S, Klencsár Z, editors. Handbook of nuclear chemistry, vol. 2. Dordrecht: Kluwer Academic Publishers; 2003. p. 85–116.
55. Evans BR, Shah R. Development of approaches for deuterium incorporation in plants. Meth Enzymol. 2015;565:213–43. https://doi.org/10.1016/bs.mie.2015.07.014.
56. Balasubramanian B, Pogozelski WK, Tullius TD. DNA strand breaking by the hydroxyl radical is governed by the accessible surface areas of the hydrogen atoms of the DNA backbone. Proc Natl Acad Sci. 1998;95:9738–43. https://doi.org/10.1073/pnas.95.17.9738.
57. Ingle S, Azad RN, Jain SS, Tullius TD. Chemical probing of RNA with the hydroxyl radical at single-atom resolution. Nucleic Acids Res. 2014;42:12758–67. https://doi.org/10.1093/nar/gku934.
58. HL S. Non-statistical isotope distribution in natural compounds: mirror for their biosynthesis and key for their origin assignment Stable isotopes in the biosphere. 1995.
59. Schmidt H, Werner RA, Eisenreich W. Systematics of 2 H patterns in natural compounds and its importance for the elucidation of biosynthetic pathways. Phytochem Rev. 2003;2:61–85.
60. Robins RJ, Billault I, Duan J, Guiet S, Pionnier S, Zhang B. Measurement of 2 H distribution in natural products by quantitative 2 H NMR: an approach to understanding metabolism and enzyme mechanism? Phytochem Rev. 2003;2:87–102. https://doi.org/10.1023/B:PHYT.0000004301.52646.a8.
61. Katz JJ, Crespi HL. Deuterated organisms: cultivation and uses: living organisms of unusual isotopic composition can be used for magnetic resonance studies. Science. 1966;151(3715):1187–94.
62. Nett RS, Guan X, Smith K, Faust AM, Sattely ES, Fischer CR. D2O labeling to measure active biosynthesis of natural products in medicinal plants. AIChE J. 2018;64(12):4319–30.
63. Katz JJ. Chemical and biological studies with deuterium (Vol. 39). Pennsylvania State University. 1965.
64. Richet P, Bottinga Y, Janoy M. A review of hydrogen, carbon, nitrogen, oxygen, sulphur, and chlorine stable isotope enrichment among gaseous molecules. Annu Rev Earth Planet Sci. 1977;5:65–110.
65. Pouyssegur J, Chambard JC, Franchi A, Paris S, Van Obberghen-Schilling E. Growth factor activation of an amiloride-sensitive Na /H exchange system in quiescent fibroblasts: coupling to ribosomal protein S6 phosphorylation. Proc Natl Acad Sci. 1982;79:3935–9. https://doi.org/10.1073/pnas.79.13.3935.
66. Pouysségur J, Sardet C, Franchi A, L'Allemain G, Paris S. A specific mutation abolishing Na /H antiport activity in hamster fibroblasts precludes growth at neutral and acidic pH. Proc Natl Acad Sci. 1984;81:4833–7. https://doi.org/10.1073/pnas.81.15.4833.
67. Perona R, Serrano R. Increased pH and tumorigenicity of fibroblasts expressing a yeast proton pump. Nature. 1988;334:438–40.
68. Somlyai G, Jancsó G, Jákli G, Vass K, Barna B, Lakics V, Gaál T. Naturally occurring deuterium is essential for the normal growth rate of cells. FEBS Lett. 1993;317:1–4. https://doi.org/10.1016/0014-5793(93)81479-J.
69. Kotyk A, Dvořáková M, Koryta J. Deuterons cannot replace protons in active transport processes in yeast. FEBS Lett. 1990;264:203–5. https://doi.org/10.1016/0014-5793(90)80248-H.
70. Laskay G, Somlyai G, Jancsó G. Reduced deuterium concentration of water stimulates O2-uptake and electrogenic H -efflux in the aquatic macrophyte Elodea Canadensis. Jpn J Deuterium Sci. 2001;10:17–23.
71. Kreuzer-Martin HW, Lott MJ, Ehleringer JR, Hegg EL. Metabolic processes account for the majority of the intracellular water in log-phase *Escherichia coli* cells as revealed by hydrogen isotopes. Biochemistry. 2006;45(45):13622–30.

72. Boros LG, D'Agostino DP, Katz HE, Roth JP, Meuillet EJ, Somlyai G. Submolecular regulation of cell transformation by deuterium depleting water exchange reactions in the tricarboxylic acid substrate cycle. Med Hypotheses. 2016;87:69–74. https://doi.org/10.1016/j.mehy.2015.11.016.
73. Somlyai G, Nagy LI, Puskás LG, Papp A, Kovács BZ, Fórizs I, et al. Deuterium content of the organic compounds in food has an impact on tumor growth in mice. Curr Issues Mol Biol. 2022;45(1):66–77.
74. Somlyai G. Deuterium depletion: a new way in curing cancer and preserving health. ATP Ltd. 2022;60.
75. Yang Y, Lane AN, Ricketts CJ, Sourbier C, Wei M, Shuch B, Pike L, Wu M, Rouault TA, Boros LG. Metabolic reprogramming for producing energy and reducing power in fumarate hydratase null cells from hereditary leiomyomatosis renal cell carcinoma. PLoS ONE. 2013;8: e72179. https://doi.org/10.1371/journal.pone.0072179.
76. Boros LG. Biological Nanomechanics: ATP Synthesis and Deuterium Depletion, Jo Anne Brasel Basic Science Seminar – Los Angeles Biomedical research Institute at the Harbor-UCLA Medical Center. 2016.
77. Dorgan LJ, Schuster SM. The effect of nitration and D2O on the kinetics of beef heart mitochondrial adenosine triphosphatase. J Biol Chem. 1981;256:3910–6. https://doi.org/10.1016/S0021-9258(19)69545-1.
78. Robins RJ, Remaud GS, Billault I. Natural mechanisms by which deuterium depletion occurs in specific positions in metabolites. Eur Chem Bull. 2012;1:39–40.
79. Bernardi P, Rasola A, Forte M, Lippe G. The mitochondrial permeability transition pore: channel formation by F-ATP synthase, integration in signal transduction, and role in pathophysiology. Physiol Rev. 2015;95:1111–55. https://doi.org/10.1152/physrev.00001.2015.
80. Urbauer JL, Dorgan LJ, Schuster SM. Effects of deuterium on the kinetics of beef heart mitochondrial ATPase. Arch Biochem Biophys. 1984;231:498–502. https://doi.org/10.1016/0003-9861(84)90413-2.
81. Olgun A. Biological effects of deuteronation: ATP synthase as an example. Theor Biol Med Model. 2007;4:1–4. https://doi.org/10.1186/1742-4682-4-9.
82. Guengerich FP. Kinetic deuterium isotope effects in cytochrome P450 reactions. In: Anonymous Methods in enzymology, Elsevier, 2017; 217–238. https://doi.org/10.1016/bs.mie.2017.06.036.
83. Alexander M. Dependence of the enzymatic velocity on the substrate dissociation rate. J Phys Chem. 2017;121:3437–42.
84. Chira S, Raduly L, Braicu C, Jurj A, Cojocneanu-Petric R, Pop L, Pileczki V, Ionescu C, Berindan-Neagoe I. Premature senescence activation in DLD-1 colorectal cancer cells through adjuvant therapy to induce a miRNA profile modulating cellular death. Exp Ther Med. 2018;16:1241–9. https://doi.org/10.3892/etm.2018.6324.
85. Lajos R, Braicu C, Jurj A, Chira S, Cojocneanu-Petric R, Pileczki V, Berindan-Neagoe I. A miRNAs profile evolution of triple negative breast cancer cells in the presence of a possible adjuvant therapy and senescence inducer. J BUON. 2018;8(10):692–705.
86. Basov A, Fedulova L, Baryshev M, Dzhimak S. Deuterium-depleted water influence on the isotope 2H/1H regulation in body and individual adaptation. Nutrients. 2019;8:1903.
87. Boros LG, Seneff S, Túri M, Palcsu L, Zubarev RA. Active involvement of compartmental, inter-and intramolecular deuterium disequilibrium in adaptive biology. Proc Natl Acad Sci. 2024;121(37): e2412390121.
88. Schleucher J, Vanderveer P, Markley JL, Sharkey TD. Intramolecular deuterium distributions reveal disequilibrium of chloroplast phosphoglucose isomerase. Plant, Cell Environ. 1999;22:525–33. https://doi.org/10.1046/j.1365-3040.1999.00440.x.
89. Boros LG, Collins TQ, Somlyai G. What to eat or what not to eat—that is still the question. Neuro Oncol. 2017;19:595–6. https://doi.org/10.1093/neuonc/now284.
90. Lecchi P, Abramson FP. An innovative method for measuring hydrogen and deuterium: chemical reaction interface mass spectrometry with nitrogen reactant gas. J Am Soc Mass Spectrom. 2000;11:400–6. https://doi.org/10.1016/S1044-0305(00)00103-3.
91. Markai S, Marchand PA, Mabon F, Baguet E, Billault I, Robins RJ. Natural deuterium distribution in branched-chain medium-length fatty acids is nonstatistical: a site-specific study by quantitative 2H NMR spectroscopy of the fatty acids of capsaicinoids. ChemBioChem. 2002;3:212–8. https://doi.org/10.1002/1439-7633(20020301)3:2/3%3c212::AID-CBIC212%3e3.0.CO;2-R.
92. Boros LG. Basic-Science-Brasel April28 2015 D2O-H2O H-bonding-posted. 2015. https://www.researchgate.net/profile/Laszlo-Boros-2/publication/275769534_Basic-Science-Brasel_April28_2015_D2O-H2O_H-bonding-posted/links/5546207a0cf234bdb21d8a1a/Basic-Science-Brasel-April28-2015-D2O-H2O-H-bonding-posted.pdf.
93. Basov AA, Bykov IM, Baryshev MG, Dzhimak SS, Bykov MI. Determination of deuterium concentration in foods and influence of water with modified isotopic composition on oxidation parameters and heavy hydrogen isotopes content in experimental animals. Vopr Pitan. 2014;83(5):43–50.
94. Woodyatt RT. Objects and method of diet adjustment in diabetes. Arch Intern Med. 1921;28:125–41. https://doi.org/10.1001/archinte.1921.00100140002001.
95. Wilder RM. The effect on ketonemia on the course of epilepsy. Mayo Clin Bull. 1921;2:307–8.
96. Peterman MG. The ketogenic diet in epilepsy. J Am Med Assoc. 1925;84:1979–83. https://doi.org/10.1001/jama.1925.02660520007003.
97. Seyfried TN, Flores RE, Poff AM, D'Agostino DP. Cancer as a metabolic disease: implications for novel therapeutics. Carcinogenesis. 2014;35:515–27. https://doi.org/10.1093/carcin/bgt480.
98. Zhou W, Mukherjee P, Kiebish MA, Markis WT, Mantis JG, Seyfried TN. The calorically restricted ketogenic diet, an effective alternative therapy for malignant brain cancer Nutr. Metab. 2007;4:1–15. https://doi.org/10.1186/1743-7075-4-5.
99. Somlyai G, Nagy LI, Puskás LG, Papp A, Kovács BZ, Fórizs I, Czuppon G, Somlyai I. Deuterium content of the organic compounds in food has an impact on tumor growth in mice. Curr Issues Mol Biol. 2022;45:66–77. https://doi.org/10.3390/cimb45010005.