

TABLE 3Subject responses to a reference dose of [¹³C₁₀]retinyl acetate and a Golden Rice meal with [²H₉]-carotene¹

Subject no.	GR β-C	[¹³ C ₁₀]RAc	AUC[² H ₅]retinol	AUC[¹³ C ₁₀]retinol	Retinol equivalent	Conversion factor	
						By weight	By mole
	<i>mg</i>	<i>mg</i>	<i>μg · d</i>	<i>μg · d</i>	<i>mg</i>		
1	0.99	1.01	19.4	67.5	0.25	4	2.1
2	1.53	1.01	38.8	57.9	0.94	2.6	1.4
3	0.99	0.43	74.3	53.9	0.51	1.9	1
4	0.99	1.01	34.4	124.2	0.24	4.1	2.2
5	1.53	1.01	32.8	119.9	0.24	6.4	3.4
Mean ± SD	1.21 ± 0.30	0.89 ± 0.26	39.9 ± 20.5	84.7 ± 34.5	0.36 ± 0.17	3.8 ± 1.7	2.0 ± 0.9
SD (% of mean)	24.8	29.2	51.4	40.7	47.2	44.7	45.0
Median	0.99	1.01	34.4	67.5	0.25	4.0	2.1
Mean-median difference	0.22	-0.12	5.5	17.2	0.11	-0.2	-0.1
Mean-median difference, SD	0.73	-0.46	0.27	0.50	0.65	-0.12	-0.11

¹ GR β-C, Golden Rice β-carotene; RAc, retinyl acetate; AUC, area under the curve.

of its biomathematical deficits. This would not be of great concern if the data were used to justify the statement that β-carotene can be absorbed from rice. Unfortunately, the data are used to advertise for the suggested benefits of the technology of genetically modified organisms in populations who may not be able to qualify the study results and conclusions drawn. Apart from this larger, principal, discussion, there are 2 critical questions regarding the data presented in the study.

In **Table 3**, the authors present their main findings. The table is reproduced here with the addition (in the lower section in bold type) of the median and the magnitude of the SD and the mean-median difference and its magnitude (calculated from the data provided by the authors in the upper lines). The means and SDs on the basis of 5 probands with large interindividual variability is a weak basis for far-reaching nutritional conclusions. The SDs of the results range from 29% to 51% of the mean in a nonnormally distributed data set. Therefore, the statement “our analysis showed a very efficient bioconversion of β-carotene to vitamin A” is based on 2 of 5 values above the median in Table 3. Even considering the limited amount of intrinsically labeled β-carotene-containing rice available—with ≈20 μg β-carotene/g rice—it is to be questioned why the research group did not choose a more homogenous study population at least in terms of the variables of age, sex, and nutritional and vitamin A status, at the start.

A second question concerns why the authors did not use a dietary approach more similar to the diets of the individuals who were suggested to benefit from the consumption of this β-carotene-containing rice. One of the arguments used for advertising Golden Rice is that the people at risk of vitamin A deficiency have such poor diets that other sources of β-carotene and vitamin A are not accessible to them. Because diet definitely has an effect on the bioavailability of β-carotene from any β-carotene-containing food, the choice for a study diet that included meat, oil, and nuts, which does not represent a poor diet, is of concern. Therefore, the results of the study do not much help us in preventing vitamin A deficiency in populations at risk. The argument of a better conversion rate with β-carotene-containing rice may at best be interpreted as follows: This rice is to be considered as one means of providing β-carotene besides the known vegetables and algae and in absence of animal-derived dietary sources of vitamin A. The suggested superior conversion rate alone does not solve all intrinsic nutritional, medical, and social problems of the “Golden Rice approach” in preventing vitamin A deficiency.

More research in the prevention of vitamin A deficiency is required, and animal studies in piglets may be an appropriate model

to investigate the different approaches of supplementation, fortification, natural β-carotene from the diet, and nutrient-oriented plant breeding before humans are further exposed to studies that obviously do not address potential health risks.

The author had no conflict of interest.

Michael B Krawinkel

Institute of Nutritional Sciences
Justus-Liebig-University
Giessen
Germany

E-mail: michael.krawinkel@ernaehrung.uni-giessen.de

REFERENCE

1. Tang G, Qin J, Dolnikowski GG, Russell RM, Grusak MA. Golden Rice is an effective source of vitamin A. *Am J Clin Nutr* 2009;89:1776–83.

doi: 10.3945/ajcn.2009.28142.

Reply to MB Krawinkel

Dear Sir:

We appreciate the interest from Krawinkel in our recent publication on the vitamin A equivalency of Golden Rice (1), in which we used stable isotope methodologies and a single serving (per subject) of Golden Rice (a transgenic rice that produces β-carotene in the grain) to study β-carotene absorption and bioconversion to vitamin A in 5 healthy adult subjects in Boston, Massachusetts. We showed that Golden Rice β-carotene in the dose provided (≈1 mg) was effectively converted to vitamin A. Although Krawinkel acknowledges that our study provides evidence for β-carotene uptake, he raises 2 concerns about the bioconversion results: one concern relating to the data analysis and the other relating to the selection of study subjects.

Krawinkel believes that the reported “effective” bioconversion efficiency of Golden Rice β-carotene to vitamin A (mean: 3.8 to 1, by weight) is questionable because 2 of 5 bioconversion values

fell above the median value. This statement makes little sense, because, by definition, 2 of any 5 values will be above the median. However, it should be noted that the range of values observed in our 5 subjects was 1.9–6.4 to 1 (by weight); therefore, all 5 individuals showed a better bioconversion of Golden Rice β -carotene than the current bioconversion value (12 to 1, by weight) used by the Food and Nutrition Board, Institute of Medicine, in its most recent Dietary Reference Intake recommendations for vitamin A (2). Additionally, the bioconversion values for Golden Rice β -carotene in these 5 subjects were lower (ie, more effective conversion) than the values of many foods previously studied, including fruits, sweet potato, carrots, and several green leafy vegetables (*see* reference section in reference 1).

With regard to the selection of study subjects, Krawinkel is concerned that this current study was not conducted in individuals from vitamin A–deficient populations or with the use of diets that are more representative of these populations. As noted in our article, we recognize that additional studies are needed in at-risk populations, including children, and in fact these studies are already in progress. Furthermore, we suggested that our bioconversion values could be used to provide estimates of what Golden Rice might provide to children, in terms of dietary vitamin A equivalents, but we also noted that longer-term trials in which Golden Rice is incorporated into daily diets are needed to assess its effectiveness in improving vitamin A status at the population level. Thankfully, with our current bioconversion estimates now determined, these types of studies can be designed in a sensible and scientifically informed manner.

None of the authors had a conflict of interest.

Guangwen Tang
Robert M Russell
Jian Qin
Gregory G Dolnikowski

Jean Mayer USDA Human Nutrition Research
Center on Aging
Tufts University
711 Washington Street
Boston, MA 02111
E-mail: guangwen.tang@tufts.edu

Michael A Grusak

USDA/ARS Children's Nutrition Research Center
Department of Pediatrics
Baylor College of Medicine
1100 Bates Street
Houston, TX 77030

REFERENCES

1. Tang G, Qin J, Dolnikowski GG, Russell RM, Grusak MA. Golden Rice is an effective source of vitamin A. *Am J Clin Nutr* 2009;89:1776–83.
2. National Academy of Sciences, Institute of Medicine, Food and Nutrition Board. Dietary Reference Intakes for vitamin A: vitamin K, arsenic, boron, chromium, copper, iodine, iron, manganese, molybdenum, nickel, silicon, vanadium, and zinc. A report of the Panel on Micronutrients, Subcommittees on Upper Reference Levels of Nutrients and of Interpretation and Use of Dietary Reference Intakes, and the Standing Committee on the Scientific Evaluation of Dietary Reference Intakes. Washington, DC: National Academy Press, 2001.

doi: 10.3945/ajcn.2009.28268.

The evidence-based Mediterranean diet reduces coronary heart disease risk, and plant-derived monounsaturated fats may reduce coronary heart disease risk

Dear Sir:

In the May 2009 issue of the Journal, an article by Jakobsen et al (1) contributes to the literature by analyzing dietary fat and the associated risk of coronary disease by using a pooled analysis of 11 studies. The editorial (2) accompanying this article suggests that the data presented in the article “raise some concern about advice to eat a Mediterranean diet.” The editorial also appears to suggest that advice to follow the Mediterranean diet does not represent “evidence-based medicine.”

The benefits of a Mediterranean diet are, in fact, supported by the highest level of evidence. There is a randomized trial in cardiac patients in whom the Mediterranean diet showed a significant reduction in total mortality (3). Of note, only 4 valid randomized clinical trials have shown a significant benefit of dietary intervention on total mortality: 3 trials involved the intake of fish or fish-derived omega-3 (n-3) fatty acids (4–6) and one randomized trial involved the Mediterranean diet (3). A randomized clinical trial that shows a statistically significant benefit in total mortality, rather than a benefit for a surrogate endpoint, is the pinnacle of evidence-based medicine.

Supporting evidence for the benefit of the Mediterranean diet includes population studies of a number of populations with well-characterized diets. The Cretan Mediterranean diet at the time of the Seven Countries Study had 31% of caloric intake from olive oil and 90% from plant-based sources (7). The Mediterranean diet in each of the 5 separate populations in Greece and Italy, all of whom had fat intake predominantly based on plant sources of monounsaturated fatty acids (MUFAs; olive oil), was associated with low rates of coronary heart disease (CHD) (8). A subsequent study conducted in Greece followed 22,000 individuals and found that greater adherence to the traditional Mediterranean diet was associated with a significant reduction in CHD and lower total mortality (9). Hence, the Mediterranean diet has multiple levels of evidence of benefit and is unique in being a comprehensive dietary approach for which a randomized clinical trial has shown a significant reduction in mortality.

In regard to the article by Jakobsen et al (1), the authors suggest in their conclusions that the replacement of saturated fatty acids (SFAs) with polyunsaturated fatty acids (PUFAs), rather than with MUFAs, prevents CHD. Also, the article's Table 2 lists information on “MUFAs for SFAs.” Similarly, the Discussion, with regard to the CHD risk, refers to “a lower intake of SFAs and a concomitant higher energy intake from MUFAs.” However, the concept that this study provides information on MUFAs replacing SFAs rather than MUFA intake in conjunction with SFA intake appears to be a misinterpretation of the data.

In populations studied by Jakobsen et al (1), MUFA intake was actually linked with SFA intake, rather than replacing SFA intake. The main sources of MUFA intake in the groups analyzed by Jakobsen et al were meat and dairy products (1). Because meat and dairy products contain both MUFAs and SFAs, the ingestion of these types of foods does not provide reliable information on the effects of MUFA intake being replaced by SFA intake. For example, 200 calories of ground beef contains an average of \approx 5 g SFAs and 6 g MUFAs (10). The intake of that ground beef necessarily entails both SFA and MUFA intake. Statistical manipulation cannot validly convert this to the equivalent of the replacement of SFA intake by MUFA intake.