

5th Amino Acid Assessment Workshop

Comparative Species Utilization and Toxicity of Sulfur Amino Acids¹

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ABSTRACT Animal studies have shown that several methionine (Met) and cysteine (Cys) analogs or precursors have L-Met- and L-Cys-sparing activity. Relative oral bioavailability (RBV) values, with the L-isomer of Met and Cys set at 100% (isosulfurous basis), are near 100% for D-Met for animals but only about 30% for humans. Both the OH and keto analogs of Met have high RBV-sparing values, as does N-acetyl-L-Met (the D-isomer of acetylated Met has no bioactivity). L-Homocysteine has an RBV value of about 65% for Met sparing in rats and chicks, but D-homocysteine has little if any Met-sparing activity. S-Methyl-L-Met can partially spare Met, but only when fed under dietary conditions of choline/betaine deficiency. Relative to L-Cys, high RBV values exist for L-cystine, N-acetyl-L-Cys, L-homocysteine, L-Met, and glutathione, but D-cystine, the keto analog of Cys, L-cysteic acid, and taurine have no Cys-sparing activity. L-2-Oxothiazolidine-4-carboxylate has an RBV value of 75%, D-homocysteine 70%, and DL-lanthionine 35% as Cys precursors. Under dietary conditions of Cys deficiency and very low inorganic sulfate (SO₄) ingestion, dietary SO₄ supplementation has been shown to reduce the Cys requirement of several animal species as well as humans. Excessive ingestion of Met, Cys, or cystine has also been studied extensively in experimental animals, and these sulfur amino acids (SAA) are well established as being among the most toxic of all amino acids that have been studied. Even though Cys and its oxidized product (cystine) are equally efficacious at levels at or below their dietary requirements for maximal growth, Cys is far more toxic than cystine when administered orally in the pharmacologic dosing range. Isosulfurous (excess) levels of cystine, N-acetyl-L-Cys, or glutathione are far less growth depressing than L-Cys when 6 to 10 times the minimally required level of these SAA compounds are fed to chicks. *J. Nutr.* 136: 1670S–1675S, 2006.

KEY WORDS: • methionine • cysteine • cystine • homocysteine • N-acetyl-L-cysteine

Sulfur amino acid (SAA)³ nutrition and metabolism have been studied extensively, from both a basic and applied standpoint. Methionine (Met) is the first limiting amino acid (AA) in virtually all poultry diets, primarily because avian diets around the world are based on soybean meal, a protein source that is deficient in SAA. Methionine, however, is also of great interest metabolically because of its role in transmethylation and its transsulfuration to cysteine (Cys). Cysteine, too, is of great interest because of its role in protein synthesis, protein structure, and as a precursor of glutathione (GSH), taurine, coenzyme A, and active sulfate (for 3'-phosphoadenosine-5'-phosphosulfate, i.e., PAPS) biosynthesis.

The review that follows emphasizes SAA animal studies and focuses on 1) transsulfuration efficiency and cyst(e)ine (Cys +

cystine) sparing of the Met requirement, 2) Met and Cys precursors, and 3) relative toxicity of SAA. A comprehensive review of SAA metabolism has been published recently (1).

Transsulfuration and the Cys-sparing effect

Transsulfuration involves transfer of the sulfur from Met to serine, resulting in Cys biosynthesis (2–6). On a molar basis, Met is 100% efficient as a precursor of Cys (7,8). The reaction between Cys and cystine is freely reversible such that both compounds are equal in furnishing Cys bioactivity for support of protein synthesis. In young, rapidly growing animals, cyst(e)ine can furnish 50% of the requirement (wt:wt) for SAA (7–14). For older animals (i.e., adult maintenance), cyst(e)ine can furnish >50% of the SAA requirement (15–18).

Young et al. had questioned whether Cys can spare Met in adult humans (19,20). Data from Di Buono et al. (21,22), however, showed that the Met requirement of adult men was roughly one-half as high when determined in the presence of excess dietary Cys as when determined with Met alone (i.e., no dietary Cys). Their results suggested that excess dietary Cys lowers the dietary Met requirement by increasing the remethylation of homocysteine (Hcy) to Met and decreasing the flux of Hcy transsulfuration to Cys. Dietary SAA requirements of humans are expressed as mg·kg⁻¹·d⁻¹. Therefore, the molecular weight difference between Met (149.2 mg/mmol)

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³ Abbreviations used: AA, amino acid; Cys, cysteine; GSH, glutathione; Hcy, homocysteine; Met, methionine; OH-Met, DL-hydroxy analog of Met; PAPS, 3'-phosphoadenosine-5'-phosphosulfate; RBV, relative oral bioavailability; SAA, sulfur amino acid(s); SAM, S-adenosylmethionine; SMM, S-methylmethionine.

and Cys (121.2 mg/mmol) comes into play. Thus, even though transsulfuration conversion of Met sulfur to Cys sulfur is 100% efficient (7,8,11,13,23), 149.2 mg of Met (1 mmol) yields only 121.2 mg (1 mmol) of Cys. This, then, should result in a lower total SAA requirement when a proper ratio of Met and Cys is consumed than when Met alone is used to meet the SAA requirement.

As illustrated by the work of Graber and Baker (7,24), 3 separate bioassays (requirement studies) are necessary to clarify the issue of Met sparing by Cys, and purified amino acid diets are required for all 3 bioassays (Table 1). Requirements were based on quantities of SAA needed to achieve maximal body weight gain and food utilization. In several instances where SAA requirement studies have been done, only Assays 1 and 2 have been completed, and these 2 assays lead to an erroneous estimate of Cys sparing. Hence, the results of Assays 2 and 3 make it clear that Cys can furnish 50% (wt:wt) of the dietary requirement for SAA, whereas Assays 1 and 2 suggest that Cys can furnish 55% ($700 - 314 \div 700$) of the total requirement for SAA.

The issue becomes even more complicated in practice when intact proteins furnish the SAA that are ingested. Hence, analytic problems exist in accurate quantification of Met and cyst(e)ine in intact proteins and diets. Also, protein-bound cyst(e)ine is well known to be poorly digestible relative to Met (25–27). These factors make it extremely difficult to determine precisely the percentage that Cys can contribute to the total SAA requirement of both animals and humans. Inorganic sulfate, too, is a factor that can influence the Cys-sparing effect. Work with chicks (8,28) and rats (29) has shown that 200 mg/kg sulfate addition to a Met-adequate diet that is deficient in Cys and devoid of sulfate can produce a marked growth response. Presumably, sulfate under these conditions is being used for PAPS biosynthesis and thereby (indirectly) sparing Cys so that more of the Cys can be used for synthesis of protein, GSH, and (or) taurine. This sulfate-sparing effect has also been observed in humans (30). However, virtually all animal and human diets contain surfeit sulfate (from SAA metabolism, sulfate salts, and food sources) such that sulfate sparing of Cys is primarily of academic interest.

A fourth bioassay may be helpful if questions persist about the efficiency with which Met furnishes Cys via transsulfuration. This (slope-ratio) assay uses the Met requirement (314 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$) established in Assay 2 (Table 1) wherein the

assay diet contained excess Cys. The basal diet for this assay would therefore provide no Cys but enough Met to furnish a Met intake of $314 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$. Then, dietary levels of Met or Cys would be supplemented to provide 0, 125, or 250 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ of L-Met or L-Cys (i.e., 3 levels of each SAA below the requirement). If done carefully, slope (weight gain in grams vs. intake in milligrams) of the Met response curve should be about 81% that of the Cys response curve in a common-intercept multiple linear regression model (7,8,23). If an assay such as this is done using indirect (e.g., phenylalanine) oxidation methodology in either animals or humans, one would expect slope of the Cys response curve to be more steeply negative than that of the Met response curve.

SAA precursors

Met and Cys isomers. The D-isomer of Met is utilized well as an L-Met precursor, except in apes and humans (14,30–39). Indeed, although the efficacy of D-Met for growth of pigs and dogs is 100% (35,38), the efficacy of D-Met for supporting nitrogen balance of adult humans is only about 30% (30,31).

In species obtaining good efficacy from D-Met, the keto analog must obviously be formed, and this must be subsequently transaminated to L-Met. Although keto-Met is not formed in the (major) transsulfuration pathway of Met degradation, an alternative pathway exists wherein keto-Met is formed (40,41), that is, under conditions of high Met intakes. The keto analog of Met is also an intermediate in the conversion of the DL-OH analog of Met to L-Met. Thus, the keto analog of Met has been shown to have good L-Met efficacy in the chick (42). The keto analog of Cys is not produced in metabolism, so neither the keto analog (43) nor D-Cys (44) has L-Cys bioactivity.

Hydroxy analog of Met. The α -hydroxy analog of DL-Met (OH-Met) is an important commercial product. The compound is made chemically, and therefore, it is a 1:1 mixture of D- and L-OH-Met (45). Considerable controversy (46,47) has surrounded the bioactivity of OH-Met, which is available commercially as the calcium salt (86% of the sulfur in Met) or the free acid (88% of the sulfur in Met). It is now well established that 2 separate enzymes are necessary to convert OH-Met to the α -keto analog of Met, a dehydrogenase for D-OH-Met and an oxidase for L-OH-Met (48). The keto analog of Met is then transaminated to Met, with branched-chain AA being principal amino donors in avians, but glutamine being the main amino donor in rats (49). Baker and Boebel (45) in chicks and Friedman and Gumbmann (36,50) in mice showed with purified diets that D-OH-Met is more active than L-OH-Met in stimulating growth of animals fed SAA-deficient diets.

Does OH-Met free acid have 88% L-Met bioactivity (weight or concentration basis)? This is what one would expect if OH-Met yielded L-Met with 100% molar efficiency. In avians, Potter (46) estimated, based on an extensive literature review, that OH-Met has 75% of the molar activity of L-Met. This translates to 66% efficacy on a weight or concentration basis ($88\% \times 0.75 = 66\%$). Table 2 shows OH-Met as having 80% molar efficacy in chicks (14,51). The L-Met-sparing value of OH-Met in pigs is equivocal, with published molar values ranging from 75% (52) to 100% (38,53). DL-OH-Met also is used clinically for renal patients (54), but its efficacy relative to L-Met is not known (55).

Glutathione, taurine, lanthionine and S-methylmethionine. Glutathione (γ -glutamylcysteinylglycine, i.e., GSH), taurine, lanthionine, S-methyl-L-Met (SMM), and dimethylsulfoniopropionate are found in food and feed ingredients consumed by animals and humans (56–61). Taurine and

TABLE 1

Illustration of 3 separate bioassays required to evaluate methionine sparing by cyst(e)ine¹

Requirement bioassay	Dietary condition	Result
1. Met	No dietary Cys	700
2. Met ²	Excess dietary Cys	314
3. Cys ³	Dietary Met at 314	314

¹ Illustration from SAA requirement studies in young chicks by Graber and Baker (7,24). All requirement values expressed as $\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$.

² The difference between 700 (Assay 1) and 314 (Assay 2) is 386 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, which is an incorrect estimate of the Cys requirement.

³ The total SAA requirement is $314 + 314 = 628 \text{ mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, lower than the 700 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ estimated for all Met in Assay 1. The correct estimate of the Cys requirement is 314 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$, which is 81% of the 386 $\text{mg}\cdot\text{kg}^{-1}\cdot\text{d}^{-1}$ (fallacious) estimate arrived at in Assays 1 and 2. Note that 81% is the same percentage arrived at by dividing the molecular weight of Cys (121.2) by the molecular weight of Met (149.2).

TABLE 2

Relative utilization of sulfur amino acid isomers, analogs, and precursors¹

Amino acid	Chick	Rat	Mouse	Pig	Dog	Human
L-Met	100	100	100	100	100	100
D-Met	90	90	75	100	100 ²	30 ³
DL-Met	95	95	88	100	100	65
DL-OH-Met	80	70	70	80	NA	NA
Keto-Met	90	NA	NA	NA	NA	NA
L-Met sulfone	NA	0	0	NA	NA	NA
L-Met sulfoxide	NA	60	85	NA	NA	NA
N-acetyl-L-Met	100	100	90	NA	100	NA
N-acetyl-D-Met	0	0	25	NA	0	NA
L-Hcy	65	65	NA	NA	NA	NA
D-Hcy	7	NA	NA	NA	NA	NA
S-Methyl-L-Met	+ ⁴	+ ⁴	NA	NA	NA	NA
L-Cys	100	100	100	100	100	100
L-cystine	100	NA	NA	100	NA	NA
D-cystine	0	0	0	NA	0	NA
Keto-Cys	NA	0	NA	NA	NA	NA
L-Cysteic acid	NA	0	NA	NA	NA	NA
DL-Lanthionine	35	NA	35	NA	NA	NA
GSH	100	100	NA	NA	NA	NA
N-Acetyl-L-Cys	100	100	100	100	NA	NA
S-Methyl-L-Cys	NA	NA	0	NA	NA	NA
L-Hcy	100	NA	NA	NA	NA	NA
D-Hcy	70	NA	NA	NA	NA	NA
L-Met	100	100	NA	100	NA	100
Taurine	0	0	NA	NA	NA	NA
L-OTC	80	70	NA	NA	NA	NA

¹ Values are expressed as growth efficacy percentages (molar or isosulfurous basis) of the L-isomer, which in all cases is presumed to represent 100% oral utilization (14); NA = data unclear or not available.

² Efficacy of D-Met is also near 100% in growing kittens.

³ Efficacy is about 30% in monkeys also.

⁴ Met sparing present in chicks when both dietary Met and choline (or betaine) are deficient; choline sparing definitely occurs in both chicks and rats.

GSH are constituents of animal-based products, but GSH is also present in some plant-based food products. Lanthionine is a cross-linked SAA that is formed in food products that have been exposed to heat. It is prominent in feather meal and poultry by-product meals used in animal feeds. Only plant-based foods contain SMM.

Taurine has no SAA-sparing activity in either chicks (8) or rats (62), although it may be limiting in diets for neonatal infants (63). Glutathione is fully effective on a molar basis in furnishing L-Cys (42,64,65). Lanthionine in foods can exist in 8 different isomeric forms (66–68). That absorbed from the gut can be cleaved by cystathionase (69), releasing either D- or L-Cys. Robbins et al. (70) conducted a quantitative study in chicks that suggested that DL-lanthionine has 35% L-Cys bioactivity.

S-Methylmethionine (SMM) is an analog of S-adenosylmethionine (SAM), with a methyl group substituted for the adenosyl group. This compound is unique to plants and is found in measurable-to-high concentration in corn, cabbage, tomatoes, celery, spinach, garlic, and in soy flours and meals (60,61,71–73). Several rodent studies have suggested that SMM has Met-sparing activity (74–77), but recent chick work (61) has shown that L-SMM will spare Met only under conditions where diets are limiting in choline and betaine. With diets adequate in Met but deficient in choline, SMM has been suggested as being capable of directly methylating phosphatidylethanolamine to form phosphatidylcholine and then choline (61).

SAA oxidation products. Methionine and cyst(e)ine in foods are subject to oxidative losses wherein Met is converted to either Met sulfoxide or Met sulfone, and Cys is oxidized to cysteic acid. These compounds are often found in milk-based foods because hydrogen peroxide is frequently used for sterilization purposes (78–80). Neither L-Met sulfone nor L-cysteic acid has SAA bioactivity when fed to rats (81), but L-Met sulfoxide has 60% and 85% bioactivity for rats and mice, respectively (14).

Homocyst(e)ine. Considerable research has been carried out with Hcy, an intermediate in the transsulfuration pathway (82). This AA is not a constituent of body proteins, but it accumulates in tissues and body fluids of patients afflicted with homocystinemia and homocystinuria (83). Homocysteine has also been implicated as a causative factor in vascular disease. In virtually all cases where Hcy or its oxidation product (homocystine) has been used in nutrition research, the racemic DL mixture has been used, yet the efficacy of the separate isomers was not known. Potentially, Hcy (or homocystine) could serve as a precursor for either Cys or Met. Work with chicks and rats from our laboratory established that D- and L-Hcy have considerably different bioactivities when serving as an oral source of Met or Cys (84,85). As might be expected, both isomers of Hcy are more effective precursors of L-Cys than of L-Met. With diets adequate in Cys and deficient in Met, L-Hcy had 65% of the growth-promoting activity of L-Met, whereas D-Hcy was only 7% as effective as L-Met (14).

Palatable SAA precursors for food supplementation. Although supplementation of animal diets with either DL-Met or DL-OH-Met has become common, adding bioavailable SAA activity to diets for humans has been held back because 1) Met and OH-Met are unpalatable to humans, 2) L-Cys is too toxic for routine use, and 3) L-cystine is relatively insoluble, making it inappropriate for liquefied diets (i.e., enteral and parenteral applications). Although GSH (Cys precursor) is soluble as well as palatable, it is expensive and also unstable. Thus, there is great interest in finding palatable and soluble precursors of Met or Cys for human applications. Acetylation of the α -amino group of either L-Met or L-Cys results in compounds that are palatable (86,87) and have full SAA bioactivity (88–91), although N-acetyl-D-Met has no Met-sparing activity (35,88,89). An added virtue of N-acetyl-L-Met is that it is an effective precursor of both Met and Cys, whereas N-acetyl-L-Cys can provide only Cys bioactivity. Moreover, acetylation of the α -amino group of Met or Cys protects these SAA against Maillard destruction (92). Clinical interest in both N-acetyl-L-Cys and lipoic acid (causes increased intracellular cysteine and GSH) has increased in recent years. Thus, the antioxidant activity of these compounds has been of interest in treating chronic bronchitis, acetaminophen hepatotoxicity, diabetes, cancer, sepsis, HIV infection, heart disease, and acute myocardial infarction (93–96).

Williamson and Meister (97) identified a new Cys precursor, L-2-oxothiazolidine-4-carboxylic acid (OTC), and this compound can serve as an oral precursor of L-Cys (or GSH). Subsequent work indicated that OTC has 80% and 70% L-Cys bioactivity in chicks and rats, respectively (98). Other L-Cys precursors have also been shown to be effective precursors of L-Cys, although quantitative efficacy values are not available. Thus, for improving glycemic control in diabetic mice, orally administered N-acetyl-L-Cys, S-allyl-L-Cys, S-ethyl-L-Cys, S-methyl-L-Cys, and S-propyl-L-Cys were all found to be efficacious (96).

SAA toxicity

Because excess ingestion of Met causes a greater growth depression than that caused by other AA (99–102), the

literature is extensive on Met imbalance and toxicity (103,104). Less is known about cyst(e)ine toxicity, but both Cys and its oxidation product cystine are well established as being relatively toxic at high levels of intake (103,104). It is not my intent to repeat the information contained in these excellent and comprehensive reviews. Instead, a brief summary will be given of newer information on SAA toxicity.

It is clear that the growth depressions and biochemical lesions caused by excess Met consumption are different from those caused by excess Cys or cystine consumption. Indeed, although considerable work has been done on metabolites of Met (e.g., Hcy and cystathionine) and Cys (e.g., taurine, cysteic acid, sulfate), it appears that excess Met and cyst(e)ine per se are primarily causative. Supplemental glycine is definitely ameliorative of Met toxicity, but whether this is because of its role in detoxifying the methyl group of Met (i.e., for synthesis of either sarcosine or creatine) or for its role as a precursor of serine (i.e., for synthesis of cystathionine from Hcy) is not clear. However, supplemental glycine and to a lesser extent serine definitely enhance methionine oxidation (105). Nothing as yet has been shown to ameliorate cyst(e)ine toxicity, at least nothing in the way of an AA supplement.

Most of the work that has been done with excess dietary levels of cyst(e)ine has used cystine rather than Cys. And even though the oxidized form (cystine) and reduced form (Cys) of these SAA are equal for promoting growth of animals fed diets deficient in cyst(e)ine and adequate in Met (7,23), they produce very different results when administered in the pharmacologic dosing range (106). Cysteine is absorbed from the gut faster than cystine (107) and is a strong reducing agent (108). Moreover, it has the ability to chelate trace minerals in the gut and in the body (106), and with its free sulfhydryl group it can readily bind plasma proteins (109). Harper et al. (103) observed 50% mortality in rats fed a casein diet (10 g/100 g) supplemented with 2.4 g/100 g L-Cys free base.

We recently studied graded levels of supplemental SAA (0, 1, 2, 3, or 4 g/100 g) added to a standard corn-soybean meal diet (23 g/100 g protein) for young chicks (R. N. Dilger and D. H. Baker, University of Illinois, unpublished data). Thus, 0, 1, 2, 3, or 4 g/100 g of L-Met, L-Cys, or L-cystine as well as levels of *N*-acetyl-L-Cys equimolar to the L-Cys addition were supplemented. Because the basal diet contained Met and cyst(e)ine at their required concentrations for maximal chick growth (i.e., 0.50 g/100 g of each), the supplemental SAA concentrations represented 0, 3, 5, 7, and 9 times the required level of either Met or Cys. The 1 g/100 g additions, regardless of SAA source, had no effect on growth rate. Likewise, 2 g/100 g of supplemental cystine or *N*-acetyl-L-Cys were without effect on chick growth. This same level of supplemental Met, however, depressed weight gain by 34%, and 2 g/100 g of added L-Cys reduced weight gain by 10%. At 3 g/100 g of L-Cys, half of the chicks died by day 5 of the 9-d bioassay; and 92% mortality occurred by day 5 when 4 g/100 g of L-Cys was supplemented. No mortality occurred at any level of supplemental Met, cystine, or *N*-acetyl-L-Cys, although the growth depression at 4 g/100 g of Met was severe (94%). With 4 g/100 g of supplemental L-cystine or an isosulfurous level of *N*-acetyl-L-Cys, growth depressions were 20% and 34%, respectively. That excess dietary L-cystine and *N*-acetyl-L-Cys were far less noxious than L-Cys suggests these SAA compounds may have been absorbed from the gut more slowly than Cys, and with *N*-acetyl-L-Cys, it may have been deacetylated more slowly such that tissue concentrations of Cys could not reach the same levels as those caused by Cys itself. How the intestine metabolizes Cys, cystine, and *N*-acetyl-L-Cys is not clear, but it is well established that as much as half of whole-body Cys oxidation occurs in splanchnic tissues (110–

112). Also, the gut is capable of not only substantial Cys oxidation but also GSH synthesis. Clearly, something is different in how the body handles oral L-Cys, L-cystine, and *N*-acetyl-L-Cys, resulting in a different toxicity profile for each compound. Pharmacokinetic studies with *N*-acetyl-L-Cys have demonstrated that <10% of orally administered *N*-acetyl-L-Cys is absorbed into portal blood as *N*-acetyl-L-Cys per se (113). Thus, first-pass metabolism in the gut wall causes formation of cysteine, GSH, and inorganic sulfate.

Among the most consistent and noteworthy features of Met toxicity is splenic hemosiderosis caused by hemolytic anemia (40,41,104,114). Excess dietary Hcy does not cause this biochemical lesion, but supplemental glycine does have some efficacy in lowering iron deposition in the spleen caused by a large excess of Met (114). It appears, therefore, that intermediates in the alternate transaminative pathway of Met degradation (e.g., 3-methylthiopropionate) are responsible for the marked iron deposition in the spleen of animals consuming large excesses of Met. Indeed, graded Met dosing studies have revealed that blood hemoglobin is inversely proportional and spleen iron concentration directly proportional to the weight gain depression caused by excess dietary Met (114).

With excess cyst(e)ine ingestion, brain lesions and retinal degeneration are the most outstanding features (115,116), although with the reduced compound (Cys) most would agree that death is the most pernicious feature. Fortunately, most of the clinical uses for cyst(e)ine (93,94,117–119) have employed *N*-acetylcysteine, a compound that, based on rat and chick studies, is much safer than Cys itself.

Recapitulation

Both Met and Cys have a multitude of functions in the body apart from their role in protein synthesis. Methionine via SAM is important in methylation reactions, and it also functions to provide Cys via transsulfuration. Cysteine is a precursor for GSH, taurine, PAPS, and coenzyme A, and it plays an important role in protein structure and as an acceptor of Se for synthesis of selenoproteins and enzymes. It is the first limiting AA for endogenous protein synthesis (120), and it is a major AA constituent of specialized proteins such as metallothionein (MT), Cys-rich intestinal protein (CRIP), and gut mucin. In its reduced state, Cys can bind or chelate several trace elements, which likely explains why it is well established as being capable of increasing iron and zinc absorption but decreasing copper absorption and excretion (106,121–125). Cysteine is also a strong reducing agent, and it has even been proposed to be a cytokine (126).

Both Met and Cys are quite toxic at dietary concentrations 5 times or more above required levels. It seems very questionable whether any Met or cyst(e)ine compound should be available as an over-the-counter nonprescription product.

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