ORIGINAL ARTICLE

Large inter-individual variation in isoflavone plasma concentration limits use of isoflavone intake data for risk assessment

V van der Velpen1, PC Hollman1,2, M van Nielen1, EG Schouten1, M Mensink1, P van’t Veer1 and A Geelen1

BACKGROUND/OBJECTIVES: Isoflavones are present in soy foods and soy-based supplements. Despite low plasma isoflavone concentrations in the general Western population, concentrations in supplement users exceed those suggested to be beneficial for health in Asian populations, raising concerns for adverse effects. To aid risk assessment, quantification of the relation between isoflavone intake and plasma concentrations is essential.

SUBJECTS/METHODS: Plasma samples were collected from postmenopausal women in three placebo-controlled crossover studies with 8-week periods for supplements (two studies, ~100 mg isoflavones/day, n = 88) or 4-week periods for soy foods (one study, ~48 mg isoflavones/day, n = 15). Plasma isoflavone concentrations (daidzein, equol, genistein and glycitein) were quantified using high-performance liquid chromatography and electrochemical detection. The association between plasma concentrations and isoflavone intake, equol producer status, intake–producer interaction and background dietary intake was assessed based on the assumption of a log-linear relation.

RESULTS: Median plasma total isoflavone concentrations after the soy food and supplement interventions were respectively 2.16 and 3.47 μmol/l for equol producers and 1.30 and 2.39 μmol/l for non-producers. Regression analysis showed that doubling isoflavone intake increased plasma concentrations by 55–62% (± s.e. 1–2%, R² > 0.87) for daidzein, genistein, equol (only for producers) and total isoflavones; for glycitein the association was weaker (15 ±1%, R² = 0.48). Adjustments for energy, carbohydrate and fat intake did not affect these estimates. Inter-individual variation, estimated based on repeated measures in one of the studies, was 30–96%.

CONCLUSIONS: Although the relation between isoflavone intake and plasma concentrations was adequately quantified, the use of isoflavone intake data for risk assessment needs caution due to large inter-individual variation in plasma concentrations.

European Journal of Clinical Nutrition (2014) 68, 1141–1147; doi:10.1038/ejcn.2014.108; published online 18 June 2014

INTRODUCTION

Isoflavones, present in soy products, are suggested to relieve menopausal complaints1–4 and to have a number of other beneficial health effects, such as prevention of osteoporosis and cardiovascular disease.5–7 At higher doses, uncertainty exists regarding potentially detrimental effects on thyroid function and risk of breast and endometrium cancer, because long-term human trials are currently lacking.8–10

The glucosides daidzin, genistin and glycitin are the main isoflavones in soy, whereas their malonyl and acetyl equivalents as well as the aglycones daidzein, genistein and glycitein occur in much lower quantities.9 The various isoflavones have specific pharmacokinetic characteristics, for example, isoflavone glucosides are more bioavailable than their aglycones;10 daidzein is rapidly excreted in urine, whereas genistein enter hepatocellular recycling.10,11 In addition, 20–30% of the Western population are so-called equol producers; they can convert daidzein into the more active metabolite equol by their gut bacteria.12 Furthermore, isoflavone plasma concentrations can be influenced by isoflavone source, food matrix, diet, frequency of ingestion, gender and age.10 Mean isoflavone intake is low (0.5–0.8 mg/day) across the European population and remains well below the intake in Asian countries even for vegetarians and vegans (22.4 mg/day).13 Mean plasma concentrations were estimated to be < 0.01 μmol/l in the European population and 0.23 μmol/l for vegetarians and vegans.14 In Japan, mean intakes of daidzein and genistein are 18.3 and 31.4 mg/day, resulting in plasma concentrations of 0.12 and 0.48 μmol/l, respectively.15 On average, supplement users in Western countries consume 50 mg of isoflavones/day, but soy-based supplements can contain up to 107 mg aglycone equivalents of isoflavones.16–18 Two intervention studies demonstrated that an intake of 100 mg isoflavones/day resulted in total circulating isoflavones of 1.12 and 4.50 μmol/l.19,20 This illustrates that postmenopausal women taking isoflavone supplements, for example, to relieve their menopausal complaints can be exposed to higher isoflavone concentrations than Asians who regularly consume soy products.

For risk assessment, insight into isoflavone plasma concentrations resulting from these higher isoflavone intake ranges is important. Isoflavone pharmacokinetics as well as positive correlations and dose-response curves between intake and circulating isoflavones have previously been thoroughly characterized.21–26 However, because of the small sample sizes (n = 10–18), these data are not suitable for risk assessment and a quantitative description of the relation between isoflavone intake and plasma concentrations in a much larger group of...
postmenopausal women is needed. We aimed to quantify this relation based on intakes of two different isoflavone supplements and a soy food, taking into account relevant factors like equal-producing phenotype and background dietary intake.

MATERIALS AND METHODS

Trials and subjects

For this study, data from three randomized crossover trials were used: the ISO study, the ISO II study and the SOY study. All studies were conducted at the Department of Human Nutrition of Wageningen University and were performed according to the guidelines laid down in the Declaration of Helsinki. All procedures were approved by the medical ethical review board of this University and written informed consent was obtained from all subjects.

Thirty postmenopausal women participated in the double-blind ISO study of which all participants were equal producers, characterized at screening. The study was registered at clinicaltrials.gov under NCT01232751. The ISO II study, hereafter named the GD (genistein/daidzein) study, was a double-blind trial with two arms in which 72 postmenopausal women participated, 36 in each arm. The two arms were either a daidzein-rich supplement (DAI) or a genistein-rich supplement (GEN), both against placebo. Equal producers, characterized at screening, were randomized between the two arms. The study was registered at clinicaltrials.gov under NCT01556737.

Both double-blind trials included two 8-week intervention periods with one 8-week washout period in between and had the same in- and exclusion criteria, previously reported in van der Velpen et al. In the ISO study, postmenopausal status was defined as 3 months absence of menses and if shorter than 1 year this was complemented with an follicle study, postmenopausal status was defined by a waist circumference ≥ 80 cm, were included. During each 4-week intervention period, the participants consumed a soy protein-rich diet or a mixed protein diet (control diet), with a 4-week washout period in between. The study was registered at clinicaltrials.gov under NCT01694056.

Table 1. Subject characteristics, isoflavone content of supplements and soy foods and background dietary intake

|                      | ISO (n = 21) | GD DAI (n = 32) | GD GEN (n = 35) | SOY (n = 15) |
|----------------------|-------------|----------------|----------------|-------------|
|                      | Mean ± s.d. | Mean ± s.d.    | Mean ± s.d.    | Mean ± s.d. |
| Age (years)a         | 60.3 ± 6.2  | 62.2 ± 5.3     | 62.7 ± 5.4     | 61.2 ± 5.4  |
| BMI (kg/m²)          | 25.7 ± 4.0  | 25.2 ± 3.1     | 25.0 ± 3.6     | 25.4 ± 4.1  |
| Body weight (kg)     | 73.0 ± 13.3 | 71.4 ± 9.8     | 69.5 ± 11.0    | 69.4 ± 12.6 |
| No of equol producers (%)b | 21 ± 100 | 8 ± 25 | 9 ± 26 | 4 ± 27 |
| Total isoflavone intake (mg/day)c | 93.9 ± 52.3 | 100.1 ± 50.8 | 104.2 ± 58.0 | 48.3 ± 15.9 |
| Daidzin              | 3.2 ± 3.7   | 0.5 ± 0.7      | 4.0 ± 0.7      | 2.3 ± 0.7   |
| Genistin             | 11.4 ± 16.5 | 42.0 ± 21.4    | 16.5 ± 21.4    | 21.4 ± 6.0  |
| Genistein            | 0.4 ± 0.4   | 0.7 ± 0.4      | 0.4 ± 0.7      | 6.0 ± 0.7   |
| Glycitin             | 23.8 ± 26.3 | 9.8 ± 9.8      | 26.3 ± 9.8     | 2.3 ± 2.3   |
| Glycitein            | 2.0 ± 1.5   | 0.4 ± 0.4      | 1.5 ± 0.4      | 0.5 ± 0.5   |
| Energy intaked (kJ/day) |           |                |                |             |
| Intervention         | 8726 ± 2304 | 7626 ± 2244    | 7869 ± 1946    | 9126 ± 1801 |
| Placebo              | 8377 ± 2264 | 7819 ± 2675    | 7359 ± 1938    | 9021 ± 1674 |
| Carbohydrate intake (g/day) |         |                |                |             |
| Intervention         | 237 ± 62   | 197 ± 67       | 217 ± 65       | 263 ± 57    |
| Placebo              | 228 ± 60   | 208 ± 80       | 203 ± 62       | 274 ± 55    |
| Fat intake (g/day)   |             |                |                |             |
| Intervention         | 87 ± 32    | 73 ± 29        | 73 ± 27        | 67 ± 13     |
| Placebo              | 81 ± 32    | 76 ± 32        | 68 ± 24        | 63 ± 12     |

Abbreviations: BMI, body mass index; DAI, daidzein-rich supplement; GD, genistein/daidzein; GEN, genistein-rich supplement. *Age, BMI and body weight are determined at the start of the studies. Number of equal producers as determined at the end of the intervention. Glucosides daidzin, genistin and glycitin calculated as aglycone equivalents. Diet data for GD DAI arm for n = 31.
macronutrient composition (21 energy% protein, 26 energy% fat and 51 energy% carbohydrates). The soy protein diet contained ~30 gram of soy protein/day, in the form of soy-based meat analogues and soy nuts provided by Alpro (Ghent, Belgium) containing ~48 mg isoflavones (18 mg daidzein, 26 mg genistein and 3 mg glycitein, Table 1). During the 1-week run-in period and the 4-week washout period, participants were not allowed to eat soy foods.

Background dietary intake
To monitor background dietary intake during the ISO and GD studies, the participants were asked to fill out a semi-quantitative validated food frequency questionnaire consisting of 125 items at the end of each 8-week intervention period.28 Background dietary intake in the SOY study was derived from duplicate portions of both experimental diets in which energy, fat, protein, ash and dry matter contents were analysed. Carbohydrate content was calculated by subtracting protein, fat, ash and moisture content from the total sample weight. Mean energy and nutrient intake per participant was calculated from food tables29 and adjusted for the duplicate diet analysis.

Sample collection
In the ISO study, plasma samples were collected halfway and at the end of each 8-week intervention period. During the GD study and SOY study, plasma was collected after each intervention period. Fasting venous blood samples were collected into 6 ml EDTA vacutainers (Becton Dickinson (BD), Breda, the Netherlands) and centrifuged for 10 min at 1190 g. Samples were collected into 6 ml EDTA vacutainers (Becton Dickinson (BD), Franklin Lakes, NJ, USA) and centrifuged for 10 min at 1190 g. In the ISO study, plasma samples were collected halfway and at the end of the 8-week intervention period.28

Data analysis
In the ISO study, one outlier was detected for all plasma concentrations (8 s.d. from mean) and excluded from the analysis. The GD study had three dropouts and the SOY study had one dropout. Ten subjects participated in more than one of the studies; these subjects were excluded from the study with most equal producers, resulting in 103 subjects, that is, ISO study n = 21, GD study DAI arm n = 32, GEN arm n = 35 and SOY study n = 15. Each subject contributed two data points (206 observations), one after the placebo or mixed protein period (unexposed) and one after the intervention period of each trial (exposed). Although these data are paired, they were considered statistically independent because plasma concentrations for unexposed were close to zero and not correlated to the concentration for exposed and there was no overlap in study subjects.

Linear regression analysis was used to explain the total and component-specific concentrations of isoflavones in plasma by intake (in μmol/kg body weight (BW)). Both dose and plasma concentrations (μmol/l) were loge-transformed and all models were adjusted for study (ISO study, GD study and SOY study). The data were loge-transformed as this improved the R² of the model compared with normal linear regression. For daidzein, equol and total isoflavones, the model also accounted for equol producer status (prod; 1 for producer, 0 for non-producer) and its interaction with intake:

\[
\log_e(\text{conc}) = \beta_0 + \beta_1 \times \log_e(\text{dose}) + \beta_2 \times \text{prod} + \beta_3 \times \text{prod} \times \log_e(\text{dose}) + \epsilon
\]

when original values for concentration were 0, 0.5 times the limit of detection was used to enable loge transformation of the data, that is, 0.02 for daidzein, equol, genistein and total isoflavones and 0.055 for glycitein. When intake was zero, a dose of 0.01 μmol/kg BW was used. To account for the role of the background diet, a second model was further adjusted for energy intake (continuous in kJ/day), carbohydrate intake (g/day) and fat intake (g/day). Dietary intake data from one participant in the GD DAI arm was missing.

To estimate inter- and intra-individual variation at a high supplement dose, loge-transformed plasma isoflavone concentrations after 4 and 8 weeks of isoflavone supplementation were used (ISO study, n = 29). Variance between subjects and total variance were obtained by the varcomp procedure and the mean square error of the regression model (MSEmodel). Coefficients of variation were obtained as CVbetween (%) = sqrt(MSEbetween)/(exp(Variance between−1)) × 100 and analogously for CVtotal and MSEmodel.30 Differences between plasma concentrations after 4 and 8 weeks of exposure to 94 mg isoflavones/day in the ISO study were tested with a paired t-test (P-value < 0.05; SAS v9.2, SAS Institute Inc, Cary, NC, USA).

Table 2. Mean (± s.d.) plasma isoflavone concentrations in equol producers and non-producers after the interventions

|                  | ISO study* | GD study DAI | GD study GEN | SOY study |
|------------------|------------|--------------|--------------|-----------|
|                  | (EP n = 21) | (EP n = 8, NP n = 24) | (EP n = 9, NP n = 26) | (EP n = 4, NP n = 11) |
| **Daidzein**     |            |              |              |           |
| EP               | 1.75       | 1.22         | 1.07         | 0.60      |
| NP               | 0.79       | 1.06         | 0.56         | 0.40      |
| **Equol**        |            |              |              |           |
| EP               | 1.20       | 0.72         | 0.61         | 0.39      |
| NP               | 0.52       | 0.58         | 0.28         | 0.15      |
| **Genistein**    |            |              |              |           |
| EP               | 0.69       | 0.40         | 1.19         | 1.16      |
| NP               | 0.52       | 0.33         | 0.90         | 0.87      |
| **Glycitein**    |            |              |              |           |
| EP               | 0.44       | 0.19         | 0.02         | 0.00      |
| NP               | 0.40       | 0.17         | 0.05         | 0.00      |
| **Total**        |            |              |              |           |
| EP               | 4.07       | 2.53         | 2.90         | 2.16      |
| NP               | 1.55       | 1.25         | 1.48         | 1.48      |

Abbreviations: DAI, daidzein-rich supplement; EP, equol producer; GD, genistein/daidzein; GEN, genistein-rich supplement; NA, not applicable; NP, non-producer. *The ISO and GD studies provided ~100 mg isoflavones/day (aglycone equivalents) as supplements for 8 weeks, the SOY study provided ~ 48 mg/day as soy protein diet for 4 weeks. 30Total isoflavones are the sum of daidzein, equol, genistein and glycitein.
**RESULTS**

In the studies with isoflavone supplements (~100 mg/day), the mean total isoflavone intake after 8 weeks exposure to isoflavones (daidzein, equol, genistein and glycitein) was 3.47 μmol/l for equol producers (n = 38) and 2.39 μmol/l for non-producers (n = 50). After the 4-week intervention with soy protein (~48 mg isoflavones/day), the mean total isoflavone concentration was 2.16 μmol/l for equol producers (n = 4) and 1.30 μmol/l for non-producers (n = 11, Table 2). For all studies at the end of the placebo or mixed protein period, 86% of the measured daidzein concentrations were below the quantification limit of the method; this was respectively 96, 96 and 100% for equol, genistein and glycitein.

Significant linear associations between natural logarithm (log_{10}) of plasma concentration and log_{10} of intake per kg BW (dose) were observed in non-producers for daidzein (β_{1} = 0.66), genistein (β_{1} = 0.70), glycitein (β_{1} = 0.20) and total isoflavones (β_{1} = 0.67, Table 3). In these non-producers, the regression coefficient of equol concentration on daidzein intake was β_{1}+β_{3} = 0.0, whereas in equol producers this was β_{1}+β_{3} = 0.63 (data from literature). Furthermore, for equol producers, the association between plasma daidzein and intake was β_{1}+β_{3} = 0.64 and for total isoflavones it was β_{1}+β_{3} = 0.74. This linear model on the log_{10}--log_{10} scale can be interpreted on a normal scale as concentration = e^{β_{1}+β_{3}} × dose^{β_{3}} with β_{0} (intercept) and β_{1} (dose, Figure 1), β_{2} (producer status) and β_{3} (intake-producer status interaction) were only relevant for equol producers for daidzein, equol and total isoflavone plasma concentrations. When isoflavone intake doubles from 1.5 to 3 μmol/kg BW, the equation is as follows: \( (1.5/3.0)^{β_{3}} = (2)^{0.67} = 1.59× \) fold or 59%. So, total isoflavone plasma concentrations in non-producers increase by 59% when their intake doubles.

Except for glycitein (\( R^2 = 0.48 \)), the explained variances of the models were higher than 0.87.

Inclusion of energy (kJ/day), carbohydrate and fat intake (g/day) in the model as background dietary intake did not change the associations (data not shown).

Figure 2 shows that the relation between intake and plasma concentration, calculated as the concentration divided by the dose, for soy foods is not different than that for isoflavone supplements.

Among the equol-producing women in the ISO study, plasma concentrations of the individual isoflavones after 4 and 8 weeks of exposure were similar (results not shown). In this study, within-person CV is smaller than between-person CV for all individual and total isoflavones, resulting in a large intraclass correlation coefficient (Table 4). The CVs between persons were 30–45% for all isoflavones, except for genistein (96%). The CV for MSEE_{model} comprising the inter- and intra-individual variation, was 31% for equol and ranged from 59 to 87% for the other isoflavones.

**DISCUSSION**

In this study, plasma isoflavone concentrations from 103 postmenopausal women participating in three intervention studies were evaluated after exposure to either isoflavone supplements or soy foods. A log-linear regression model showed that over a range of total isoflavone intakes from 0 to 100 mg/day, doubling of the dose (per kg BW) increased plasma concentrations from 55 to 62% (± s.e. 1–2%) for daidzein, genistein, equol (only in producers) and total isoflavones (\( R^2 = 0.87 \)). For glycitein, with an intake range of 0–28 mg/day, the observed increase was much smaller (15 ±1%, \( R^2 = 0.47 \)). Including background dietary intake in the model did not affect the associations. Both visual inspection of the regression model and quantification with ISO study data indicated large inter-individual variation of isoflavone plasma concentrations at this intake range.

We studied the isoflavone dose–concentration relation among 103 postmenopausal women, which is a relatively large sample size compared with other studies (n = 39–76).\(^{19,20}\) The percentage of equol producers in the studies (23–27%) was similar to that in the data from literature.\(^{12}\) Results from three intervention studies are presented, covering isoflavone intake from 0 to 100 mg/day. The three studies, having small differences in duration and dose, are comparable because they were conducted in postmenopausal women using similar determination of isoflavones with regard to lab, methods and reference materials. We demonstrated that data from 4 and 8 weeks of exposure could be combined in the repeated measurements of the ISO study, also supported by calculations from literature.\(^{31}\) and that food matrix did not influence the comparability of the studies.

The outcomes of our model suggested that production of equol did not affect daidzein plasma concentrations, as these concentrations increased equally for producers and non-producers (56 and 58%, respectively) on doubling the daidzein intake (Table 3). Equol plasma concentrations, only relevant for producers, did depend on daidzein intake as doubling intake increased plasma equol concentration by 55%. Together, this resulted in higher increases in total plasma isoflavone concentrations in equol producers (67%) than in non-producers (59%) on doubling daidzein intake. Previous literature is not consistent whether equol is produced at the expense of daidzein plasma concentrations,\(^{32–34}\) which might partly be explained by differences in the pharmacokinetics of daidzein and equol.\(^{35}\)

Our model was limited to daidzein, equol, genistein and glycitein, because other isoflavones or metabolites, like the gut metabolite O-desmethylangolensin, were not measured in these studies. In the model, we assumed that the ability to produce equol would influence daidzein, equol and total isoflavone concentrations and that a linear relation between the natural logarithms of intake and plasma concentrations existed. By using log_{10} transformations of both intake and concentration,

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**Table 3.** Outcomes of the linear regression model on log_{10}-transformed intake (μmol/kg BW) and log_{10}-transformed plasma concentrations (μmol/l)\(^{a}\)

|                | Non-producers\(^b\) | Producers\(^c\) |
|----------------|----------------------|-----------------|
|                | β_{0}  | 95% CI   | β_{1} × dose  | 95% CI   | % Change at doubling | β_{0}+β_{1} | 95% CI   | (β_{0}+β_{1}) × dose  | 95% CI   | % Change at doubling | R\(^2\) |
| Daidzein       | −0.54  | −0.70, −0.38 | 0.66      | 0.61, 0.71 | 58 | −0.49  | −0.74, −0.24 | 0.64      | 0.59, 0.70 | 56 | 0.87 |
| Equol          | −3.92  | −3.98, −3.85 | 0.00      | −0.02, 0.02 | 0 | −1.12  | −1.23, −1.02 | 0.63      | 0.61, 0.66 | 55 | 0.96 |
| Genistein      | −0.66  | −0.78, −0.54 | 0.70      | 0.67, 0.74 | 62 |          |          |          |          |    |      |
| Glycitein      | −2.14  | −2.26, −2.01 | 0.20      | 0.17, 0.24 | 15 |          |          |          |          |    |      |
| Total          | −0.39  | −0.55, −0.23 | 0.67      | 0.63, 0.72 | 59 | −0.06  | −0.31, 0.18 | 0.74      | 0.68, 0.79 | 67 | 0.90 |

Abbreviations: BW, body weight; CI, confidence interval. \(^a\)The log-linear regression model: log_{10}(conc) = β_{0}+β_{1} × log_{10}(dose)+β_{2} × prod+β_{3} × prod × log_{10}(dose)+ε. \(^b\)The model was adjusted for study (ISO, GD or SOY). \(^c\)The model was adjusted for study (ISO, GD or SOY), equol producer status (β_{0}) and log_{10}-transformed intake–producer status interaction (β_{1}).
homogeneity of the variance of error terms was allowed for while the back-transformed curve flattened down at higher doses. Without these log transformations and inclusion of the unexposed data, the model fit would be less (data not shown). The high explained variances of the models ($R^2 > 0.87$) indicated a good model fit, except for glycitein (Table 3), although plasma isoflavone concentrations varied substantially between individuals (Figure 1). This variation proved to be large when quantified by CV and intraclass correlation coefficient with ISO study data and the $MSE_{model}$ for the regression model (Table 4). Differences between these measures of variance can be explained by the number of studies and therefore supplements included. In previous studies

![Exponential regression lines](image1)

**Figure 1.** Exponential regression lines for the association between isoflavone intake ($μmol/kg BW$) and plasma concentration ($μmol/l$) combined with individual data. Isoflavone intake and plasma concentration on the x and y axes refer to specific isoflavones; (a) shows daidzein intake with daidzein plasma concentration and daidzein intake with plasma equol concentration; (b) shows genistein intake with genistein concentration and total isoflavone intake with total isoflavone concentration.

![Relative plasma isoflavone concentrations](image2)

**Figure 2.** Relative plasma isoflavone concentrations of equol producers (a) and non-producers (b) in the three studies. Relative concentrations were calculated by dividing plasma concentrations in $μmol/l$ by intake in $μmol/kg BW$. The bar for equol concentration is placed on top of the bar for daidzein concentration.
with isoflavone supplements, inter-individual variation in plasma isoflavone concentrations was quantified as 162–1596-fold for the individual isoflavones.19,20 Inter-individual variation might be caused by differences in uptake efficiency and metabolism, which in turn might be influenced by microbiota10 or genetic variation in transporter genes.36 Other studies hypothesized that fat, carbohydrate and fibre intake could explain inter-individual variation.37,38 Therefore, we complemented our model with energy, fat and carbohydrate intake data. Fibre intake data could not be extracted from the food frequency questionnaire used. This adjustment did not change the observed associations and suggests that background dietary intake did not explain the observed inter-individual variation. However, the relatively high CV% of the method might have influenced the observed inter-individual variation to a limited extent.

Postmenopausal women produce little endogenous estradiol and are therefore considered susceptible to the potentially beneficial or even adverse health effects of isoflavones when using these supplements. Our study confirmed that supplement intake by postmenopausal women led to high concentrations of circulating isoflavones compared with soy food intake in Japanese populations.15 For risk assessment purposes, plasma isoflavone concentrations from 103 postmenopausal women in this study could be explained by isoflavone intake and equal producer status at a relevant intake range of 0–100 mg isoflavones/day.

Despite the adequate explanation of plasma isoflavone concentrations over this intake range, the large inter-individual variation will restrict the use of this model for future risk assessment to the population level and cannot be applied to predict plasma concentrations in individuals.

CONFlict OF I nterest
The authors declare no conflicts of interest.

ACKNOWLEDGEMENTS
We would like to thank Dini Venema for her excellent technical assistance with the HPLC analysis and Elis Siebelink, Corine Perenboom, Saskia Meyboom and Karin Borgonjen for providing the FFQ data. Furthermore, thanks to Springfield Nutraceuticals and Alpro for providing the supplements and soy foods. The ISO and ISO II (GD) studies were funded by the Dutch Food Safety Authority (nWVA), and the SOY study was funded by the Alpro Foundation.

Table 4. Between-person and total variance, coefficient of variation (%) and ICC of isoflavone concentrations 4 and 8 weeks after supplementation with 94 mg isoflavones (aglycone equivalents) in the ISO study in 29 equol-producing postmenopausal women

| Isoflavone | CV_within | CV_total | ICC | MSE model |
|-----------|-----------|----------|-----|-----------|
| Var_within | Var_total |           |     |           |
| Daidzein   | 0.18      | 0.44     | 0.27| 0.56      | 0.67 | 0.52 | 0.83 | 1   |
| Equol      | 0.18      | 0.45     | 0.27| 0.56      | 0.67 | 0.67 | 0.31 | 31  |
| Genistein  | 0.65      | 0.96     | 0.81| 0.12     | 0.80 | 0.32 | 61  | 32  |
| Glycitein  | 0.19      | 0.46     | 0.56| 0.87      | 0.34 | 0.30 | 59  | 59  |

Abbreviations: CV, coefficient of variation; ICC, intraclass correlation coefficient; MSE, mean square error; Var, variance. 1CV% of coefficient of variation between persons from loge-transformed concentration data calculated as the square root of the exponent of the variance minus 1.

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