Dietary Soy and Soy Isoflavones Have Gender-Specific Effects on Plasma Lipids and Isoflavones in Golden Syrian F_{1}B Hybrid Hamsters

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ABSTRACT The specific components of soy responsible for its beneficial effects on plasma lipids are unknown. Golden Syrian F_{1}B Hybrid hamsters (75 male, 74 female) were evaluated for the effect of dietary soy and soy isoflavones on plasma lipids. They were fed the following diets for 16 wk: casein/lactalbumin (C/L), soy protein with isoflavones [Soy(+)], soy protein with isoflavones removed [Soy(−)], Soy(−) plus isoflavone extract (IF), and C/L + IF. At necropsy, plasma total cholesterol, HDL cholesterol (HDLc), LDL + VLDL cholesterol (LDL + VLDLc), isoflavones, and uterine and accessory gland weights were measured. Male hamsters fed the three soy-containing diets had lower LDL + VLDLc concentrations than those fed the two C/L diets (P < 0.01), and those fed Soy(−) + IF did not differ from those fed Soy(+). In females, diet did not affect plasma LDL + VLDLc concentration. Females fed Soy(+) or Soy(−) had higher HDLc (P < 0.05) than those fed C/L. HDLc was not affected by diet in males. Due to higher equal production (P < 0.01), males had greater plasma isoflavone concentrations (P < 0.01) than females. There was a positive association between plasma total isoflavones and LDL + VLDLc (r = 0.65, P < 0.05) in females. These data suggest gender differences in plasma lipid and isoflavone responses to soy-based diets in Syrian F_{1}B Hybrid hamsters, which offer an opportunity to explore effects of sex hormones on isoflavone metabolism and the effects of isoflavones on lipid metabolism. J. Nutr. 132: 3585–3591, 2002.

KEY WORDS: • soy protein • isoflavones • lipids • hamsters

In October 1999, the U.S. Food and Drug Administration concluded that "25 g of soy protein a day, as a part of a diet low in saturated fat and cholesterol, may reduce the risk of heart disease." Over the past several decades, there have been major national and international research efforts to determine the components of soy that provide cardiovascular benefits. The amino acid composition, specific protein fractions and isoflavones are among the components of soy that have been investigated.

Many believe that the isoflavones are largely responsible for the benefits of soy. Supporting this hypothesis are several recent studies in humans consuming soy protein diets that contained increasing amounts of isoflavones. Individuals consuming diets with the highest isoflavone content had 7–10% lower plasma LDL cholesterol (LDLc)\(^2\) concentrations compared with those consuming isoflavone-free diets (1–4). Several studies in nonhuman primate models have reported that isoflavone-extracted soy protein is less effective in improving plasma lipoprotein concentrations than intact soy protein.

Comparison of intact soy protein [(Soy(+)) with soy protein that has been alcohol washed to remove isoflavones [Soy(−)] has been the basis of several studies in monkeys (5–7). In these studies, monkeys fed Soy(+) diets tended to have higher HDL cholesterol (HDLc) concentrations and lower LDL + VLDL cholesterol (LDL + VLDLc) concentrations than those fed Soy(−). An inhibition of atherosclerosis in mice fed Soy(+) diets has also been reported (8–10).

The results of these studies suggest that the beneficial effects of soy might be due to the isoflavones; however, definitive evidence has not been reported. To the contrary, using the cynomolgus monkey model, neither Greaves et al. (11) nor Anthony et al. (12) could demonstrate a lipid-lowering effect of soy isoflavone extracts when added back to the diet after extraction. Similarly, pills containing isolated isoflavones have not improved plasma lipid concentrations in several studies (13–15). Alcohol extraction may alter the effectiveness of the soy isoflavones on cardiovascular risk factors, suggesting that intact soy with naturally occurring isoflavones may provide the most benefit for reducing the risk of atherosclerosis. Alternatively, alcohol extraction may also remove or alter other compounds in soy, such as soy globulins, which may be responsible for lipid lowering (16).

There are numerous soy component questions still to be explored. This could be done most efficiently using a suitable...
laboratory small animal model. We chose to evaluate Golden Syrian F$_1$B Hybrid hamsters for several reasons: they are readily available from a reputable supplier; large numbers can be maintained in a relatively small housing space; and they have responses similar to those of humans with respect to dietary influences on blood lipids and the development of atherosclerotic lesions. As in humans, male and female hamsters differ in plasma lipid concentrations and atherosclerosis susceptibility (17–19). Male F$_1$B Hybrid hamsters fed moderately atherogenic diets have elevated plasma concentrations of triglycerides, total cholesterol and increased atherosclerosis. However, intact female F$_1$B Hybrid hamsters fed these diets, like human premenopausal women, do not exhibit plasma lipid elevations and atherosclerosis (18,19). Both ovariectomized F$_1$B Hybrid hamsters and surgically or naturally post-menopausal women develop elevated plasma lipid concentrations and lose their protection from atherosclerosis (18). The objective of the present study was to examine gender differences in intact female and male F$_1$B Hybrid hamsters fed soy-based diets.

MATERIALS AND METHODS

Hamsters. Golden Syrian F$_1$B Hybrid hamsters (n = 149; 75 male and 74 female) were obtained from Bio Breeders (Warterton, MA) at 8 wk of age. They were housed in same-sex groups of three in a shoebox cage in a controlled environment (23°C, 12-h light:dark cycle). The hamsters were allowed a 4-wk acclimation period during which they consumed a casein/lactalbumin (C/L) control diet (Table 1) and water ad libitum. All procedures involving hamsters were conducted in compliance with state and federal laws, standards of the U.S. Department of Health and Human Services, and guidelines established by the Wake Forest University School of Medicine Animal Care and Use Committee.

Study design. After the 4-wk acclimation period, the hamsters were assigned randomly to one of the following five diet groups: 1) C/L control (n = 15 female, n = 15 male); 2) unextracted soy protein with isoflavones intact, [Soy(+); n = 15 female, n = 15 male]; 3) soy protein with isoflavones removed by alcohol extraction [Soy(−); n = 12 female, n = 18 male]; 4) C/L with isoflavone concentrate added [C/L + IF; n = 14 female, n = 15 male]; 5) Soy(+) plus isoflavone concentrate added back [Soy(+) + IF; n = 18 female, n = 12]. The treatment diets were fed for 16 wk.

Diet. The compositions of experimental diets are presented in Table 1. Isoflavone concentrate (IF) was added to a C/L-based diet and Soy(−) diet to make the isoflavone content of these two diets equivalent to the Soy(+) diet. Soy protein isolates and isoflavone concentrate were provided by Dupont Protein Technologies (St Louis, MO).

All diets were prepared in our diet laboratory and were formulated to be equivalent in cholesterol and macronutrient concentrations, i.e., protein, fat and carbohydrate. DL-Methionine was added to the soy-containing diets to make the concentration of sulfur-containing amino acids comparable to that in C/L diets.

Body weight. Each cage of three hamsters received 39 g food/day; thus, 13 g (159.1 kJ) was available to each hamster per day. Body weights were measured at baseline and weekly thereafter throughout the study.

Plasma lipids and lipoproteins. At necropsy, blood was collected from the left ventricle into evacuated tubes containing heparin. The blood was stored on ice until centrifugation (1000 × g, 25 min) and plasma collection. Plasma was analyzed for plasma total cholesterol (TC) and HDL-C. TC was measured by enzymatic techniques based on the methods of Allain et al. (20). The concentration of HDL-C was measured after using a heparin–manganese precipitation procedure (21). The plasma concentration of LDL + VLDL-C was calcu-
lated as the difference between TC and HDLC. All assays were done on a COBAS FARA II autoanalyzer.

**Plasma isoflavones.** To obtain a sufficient quantity of blood to measure plasma isoflavone concentrations, we pooled blood samples from several hamsters. For the females, 19 pools (averaging 3 hamsters per pool) were prepared, resulting in 3–5 pools per treatment group. The males were slightly smaller and required an average of 5 hamsters per pool for a total of 12 pools (n = 2–3 pools/treatment group).

Plasma isoflavone concentrations were determined using specific ELISA techniques for genistein, daidzein and equol as previously described (22,23). The isoflavone ELISA techniques have been compared to HPLC-diode array detection procedures and were found to give similar values (24).

Before the assays were conducted, samples were hydrolyzed and extracted using ethyl acetate. Plasma (500 µL) was incubated with 1.5 mL of a β-glucuronidase-aryl sulfatase solution in acetate buffer (0.1 mol/L pH 5) for 48 h at 37°C as described (25). As a control for the enzyme activity, 500 µL of daidzein (480 nmol/L) or genistin (nmol/L) was analyzed in parallel and under the same conditions. The phytoestrogens in the aglycone form were then extracted with 4.0 mL of acid ethyl acetate. As an extraction control, a solution of genistin (370 nmol/L) was extracted in parallel. Standards were prepared using isoflavones synthesized according to Pelissero et al. (26) and stored at 4°C when not used. Wells were coated with the Thy-1 hapten conjugates (200 µL/well) in a carbonate buffer solution (0.05 mol/L, pH 9.6) overnight at 4°C. The same hapten was used for coating as for immunization, i.e., the assays were hapten homologous.

The interassay variations were 13.1% for genistein, 12.8% for daidzein and 13.6% for equol measured when the same sample was measured on 10 different plates. The intra-assay variations were 4.8, 5 and 5% for genistein, daidzein and equol, respectively, when the same sample was measured 12 times on the same plate. The samples were diluted 1:5 or greater as needed. Assay sensitivity was 5 and 5% for genistein, daidzein and equol assay, respectively, when immunization, i.e., the assays were hapten homologous.

Cross-reactivities of the antibodies used in the ELISAs were: 1) anti-equol antibody: 0.12% for daidzein, 0.015% for genistein and <0.05% for all other isoflavones tested; 2) anti-genistein antibody: 53% for biochanin A, 5.25% for chrysin, 2.08% for formononetin, 2.05% for daidzein, 1.35% for apigenin, and <1% for all other isoflavones tested including equol (0.062%); 3) anti-daidzein antibody: 51.5% for formononetin, 5.22% for genistein, 1.78% for biochanin A, and <1% for all other isoflavones tested including equol (0.19%). The high cross-reactivities of the anti-genistein antibody with biochanin A, genistein’s parent isoflavone, and the anti-daidzein antibody with formononetin, daidzein’s parent isoflavone, are not unexpected. Because formononetin and biochanin A are not present in soy or in any of the dietary ingredients used in the current study, these cross-reactivities do not affect the isoflavone analyses.

**Post-mortem evaluations.** At the end of the study the hamsters were randomly assigned to a necropsy date. Necropsies were conducted in the morning with hamsters from different dietary treatments and both genders included each necropsy day. Hamsters were anesthetized with an intraperitoneal injection of a mixture of ketamine/xylazine doses of 60 and 5 mg/kg, respectively. Once fully anesthetized, a 20-gauge needle (with syringe attached) was inserted into the left ventricle and the hamster was killed by exsanguination. This allowed maximum blood volume collection for plasma lipid and isoflavone determination.

Reproductive organs were collected from both males and females. After the entire female reproductive tract was removed, the uterus was dissected away and weighed. The male reproductive organs were removed, weighed and stored in paraformaldehyde as follows: accessory glands (prostate and seminal vesicles), left testis and right testis. The uterus and ovaries of the females and the accessory glands of the males were embedded in paraffin, sectioned at 5-µm thickness, and stained with hematoxylin and eosin. A board-certified veterinary pathologist examined all sections for evidence of estrogen-like effects.

**Statistical analyses.** Data were analyzed by ANOVA using the General Linear Models (Proc GLM) of SAS (Version 6.12 for Windows; SAS Institute, Cary, NC). Plasma lipid and isoflavone concentrations were analyzed for differences due to gender, diet and gender × diet interactions. Body weight, normalized uterine weight (uterine weight/100 g body weight), normalized sex gland weight and normalized testicular weights were analyzed for differences among dietary treatments. A P-value < 0.05 was considered significant. Pooled variance t tests (comparable to Fisher’s least significant difference test) were used for post-hoc comparisons. To evaluate the relationship between plasma isoflavone concentration and plasma lipid concentration changes, the plasma isoflavone data from each pool and the mean plasma lipid data from hamsters making up the pool were analyzed with Proc Corr of SAS.

**RESULTS**

**Body weight.** At the initiation of the study, females weighed ~10 g more than males (140 vs. 130 g). By the end of the treatment period, both females and males had gained ~30 g and there were no differences among the dietary groups or differences between the genders (P > 0.10).

**Plasma lipid determinations.** Gender affected (P < 0.01) LDL + VLDLC concentrations (Fig. 1). Males fed C/L, Soy(-), and C/L + IF had greater LDL + VLDLC concentrations than females fed the same diets (P < 0.05). There were no differences (P > 0.10) in plasma LDL + VLDLC concentrations in females fed any of the diets; however, male hamsters fed soy-based diets had lower LDL + VLDLC than those fed C/L or C/L + IF diets (P < 0.01). Males fed Soy (+) had lower (P < 0.01) plasma LDL + VLDLC concentrations than those fed Soy(-). In males, the addition of IF back to Soy(-) resulted in LDL + VLDLC concentrations that were intermediate to and not different from those in hamsters fed Soy(-) and Soy(+) (P > 0.10). The addition of IF back to C/L did not lower plasma LDL + VLDLC concentrations in either males or females (P > 0.10).

In contrast to LDL + VLDLC, gender and diet did not interact to affect HDLC. Females fed Soy(-) had higher (P < 0.05) HDLC than males fed Soy(-) (Fig. 2). There were no differences (P > 0.10) in HDLC among the male hamsters fed the various diets. Female hamsters fed Soy(+) and Soy(-),
had higher (P < 0.05) HDLC concentrations than females fed C/L.

**Plasma isoflavone determinations.** Only hamsters fed the isoflavone-containing diets had detectable plasma isoflavones. Gender affected genistein, daidzein and equol concentrations, as well as their relative proportions to one another (Fig. 3). Female hamsters fed either Soy(+) or C/L + IF had higher (P < 0.05) concentrations of genistein than males fed the same diets. Males fed Soy(−) + IF tended (P = 0.053) to have higher daidzein concentrations than males fed Soy(+).

Female hamsters fed the C/L + IF diet had greater (P < 0.05) equol concentrations than those fed Soy(+) or Soy(−) + IF. Male hamsters fed diets with isoflavones added back [C/L + IF and Soy(−) + IF] had greater (P < 0.01) equol concentrations than males fed Soy(+). Males had greater (P < 0.01) equol concentrations than females fed all three isoflavone-containing diets.

Isoflavone proportions varied among the diet groups in females. Equol comprised a greater (P < 0.05) proportion of the total plasma isoflavone concentration in females fed C/L + IF (79.00 ± 3.10%) than in those fed Soy(+) (66.24 ± 2.68%), and tended to be a greater (P = 0.09) than in those fed Soy(−) + IF (71.84 ± 2.40%). Isoflavone proportions did not differ (P > 0.10) among males fed the isoflavone-containing diets. Similar to the total isoflavone concentrations, males had higher proportions of equol than females fed the same isoflavone-containing diets (P < 0.05).

Correlations of genistein, daidzein and equol with one another revealed some differences between genders. Genistein was significantly correlated (r = 0.75, P < 0.01) with daidzein in females, but only tended (r = 0.69, P = 0.085) to be correlated with daidzein in males. In males, equol was correlated with genistein (r = 0.92, P < 0.01), and tended to be correlated with daidzein (r = 0.72, P = 0.06).

Although there was no effect (P > 0.10) of isoflavone-containing diets on the concentration of LDL + VLDLC in the female hamsters (Fig. 1), a positive association was observed (Fig. 4) between plasma total isoflavone concentration and LDL + VLDLC concentrations (r = 0.65, P = 0.02). A similar but nonsignificant (r = 0.48, P = 0.28) positive association was seen in the male hamsters. The lack of any overlap in the plasma isoflavone concentrations of males and females further demonstrated the gender difference in isoflavone metabolism (Fig. 4).

**Post-mortem evaluations.** In males, neither testicular nor accessory gland (seminal vesicles plus prostate) normalized weights differed (P > 0.10) among the treatment groups nor were there effects of treatment (P > 0.10) on normalized uterine weight in the females. No histological abnormalities were observed in any of the tissues examined.
DISCUSSION

Golden Syrian F1B Hybrid hamsters offer a number of opportunities for research on soy and soy components. Most notably they provide the opportunity to explore gender differences in plasma lipids and atherosclerosis. Ovarian hormones presumably modulate the protection of intact female hamsters from hyperlipoproteinemia and atherosclerosis because ovariectomized F1B Hybrid hamsters are reported to lose that protection (18). It is not known whether the susceptibility of the male hamsters to elevated plasma lipid concentrations and atherosclerosis is dependent on testicular-derived androgens.

Major gender differences were noted in the plasma lipid responses of the F1B Hybrid hamsters to the various diets. When Soy(+)/H11001 was fed to male hamsters, a large reduction in LDL + VLDLC concentrations and a small (P = 0.14) increase in HDLC were noted compared with those fed the C/L diet. This was in contrast to female F1B Hybrid hamsters fed Soy(+)/H11001 where there was no effect on LDL + VLDLC concentration, but there was significant increase in plasma HDLC compared with those fed the C/L diet. Unlike the results of the current study, a study in nonhuman primates (28), found no difference between males and females in their plasma lipid responses to Soy(+). In that study, both males and females fed Soy(+)/H11001 had significantly lower LDL + VLDLC and higher HDLC than those fed C/L. It is unclear whether the gender differences in F1B Hybrid hamsters may be different from observations in humans. Crouse et al. (1) found that LDLC was reduced in both men and women after consuming diets that contained at least 60 mg of isoflavones/25 g soy protein (comparable to the soy used in our study). Similarly, in a meta-analysis of the effects of soy protein intake on serum lipid concentrations in humans (29), reductions in LDL + VLDLC concentrations were noted in both genders, although a comparison between genders was not made. Although Teede and co-workers (30) observed a reduction in LDL/HDL the ratio in males and postmenopausal females receiving a soy protein isolate (118 mg of isoflavones in 40 g of soy protein), differences between genders were not evident.

Currently there is a great interest in whether and to what extent, the isoflavones in soy affect plasma lipids and atherosclerosis risk. To investigate this, we compared the soy diet with isoflavones intact, Soy(+), with a soy diet in which the isoflavones had been extracted, Soy(−). There were important gender differences in the effects of Soy(+)/H11001 and Soy(−)/H11001 on plasma lipoprotein concentrations in the F1B Hybrid hamsters. Among females, there were no differences between hamsters fed Soy(+)/H11001 and Soy(−)/H11001 diets in HDLC or LDL + VLDLC concentrations. In contrast, there were clear differences in the response of the male hamsters to the Soy(+)/H11001 vs. Soy(−)/H11001 diets. Males fed Soy(+)/H11001 had significantly lower LDL + VLDLC but there was no difference in HDLC. The response of male F1B Hybrid hamsters appears to be comparable to men (1) and male nonhuman primates (7,28), whereas intact female F1B Hybrid hamsters were unlike either pre- or postmenopausal monkeys (5,6,28) in that those fed Soy(+)/H11001 and Soy(−)/H11001 diets did not differ in LDL + VLDLC or HDLC concentrations.

Our group has conducted several studies that compare the effects of Soy(+)/H11001 and Soy(−)/H11001 fed to male, intact female and ovariectomized female cynomolgus monkeys. With the exception of the male rhesus monkeys' HDLC response (6), the Soy(+)/H11001 diets in these studies consistently resulted in a 20–30% reduction of LDL + VLDLC and an increase of 10–20% in HDLC (5,6,7,28). However, there are mixed results from studies comparing different effects of Soy(+)/H11001 and Soy(−)/H11001 on plasma lipids and lipoproteins of humans. Crouse et al. (1) demonstrated that there were increasing reductions in LDLC with increasing isoflavone content (3, 27, 37, and 62 mg of isoflavones) of dietary soy supplements, as well as slight but nonsignificant increases in HDLC in adult men and women. Premenopausal women consuming high isoflavone supplements (128 mg) had the greatest reductions (7–10%) in LDLC compared with the control diet during the midfollicular and periovulatory phases of the menstrual cycle compared with the low isoflavone (64 mg) and Soy(−)/H11001 (10 mg) supplements (3). Similarly, Wangen et al. (4) observed a significant decrease in plasma concentrations of LDLC in postmenopausal women consuming 132 mg of isoflavones in soy protein/d for 93 d compared with women consuming 7.1 mg of isoflavones/d, but no effect on HDLC was observed. In contrast to these studies, treatment of perimenopausal women with soy containing 80 mg of isoflavones/d for 24 wk did not alter their lipid profiles (31). Recently, Meinertz and co-workers (32) reported that both Soy(+)/H11001 and Soy(−)/H11001 reduced LDLC concentrations in normocholesterolemic men and women compared with the self-selected, baseline diets, but there was no difference in LDLC compared with the casein diet. Interestingly, a decrease in HDLC compared with baseline for all diets [casein, Soy(−)/H11001, Soy(+)/H11001] was also reported. Among these diets however, only Soy(+)/H11001 significantly increased HDLC concentration compared with the casein diet.

The fact that Soy(+)/H11001 appears to be more beneficial than soy without its isoflavones has led to interest in soy isoflavone extracts. Greaves et al. (11) were unable to achieve the plasma lipid-lowering effects of soy protein when the exact amounts of soy isoflavones contained in soy protein were added back to a diet containing casein and lactalbumin. Similarly, Anthony et al. (12) were unable to achieve plasma lipid lowering in male and postmenopausal monkeys by adding soy isoflavone extract to Soy(−)/H11001. These findings appear to be consistent with the observations in humans (13,15,33,34). However, Han et al. (35) recently reported significant reductions in LDLC and elevations in HDLC concentrations in postmenopausal women given capsules of soy isoflavones in 3 divided daily doses equal to 100 mg/d.

In the present study, there were no effects in female F1B Hybrid hamsters of adding isoflavone concentrate (IF) to either C/L or Soy(−)/H11001. In contrast, in the male F1B Hybrid hamsters, the effect of adding IF to Soy(−)/H11001 was to make their LDL + VLDLC concentrations intermediate to those in the Soy(−)/H11001 and Soy(+)/H11001 groups and not different from either. The addition of IF extract to the casein diet did not alter the lipid profile relative to male hamsters fed the C/L diet. In contrast to our results, Balmir et al. (36) demonstrated LDL lowering in male hamsters by adding an isoflavone extract to a CL diet.

The dramatically higher plasma isoflavone concentrations in male hamsters compared with the females was unexpected. The gender differences may relate to some aspect of absorption or metabolism and not food consumption because weight gains did not differ. We can find no evidence in the literature to suggest the mechanism by which plasma isoflavone concentrations might be different in male and female hamsters.

The positive association between plasma total isoflavones and LDL + VLDLC is of interest. We are uncertain whether this is a causal association, but a similar relationship was detected in a study with nonhuman primates (37). In contrast, a study in men reported an inverse association between plasma isoflavones and TC concentrations (38). However, there are few studies in humans that have measured plasma isoflavones, and it is uncertain whether high plasma concentrations are
associated with high or low urinary excretion of isoflavones. One possible reason for the positive association between plasma isoflavones and LDL+VLDL concentrations in our study could be that both isoflavones and cholesterol are recirculated in the enterohepatic circulation (39,40). It is possible that there is greater recirculation of both isoflavones and cholesterol in some individuals and, by the same token, a similarly lower rate of excretion of both cholesterol and isoflavones. Another possible explanation for the positive association between plasma isoflavones and LDL+VLDL is that there is a parallel absorption of the isoflavones and cholesterol, resulting in a positive association in the plasma. The F,B hybrid hamsters should lend themselves well to further research on this observation.

The abundance of equol in the plasma of the hamsters fed the isoflavone-containing diets is comparable to observations in mice (10) and rats (41). Additionally, we reported that ~70% of the plasma isoflavones of cynomolgus monkeys fed soy is equol (5). The production of such large quantities of equol in animal models is unlike the majority of humans. Only ~2–10% of human subjects produce large quantities of equol (42). We cannot determine whether the association of increasing plasma isoflavones with increasing LDL+VLDL is or is not due to equol because the relative amounts of the various isoflavones are correlated one with another.

We found no effect of the soy or soy isoflavone–containing diets on the reproductive organ relative weights of either the male or female hamsters, consistent with our earlier studies of nonhuman primates (6). However, increased uterine weight in rats fed isoflavones at pharmacologic doses has been reported (43).

Overall, the F,B Hybrid hamster has both similarities and dissimilarities to human and nonhuman primates in responses to soy-containing diets. The model, however, does offer opportunities to explore gender differences, in particular, effects of both male and female sex hormones on isoflavone metabolism and the effects of isoflavones on lipid metabolism.

ACKNOWLEDGMENTS

The authors gratefully acknowledge Matthew Dwyer, Timothy Vest and Maryanne Post for the care and handling of the hamsters and sample collection and J. Mark Cline for histological assessment of the reproductive tissues.

LITERATURE CITED


