参考資料２－４

経口毒性と吸入毒性の比較に関する論文（暫定版）

Subacute (28-day) toxicity of furfural in Fischer 344 rats: a comparison of the oral and inhalation route. 2004. *Food and Chemical Toxicology.* 42 1389-1399.

要約

投与経路の違いによる外挿、すなわち経口毒性試験データから吸入曝露の限界値（limit value）を導くことができるか、フルフラール（furfural）を用いF344 ラットにおける亜急性経口及び亜急性吸入毒性試験を実施した。1 群雌雄各 5 匹のラットに投与量 6-192 mg/kg bw/日（6 群設定）で 28 日間強制経口投与、または濃度 20-1280 mg/m³（7 群設定：6 時間/日、5 日間/週）あるいは 160-1280 mg/m³（4 群設定：3 時間/日、5 日間/週）で 4 週間吸入曝露した。コントロール群は媒体（コーンオイル）投与または清浄空気の曝露とした。

フルフラールの最高用量における経口投与（初期で 192 mg/kg bw/日、その後 144 mg/kg 体重/日に低下、最後は 120 mg/kg 体重/日）で死亡（雄 1/6 例、雌 4/6 例）と雌の生存例における肝臓と腎臓の絶対および相対重量の増加が認められた。6 時間/日吸入曝露において、640 mg/m³以上の高濃度群においては曝露後 1-8 日内で死亡が認められた。6 時間/日吸入曝露の 320 mg/m³以下および 3 時間/日吸入曝露の 640 mg/m³の濃度群では重篤な臨床症状は認められなかった。対照的に病理組織学的検査では、鼻部の変化が 6 時間/日吸入曝露の最低濃度である 20 mg/m³群でも認められた。曝露濃度が高くなるほど、鼻部変化の頻度、程度は増加し，部位は鼻の前部から後部へと広がり嗅上皮も含まれていた。

経口毒性試験の無毒性量（NOAEL）は 96 mg/kg bw/日と結論された。全身的な吸入毒性の NOAEL もほぼ同濃度、すなわち 100%の吸収率と仮定すると 92 mg/kg bw/日（6 時間/日曝露の 320 mg/m³群または 3 時間/日曝露の 640 mg/m³群に相当）であった。最低濃度の 20 mg/m³群（6 mg/kg bw/日相当）で病理組織学的に鼻部の変化が認められたことは、フルフラールのような局所作用を有する物質に対しては経口経路から吸入経路への外挿は有効ではない。

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Subacute (28-day) toxicity of furfural in Fischer 344 rats: a comparison of the oral and inhalation route

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Abstract

The subacute oral and inhalation toxicity of furfural vapour was studied in Fischer 344 rats to investigate whether route-to-route extrapolation could be employed to derive the limit value for inhalation exposure from oral toxicity data. Groups of 5 rats per sex were treated by gavage daily for 28 days at dose levels of 6–192 mg/kg bw/day, or exposed by inhalation to concentrations of 20–1280 mg/m^3 (6 h/day, 5 days/week) or 160–1280 mg/m^3 (3 h/day, 5 days/week) for 28 days. Controls received vehicle (corn oil) or were exposed to clean air.

Daily oral treatment with the highest dose of furfural (initially 192 mg/kg bw/day, later reduced to 144 mg/kg bw/day and finally to 120 mg/kg bw/day) resulted in mortality, and in increases in absolute and relative kidney and liver weight in surviving females of this group. Exposure of rats by inhalation for 6 h/day, 5 days/week for 28 days induced mortality at concentrations of 640 mg/m^3 and above within 1–8 days. At 640 mg/m^3 (3 h/day) and at 320 mg/m^3 (3 and 6 h/day) and below, however, exposure was tolerated without serious clinical effects. In contrast, histopathological nasal changes were seen even at the lowest concentration of 20 mg/m^3. With increasing exposure concentration, the nasal effects increased in incidence and severity and also expanded from the anterior part to the posterior part, including the olfactory epithelium.

It was concluded that the no-observed-adverse-effect level (NOAEL) for oral toxicity was 96 mg/kg bw/day. The NOAEL for systemic inhalation toxicity was comparable, i.e. 92 mg/kg bw/day (corresponding to 320 mg/m^3 (6 h/day) or 640 mg/m^3 (3 h/day)) assuming 100% absorption. The presence of the histopathological nasal changes at the lowest tested concentration of 20 mg/m^3 (corresponding to 6 mg/kg bw/day) proves that for locally acting substances like furfural extrapolation from the oral to the inhalation route is not valid.

Keywords: Furfural; Oral; Inhalation; Subacute toxicity; Fischer rat; Route-to-route extrapolation

1. Introduction

Furfural (CAS Reg. no. 98-01-1) is a colourless, readily volatile oily liquid, with a pungent aromatic odour. It is used in solvent extraction processes in the petroleum refining industry and has a wide variety of other uses such as a solvent, an ingredient of phenolic resins, chemical intermediate, weed killer, fungicide and also as a flavouring agent (Kirk-Othmer, 1984). Furfural as a natural volatile compound has been identified in many foods, e.g. fruits, vegetables, bread, and beverages such as cognac, rum, malt whiskey, port wine, and coffee (Maarsse and Visscher, 1989). At the workplace, furfural may enter the body by the respiratory as well as the percutaneous route, the absorbed portion of the vapour by the skin corresponding to about 20% of the amount absorbed by the lungs (Flek and Sedivic, 1978). The lungs will retain about 78% furfural of the inhaled amount (Flek and Sedivic, 1978). Following oral intake in rats, highest concentrations, proportional to dose, were found in liver and kidneys. The lowest concentration was observed in the brain (Nomeir et al., 1992). Furfural is cleared from the body by rapid liver metabolism and excretion. The biotransformation of furfural takes place in two ways: the major part is

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oxidised and conjugated with glycine to furoylglycine, the smaller part is condensated with acetic acid and also conjugated with glycine to 2-furanacryluric acid (Flek and Sedivic, 1978). The major excretion route is via the urine, whereas exhalation by expired air and faecal excretion are minor routes (Nomeir et al., 1992).

Various values for the acute inhalation toxicity of furfural have been reported in rats varying from 600 mg/m^3 (4-h LC50; RTECS, 2002), 740 mg/m^3 (1-h LC50; Gupta et al., 1991) to 4075 mg/m^3 (1-h LC50; Terrill et al., 1989). In hamsters, furfural has a low acute inhalation toxicity; a 4-h LC50 value of 13 g/m^3 was indicated (Kruysse, 1972). A 6-h LC50 value of about 1.5 g/m^3 has been reported for dogs (RTECS, 2002). These differences may indicate that metabolism plays a role. The sensory irritation potential as measured by respiratory rate depression resulted in RD50 values of about 900 and 1100 mg/m^3 in two strains of mice (Steinhagen and Barrow, 1984). Inhalation exposure of hamsters to 448 or 2165 mg/m^3 furfural for 6 h/day, 5 days/week during 13 weeks produced local toxicity especially in the nose as indicated by concentration-related focal atrophy of the nasal olfactory epithelium. No such effects were observed at the lowest concentration of 77 mg/m^3 (Feron et al., 1979). Inhalation exposure during 12 months to a concentration of 1550 mg/m^3 which was lowered after 20 weeks to 970 mg/m^3, also revealed irritation of the nasal olfactory mucosa in the same species (Feron and Kruysse, 1978). Exposure of workers to furfural concentrations exceeding the threshold limit value of 8 mg/m^3 has been reported to produce respiratory tract and/or eye irritation (Apol and Lucas, 1975; Di Pede et al., 1991).

The oral LD50 value for rats was reported to be between 50 and 127 mg/kg bw (Castelli et al., 1967; RTECS, 2002). In mice, oral LD50 values were higher, i.e. between 418 and 500 mg/kg bw (RTECS, 2002). Oral exposure of F344/N rats to furfural at dose levels of 15–240 mg/kg bw/day by gavage for 16 days resulted in mortality in 8 out of 10 rats at the highest level tested. A similar treatment of B6C3F1 mice up to dose levels of 400 mg/kg bw/day did not result in mortality. In both species, no compound-related histopathological lesions were observed. Upon treatment of the same rat strain for 13 weeks, the main effects consisted of mortality at levels of 90 and 180 mg/kg bw/day. In addition, increased absolute and relative liver and kidney weights were seen at a level of 90 mg/kg bw/day (at 180 mg/kg bw/day most rats had died). In mice survival was reduced at dose levels of 600 and 1200 mg/kg bw/day; increased liver and kidney weights were observed at levels of 75 mg/kg bw/day and higher, although dose-response relationships were not obtained. In mice, centrilobular necrosis and multifocal inflammation of the liver was reported at levels of 150 mg/kg bw/day and higher. When tested for carcinogenicity by the same treatment, it was concluded that there was some evidence of carcinogenicity based on the occurrence of uncommon cholangiocarcinomas in 2 males and bile duct dysplasia with fibrosis in two other males at a level of 60 mg/kg bw/day. In mice, it was concluded that there was clear evidence of carcinogenic activity at a level of 175 mg/kg bw/day, based on increased incidences of hepatocellular adenomas and carcinomas (Irwin, 1990).

From these data it can be concluded that the main target following oral exposure to furfural appeared to be the liver, whereas only local (nasal) effects have been reported following inhalation exposure. In the process of risk assessment, however, it is common practice to derive exposure limits for inhalation exposure from oral toxicity data. One of the criteria to perform route-to-route extrapolation is the absence of any local effects, i.e. the critical target tissue should not be at the portal of entry (Pepelko, 1987; Dourson and Felter, 1997). The present study with furfural was conducted in order to establish whether it is scientifically sound to apply route-to-route extrapolation to derive limit values for inhalation exposure from oral toxicity data. In addition to groups exposed for 6 h/day, groups exposed for 3 h/day were inserted in the present study to investigate whether daily exposure for 3 h to a given concentration would result in similar effects as daily exposure for 6 h to half that concentration.

2. Materials and methods

2.1. Animals and maintenance

Male and female, young adult, F344 (CDF(F344)/CrlBR) rats were purchased from Charles River Deutschland (Sulzfeld, Germany). The animals were acclimatised for at least 5 days before the start of the study. They were kept under conventional laboratory conditions in macrolon cages with sterilized bedding, 5 rats per sex per cage, and received RM3 rodent diet and unfluoridated tap water ad libitum. The animal rooms were ventilated with about 10 air changes per hour and were maintained at a temperature of 22 ± 3 °C and a relative humidity of at least 30% and not exceeding 70% other than during room cleaning. All animal procedures were approved by the TNO Committee on Animal Welfare.

2.2. Materials

Furfural (2-furaldehyde; CAS Reg. No. 98-01-1; purity ≥99%) was obtained from Sigma/Aldrich (Brussels, Belgium).

2.3. Atmosphere generation and analysis

Furfural vapours were generated by bubbling mass flow controlled (Bronkhorst, Hi Tec, Ruurlo, The Netherlands) amounts of nitrogen (between 27 and 1373 ml/min) through all glass evaporators filled with furfural. The evaporators were held at 23.0 °C. Each test atmosphere was passed to a separate inhalation unit (ADG Developments Ltd., Codicote, Hitchin, Herts. SG4 8UB, UK), where it was diluted with humidified compressed air. The water container used for humidification was kept at a constant temperature of 39 °C. Furfural concentrations in the test atmospheres were semi-continuously determined by infrared analysis (Bruel and Kjaer, Denmark) at a wavelength of approximately 9.8 μm. Two monitors were used, and each successively sampled by rotation one of three inhalation units during 10 min. Prior to the first exposure, the infrared analysers were calibrated one for the high levels in the range of 30–1500 mg/m^3, the other for the lower concentrations in the range of 30–200 mg/m^3 (correlation coefficients > 0.996). One day after the last exposure, the integrity of the calibration was approved again.

2.4. Experimental design and execution

2.4.1. Oral study

Male and female animals were allocated according to body weight into groups of 5 rats/sex. Each group received furfural in corn oil at 5 ml/kg bw by gastric gavage for 28 consecutive days (Table 1). Controls received vehicle only. Fresh dilutions of the test substance in the vehicle were made once per week and stored in a refrigerator. Twice per week the dose volumes were adjusted to the latest recorded body weight for each rat.

2.4.2. Inhalation study

Male and female animals were also allocated according to body weight into groups of 5 rats/sex. During exposure, the rats were individually restrained in Battelle tubes and each tube was then placed into one of the inhalation units (ADG Developments Ltd., Codicote, Herts, UK) for head/nose-only exposure to the test atmosphere. Each unit had a volume of approximately 50 l. The exposure air flows were between 15 and 28 l/min that is, 18–34 air changes per hour. Daily mean temperature of the test atmospheres was between 22.1 and 22.8 °C with standard deviations of 0.4 °C; daily mean relative humidity was 43–44% with standard deviations of 2–4%. Rats were exposed for 3 h/day or 6 h/day, 5 days/week (Table 1). Controls were exposed to clean air.

2.4.3. Clinical signs, body weight and food consumption

Each animal was observed daily to detect signs of toxicity. Body weights were measured once or twice weekly, and food consumption was recorded at weekly intervals.

2.4.4. Haematology and clinical chemistry

Haematological variables were measured in all fasted rats at the end of the treatment period and included haemoglobin concentration, packed cell volume (haematocrit), erythrocyte and thrombocyte count, prothrombin time, and total and differential leukocyte counts. The following biochemical variables were measured in plasma obtained from heparinised blood samples at the same time (Hitachi 911 analyser, Hitachi Instruments Division, Japan): albumin, alanine aminotransferase (ALAT), alkaline phosphatase, aspartate aminotransferase (ASAT), total bilirubin, calcium, chloride, cholesterol, creatinine, γ-glutamyltransferase, glucose, inorganic phosphate, phospholipids, potassium, total protein, sodium, triglycerides, and urea.

2.4.5. Pathology

At necropsy, the day after the last treatment, the animals were weighed, anaesthetised, killed by

Table 1
Dose and concentration levels used

Oral exposure	Inhalation exposure (6 h/day)			Inhalation exposure (3 h/day)		
Dose (mg/kg bw/day)	Concentration (mg/m^3)	Concentration (mg/m^3 h)	'Dose' (mg/kg bw/day)	Concentration (mg/m^3)	Concentration (mg/m^3 h)	'Dose' (mg/kg bw/day)
0	0[a]	0	0	–	–	–
6	20	120	6	–	–	–
12	40	240	12	–	–	–
24	80	480	23	160	480	23
48	160	960	46	320	960	46
96	320	1920	92	640	1920	92
192	640	3840	184	1280[a]	3840	184
–	1280[a]	7680	368	–	–	–

Groups of 5 male and 5 female rats were daily treated orally or exposed by inhalation 5 days/week with furfural for 28 days. The inhalation 'dose' was calculated as follows: [conc. (mg/m^3)/1000 l × 360 min × 0.8 l/kg bw/min].

[a] Due to mortality in the higher concentration groups on the first exposure day (see Table 2), these groups were replaced by groups exposed to 160 mg/m^3 (3 h/day), and 20 mg/m^3 (6 h/day).

exsanguination from the abdominal aorta and examined grossly for pathological changes. Adrenals, brain, heart, kidneys, liver, spleen, testes, thymus, and lungs (with trachea and larynx) were removed and weighed. Tissue samples of these organs and, from animals exposed by inhalation, samples of the complete respiratory tract, and from animals treated orally, samples of the gastrointestinal tract, were preserved in a 4% aqueous, neutral phosphate buffered formaldehyde solution. After fixation, noses were decalcified in nitric acid. Organs and tissues were embedded in paraffin wax, sectioned at 5 m and stained with haematoxyclin and eosin. The respiratory tract was processed as follows: the nose was cut at six levels (Young, 1986; Woutersen et al., 1994), the larynx was cut longitudinally at three levels, the trachea with the bifurcation was cut longitudinally alongside the bifurcation and each lung lobe was sectioned. Full microscopic examination was carried out on the kidneys, liver, lungs, spleen and thymus of all rats, on the adrenals, heart, oesophagus and stomach of all orally treated rats, and on the nose, larynx and trachea of all animals exposed by inhalation.

2.5. Statistical analysis

Body weight data were analysed by one-way analysis of co-variance (ANCOVA) using pre-exposure (day 0) weights as the covariate. Organ weights, and haematological and clinico-chemical data were analysed by one-way analysis of variance (ANOVA). If significant differences among the means were indicated, Dunnett's test was performed to determine which exposed groups differed from the control (Dunnett, 1955, 1964; Cochran, 1957; Steel and Torrie, 1960). Relative differential white blood cell counts were analysed by Kruskal–Wallis non-parametric ANOVA followed by Mann–Whitney *U*-test. The incidences of histopathological changes were analysed by Fisher's exact probability test (Siegel, 1956). All pairwise comparisons were two-tailed. Group mean differences with an associated probability of less than 0.05 were considered to be statistically significant.

3. Results

3.1. Oral study

One female and one male of the highest dose group were found dead on day 1 and 4 of the study, respectively. These animals were replaced by reserve animals. Because of these fatalities the highest dose of 192 mg/kg bw/day was lowered to 144 mg/kg bw/day for both male and female rats. Due to one additional female mortality on day 10 and one female that had to be killed in extremis on day 11, the highest dose level was further reduced to 120 mg/kg bw/day, again for both male and female animals. The animal that had to be killed in extremis showed lethargy and breathing difficulties prior to necropsy. At necropsy, the lungs of this rat were red, and a gaseous content was observed in the stomach. On the last day of the study one other female of this group was found dead (Table 2). No other treatment-related clinical signs were observed. Mean body weights were similar among the groups throughout the study, and no changes in food consumption or food conversion efficiency were observed. No treatment-related changes were observed in haematology and clinical chemistry (data not shown). Increased absolute and relative kidney weights were observed in both surviving females of the highest dose group; increased absolute and relative liver

Table 2
Mortality data

Oral exposure		Inhalation exposure (6 h/day)		Inhalation exposure (3 h/day)	
Dose (mg/kg bw/day)	Mortality M/F	'Dose'* (mg/kg bw/day)	Mortality M/F	'Dose'* (mg/kg bw/day)	Mortality M/F
0	0/0	0	0/0	–	–
6	0/0	6	0/0	–	–
12	0/0	12	0/0	–	–
24	0/0	23	0/0	23	0/0
48	0/0	46	0/0	46	0/0
96	0/0	92	0/0	92	0/0
192[a]	1/6 / 4/6	184[b]	2/5 / 3/5	184[c]	5/5 / 5/5
–	–	368[c]	5/5 / 5/5	–	–

Groups of 5 male and 5 female rats were daily treated orally or exposed by inhalation 5 days/week with furfural for 28 days.
*See for calculation of the 'inhalation dose' Table 1.
[a] One female and one male were found dead on day 1 and 4, respectively. These animals were replaced by reserve animals and the dose was reduced to 144 mg/kg bw/day. Due to two additional female fatalities, this dose level was further reduced to 120 mg/kg bw/day. One female was found dead on the last day of treatment.
[b] Since mortality occurred after one day of exposure (male), after 4 (male) and 5 (female) days, and again after 8 days (2 females), it was decided to discontinue the exposure of this group.
[c] All animals were found dead during or after the first exposure; these groups were replaced the next day by groups exposed to 160 mg/m^3 (3 h/day) and 20 mg/m^3 (6 h/day).

Table 3
Absolute and relative organ weights in female rats orally treated with furfural for 28 days

	Kidneys		Liver		Spleen	
	Absolute (g)	Relative (g/kg)	Absolute (g)	Relative (g/kg)	Absolute (g)	Relative (g/kg)
Control	1.07 ± 0.01	7.39 ± 0.04	4.04 ± 0.09	27.8 ± 0.8	0.342 ± 0.006	2.35 ± 0.03
6 mg/kg bw	1.08 ± 0.02	7.26 ± 0.06	4.37 ± 0.10	29.5 ± 0.7	0.367 ± 0.010	2.47 ± 0.04
12 mg/kg bw	1.05 ± 0.01	7.14 ± 0.07	4.25 ± 0.11	28.9 ± 0.6	0.363 ± 0.008	2.47 ± 0.06
24 mg/kg bw	1.09 ± 0.03	7.42 ± 0.10	4.33 ± 0.17	29.3 ± 0.8	0.347 ± 0.007	2.35 ± 0.03
48 mg/kg bw	1.11 ± 0.02	7.41 ± 0.02	4.43 ± 0.16	29.5 ± 0.8	0.362 ± 0.010	2.41 ± 0.06
96 mg/kg bw	1.12 ± 0.01	7.51 ± 0.09	4.37 ± 0.07	29.3 ± 0.6	0.381 ± 0.005**	2.56 ± 0.04*
192 mg/kg bw#	1.29** (1.32/1.27)	8.25** (8.37/8.13)	5.21** (4.51/5.91)	33.3 (28.7/37.9)	0.381 (0.386/0.376)	2.43 (2.45/2.41)

Groups of 5 female rats were treated orally with furfural daily for 28 days. Animals were necropsied the day after the last treatment, and organs were weighed.

#Two surviving animals only; during the course of the study, this dose level was lowered to 144 mg/kg bw/day and finally to 120 mg/kg bw/day. Statistics: ANOVA-Dunnett's test; $^{*}p < 0.05$, $^{**}p < 0.01$.

weights were observed in one of these 2 rats (Table 3). Increased absolute and relative spleen weights were observed in females treated with 96 mg/kg bw/day, but not in females of the highest dose group (Table 3). At necropsy, no treatment-related gross lesions were observed. Microscopic examination of the preserved organs did not reveal any treatment-related changes. The histopathological changes observed were considered to be common findings in rats of this strain and age. Moreover, they were about equally distributed among the groups and/or they occurred in one or a few animals only. Also in the rats that were found dead or killed in extremis, no treatment-related histopathological changes could be observed (data not shown).

3.2. Inhalation study

Mean actual concentrations of furfural were close to target concentrations, i.e. these were (±standard deviation) 20 (±1), 41 (±1), 80 (±3), 158 (±3), 316 (±8) mg/m^3 for the 6-h exposure groups and 157 (±4), 314 (±1), and 635 (±24) mg/m^3 for the 3-h exposure groups. At the end of the first exposure day, all animals exposed to 1280 mg/m^3 (3840 and 7680 mg/m^3 h) were found dead. The next morning also one male of the group exposed for 6 h to 640 mg/m^3 (3840 mg/m^3 h) was found dead. After four more animals of this group were found dead up to nominal day 8, it was decided to discontinue exposure of the remaining animals of this group (Table 2). Clinical signs during exposure consisted of breathing abnormalities, i.e. decreased breathing frequency was observed in animals exposed to 80 mg/m^3 (480 mg/m^3 h) and higher. Mean body weights were similar among the groups throughout the study, and no changes in food consumption or food conversion efficiency were observed (data not shown). Although several changes were observed in haematology and clinical chemistry (data not shown), the changes were found in one or a few groups and were not concentration-related. Therefore, they were not considered to be related to treatment, except perhaps the small increase observed in inorganic phosphate in females exposed to 320 mg/m^3 for 6 h/day (1920 mg/m^3 h). Also, the increases as well as decreases in absolute and relative liver and spleen weights (Table 4) were considered to be unrelated to treatment. At necropsy, no treatment-related gross lesions were observed. Microscopic examination of the preserved organs revealed treatment-related changes in the nasal passages only. The histopathological changes observed consisted of respiratory epithelial lesions such as squamous metaplasia and atypical hyperplasia, and olfactory epithelial changes characterised by epithelial disarrangement. The histopathological changes observed in the respiratory epithelium were seen in all 6 h/day exposure groups, i.e. at 20 mg/m^3 (120 mg/m^3 h) and higher, whereas the olfactory epithelial disarrangement was seen in the groups exposed to 80 mg/m^3 (480 mg/m^3 h) or above. In addition, at the exposure concentrations of 20 mg/m^3 (120 mg/m^3 h) and 40 mg/m^3 (240 mg/m^3 h), the transitional epithelium located in the anterior part of the nose was affected in all exposed animals, whereas the lining epithelium more posterior in the nose was affected in one or two animals of these groups only. At exposure concentrations of 80 mg/m^3 (480 mg/m^3 h) and higher, exposure-related changes of the lining epithelium more posterior in the nose were seen at a higher incidence and degree. Similar lesions were observed in animals exposed for 3 h/day, however, at a lower incidence and degree when compared to animals exposed for 6 h/day at half the concentration (Table 5).

4. Discussion

In the present oral 28-day toxicity study, daily treatment with the highest dose of furfural (initially 192 mg/kg bw/day, later reduced to 144 mg/kg bw/day and finally to 120 mg/kg bw/day) resulted in mortality in four out of 6 female rats (one was replaced due to early mortality, i.e. during the first study week) and in one out