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List of references supporting the assessment of *Glycine max* (L.) Merr., semen

Draft

The European Medicines Agency acknowledges that copies of the underlying works used to produce this monograph were provided for research only with exclusion of any commercial purpose.

An J, Tzagarakis-Foster C, Scharschmidt TC, Lomri N, Leitman DC. Estrogen receptor beta-selective transcriptional activity and recruitment of coregulators by phytoestrogens. *J Biol Chem* 2001, 276(21): 17808-17814

Anderson RL, Wolf WJ. Compositional changes in trypsin inhibitors, phytic acid, saponins and isoflavones related to soybean processing. *J Nutr* 1995, 125(3 Suppl): 581S-588S

Andres S, Abraham K, Appel KE, Lampen A. Risks and benefits of dietary isoflavones for cancer. *Crit Rev Toxicol* 2011, 41(6): 463-506

Bell DS, Ovalle F. Use of soy protein supplement and resultant need for increased dose of levothyroxine. *Endocr Pract* 2001, 7(3): 193-194

BfR (Bundesinstitut für Riskobewertung), 2007, online. Updated BfR Expert Opinion No 039/2007. Available online: http://www.bfr.bund.de/cm/349/isolated_isoflavones_are_not_without_risk.pdf (Accessed February 2015)

Blumenthal M, Goldberg A, Brinckmann J, editors. Herbal Medicine. Expanded Commission E Monographs. The American Botanical Council, Austin Texas 2000, 354-358

Bruneton J. Pharmacognosy, Phytochemistry, Medicinal Plants, 2nd ed, Lavoisier Publishing, France 1999, 147-149

Cambria-Kiely JA. Effect of soy milk on warfarin efficacy. *Ann Pharmacother* 2002, 36(12): 1893–1896

COT (Committee on Toxicity of Chemicals in Food, Consumer Products and the Environment), 2003, online. Phytoestrogens and health. Available online: <http://cot.food.gov.uk/sites/default/files/cot/phytoreport0503.pdf> (Accessed February 2015)

de Cremoux P, This P, Leclercq G, Jacquot Y. Controversies concerning the use of phytoestrogens in menopause management: bioavailability and metabolism. *Maturitas* 2010, 65(4): 334–339



- der Marderosian A, Beutler J, editors. The Review of Natural Products. Monograph: Soy. Facts and Comparisons, A Wolters Kluwer Company, <http://online.statref.com/> created December 19, 2011; modified April 10, 2015
- Du M, Yang X, Hartman JA, Cooke PS, Doerge DR, Ju YH, Helferich WG. Low-dose dietary genistein negates the therapeutic effect of tamoxifen in athymic nude mice. *Carcinogenesis* 2012, 33(4): 895-901
- Erdman JW Jr, Badger TM, Lampe JW, Setchell KD, Messina M. Not all soy products are created equal: caution needed in interpretation of research results. *J Nutr* 2004, 134(5): 1229S-1233S
- European Food Safety Authority (EFSA). Risk assessment for peri- and post-menopausal women taking food supplements containing isolated isoflavones. *EFSA Journal* 2015, 13 (10): 4246, 342 pp
- European Medicines Agency (EMA). Public statement on the allergenic potency of herbal medicinal products containing soya or peanut protein. Committee on Herbal Medicinal Products 2006, EMEA/HMPC/138139/2005
- European Medicines Agency (EMA). Guideline on Clinical Investigation of Medicinal Products for Hormone Replacement Therapy of Oestrogen Deficiency Symptoms in Postmenopausal Women (EMEA/CHMP/021/97 Rev. 1)
- Faure ED, Chantre P, Mares P. Effects of a standardized soy extract on hot flushes: a multicentre, double-blind, randomised placebo-controlled study. *Menopause* 2002, 9(5): 329–334
- Fruzza AG, Demeterco-Berggren C, Jones KL. Unawareness of the effects of soy intake on the management of congenital hypothyroidism. *Pediatrics* 2012, 130(3):e699-702
- Goodman NF, Cobin RH, Ginzburg SB, Katz IA, Woode DE. American Association of Clinical Endocrinologists Medical Guidelines for Clinical Practice for the diagnosis and treatment of menopause. *Endocr Pract* 2011, Suppl 6: 1-25
- Gu L, House SE, Prior RL, Fang N, Ronis MJ, Clarkson TB, Wilson ME, Badger TM. Metabolic phenotype of isoflavones differ among female rats, pigs, monkeys, and women. *J Nutr* 2006,136: 1215–1221
- Health Canada Monographs: Soybean extracts and isolates, October 29, 2009. Available online: http://webprod.hc-sc.gc.ca/nhp/nd-bdip/sn/atReq.do?atid=soy_extra_isolate&lang=eng (Accessed April 2015)
- Helsby NA, Chipman JK, Gescher A, Kerr D. Inhibition of mouse and human CYP 1A- and 2E1-dependent substrate metabolism by the isoflavonoids genistein and equol. *Food Chem Toxicol* 1998, 36(5): 375-82
- Hosoda K, Furuta T, Ishii K. Metabolism and disposition of isoflavone conjugated metabolites in humans after ingestion of kinako. *Drug Metab Dispos* 2011, 39(9): 1762–1767
- Jabbar MA, Larrea J, Shaw RA. Abnormal thyroid function tests in infants with congenital hypothyroidism: the influence of soy-based formula. *J Am Coll Nutr* 1997, 16(3): 280-282
- Jacobs A, Wegewitz U, Sommerfeld C, Grossklaus R, Lampen A. Efficacy of isoflavones in relieving vasomotor menopausal symptoms - A systematic review. *Mol Nutr Food Res* 2009, 53(9): 1084-1097
- Ju YH, Doerge DR, Allred KF, Allred CD, Helferich WG. Dietary genistein negates the inhibitory effect of tamoxifen on growth of estrogen-dependent human breast cancer (MCF-7) cells implanted in athymic mice. *Cancer Res* 2002, 62(9): 2474-2477

- Lethaby A, Marjoribanks J, Kronenberg F, Roberts H, Eden J, Brown J. Phytoestrogens for menopausal vasomotor symptoms. *Cochrane Database Syst Rev* 2013, Issue 12. Art. No.: CD001395. DOI: 10.1002/14651858.CD001395.pub4
- Marahatta A, Bhandary B, Jeong SK, Kim HR, Chae HJ. Soybean greatly reduces valproic acid plasma concentrations: a food-drug interaction study. *Sci Rep* 2014, 4:4362
- Markovits J, Linassier C, Fossé P, Couprie J, Pierre J, Jacquemin-Sablon A, Saucier JM, Le Pecq JB, Larsen AK. Inhibitory effects of the tyrosine kinase inhibitor genistein on mammalian DNA topoisomerase II. *Cancer Res* 1989, 49(18): 5111-5117
- Messina M. J Nutr. A brief historical overview of the past two decades of soy and isoflavone research. *J Nutr* 2010, 140(7): 1350S-1354S
- Messina MJ, Loprinzi CL. Soy for breast cancer survivors: a critical review of the literature. *J Nutr* 2001, 131(11 Suppl): 3095S-3108S
- Messina M, Redmond G. Effects of soy protein and soybean isoflavones on thyroid function in healthy adults and hypothyroid patients: a review of the relevant literature. *Thyroid* 2006, 16(3):249-58
- Misra RR, Hursting SD, Perkins SN, Sathyamoorthy N, Mirsalis JC, Riccio ES, Crowell JA. Genotoxicity and carcinogenicity studies of soy isoflavones. *Int J Toxicol* 2002, 21(4): 277-285
- Murkies AL, Lombard C, Strauss BJ, Wilcox G, Burger HG, Morton MS. Dietary flour supplementation decreases post-menopausal hot flashes: effect of soy and wheat. *Maturitas* 1995, 21(3): 189-195.
- Murkies AL, Wilcox G, Davis SR. Clinical review 92: Phytoestrogens. *J Clin Endocrinol Metab* 1998, 83(2): 297-303
- National Institute of Health (NIH). Assessing and Improving Measures of Hot Flashes, Summary of an NIH Workshop, National Institutes of Health, Bethesda, Maryland, January 20, 2004 Available at <https://nccih.nih.gov/health/hotflashes#pdf> (Accessed February 2015)
- NTP CERHR expert panel report on the reproductive and developmental toxicity of Soy formula. National Toxicology Program (NTP) US Department of Health and Human Service. April 2006. Released for public comment on May 5 2006 (71 FR 28368), 1-214
- NTP Multigenerational Reproductive Toxicology Study of genistein (CAS No. 446-72-0) in Sprague-Dawley rats (Feed Study). NTP TR 539 March 2008, 1-268
- NTP Toxicology and Carcinogenesis Studies of genistein (CAS No. 446-72-0) in Sprague-Dawley rats (Feed Study). NTP TR 545 January 2008, 1-242
- Poluzzi E, Piccinni C, Raschi E, Rampa A, Recanatini M, De Ponti F. Phytoestrogens in postmenopause: the state of the art from a chemical, pharmacological and regulatory perspective. *Curr Med Chem* 2014, 21(4): 417-36
- Setchell KD. Soy isoflavones - benefits and risks from nature's selective estrogen receptor modulators (SERMs). *J Am Coll Nutr* 2001, 20(5 Suppl): 354S-362S; discussion 381S-383S
- Setchell KD, Brown NM, Desai P, Zimmer-Nechemias L, Wolfe BE, Brashear WT, Kirschner AS, Cassidy A, Heubi JE. Bioavailability of pure isoflavones in healthy humans and analysis of commercial soy isoflavone supplements. *J Nutr* 2001, 131(4 Suppl): 1362S-1375S
- Setchell KD, Faughnan MS, Avades T, Zimmer-Nechemias L, Brown NM, Wolfe BE, Brashear WT, Desai P, Oldfield MF, Botting NP, Cassidy A. Comparing the pharmacokinetics of daidzein and genistein with the use of 13C-labeled tracers in premenopausal women. *Am J Clin Nutr* 2003, 77(2): 411-419

Singh D, Asad M. Effect of soybean administration on the pharmacokinetics of carbamazepine and omeprazole in rats. *Fundam Clin Pharmacol* 2010, 24(3): 351-355

Soukup ST, Al-Maharik N, Botting N, Kulling SE. Quantification of soy isoflavones and their conjugative metabolites in plasma and urine: an automated and validated UHPLC-MS/MS method for use in large-scale studies. *Anal Bioanal Chem* 2014, 406(24): 6007–6020

Stanosz S., Puk E., Grobelny W., Stanosz M., Kazikowska A. [Evaluation of the efficacy and tolerance of Soyfem in women in the early menopausal period.] *Przegląd Menopauzalny* 2006, 3: 182-190 [Polish]

van Duursen MB1, Smeets EE, Rijk JC, Nijmeijer SM, van den Berg M. Phytoestrogens in menopausal supplements induce ER-dependent cell proliferation and overcome breast cancer treatment in an in vitro breast cancer model. *Toxicol Appl Pharmacol* 2013, 269(2): 132-140

Vergne S, Titier K, Bernard V, Asselineau J, Durand M, Lamothe V, Potier M, Perez P, Demotes-Mainard J, Chantre P, Moore N, Bennetau-Pelissero C, Sauvant P. Bioavailability and urinary excretion of isoflavones in humans: effects of soy-based supplements formulation and equol production. *J Pharm Biomed Anal* 2007, 43(4): 1488-1494

Williamson-Hughes PS, Flickinger BD, Messina MJ, Empie MW. Isoflavone supplements containing predominantly genistein reduce hot flash symptoms: a critical review of published studies. *Menopause* 2006, 13(5): 831-839

Excluded clinical studies

Reason for exclusion: Studies on food supplements, products of unknown regulatory status, or unknown composition were excluded. Also, studies on isolated pure genistein or synthetic genistein have been excluded.

Albert A, Altabre C, Baró F, Buendía E, Cabero A, Cancelo MJ, Castelo-Branco C, Chantre P, Duran M, Haya J, Imbert P, Juliá D, Lanchares JL, Llana P, Manubens M, Miñano A, Quereda F, Ribes C, Vázquez F. Efficacy and safety of a phytoestrogen preparation derived from *Glycine max* (L.) Merr in climacteric symptomatology: a multicentric, open, prospective and non-randomized trial. *Phytomedicine* 2002, 9(2): 85-92

Albertazzi P, Steel SA and Bottazzi M. Effect of pure genistein on bone markers and hot flushes. *Climacteric* 2005, 8(4): 371-379

Campagnoli C, Abba C, Ambroggio S, Peris C, Perona M, Sanseverino P. Polyunsaturated fatty acids (PUFAs) might reduce hot flushes: an indication from two controlled trials on soy isoflavones alone and with a PUFA supplement. *Maturitas* 2005, 51(2): 127–134

Cheng G, Wilczek B, Warner M, Gustafsson JA, Landgren BM. Isoflavone treatment for acute menopausal symptoms. *Menopause* 2007, 14(3 Pt 1): 468-473

Colacurci N, Zarcone R, Borrelli A, De Franciscis P, Fortunato N, Cirillo M, Fornaro F. Effects of soy isoflavones on menopausal neurovegetative symptoms. *Minerva Ginecol* 2004, 56(5): 407–412

Crisafulli A, Marini H, Bitto A, Altavilla D, Squadrito G, Romeo A, Adamo EB, Marini R, D'Anna R, Corrado F, Bartolone S, Frisina N, Squadrito F. Effects of genistein on hot flushes in early postmenopausal women: a randomized, double-blind EPT- and placebo-controlled study. *Menopause* 2004, 11(4): 400-404

Duffy R, Wiseman H, File SE. Improved cognitive function in postmenopausal women after 12 weeks of consumption of a soya extract containing isoflavones. *Pharmacol Biochem Behav* 2003, 75(3): 721-729

- Ferrari A. Soy extract phytoestrogens with high dose of isoflavones for menopausal symptoms. *J Obstet Gynaecol Res* 2009, 35(6): 1083–1090
- Hachul H, Brandão LC, D'Almeida V, Bittencourt LR, Baracat EC, Tufik S. Isoflavones decrease insomnia in postmenopause. *Menopause* 2011, 18(2): 178-184
- Han KK, Soares JM, Haidar MA, de Lima GR, Baracat EC. Benefits of soy isoflavone therapeutic regimen on menopausal symptoms. *Obstet Gynecol* 2002, 99(3): 389–394
- Jou HJ, Ling PY, Wu SC. Comparison of 70 mg and 35 mg isoflavone soya supplement for menopause symptoms. *Int J Gynaecol Obstet* 2005, 90(2): 156–160
- Jou HJ, Wu SC, Chang FW, Ling PY, Chu KS, Wu WH. Effect of intestinal production of equol on menopausal symptoms in women treated with soy isoflavones. *Int J Gynaecol Obstet* 2008, 102(1): 44-49
- Kaari C, Haidar MA, Soares Junior JM, Nunes MG, de Azevedo Quadros LG, Kemp C, Stavale JN, Baracat EC. Randomized clinical trial comparing conjugated equine estrogens and isoflavones in postmenopausal women: a pilot study. *Maturitas* 2006, 53 (1): 49–58
- Khaodhiar L, Ricciotti HA, Li L, Pan W, Schickel M, Zhou J, Blackburn GL. Daidzein-rich isoflavone aglycones are potentially effective in reducing hot flashes in menopausal women. *Menopause* 2008, 15(1): 125-132
- Knight DC, Howes JB, Eden JA, Howes LG. Effects on menopausal symptoms and acceptability of isoflavone containing soy powder dietary supplementation. *Climacteric* 2001, 4(1): 13–18
- Kotsopoulos D, Dalais FS, Liang Y-L, McGrath BP, Teede HJ. The effects of soy protein containing phytoestrogens on menopausal symptoms in postmenopausal women. *Climacteric* 2000, 3(3): 161–167
- Levis S, Strickman-Stein N, Ganjei-Azar P, Xu P, Doerge D, Krischer J. Soy isoflavones in the prevention of menopausal bone loss and menopausal symptoms. *Arch Intern Med* 2011, 171(15): 1363–1368
- Nahas E, Nahas-Neto J, Orsatti F, Carvalho E, Oliveira M, Dias R. Efficacy and safety of a soy isoflavone extract in postmenopausal women: a randomized double-blind, and placebo controlled study. *Maturitas* 2007, 58(3): 249–258
- Nahas EP, Neto JN, De Luca L, Traiman P, Pontes A, Dalben I. Maturitas. Benefits of soy germ isoflavones in postmenopausal women with contraindication for conventional hormone replacement therapy. *Maturitas* 2004, 48(4): 372-380
- Nelson HD, Vesco KK, Haney E, Fu R, Nedrow A, Miller J, Nicolaidis C, Walker M, Humphrey L. Nonhormonal therapies for menopausal hot flashes: systematic review and meta-analysis. *JAMA* 2006, 295(17): 2057-2071
- Nikander E, Kilkinen A, Metsä-Heikkilä M, Adlercreutz H, Pietinen P, Tiitinen A, Ylikorkala O. A randomized placebo-controlled cross-over trial with phytoestrogens in treatment of menopause in breast cancer patients. *Obstet Gynecol* 2003, 101(6): 1213–1220
- Penotti M, Fabio E, Modena AB, Rinaldi M, Omodei U, Vigano P. Effect of soy-derived isoflavones on hot flushes, endometrial thickness and the pulsatility index of the uterine and cerebral arteries. *Fertil Steril* 2003, 79(5): 1112–1117
- Rossouw JE, Anderson GL, Prentice RL, LaCroix AZ, Kooperberg C, Stefanick ML, Jackson RD, Beresford SA, Howard BV, Johnson KC, Kotchen JM, Ockene J. Risks and benefits of estrogen plus progestin in

healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. *JAMA* 2002, 288(3): 321-333

Scambia G, Mango D, Signorile PG, Angeli RA, Palena C, Gallo D, et al. Clinical effects of a standardized soy extract in postmenopausal women: a pilot study. *Menopause* 2000, 7(2): 105–111

Secreto G, Chiechi LM, Amadori A, Miceli R, Venturelli E, Valerio T, Marubini E. Soy isoflavones and melatonin for the relief of climacteric symptoms: a multicenter, double-blind, randomized study. *Maturitas* 2004, 47(1): 11-20

Steinberg FM, Murray MJ, Lewis RD, Cramer MA, Amato P, Young RL, Barnes S, Konzelmann KL, Fischer JG, Ellis KJ, Shypailo RJ, Fraley JK, Smith EO, Wong WW. Clinical outcomes of a 2-y soy isoflavone supplementation in menopausal women. *Am J Clin Nutr* 2011, 93(2): 356-367

St Germain A, Peterson CT, Robinson JG, Alekel DL. Isoflavone-rich or isoflavone-poor soy protein does not reduce menopausal symptoms during 24 weeks of treatment. *Menopause* 2002, 8(1): 17–26

Taku K, Melby MK, Kronenberg F, Kurzer MS, Messina M. Extracted or synthesized soybean isoflavones reduce menopausal hot flash frequency and severity: systematic review and meta-analysis of randomized controlled trials. *Menopause* 2012, 19(7): 776-790

Upmalis DH, Lobo R, Bradley L, Warren M, Cone FL, Lamia CA. Vasomotor symptom relief by soy isoflavone extract tablets in postmenopausal women: a multicenter double-blind randomized placebo-controlled study. *Menopause* 2000, 7(4): 236–242

Yang T-S, Wang S-Y, Yang Y-C, Su C-H, Lee F-K, Chen SC, et al. Effects of standardised phytoestrogen on Taiwanese menopausal women. *Taiwan J Obstet Gynecol* 2012, 51(2): 229-235