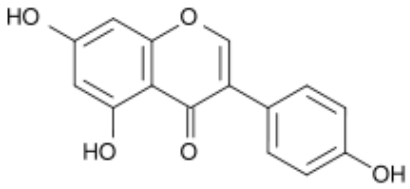
Bijlage 2 van het advies 29-2009 : Fiche Genistein

GENISTEIN

CAS no. 446-72-0

4',5,7-trihydroxyisoflavone (CAS No 446-72-0) is an Isoflavone, a member of the family of flavonoids

Chemical form



Genistein

Origin

Genistein occurs in plants mainly under the form of glycoside, genistin. Genistin has been found in kidney beans, lentils, parsley, peanuts and sage, the predominant source being soy. Beside genistin, soy beans also contain glycosides of daidzein and glycitein. Glycosides are no absorbed as such (Piskula *et al.,* 1999; Setchell *et al.,* 2002; Rowland *et al.,* 2003). For absorption to occur, isoflavones must first be hydrolysed to their aglycone. Absorbed genistein and other isoflavones are rapidly conjugated with glucuronic acid or sulfate. Conjugated genistein is excreted with the urine and, to a lesser degree, with the bile (Sfakianos *et al.,* 1997). The microbial degradation of genistein in the intestine is more important than the hepatic metabolism. The metabolism of genistein in the human body or in the digesta, does not result in the formation of unusual metabolites that might be physiologically more active than the parent compound.

Mode of action (toxicological data: Major biologic effect, active dose)

Carcinogenicity

Genistein is not genotoxic.
Carcinogenicity studies of genistein in rats showed that there were no non-neoplastic or neoplastic changes that could be attributed to the treatment, except for an increased incidence of mammary gland adenoma/adenocarcinoma and pituitary adenoma in the high dose group females with continuous genistein exposure for 2 years. In males of the high dose group, a statistically not significant increased incidence of minimal mammary gland hyperplasia was noted and the incidence of pancreatic islet adenoma/adenocarcinoma tended to be increased. With regard to the first observation, it should be noted that the ingestion of soy isoflavonoids with a genistein content of 50% at a dietary level of 12 mg/kg bw/day for a period of 3 years had no histopathological effect on the mammary gland of male Cynomolgus monkeys (Perry *et al.,* 2007).

Endocrine disrupting activity

Estrogenic activity

Genistein has estrogen agonist and antagonist actions. Genistein acts through estrogen receptor-mediated mechanisms (Galati and O'Brien, 2004). Genistein has a weak estrogenic potency. Depending upon the test system that is applied, its estrogenic potency is by a factor of 10^2 - 10^5 below that of estradiol. *In vitro* receptor binding assays yield usually the highest values while the uterotrophic assay gives the lowest value (cf. COT, 2003).
There is a considerable controversy as to whether isoflavones are net estrogen agonists or whether they act via antiestrogenic effects. Other properties that may result in isoflavone effects include antioxidant activity, inhibition of growth factor receptor signaling via tyrosine kinases, induction of apoptosis and/or induction of cell differentiation (Niculescu *et al.*, 2007).

- **Epidemiological studies**

Although convincing evidence for both the beneficial and detrimental effects of genistein exposure is limited, it has been reported to reduce mammary cancer in rats and to lower cholesterol levels in humans (cited in Henley and Korach, 2006).

Epidemiological studies (in China and Japan) and *in vitro* laboratory experiments with membrane preparations or cells in culture support the belief that flavonoids in human diet can reduce risk of various cancers, especially hormone-dependent breast and prostate cancers. From this point of view, two major soya isoflavonoids, genistein and daidzein, having weak estrogenic and anti-estrogenic activity in respect to estrogen receptor and aromatase, respectively, are suggested to account for the health beneficial properties of soy derived food (Hodek *et al.,* 2002).

A human study in which subjects were given single doses of genistein (2, 4 or 8 mg/kg; each dose was separated by 1 week) reported that after one dose, tyrosine phosphorylation was significantly changed, suggesting that soy can modulate cell-signaling pathways *in vivo* (Niculescu *et al.,* 2007).

Dietary soy isoflavones induced changes in gene expression in postmenopausal women. These genes are involved in a variety of pathways. Importantly, some of the changes were related to increased cell differentiation, increased cAMP signaling and G-protein-coupled protein metabolism and increased steroid hormone receptor activity.

Closer studies in experimental animals and human populations exposed to phytoestrogen-containing products, and particularly soy-based infant formulas, are necessary as the estrogenic activity of genistein has been shown to be associated with decreased fertility and increased sexual dysfunction in experimental animals at high doses (Galati and O'Brien, 2004).

- ***in vivo studies***

Genistein has been shown to have estrogenic activity on the uterus, mammary and hypothalamic axis in rats (Dodge, 1998).
Genistein exhibits *in vivo* estrogenic activity as well as tyrosine kinase inhibitory properties (cited in Henley and Korach, 2006).

Genistein has been associated with diminished reproductive capacity in animals and has been shown to induce uterine adenocarcinomas in a neonatal mouse model and to increase the incidence of mammary tumors in rats (cited in Henley and Korach, 2006). Genistein has genomic effects (inhibitor of protein kinases and topoisomerase, activity utero-topical of 0.005 compared to 100 for estradiol in the mouse); Genistein is a partial agonist (Pike *et al.,* 1999).

- ***in vitro* studies**

Genistein *in vitro* inhibits the production of prostatic sulphate acid molecule used as a marker of cancer activity of a cell in both cancer cell lines in the prostate and brain (Duquesnoy, 2005).

Genistein is a potent and specific *in vitro* inhibitor of tyrosine kinase action in the autophosphorylation of the epidermal growth factor receptor and is thus frequently used as a pharmacological tool (Wiseman, 2006).

Recent reports suggest that soy isoflavones, particularly genistein, can induce gene damage. Genistein induced mammalian topoisomerase-II-dependent DNA cleavage in purified broken cell preparations and induced increased DNA strand breaks as detected by COMET assay and micronucleus formation in mouse lymphoma cells in culture. It is proposed that genotoxicity arises from alterations of the DNA topoisomerase II activity, resulting in a stabilization of DNA double-strand breaks at topoisomerase II–DNA binding sites (cited in Niculescu *et al.*, 2007).

Genistein is a weak estrogen which compete with 17β-estradiol in receptor binding assays (Dodge,

1998).
Genistein exhibits a concentration-dependent ability to inhibit both growth factor-stimulated and estrogen-stimulated (reversed by 17β-estradiol) cell proliferation. Genistein at low concentrations can, in the absence of any estrogens, stimulate the growth of estrogen receptor-positive MCF-7cells. Genistein does not, however, stimulate the growth of estrogen receptor-negative breast cancer cells. Its only inhibits cell proliferation in these cell lines (Wiseman, 2006).

Receptor-binding assays indicate that genistein preferentially binds to ERβ in comparison with ERα, with relative binding affinities reported from 20 to 30 fold higher for ERβ (cited in Henley and Korach, 2006). It can also act as an estrogen agonist via both ERα and ERβ in some test systems (cited in Wiseman, 2006).

Although genistein is a much better ligand for ERβ than for the ERα (20-fold higher binding affinity), it can also act as an estrogen agonist via both ERα and ERβ in some test systems. However, genistein also behaves as a partial estrogen agonist in human kidney cells transiently expressing ERβ, suggesting that it may be a partial estrogen antagonist in some cells expressing Erβ (cited in Wiseman, 2006).

Binding affinity of genistein to recombinant human estrogen receptor (hERα) is 0.3 % of that of the hER α reference ligand 17 β-estradiol, with an IC50 of 0.6 µM. No binding of genistein was detected to recombinant progesterone receptor (hPR) (Scippo *et al*., 2004).

Characteristics of flavonoid inhibitors of human aromatase (CYP19) were not detected, Inhibition parameters were determined with human adipose cells (Ad), Ki (µM): 123 (CYP19), Inhibition parameters were determined with reconstituted expressed human CYP19. Genistein does not interfere with CYP regulation, has no effect on CYP1A1/2 (Hodek *et al.,* 2002).

The isoflavone genistein, and the other natural phenolic products curcumin and ellagic acid, are inhibitors of the P form phenol sulfotransferase, with IC50 values of 0.38 – 34.8 mM. (Galati and O'Brien, 2004).

Genistein has strong agonistic activity (>75% of the 17 β-estradiol activity) in a luciferase reporter gene assay using estrogen responsive MCF-7 cells (Willemsen *et al.,* 2004).

Using luciferase reporter gene assays, it was shown that genistein, quercetin, and chrysin are weak Aryl hydrocarbon Receptor (AhR) antagonists: they suppress the TCDD-induced response at concentrations of 20 µM and 40 µM in dioxin responsive HepG2 human hepatoma cells. They act as AhR agonists in dioxin responsive T47D human breast tumor cells and have no activity in dioxin responsive H4IIE rat hepatoma cells. Furthermore, genistein and chrysin act in synergy with 3-methylcholanthrene on the AhR activation in dioxin responsive T47D cells (Van der Heiden *et al.*, 2007). The flavanoids/TCDD concentration ratios, used in the HepG2 and T47D cell-based assays, were close to those found in the sera of humans, taking into account their diet and the background contamination by dioxin. These results suggest that a vegetable-based diet could reduce or increase the possible dioxin toxicity associated to food intake, depending of the target tissue (Van der Heiden *et al.*, 2007).

The safety of genistein has been evaluated together with other isoflavones of soy isoflavones (Munro *et al.,* 2003) and authoritative bodies (AFSSA/AFSSaPS, 2005; COT, 2003; BfR, 2007; DFG/SKLM, 2006; 6/17/2008 Page 3 of 5 AESAN, 2007). It was generally concluded that the available scientific evidence supports the safety of isoflavones as typically consumed with diets containing soy or soy products, which could result in average daily intakes of 50 - 60 mg soy isoflavones in certain populations (Munro *et al*., 2003; AESAN, 2007). Soy isoflavone intakes of up to 1 mg/kg bw/day do not raise safety concerns (AFSSA/AFSSaPS, 2005). However, individuals with hypothyroidism and women with estrogen-dependent breast disease were identified as subgroups of potential concern with regard to high intakes of soy isoflavones (COT, 2003; DFG/SKLM, 2006; BfR, 2007; Eisenbrand, 2007).
From the available scientific evidences and a long history of use in Asian countries, the safety of soy isoflavones is established even if consumed in amounts as high as 100 mg/day or more with a soy based diet. The amount of genistein ingested by adults in European countries having a low dietary soy intake with food supplements or dietetic foods is estimated at a level of up to 60 mg/adult

person/day.

A **NOAEL** at **50 mg/kg bw/d** is proposed (McClain *et al.,* 2006).
Experts of AFSSA concluded that soy isoflavone intakes of up to **1 mg/kg bw/d** do not raise safety concerns (AFSSA/AFSSaPS, 2005).

Exposure source

Soy and derivates are the main sources in food. The genistein concentration in green soybean has been reported to be 729 mg/kg wet wt (Miyamoto and Klein, 1998).
Genistein concentrations in tofu are estimated between 738 and 39250 µg/100g of food (AFSSA/AFSSaPS, 2005).
Genistein concentration in soy based dessert are estimated between 4200 et 29800 µg/100g of food (AFSSA/AFSSaPS, 2005)
The consumption of dietary complements containing isoflavones has also to be taken into account especially for menopausal and post-menopausal women.

Level of exposure

The daily intake of dietary genistin and thus genistein which is liberated from genistin in the digestive tract, varies in direct relationship with the consumption of soy and foods derived from it. An average genistein intake of about 20 – 50 mg/day has been reported, for example, from Japan, with daily intakes reaching 100 mg in the 95th percentile consumer (Messina *et al.,* 2006). In contrast, soy derived foods and food ingredients are used sparsely in Europe, except maybe among vegetarians and vegans. Accordingly, the average intake of dietary genistein (from naturally occurring genistin) varies from about 0.1 – 2 mg/day in European countries.
Mean and 95th percentile exposure level of genistein for adult population in France without soy based food were estimated to 0.0135 mg/day and 0.0348 mg/day, respectively (AFSSA/AFSSaPS, 2005).
Mean and 95th percentile exposure level of genistein and daidzein for adult population in France included consumption of soy product has been estimated to 15.4 mg/day and 44.7 mg/day, respectively (AFSSA/AFSSaPS, 2005).
Mean intake of isoflavone (genistein and daidzein) has been estimated to 0.788 mg/day in Finland by Valsta *et al.* (2003).
Mean and 95th percentile total intake of isoflavone genistein and daidzein by children between 3 and 14 year has been estimated to 0,0182 mg/day and 0.391 mg/day, respectively (AFSSA/AFSSaPS, 2005).
Franke *et al.* (1998) have estimated the exposure level of infant in US to 17.69 mg/day.
Mean intake of isoflavone by vegetarian and omnivore English population has been estimated to 7.4 and 1.2 mg/day, respectively (Ritchie *et al*., 2006). Mean daily intake for aglycone isoflavone (daidzein, genistein et glycitein) has been estimated to 3,3 mg/day and 10 mg/day for high consumer in England (Clarke and Lloyd, 2004).
An average genistein intake of 1.4 mg/day has been reported for adult vegetarians in the UK (97.5th percentile: 13.4 mg/day) (COT, 2003). Higher intakes occurred in small groups of vegan and vegetarian breast-feeding mothers (about 47 – 50 mg/day on average) (COT, 2003). A similarly high average intake (7.4 mg/day) was observed in another small group of vegetarians (Ritchie *et al.,* 2006). This figure corresponds well with the result of a survey of vegetarians in the US (7.2 mg/day) (Kirk *et al.,* 1999). Similarly high average intake (7.4 mg/day) was observed in another small group of vegetarians (Ritchie *et al.,* 2006). This figure corresponds well with the result of a survey of vegetarians in the US (7.2 mg/day) (Kirk *et al.,* 1999).
It follows from these data that genistein is consumed with a regular diet in highly variable amounts which in certain populations or population subgroups may reach 30 mg/day or more.
The highest intake of genistin/genistein in Europe results from the consumption of food supplements which contain purified extracts of soy beans with an elevated content of soy isoflavones and thus genistin. The genistein exposure from such food supplements may reach 60 mg/day or more as shown by the analyses of products sold in France, the UK and Australia (Vergne *et al.,* 2007; Setchell *et al.,* 2001; Howes and Howes, 2002).
Food supplements with soy isoflavones are typically positioned for consumption by peri- and postmenopausal women because they help women at that age to cope with climacteric symptoms

such as hot flushes (Howes *et al.,* 2006; Williamson-Hughes *et al.,* 2006). They also may help maintain bone strength by delaying bone decalcification. Furthermore, beneficial effects on glycemic control and on certain biomarkers and risk factors of cardiovascular disease have been noted (Cassidy *et al.,* 2006; Ma *et al.,* 2007).

The claimed benefits may be achieved with daily genistein intakes of 30 - 60 mg for an adult person corresponding to 1 mg/kg bw/day.

The amount of genistein ingested by adults in European countries having a low dietary soy intake with food supplements or dietetic foods is estimated at a level of up to 60 mg/adult person/day.

Levels of exposure, calculated on the basis of data collected for the Belgian food consumption inquiry (Devriese *et al.,* 2004) and on the basis of concentrations determined by Thompson *et al.* (2006) are the following:

Level of exposure for the general adult population: 0.013mg/kg bw/day (adult 60kg)

Level of exposure for the vegetarians*: 0.23 mg/kg bw/day (adult 60kg)

* The vegetarian diet differs from that general consumers in the substitution of meat consumption by vegetarian hamburgers.

TDI

TDI = 1 mg/kg bw (AFSSA/AFSSaPS. 2005)

Estrogenic potency

- Relative binding affinity

Relative binding activity of genistein is 10^2 to 10^5 weaker compared to E2.

- Uterotrophic activity

The uterine wet weights were significantly increased by genistein at 35 mg/kg /day in uterotrophic assay using Sprague-Dawley immature female rats (Kim *et al.,* 2005). In addition, the increase in uterine blotted weights also showed a similar pattern to that of uterine wet weights (Kim *et al.,* 2005).

% TDI

The level of exposure range between 0.016 – 0.833 mg/kg bw/day.

% TDI range between 0.16 – 83.3%.

But the genistein exposure from isoflavones-containing food supplements may reach 60 mg/day (the claimed benefits may be achieved with daily genistein intakes of 30 - 60 mg for an adult person corresponding to 1 mg/kg bw/day) !

Reference

AESAN. 2007. Informe del Comité Científico de la Agenica Española de Seguridad Alimentaria y Nutrición (AESAN) en relación con las consecuencias asociadas al consumo de isoflavonas. Número de referenzia: AESAN 2007-002.

AFSSA/AFSSaPS. 2005. Agence Française de Sécurité Sanitaire des Aliments/Agence Française de Sécurité Sanitaire des Produits de Santé. Sécurité et bénéfices des phyto-estrogènes apportés par l'alimentation – Recommandations, Mars 2005. http://www.afssa.fr/Documents/NUT-Ra-Phytoestrogenes.pdf

BfR. 2007. Bundesamt für Gesundheit. Isolated isoflavones are not without risk. Updated BfR Expert Opinion No. 039/2007, 3 April 2007. http://www.bfr.bund.de/cm/245/isolated_isoflavones_are_not_without_risk.pdf

Cassidy A., Albertazzi P., Nielsen I.L., Hall W., Williamson G., Tetens I., Atkins S., Cross H., Manios Y., Wolk A., Steiner C. and Branca F. 2006. Critical review of health effects of soya bean phyto-oestrogens in post-menopausal women. *Proc. Nutr. Soc*., 65, 76-92.

Clarke D.B., Lloyd A.S. 2004. dietary exposure estimates of isoflavones from the 1998 UK total diet study. *Food add. Contam.*, 21 (4), 305-3016.

COT. 2003. Committee on Toxicity of Chemicals in Food, Consumer Product and the Environment. Phytoestrogens and health. COT Report.

Devriese S., Huybrechts I., Moreau M., Van Oyen H. 2004. L'enquête de consommation alimentaire belge 1 - 2004: Rapport. Institut scientifique de santé publique, mars 2006, numéro de Dépot : D/2006/2505/17. Adresse URL: http://www.iph.fgov.be/EPIDEMIO/epien/index5.htm.

DFG/SKLM. 2006. Deutsche Forschungsgemeinschaft. Isoflavone als Phytoestrogene in Nahrungsergänzungsmitteln und diätetischen Lebensmitteln für besondere medizinische Zwecke.http://www.dfg.de/aktuelles_presse/reden_stellungnahmen/2006/download/sklm_phytoestrogene_28112006.pdf

Dodge J.A. 1998. Natural and anthopogenic environmental oestrogens: the scientific basis for risk assessment structure/activity relation ships in *Pure & Appl. Chem.,* 70 (9), 1725-1733.

Duquesnoy N. 2005. Les substances naturelles à effet oestrogénique dans l'alimentation des ruminants: revue de la littérature. *Ann. Méd. Vét.*, 149, 202-212.

Eisenbrand G. 2007. Isoflavones as phytoestrogens in food supplements and dietary foods for special medical purposes. *Mol. Nutr. Food Res*., 51, 1305-1312.

Galati G., O'Brien P. 2004. Potential Toxicity of flavonoids and other dietary phenolics : significance for their chemopreventive and anticancer properties. *Free Radic. Biol. Med.*, 37 (3), 287-303.

Franke A.A., Custer L.J., Hundahl S.A. 2004. Determinants for urinary and plasma isoflavones in humans after soy intake. *Nutr. Cancer,* 50 (2), 141-154.

Henley D.V., Korach K. S. 2006. Endocrine –disrupting chemicals use distinct mechanisms of action to modulate endocrine system function. *Endocrinology*, 147 (6), 25-32.

Hodeck P., Trefil P., Stiborova, M. 2002. Flavonoids-potent and versatile biologically active compounds interacting with cytochromes P450. *Chem.-Biol. Interact.*, 139, 1-21.

Howes J.B., Howes L.G. 2002. Content of isoflavone-containing preparations. *Med. J. Aust.,*176: 135-136.

Howes L.G., Howes J.B., Knight D.C. 2006. Isoflavone therapy for menopausal flushes: a systematic review and meta-analysis. *Maturitas,* 55 (3), 203-211.

Kim H. S., Kang T.S., Kang I.H., Kim T.S., Moon H.J., KIM I.Y., Park K.L., Lee B.M., Yoo S.D., Han S.Y. 2005. Validation study of OECD rodent uterotrophic assay for the assessment of estrogenic activity in Sprague-Dawley immature female rats. *J. Toxicol. Environ. Health A*, 68 (23-24), 2249-62.

Kirk P., Patterson R.E., Lampe J. 1999. Development of a soy food frequency questionnaire to estimate isoflavone consumption in US adults. *J. Am. Diet. Assoc.,* 99, 558-569.

Ma D.F., Qin L.Q., Wang P.Y., Katoh R. 2007. Soy isoflavone intake inhibits bone resorption and stimulates bone formation in menopausal women: meta-analysis of randomized controlled trials. *Eur. J. Clin. Nutr.* advance online publication 28 March 2007.

McClain R.M., Wolz E., Davidovich A., Pfannkuch F., Edwards J.A., Bausch J. 2006. Acute, subchronic and chronic safety studies with genistein in rats. *Food Chem. Toxicol*., 44, 56-80.

Messina M., Nagata C., Wu A.H. 2006. Estimated Asian adult soy protein and isoflavone intakes. *Nutr. Cancer,* 55 (1), 1-12.

Miyamoto J., Klein W. 1998. Natural and anthropogenic environmental oestrogens: the scientific basis for risk assessment Environmental exposure, specifies differences and risk assessment. *Pure & Appl. Chem.,* 70 (9), 1829-1845.

Munro I.C., Harwood M., Hlywka J.J., Stephen A.M., Doull J., Flamm W.G., Adlercreutz H. 2003. Soy isoflavones: a safety review. *Nutr. Rev.,* 61 (1), 1-33.

Niculescu M.D., Pop E.A., Fischer L.M., Zeisel S.H. 2007. Dietary isoflavones differentially induce gene expression changes in lymphocytes from postmenopausal women who form equol as compared with those who do not. *J. Nutr. Biochem.*; 18 (6), 380–390.

Perry D.L., Spedick J.M., McCoy T.P., Adams M.R., Franke A.A., Cline J.M. 2007. Dietary soy protein containing isoflavonoids does not adversely affect the reproductive tract of male Cynomolgus macaques (Macaca fascicularis). *J. Nutr.*, 137, 1390-1394.

Pike A.C., Brzozowski A.M., Hubbard R.E., Bonn T., Thorsell A.G., Engstrom O., Ljunggren J., Gustafsson J.A., Carlquist M. 1999. Structure of the ligand-binding domain of oestrogen receptor beta in the presence of a partial agonist and a full antagonist. *EMBO J.,* 18, 4608-4618.

Piskula M.K., Yamakoshi J., Iwai Y. 1999. Daidzein and genistein but not their glucosides are absorbed from the rat stomach. *FEBS Letters*, 447, 287-291.

Preziosi. 1998. Natural and Anthropogenic Environmental Oestrogens. The scientific basis for risk assessment. Endocrine disrupters as environmental signallers: an introduction, *Pure & Appl. Chem.* 70 (9), 1617-1631.

Ritchie M.R., Cummings J.H., Morton M.S., Steel C.M., Bolton-Smith C., Riches A.C. 2006. A newly constructed and validated isoflavone database for the assessment of total genistein and daidzein intake. Br. *J. Nutr.* 95, 204-213.

Rowland I., Faughnan M., Hoey L., Wähälä K., Williamson G., Cassidy A. 2003. Bioavailability of phyto-oestrogens. *Br. J. Nutr.,* 89 (suppl. 1), 45-58.

Scippo M-L., Argiris C., Van De Weerdt C., Muller M., Willensen P., Martial J. Maghuin-Rogister G.

2004. Recombinant human estrogen, androgen and progesterone receptors for detection of potential endocrine disruptors. *Anal. Bioanal. Chem.*, 378, 664-669.

Scippo M-L, Maghuin-Rogister G. 2007. Les perturbateurs endocriniens dans l'alimentation humaine: impact potentiel sur la santé. *Ann. Méd. Vét.,* 151, 44-54.

Setchell K., Brown N.M., Desai P., Zimmer-Nechemias L., Wolfe B.E., Brashear W.T., Kirschner A.S., Cassidy A., Heubi J.E. 2001. Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. *J. Nutr.,* 131, 1362-1375.

Setchell K., Brown N.M., Zimmer-Nechemias L., Brashear W.T., Wolfe B.E., Kirschner A.S., Heubi J.E. 2002. Evidence for lack of absorption of soy isoflavone glycosides in humans, supporting the crucial role of intestinal metabolism for bioavailability. *Am. J. Clin. Nutr.,* 76, 447-453.

Sfakianos J., Coward L., Kirk M., Barnes S. 1997. Intestinal uptake and biliary excretion of the isoflavone genistein in rats. *J. Nutr.,* 127, 1260-1268.

Thompson L.U., Boucher B. A., Liu Z., Cotterchio M., Kreiger N. 2006. Phytoestrogen Content of Foods Consumed in Canada, Including Isoflavones, Lignans, and Coumestan. *Nutr. Cancer,* 54 (2), 184–201.

Valsta LM, Kilkkinen A, Mazur W, Nurmi T, Lampi AM, Ovaskainen ML, Korhonen T, Adlercreutz H, Pietinen P. 2003. Phyto-oestrogen database of fodds and average intake in Finland. *Br H Nutr.,* 89 (1), 31-8.

Van der Heiden E., Bechoux N., Sergent T. Schneider Y.J., Muller M., Maghuin-Rogister G. and Scippo M.L. 2007. Aryl hydrocarbon receptor-mediated agonist/antagonist/synergic activities of food polyphenols are species- and tissue-dependent. *Organohalogen Comp.*, 69, 365-368

Vergne S., Titier K., Bernard V., Asselineau J., Durand M., Lamothe V., Potier M., Perez P., Demotes-Mainard J., Chantre P., Moore N., Benneteau-Pelissero C., Sauvant P. 2007. Bioavailability and urinary excretion of isoflavones in humans: effects of soybased supplements formulation and equol production. *J. Pharma. Biomed. Anal.,* 43, 1488-1494.

Willemsen P., Scippo M-L, Kausel G., Figueroa J., Maghuin-Rogister G., Martial JA., Muller M. 2004. Use of reporter cell lines for detection of endocrine –disrupter activity. *Anal. Bioanal. Chem*., 378, 655-663.

Williamson-Hughes P.S., Flickinger B.D., Messina M.J., Empie M.W. 2006. Isoflavone supplements containing predominantly genistein reduce hot flash symptoms: a critical review of published studies. *Menopause,* 13 (5), 831-839.

Wiseman H. 2006. in Flavanoids: chemistry, biochemistry and applications edited by Ø y vind M. Andersen, Kenneth R. Markham. Published in 2006 by CRC Pres Taylor and Francis group.