# Effects of cow*s milk consumption on estrogen levels in human male volunteers

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Other condition |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON34786

**Source**
ToetsingOnline

**Brief title**
Estrogen intake via cow*s milk

### Condition

- Other condition

**Synonym**
niet van toepassing

**Health condition**

humane blootstelling aan estrogenen via melkconsumptie

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Universiteit Utrecht
**Source(s) of monetary or material Support:** Voedsel en Waren Autoriteit

## Intervention

**Keyword:** cows' milk, estrogens, exposure, risk assessment

## Outcome measures

### Primary outcome

Changes in the levels of estrogens, testosterone and metabolites in urine

resulting from milk consumption.

### Secondary outcome

Hormone extracts of the urine samples are tested in two in vitro bio-assays for

detection of estrogenic and androgenic activity.

# Study description

### Background summary

It is known since long that cow*s milk contains hormones, such as estrogens, progesterone and growth factors. However, hormone levels in commercial milk production have increased because lactation in new breeds of cows continues throughout almost the entire pregnancy.
Because of the increased levels of estrogens in cow*s milk and the high consumption of milk products in the Dutch population, it is of concern whether intake of hormones via cow*s milk consumption could result in endocrine effects in humans. Beside the possibility of endocrine disruption, relations between milk consumption and prevalence of hormone-dependent cancers (e.g. breast- and prostate cancers) have been suggested. Although clear epidemiological evidence is currently lacking, it is worth investigating which hormones in milk are most critical for these adverse effects. Exposure to estrogens appears to be important in this possible relationship between milk consumption and hormone-dependent cancers, as estrogens are critically involved in hormone-dependent cancers. On one hand estrogens interact with the estrogen receptor to induce cell proliferation. On the other hand, metabolites of estrogens interact with the estrogen receptor and the DNA, thereby inducing

genotoxicity. Both mechanisms explain the carcinogenic properties of estrogens. Preliminary data from a very recent Japanese study indicates increases in systemic estrogen concentration after a single consumption of 600 ml commercial milk.
In the Dutch situation can be expected that an additional intake of estrogens takes place by means of the consumption of dairy products. It remains however the question whether this additional exposure to estrogens from dietary intake results in changes in systemic (internal) concentrations, and whether this can be responsible for the observed changes in growth and development of juveniles and the higher incidence of hormone-dependent cancers. The association between the high dairy consumption in our country and before mentioned changes in growth and development as well as higher tumor incidence is at present only based on speculation. Other lifestyle factors, dietary factors and improved medical care during the last fifty years could also be involved.
To reveal a possible causal connection between dietary estrogens and changes in growth and development or higher tumor incidence, it must first be investigated whether Dutch dairy consumption can lead to increased systemic estrogen concentrations. If internal concentrations are not significantly influenced by cow*s milk consumption, the risk of these hormones can be considered then as nil in this specific situation. It is known from pharmacology that natural estrogens are taken up poorly after oral intake. It is not unlikely that a potential increase of systemic concentrations is reduced by first pass metabolism in the liver. Phase II sulfate and glucuronidic metabolites are formed, that are rapidly excreted from the body. It can however not be excluded that re-uptake of estrogens via the entero-hepatic pathway also occurs, possibly resulting in increases in systemic concentrations in blood and tissues. Estrogens taken up from the cow*s milk may also be metabolized to hydroxylated metabolites in the liver. Some of these metabolites also exhibit estrogenic activity and are possibly carcinogenic.

## Study objective

The aim of this study is to investigate whether weeklong dietary intake of estrogens via high cow*s milk consumption in the Dutch population increases systemic estrogen concentrations. To this aim, estrogen levels are measured in urine samples of volunteers.
In the urine samples, estrogen concentrations (17β-estradiol en estrone) are measured at the division Veterinary and Public Health (VPH) at the Institute for Risk Assessment Sciences (IRAS) at Utrecht University (Faculty Veterinary Medicine). Measurements of estrogen metabolites are also included. Because of the close association between estrogens and androgens, testosterone measurements are also included. To investigate total amount of estrogenic compounds excreted via urine, sum estrogenic activity will be investigated by using in vitro screening of urine extracts (see below in study design).

## Study design

Volunteers will be asked to drink 1.5 l cow*s low-fat (*halfvolle*) milk per day for 7 days. The resulting daily intake of 1.5 l is considered a high-intake scenario, while average daily intake of cow*s milk in the Netherlands is estimated to be 270 ml (in 19-30 year olds). Before the study, a screening questionnaire and an informed consent form have to be filled out. 3 days prior to the intervention and during the intervention, the volunteers will remove dairy products from their diet, as well as other foodstuffs containing large amounts of phytoestrogens (specified in volunteer*s information). It is expected that dietary estrogens are cleared from the body within this period. Examples for meals appropriate during the study are suggested. Supplied food questionnaires (qualitative) have to be filled out daily. At 8 days during the study, volunteers are asked to collect morning urine, and they are invited to the IRAS in the morning. At these meetings, urine sample vials and milk are distributed, and urine samples handed in. The volunteers receive a simple breakfast to-go. The volunteers will be asked for their body weight and length.

Urinary excretion of hormones is used in this study to examine changes in internal concentrations. In the urine, 17β-estradiol and estron are measured as a measure for systemic exposure. To investigate possible effects on the estrogen/androgen balance, testosterone is also measured in the urine samples. The hormones in the urine will be measured by LC-MS/MS at the division Veterinary and Public Health of the IRAS. Hormone extracts of the urine samples are also tested in two in vitro bio-assays for detection of estrogenic and androgenic activity. These are ER-Calux and AR-Calux, in vitro assays using a genetically modified mammal cell line. Analysis of estrogen metabolites will also be included. The results of this research will be published in the open scientific literature. The data will also be made available to the RIVM for possible pharmacokinetic modeling. To this aim, the volunteers will be asked for their body weight and length.

**Intervention**

Volunteers will be asked to drink 1.5 l cow*s low-fat (*halfvolle*) milk per day for 7 days. 3 days prior to the intervention and during the intervention, the participants will remove dairy products from their diet, as well as other foodstuffs containing large amounts of phytoestrogens. Supplied food questionnaires (qualitative) have to be filled out daily (in total 31 days). At 8 days during the study, volunteers are asked to collect morning urine, and they are invited to the IRAS. At these meetings, urine sample vials and milk are distributed, and urine samples handed in. The volunteers receive a simple breakfast to-go. A compensation of 150 ¤ will be given to the volunteers after the study. Milk will be supplied by the research team to the volunteers. The volunteers will be asked to inform the researchers about their body weight and length.

**Study burden and risks**

The inclusion and exclusion criteria are designed to avoid health risk related to milk consumption (mainly allergic reactions). Prior to and during the intervention, volunteers will have to avoid certain foodstuffs. These are listed in the information for volunteers and example meal recipes are suggested. During the study, volunteers will have to fill in daily food questionnaires (in total 31 days). Furthermore, only non-invasive (urine) sampling will occur during this study.

## Contacts

**Public**
Universiteit Utrecht

Yalelaan 2
3584CM Utrecht
Nederland
**Scientific**
Universiteit Utrecht

Yalelaan 2
3584CM Utrecht
Nederland

## Trial sites

### Listed location countries

Netherlands

## Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

### Inclusion criteria

Volunteers (20) will be recruited at the campus of Utrecht University (de Uithof, living within 30 min travel). Healthy young males (20-23 year-old) are selected to reduce the possibility of confounding (see also exclusion criteria). A person is regarded healthy if they have none of

the health problems described under exclusion criteria. Only Dutch Caucasian males are selected because of their likely encounter with dairy products, limiting the risk of health problems due to milk allergies or lactose intolerance during the study. Males are chosen for their low estrogen levels, making it possible to measure subtle concentration changes in urine. In addition, participants should have an adequate command of Dutch in order to avoid language problems with filling out questionnaires.

### Exclusion criteria

Volunteers that have dairy intolerance or allergies are excluded to avoid health problems due to the nature of the study. Potential volunteers with a deficiency in liver metabolism or hormonal afflictions are excluded from this research to avoid confounding of the results on urinary hormone levels. Vegetarians are excluded from this study because of a possible high dietary intake of phytoestrogens. Smokers are excluded in view of induction of cytochrome P450 enzymes. Participation in other medical-scientific investigations could result in confounding in all involved studies. Women are excluded because of monthly menstrual-cycle related variations in systemic estrogen levels and children are excluded because of ethical reasons.

## Study design

### Design

**Study type:** Interventional

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| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

### Recruitment

NL

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| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 12-04-2010 |
| Enrollment: | 20 |
| Type: | Actual |

## Ethics review

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| Approved WMO Date: | 01-04-2010 |
| Application type: | First submission |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 21-05-2010 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |
| Approved WMO Date: | 05-11-2010 |
| Application type: | Amendment |
| Review commission: | METC Universitair Medisch Centrum Utrecht (Utrecht) |

# Study registrations

## Followed up by the following (possibly more current) registration

No registrations found.

## Other (possibly less up-to-date) registrations in this register

No registrations found.

## In other registers

| Register | ID |
|---|---|
| CCMO | NL29765.041.10 |