Dietary Lignins Are Precursors of Mammalian Lignans in Rats

Aynun Nahar Begum, Catherine Nicolle, Isabelle Mila,* Catherine Lapierre,* Kazutane Nagano,† Kazuhiko Fukushima,† Satu-Maarit Heinonen,** Herman Adlercreutz,** Christian Rémésy and Augustin Scalbert†

Unite des Maladies Metaboliques et Micronutrients, INRA Theix, 63122 Saint-Genes-Champanelle, France; *UMR de Chimie Biologique, INRA-INAPG, Institut National Agronomique Paris-Grignon, 78850 Thiverval-Grignon, France; †Graduate School of Bioagricultural Sciences, Nagoya University, Nagoya 464-8601, Japan; and **Institute for Preventive Medicine, Nutrition, and Cancer, Folkhalsan Research Center, and Division of Clinical Chemistry, University of Helsinki, PL 63, FIN-00014, Helsinki, Finland

ABSTRACT The mammalian lignans enterolactone (ENL) and enterodiol, commonly found in human plasma and urine, are phytoestrogens that may contribute to the prevention of breast cancer and coronary heart disease. They are formed by the conversion of dietary precursors such as secoisolariciresinol and matairesinol lignans by the colonic microflora. The identification of lignins, cell-wall polymers structurally related to lignans, as precursors of mammalian lignans is reported here for the first time. In study 1, rats were fed rye or wheat bran (15% diet) for 5 d. Untreated brans and brans extracted with solvents to remove lignans were compared. ENL was estimated in urine samples collected for 24 h by time-resolved fluoroimmunoassay. ENL urinary excretion was reduced from 18.6 to 5.3 nmol/d (n = 8; P < 0.001) when lignans were removed from rye bran and from 30.5 to 6.2 nmol/d (P < 0.001) when they were removed from wheat bran. These results suggest that lignins, embedded in the cell wall and retained in the bran during solvent extraction, account for 26–32% of the ENL formed from cereal brans. In study 2, rats were fed a deuterated synthetic lignin (0.2% diet) together with wheat bran (15%) for 3 d. The detection of deuterated ENL by LC-tandem MS in urine (20 nmol/d) clearly confirms the conversion of lignin into mammalian lignans. More research is warranted to determine the bioavailability of lignins in the human diet. J. Nutr. 134: 120–127, 2004.

KEY WORDS: lignins • lignans • enterolactone • phytoestrogens • rats

Phytoestrogens are plant constituents with estrogenic properties that have been implicated in the prevention of breast and prostate cancers, osteoporosis or cardiovascular diseases (1,2). The most largely studied phytoestrogens are the soy isoflavones. Lignans form another class of phytoestrogens. Two main lignans, enterolactone (ENL) and enterodiol (END) (Fig. 1) were first detected in human urine and plasma and were called “mammalian lignans” (3,4). They bind weakly to estrogen receptors (5), have estrogenic effects in cultured cells (6,7) and can modulate the response to endogenous estrogens (8,9).

ENL and END result from the conversion of some dietary precursors by the colonic microflora (10–12). The main precursors identified to date are secoisolariciresinol (SECO) and matairesinol (MAT), which are abundant in flaxseed (Fig. 1) (10,13,14) and present in low amounts in several other food sources (15–17). Other lignan precursors were recently identified by incubating human fecal microflora (18) or feeding rats pure compounds (19,20); these include pinoresinol (PIN), lariciresinol (LAR) and 7-hydroxymatairesinol.

Animal experiments suggest that lignans may play a role in the prevention of cancers. Supplementation of the diet with plant lignans delays the progression of chemically induced mammary tumorigenesis in rats (21–23). Inverse associations between the plasma concentration or urinary excretion of lignans and the risk of breast cancers were also observed (24–28). The effect of mammalian lignans on prostate cancer was also examined. ENL and END inhibit the growth of human prostate cancer cell lines in vitro (29). However the dose used was much higher than that observed in vivo and no association was found between the excretion of ENL and prostate cancer in a case-control study (30).

Lignans may also influence bone metabolism and prevent osteoporosis. Continuous administration of SECO with the diet to nursing rat dams improved bone strength of young female offspring (31). In humans, the levels of ENL urinary excretion were lower in Korean postmenopausal women with osteoporosis compared with healthy women (32). However,
are generally associated with a high intake of dietary human tissues. High ENL and END levels in urine or plasma not explain the general occurrence of mammalian lignans in low consumption of disease risk, little is known concerning their dietary origin. Despite the potential importance of lignans in reducing disease risk, little is known concerning their dietary origin. Flaxseed was recognized as a rich source of lignans and continues to be their best dietary source (34,35). However, the low consumption of flaxseed in most human populations cannot explain the general occurrence of mammalian lignans in human tissues. High ENL and END levels in urine or plasma are generally associated with a high intake of dietary fiber and with the consumption of whole-grain food and fruit and vegetables (16,27,36–40). It was suggested that the lignans contained in these food sources were the precursors of ENL and END. However, two studies in which rats or humans were fed whole-meal cereals or cereal bran showed that the content of SECO and MAT, the two main lignans identified in cereals, was too low by a factor of 5–25 to explain the levels of ENL and END excreted in urine (36,41). The recent identification of a number of lignans in rye (18) and other cereals still does not completely explain the urinary excretion of ENL and END. This suggests the existence of other precursors.

We propose here that lignins are major dietary precursors of mammalian lignans. Lignins are structurally related to lignans but differ from them by their polymeric nature and distribution in plants. They are cell-wall polymers made of phenylpropane units (Fig. 2) (42). The most common monomers in lignins are guaiacylpropane units (G); lignins are therefore structurally closely related to SECO and MAT (Fig. 1). Some lignins, like those in cereals, also contain syringylpropane (S) and p-hydroxyphenylpropane (H) units. They cannot be easily extracted by solvents unless they are chemically or physically degraded into smaller fragments. Lignins are found in vessels and secondary tissues of all higher plants. They are thus present in a large variety of foods, and are particularly abundant in cereal brans (43). In contrast, lignans are dimers of phenylpropane units, present in vacuoles and extractable by organic solvents (44). They are usually specific to a plant species such as SECO in flaxseeds.

In the present work, we fed rats cereal brans that had and had not had lignans removed by solvent extraction to examine the respective contribution of plant lignans and lignins to the formation of mammalian lignans. We also fed rats a deuterated synthetic lignin and measured the excretion of deuterated ENL in urine. We demonstrate for the first time that lignins are precursors of lignan phytoestrogens.

**MATERIALS AND METHODS**

**Preparation of cereal brans.** Untreated rye and wheat brans were kindly supplied by Celnat (St Germain Laprade, France). Insoluble and soluble dietary fiber were determined on brans by a combination of enzymatic and gravimetric methods (45). To prepare extractive-free brans, 400 g wheat or rye bran were successively extracted in a Soxhlet by ethanol/toluene 2:1 (v/v), ethanol, and water. Extracted brans were then dried at 50°C for 2 d. The weight loss gave the total extractive contents (Table 1). To prepare lignin-enriched wheat bran, the extractive-free wheat bran suspended in water (40 g/L) was hydrolyzed by Onozuka cellulase (Yakult & Company, Tokyo, Japan) in 0.05 mol/L acetate buffer, pH 4.7, for 70 h at 37°C. The insoluble residue was recovered by centrifugation (75,000 × g, 45 min), washed three times with water and freeze-dried. Lignins were determined by the Klonov gravimetric method on the extractive-free and lignin-enriched brans. This gravimetric determination systematically includes a correction for ash-forming compounds present in bran samples (46). The monomeric composition of bran lignins was determined by thiocellulolytic analysis of the lignin-derived monomers by GC-MS as their trimethylsilyl derivatives (47). Thiocellulolytic analysis of plant tissues coupled with GC-MS of the lignin-derived products makes it possible to detect small amounts of lignin without interference from other phenolics such as bran ferulic acid esters (47). During this reaction, thioethylated H, G and S monomers are formed from the H, G and S lignin units involved in above B-O-4 ether bonds, the most frequent interunit linkages of native lignin.

**Determination of lignins in brans.** The GC-MS method used for analysis of plant lignans MAT and SECO, isolariciresinol (ISOL), LAR, PIN and syringaresinol (SYR) in different brans was optimized from previously published method for the analysis of isoflavonoids and lignans in food matrices (48). Duplicate analyses were carried out for each sample. To clearly differentiate the lignans from the lignins, an additional extraction step was added to the sample pretreatment method. The lignans were extracted from brans or the control purified diet (50 mg) with acetone/water 7:3 (2 mL) at room temperature for 2 min three times. This additional step was necessary because part of...
the insoluble lignins were degraded to lignans when the following sample pretreatment method was applied directly to the brans or to the residue of selected samples, obtained after acetone/water extraction (S. Heinonen, H. Adlercreutz, A. Scibert, unpublished results). Furthermore, all lignans are extractable by aqueous acetone. The supernatant obtained after centrifugation (5000 × g, 10 min) was dried under a nitrogen flow and used for further analyses. Deuterated internal standards (deuterated SECO and anhydrosecoisolariciresinol) were simultaneously added dropwise using a micro-pump (15,000 × g, 30 min), dissolved in dichloroethane/ethanol 2:1 (v/v)(50 mL) and added dropwise to excess diethyl ether with vigorous stirring to eliminate the low-molecular-weight products such as monomers, dimers (= lignans) or trimers. The precipitate was recovered by centrifugation (15,000 × g, 30 min, 4°C) and washed five times with diethyl ether (5 × 40 mL). The elimination of lignans was confirmed by silica gel TLC with 1,2-dichloroethane/MeOH 20:1 (v/v) as eluant. The insoluble DHP was dried over phosphorus oxide in vacuo (yield, 1.3 g).

The DHP was characterized by thioacidolysis (50). The main monomeric products were 2-methoxy-4-(1,2,3-tris-ethylsulfanylpropyl)-phenol (I), 4-(1,3-bis-ethylsulfanyl-propyl)-2-methoxy-phenol (II) and 4-(3-ethylsulfanylpropenyl)-2-methoxy-phenol (III) with respective yields of 649, 263 and 127 μmol/g (Fig. 3). The high yield of (II) and (III) indicates a high content of β-O-4-linked coniferyl alcohol end-groups compared with natural lignins (50,51). Intermediate linkages were also quantified by thioacidolysis followed by Raney nickel desulfuration (52). The main dimers recovered were of the β-5 type (IV and V) and β-β type (VI) (53,54, respectively, of the total dimers) originating from phenylcoumaran and PIN structures, respectively.

**Rats, diet and sampling procedure.** Male Wister rats (Iffa-credo, L’Arbresle, France) weighing ~100–120 g were used. Rats were housed two per cage in a room maintained at 22°C with a 12-h light/dark cycle (light from 0800 to 2000 h) with access to food from 1600 to 2000 h. Rats were maintained and handled according to the recommendations of the Institutional Ethics Committee (Institut National de la Recherche Agronomique), according to decree no. 87–848.

In study 1, 48 rats were first adapted for 18 d to a semisynthetic basal diet. The basal diet consisted of casein (150 g/kg diet), wheat starch (755 g/kg diet), mineral mixture (35 g/kg diet), vitamin mixture (10 g/kg diet) and peanut oil (50 g/kg diet). The mineral mixture AIN-93M and vitamin mixture AIN-76A supplemented with choline were used (ICN Biochemicals, Aurora, OH) (33). After adaptation to the basal diet, rats were moved to metabolic cages, randomly assigned to 6 groups and different brans were added to the diets in place of an equivalent weight amount of starch. The six groups of rats were thus equivalent in weight and composition. More peroxidase (5.0 mg) was then added to the reaction mixture and stirred for an additional 24 h. The resulting insoluble polymer was separated by centrifugation (15,000 × g, 30 min), dissolved in dichloroethane/ethanol 2:1 (v/v)(50 mL) and added dropwise to excess diethyl ether with vigorous stirring to eliminate the low-molecular-weight products such as monomers, dimers (= lignans) or trimers. The precipitate was recovered by centrifugation (15,000 × g, 30 min, 4°C) and washed five times with diethyl ether (5 × 40 mL). The elimination of lignans was confirmed by silica gel TLC with 1,2-dichloroethane/MeOH 20:1 (v/v) as eluant. The insoluble DHP was dried over phosphorus oxide in vacuo (yield, 1.3 g).

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intakes did not differ during the urine collection period and were
controls, and urine samples were collected for 24 h on these 3 d. All
Three other rats were fed the original 15% wheat bran diet as
same wheat bran diet to which was added 0.2% labeled DHP for 3 d.
showing the highest level of lignan excretion were selected for
feeding the DHP diet. This was done to maximize the chances of
detecting labeled ENL when feeding low amounts of labeled DHP to
rats. On d 15, the three selected rats were fed the
original 15% wheat bran diet supplemented with DHP and the control diet, respectively.


g/d in rats fed rye, extracted rye, wheat, extracted wheat, lignin-enriched wheat brans and controls diets, respectively.

In study 2, 12 rats were first fed the same 15% wheat bran diet as
above for 14 d. They were moved to metabolic cages on d 10 and
urine samples were collected for 24 h as described above on d 10 and
11. ENL was estimated in these urine samples and the three rats
showing the highest level of lignan excretion were selected for
feeding the DHP diet. This was done to maximize the chances of
detecting labeled ENL when feeding low amounts of labeled DHP to
a limited number of rats. On d 15, the three selected rats were fed the
same wheat bran diet to which was added 0.2% labeled DHP for 3 d.
Three other rats were fed the original 15% wheat bran diet as
controls, and urine samples were collected for 24 h on these 3 d. All
rats consumed their feed ad libitum throughout the experiment. Food
intakes did not differ during the urine collection period and were
(1.7, 19.8 ± 2.8 g dry matter/d in rats fed rye, extracted rye, wheat, extracted wheat, lignin-enriched wheat brans and controls diets, respectively.

Time-resolved fluoroimmunoassay (TR-FIA) for ENL. This
immunoassay allows the specific estimation of ENL at a low concentra-
tion with very low cross-reaction for END (0.28%) and no inter-
ference from other compounds that have been investigated (54–56).

The assay was carried out as previously described (41). Briefly, urine
samples were treated with β-glucuronidase and sulfatase and ENL
estimated using the DELFIA kit (Wallac Perkin Elmer, Turku, Finland) and a Victor 1420 multilabel counter.

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Results

Enterolactone formed from cereal brans. Rye and wheat
brans were used as dietary sources of lignans and supplemented
to the purified diet of rats. Some of these brans were extracted
successively with a Soxhlet by ethanol/toluene, ethanol and
water to remove lignans. Lignans were analyzed in both un-
treated brans and extractive-free brans. The total concentra-
tions of lignans were 3335 and 139 μg/100 g for the untreated
and extractive-free rye brans, respectively, and 2764 and 89
μg/100 g for the untreated and extractive-free wheat brans,
respectively (Table 1). Extractive-free brans then contained
virtually no lignans (96–97% removed) but still contained
lignins (7.0 and 5.5 g/100 g for rye and wheat, respectively;
Table 1), which cannot be extracted by solvents.

The bran-supplemented diets were fed to the rats for 5 d
and ENL estimated in urine samples collected for 24 h by
TR-FIA assay (Table 2). The ENL excretion did not differ
significantly between rats fed untreated rye and wheat brans.
When these brans were extracted with a Soxhlet, the excre-
tion of lignans was significantly reduced (Table 1). The
value in rats fed untreated brans but was still 5–6 times
higher than that for control rats (P < 0.001). This shows that
the nonextractable materials in brans still contain ENL pre-
cursors different from lignans.

To examine whether these nonextractable ENL precursors
could be lignins, we established unequivocally the occurrence of
lignins in extractive-free brans using thioacidolysis. The detection of the three thioethylated H, G and S monomers demonstrates that the three lignin units H, G and S are
present in the extractive-free bran samples (Table 1). To further establish the involvement of native lignins in the
formation of urinary lignans, we treated the extracted wheat
bran with a commercial mixture of cellulases and hemicellu-
lases. This treatment removed part of the cell-wall polysac-
charides, resulting in a 310% increase in the lignin content in
this enzyme-treated bran (Table 1). The amount of this enzyme-treated bran added to the diet was determined to provide the same lignin amount to the rats as was given with the diet supplemented with the extractive-free wheat bran (Table 2). The level of ENL urinary excretion was close to that of rats fed the extractive-free wheat bran diet although the amount of bran ingested by the rats was only 31%. The ENL excretion level thus appears to depend in part on the amount of lignins ingested with the diet.

Enterolactone formed from lignin dehydropolymers. Three rats were first fed a diet supplemented with 15% wheat bran for 14 d. A labeled lignin dehydrogenation polymer (DHP) was then added to this same diet (0.2%) for three more days and urine samples were collected for 24 h over these 3 d. The DHP group was compared with the control group fed the diet supplemented with wheat bran only. The excretion of both unlabeled and labeled-ENL was followed in urine by LC-ESI-MS/MS (Fig. 4). Feeding the labeled DHP greatly increased D_2-ENL excretion compared with the control rats (19.9 vs. 0.9 nmol/d, \( P < 0.001 \) at d 3 of the DHP diet) (Fig. 5). Excretion levels of unlabeled ENL did not differ between the DHP-fed rats and control rats (the higher means for the DHP-fed rats is explained by the selection of the best lignan producers for feeding the labeled-DHP; see experimental section). The D_2-ENL/nonlabeled ENL in the urine of the DHP-fed rats increased after d 1–2 of feeding the labeled DHP, reflecting the time needed for the DHP to be metabolized by the cecal microflora after ingestion. These results show unambiguously that lignins can be degraded into ENL, in a way similar to lignans.

The presence of END was determined in the urine of rats by tandem MS (m/z 301/253). Levels of excretion were low and did not exceed 1.1 nmol/d in rats fed the 15% wheat bran diet. No labeled END (m/z 305/257) could be detected in rats fed the labeled DHP.

**DISCUSSION**

Mammalian lignans differ from all other polyphenols detected in human plasma or urine because not all of the dietary precursors that explain their concentrations or levels of excretion have been identified. The most evident dietary sources of mammalian lignans are plant lignans. However, the number of plant foods containing significant amounts of lignans is very limited.

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**TABLE 2**

**Polyphenol intake and enterolactone (ENL) urinary excretion in rats consuming diets supplemented with different cereal brans**

<table>
<thead>
<tr>
<th>Diet</th>
<th>Bran in diet</th>
<th>Lignin intake</th>
<th>Lignan intake</th>
<th>ENL excretion^1</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>g/100 g</td>
<td>mg/d</td>
<td>Total</td>
<td>ENL precursors^2</td>
</tr>
<tr>
<td>Rye bran</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>15.0</td>
<td>159</td>
<td>246.6</td>
<td>61.3</td>
</tr>
<tr>
<td>Extractive-free</td>
<td>10.7</td>
<td>142</td>
<td>7.2</td>
<td>2.0</td>
</tr>
<tr>
<td>Wheat bran</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Untreated</td>
<td>15.0</td>
<td>138</td>
<td>217.7</td>
<td>45.0</td>
</tr>
<tr>
<td>Extractive-free</td>
<td>10.2</td>
<td>108</td>
<td>4.3</td>
<td>0.2</td>
</tr>
<tr>
<td>Extractive-free and treated with cellulases</td>
<td>3.2</td>
<td>99</td>
<td>0.4</td>
<td>0.0</td>
</tr>
<tr>
<td>Control</td>
<td>—</td>
<td>—</td>
<td>2.4</td>
<td>0.2</td>
</tr>
</tbody>
</table>

^1 Values are means ± SD, \( n = 8 \). Means without a common letter differ, \( P < 0.001 \).

^2 Main enterolactone precursors are secoisolariciresinol + matairesinol + lariciresinol + pinoresinol.
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limited. Flaxseed contains SECO and MAT (14), and sesame seeds contain sesamin and other furanolignans (57). However, both foods are generally consumed in limited amounts and cannot explain the systematic excretion of mammalian lignans in urine. A large variety of grains, fruits, vegetables and beverages such as tea or coffee were also found to contain small amounts of SECO (< 3.5 mg/100 g) and traces of MAT (16,17).

In the present work, if we assume an average recovery yield of 32% in urine (58), SECO and MAT could account for no more than 20 and 14% of the ENL excreted in the urine of rats fed the diets supplemented with rye and wheat brans, respectively, and for 0 and <6%, respectively, when the same brans were previously extracted to remove the major part of the lignans. Other lignans such as PIN and LAR were also shown to be metabolized in high yields into ENL and END when incubated in vitro with a human fecal microflora (18). PIN and LAR were thus also estimated in the bran diets, in addition to SECO and DHP. If we assume that more than 20% of ENL excreted in the urine of rats fed the diets supplemented with rye and wheat brans, respectively, but for only 13 and 1%, respectively, when both brans were previously extracted with solvents. This clearly suggests the presence of other precursors.

The contribution of plant lignans to the formation of mammalian lignans could be somewhat underestimated because SYR, the major lignan in rye and wheat bran (3 times more abundant than SECO, MAT, PIN and LAR taken together), can also be converted to ENL and END, although in a yield which does not exceed 7% of those of the other four lignans (18).

Lignins are structurally related to lignans and may also be metabolized into mammalian lignans. Lignins were unequivocally detected by thioacidolysis in rye and wheat brans where they account for ~5% of their weight (Table 1). Native lignins cannot be isolated without substantial degradation due to their insoluble and cross-linked nature (59). To examine whether lignins are effective precursors of mammalian lignans, a lignin-enriched wheat bran and a deuterated synthetic lignin (DHP) were prepared and fed to rats. When the lignin-enriched extractive-free wheat bran (310% lignin-enriched) was compared with the extractive-free wheat bran, ENL yields were similar when calculated on a lignin intake basis (78 and 58 nmol/g, respectively).

It is difficult to obtain pure lignins from complex plant materials and more particularly from materials such as brans, which have a relatively low lignin content compared with other lignocellulosic materials such as wood. For this reason, we prepared a synthetic lignin, free of any other contaminants. The synthetic lignins are prepared by oxidative polymerization of coniferyl alcohol and are called dehydrodimers (DHP). To differentiate ENL originating from the degradation of DHP from that originating from other constituents of the diet, a labeled DHP was prepared from [γ,γ-D]-coniferyl alcohol. In the labeled DHP, the distal carbon of the propane side chain of most of the monomeric units carries two deuterium atoms in the place of hydrogen. The ENL that would result from the metabolism of the labeled lignins by the rat microflora would then carry two deuterium atoms.

When the labeled DHP was fed to rats, D2-ENL was specifically detected, showing that lignins can be metabolized into ENL in rats. The yield of D2-ENL was 655 nmol/g DHP (195 μg/g). This yield is ~10 times higher than that calculated for bran lignins. These differences could be explained either by a limited accessibility to the substrate for bran lignins embedded in the cell wall or to structural differences between native bran lignins and synthetic lignins. To examine the first possibility, extractive-free wheat bran was thinly ground with a Retsch grinder (particle size < 0.5 mm) and fed to rats (not shown). The ENL urinary excretion was not affected by grinding. Therefore, a difference in substrate accessibility cannot be responsible for the difference in ENL yields between native and synthetic lignins.

The most likely explanation is a difference in the structure of the synthetic DHP compared with the bran native lignins. The precursors of mammalian lignans within the lignin are most likely the PIN and LAR structures (see dotted line circles, Fig. 2). The content of such structures in the DHP was determined by thioacidolysis followed by reduction with Raney nickel desulfuration (see experimental section). The PIN structures accounted for 23% of the total dimers recovered after such a chemical degradation. This value is much higher than that commonly observed for native lignins such as those present in a wheat bran and this difference most likely explains the high yield of ENL formation observed when the DHP is fed to the rats (60).

Lignins, because of their polymeric nature and of their embedding in the cell wall, are usually considered inert in the digestive tract. However, the present results show that they are metabolized by the gut microflora to form part of the ENL excreted in urine. Similarly, proanthocyanidins, natural phenolic polymers with antimicrobial properties, were also shown to be degraded into various phenolic acids by the gut microflora (61–63). Another observation not previously noted is the absence of optical activity of ENL and END excreted in urine (64). A lignin origin for mammalian lignans is consistent with the absence of optical activity of lignins due to their biosynthesis through radical polymerization (65). This contrasts with the biosynthesis of plant lignans, which is stereospecific and leads to the formation of optically active lignans (66,67).

The respective contributions of lignins and plant lignans to the genesis of mammalian lignans can be evaluated from the comparison of the ENL excreted in urine after feeding whole brans or extractive-free brans (Table 2). Lignins account for 32 and 26% of the ENL excreted in the rats fed rye and wheat brans, respectively. Lignans present in brans would account for the remaining fraction.

The SECO and MAT intakes in Western populations were calculated using the SECO and MAT content in foods and beverages previously published (68). An intake of 1.5–3 μmol/d was determined for SECO and MAT in two Dutch and American cohorts (69,70), but this value could be 10 times higher if other lignans such as those estimated here in cereal brans were considered (70). The intake of these lignans explains in part the urinary excretion levels of mammalian lignans (6.5–27 μmol/d) in various populations (71). However, previously published lignan content values in food may be overestimated. Indeed, the analytical method used differs from the one used here by the mode of extraction of the lignans (48) and also gives positive values for SECO and other lignans when applied to a lignan-free lignin sample (S. Heimonen, H. Adlercreutz and A. Scalbert, unpublished results). Food composition tables for lignins do not exist. More data on lignan and lignin contents in foods will be required to determine their respective contributions to the mammalian lignan formation.

LITERATURE CITED


