

January 11, 2005

COURTNEY M. PRICE  
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*FYI-0105-01485*

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Dear Mr. Auer:

The American Chemistry Council makes available to the public and appropriate government agencies final reports of environmental, health, and safety research that it manages. In keeping with this policy, the following reports that the American Chemistry Council's Olefins Panel recently conducted are enclosed:

- "2-Methyl-2-Butene Acute Toxicity to *Daphnia Magna*,"
- "2-Methyl-2-Butene Algal Growth Inhibition Assay,"
- "2-Methyl-2-Butene Dose Range Finding Study in rats by Inhalation Exposure,"
- "2-Methyl-2-Butene Identification and Determination of Purity,"
- "2-Methyl-2-Butene Assessment of Biodegradability Using the Closed Bottle Method,"
- "2-Methyl-2-Butene Acute Toxicity to Rainbow Trout (Semi-Static Exposure Conditions)," and
- "2-Methyl-2-Butene 4 Week General Toxicity and Reproduction/Development Toxicity Screening Test by Inhalation Exposure to Rats (OECD 422 Guidelines)."

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The enclosed reports do not include confidential information.

If you have any questions, please call the Olefins Panel Manager of my staff at 301-924-

2006



Sincerely yours,

Enclosure



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282840

## ROBUST SUMMARY

### Acute Toxicity to *Daphnia Magna*

<p><b><u>Test Substance</u></b></p> <p>Remarks</p> <p><b><u>Method</u></b></p> <p>Method/guideline followed GLP Year Test type Species Exposure period Limit test Analytical monitoring Study Design</p> <p>Evaluation of data</p>	<p>2-methyl-2-butene ( No. 513-35-9) The test substance was stable for the duration of all the studies performed by the test house.</p> <p>OECD Guide-line 202 and EC Directive 92/96 C2 Yes 2002 Static <i>Daphnia magna</i> (Crustacea) 48 hours No Yes The study was conducted in completely filled (no headspace) and sealed vessels because of the volatility of 2-methyl-2-butene. The test media were prepared, either directly or by dilution, from an aqueous preparation in which the test substance was stirred in a sealed vessel in the dark for approximately 24 hours. After being allowed to stand for approximately 30 minutes to obtain an equilibrium concentration of 2-methyl-2-butene, aliquots of medium were removed from the middle of the vessel and used to fill replicate vessels at each concentration.</p> <p>Groups of twenty <i>Daphnia</i>, less than 24 hours old, were exposed for 48 hours to 2-methyl-2-butene, prepared in Elendt M4 medium at nominal concentrations of 2.13, 4.70, 10.3, 22.7 and 50.0 mg/l. The exposure levels were monitored by measuring the concentrations of 2-methyl-2-butene in samples of the test media using a GLC method of analysis.</p> <p>Observations of the <i>Daphnia</i> in each control and test vessel were made after 24 and 48 hours.</p> <p>EC<sub>50</sub> values were estimated either by the moving average method or by non-linear interpolation between the two concentrations which bracket the 50% effect level using a computer program (Stephan:1977;1982); the program uses the number of <i>Daphnia</i> exposed and the number immobile at each nominal and measured concentration.</p> <p>The “no observed effect concentration” (NOEC) was derived by direct inspection of the data on the immobility of the animals. An incidence of more than 10% is considered to be significant.</p>
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## ROBUST SUMMARY

### Algal growth inhibition assay

<u><b>Test Substance</b></u>	
Remarks	2-methyl-2-butene (CAS No. 513-35-9) also known as 2-methyl, 2-butene. The test substance was stable for the duration of all the studies performed by the test house.
<u><b>Method</b></u>	
Method/guideline followed	OECD Guide-line 201, EC Directive 92/69 C3, US EPA TSCA 797.1050 & 797.1060
GLP	Yes
Year	2003
Endpoint	Growth rate
Species	<i>Pseudokirchneriella subcapitata</i> (formerly <i>Selenastrum capricornutum</i> ) (Algae)
Exposure period	96 hours
Limit test	No
Analytical monitoring	Yes
Study Design	The study was conducted in completely filled (no headspace) and sealed vessels because of the volatility of 2-methyl-2-butene. The test media were prepared, either directly or by dilution, from an aqueous preparation in which the test substance was stirred in a sealed vessel for approximately 23 hours in the dark. After being allowed to stand for at least one hour to obtain an equilibrium concentration of 2-methyl-2-butene, aliquots of medium were removed from the middle of the vessel and after dilution and inoculated with algal cells, was used to fill the test vessels. The cultures were incubated in an orbital incubator under continuous illumination at temperatures ranging from 22.3 to 23.4°C for 96 hours. Replicate algal cultures, with an initial cell density of $1 \times 10^4$ /ml, were exposed to 2-methyl-2-butene at nominal concentrations of 3.20, 7.04, 15.5, 34.1 and 75 mg/l.  The exposure levels were monitored by measuring the concentrations of isoprene in samples of the test media using a GLC method of analysis.
Evaluation of data	Cell densities were measured daily to monitor growth, and the test results are expressed in terms of the area under the growth curve and growth rate. The area under the growth curve and the average specific growth rate are taken to be an index of growth and are calculated mathematically.

	<p>The <math>E_bC_{50}</math> ("x" h) is the median effect concentration for inhibition of growth based on a comparison of areas under the growth curves after "x" hours. The <math>E_bC_{50}</math> was calculated using the moving average method of a computer program (Stephan:1977, 1982) which uses percentage effect and the nominal and measured test concentration in test samples.</p> <p>The <math>E_rC_{50}</math> ("x"- "y" h) is the median effect concentration for inhibition of growth based on a comparison of growth rates from "x" to "y" hours. The <math>E_rC_{50}</math> was calculated by either the moving average method or by non-linear interpolation between the two concentrations which bracket the 50% effect level of a computer program (Stephan:1977, 1982); the program uses percentage effect and the nominal and measured test concentration in test samples.</p> <p>The "no observed effect concentrations" (NOEC) was determined using Dunnett's multicomparison test to compare the percentage inhibition in the test group with that for the control cultures (Dunnett:1955, 1964).</p>
<b><u>Results</u></b>	<p>The measured concentrations of 2-methyl-2-butene ranged between 19 and 27% of their nominal values at the start of the test and between 22 and 29% of nominal after 96 hours. Based on an arithmetic mean, the overall mean measured levels of 2-methyl-2-butene were 0.689, 1.53, 3.61, 7.22 and 21.1 mg/l.</p>
	<p>Area under the growth curve (measured concentrations):  <math>E_bC_{50}</math> (72 h) : 10.5 mg/l (95% confidence limits, 9.55 &amp; 11.7 mg/l)  <math>E_bC_{50}</math> (96 h) : 10.1 mg/l (95% confidence limits, 9.21 &amp; 11.1 mg/l)  No observed effect concentration (NOEC) : 3.61 mg/l</p> <p>Average specific growth rate (measured concentrations):  <math>E_rC_{50}</math> (0-72 h) : 12.0 mg/l (95% confidence limits, 7.22 &amp; 21.1 mg/l)  <math>E_rC_{50}</math> (0-96 h) : 13.2 mg/l (95% confidence limits, 12.2 &amp; 14.3 mg/l)  No observed effect concentration (NOEC) : 7.22 mg/l</p>
Observations	<p>After 96 hours of exposure, the majority of the cells at 21.1 mg/l were swollen and/or mis-shapen.</p>
<b><u>Conclusions</u></b>	<p>After 72 and 96 hours of exposure to 2-methyl-2-butene, the <math>E_bC_{50}</math> values were 10.5 and 13.2 mg/l respectively; the <math>E_rC_{50}</math> values were 12.0 and 13.2 mg/l respectively.</p>
<b><u>Data Quality</u></b>	<p>The "no observed effect concentration" (NOEC) for area under the growth curve and growth rate respectively, were 3.61 and 7.22 mg/l.  Valid without restrictions</p>
<b><u>Reference:</u></b>	<p>Huntingdon Life Sciences Ltd. 2003. Algal growth inhibition assay. Project ID CSS 003 Huntingdon Life Sciences Ltd., Cambridgeshire, England</p>
<b><u>Other</u></b> Last changed	<p>21 January 2004  Robust summary prepared by contractor to Olefins Panel</p>

**2-METHYL-2-BUTENE**  
**DOSE RANGE FINDING STUDY IN RATS**  
**BY INHALATION EXPOSURE**  
**ACC Reference Number: OLF-63.0-HVP3-HLS**

**Sponsor**

American Chemistry Council,  
1300 Wilson Boulevard,  
Arlington,  
VA 22201,  
USA.

**Research Laboratory**

Huntingdon Life Sciences Ltd.,  
Woolley Road,  
Alconbury,  
Huntingdon,  
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ENGLAND.

Report issued: 22 April 2004

## SUMMARY

This study was performed to assess the effect of the test substance, 2-methyl-2-butene, on pregnant female rats to establish suitable dosages for a 4-week general toxicity and reproductive/developmental toxicity screening study.

Three groups, each of 6 time-mated female Crl:CD<sup>®</sup> rats, were exposed to an aerosol of 2-methyl-2-butene, 6 hours a day, from Days 12-19 after mating using a whole body exposure system. A fourth group, also of 6 females, acted as a control and was exposed to air only. The doses of 2-methyl-2-butene administered were 2000, 4000 and 7000 ppm for Groups 2, 3 and 4 respectively.

During the study, clinical signs, bodyweight and food consumption were recorded. On Day 20 of pregnancy the animals were killed, examined macroscopically, and the uterus excised for examination of litter parameters.

The following comments in relation to principal findings are made in summary:

### **Achieved concentration**

The chamber mean analysed concentration over the duration of the study were 0 (Control), 1971, 4027 and 7109 ppm in Group 1 to 4 respectively.

### **Clinical signs and mortality**

There were no treatment related clinical observations and no deaths amongst adult females.

### **Bodyweight**

Bodyweight gain in the test animals was transiently lower than controls during the first 4 days of the exposure period, however there was no dosage relationship established.

### **Food consumption**

Food consumption of the test animals was lower than that of the control during the dosing period.

### **Macroscopic pathology**

No treatment related macroscopic changes were noted.

### **Litter parameters**

There were no obvious effects of treatment on the *in-utero* parameters investigated. External necropsy examination of foetuses at Day 20 after mating revealed no abnormalities.

### **Conclusion**

It was concluded that pregnant females would tolerate exposures up to 7000 ppm and that this concentration would be suitable for use in the subsequent OECD 422 study.

CSS 007/032061

**2-METHYL-2-BUTENE**  
**IDENTIFICATION AND DETERMINATION OF PURITY**  
**(ACC Reference Number OLF-63.0-HPV3-HLS)**

**Sponsor**

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Report issued: 22 April 2004

**SUMMARY**

The study was designed to characterise 2-methyl-2-butene using a gas chromatographic method to determine the mass percent concentration and identification by retention time and to assess its stability for the duration of toxicity testing performed at Huntingdon Life Sciences.

The results from the tests are as follows:

Component	Initial purity (mass %) (2 August 2001)	Final purity (mass %) (12 December 2002)
2-methyl-2-butene	98.0	97.8

The GC retention times obtained for the reference standard and test samples confirm the identity of the test material as 2-methyl-2-butene. The results also confirm the stability of the compound throughout the period of 16 months during which the biological testing was performed.

## ROBUST SUMMARY

<p><b><u>Test Substance</u></b> Remarks</p>	<p>2-methyl-2-butene (CAS No. 513-35-9). The test substance was stable for the duration of all studies performed at the test house.</p> <p>The carbon content of the test substance was determined before the start of the Closed Bottle test using a CEC Model 440 Elemental Analyser. The measured carbon content (85.47%) was equivalent to 99.8% of the theoretical value (85.63%), which was calculated using the empirical formula of 2-methyl-2-butene which comprised 98.2% of the test substance.</p>
<p><b><u>Method</u></b> Method/guideline followed</p> <p>GLP Year Type Inoculum Concentration Contact time</p>	<p>OECD Guideline 301D and EC Directive 92/69, C.4-E and EPA OPPTS 835.3110.</p> <p>Yes 2001 - 2002 Aerobic Domestic sewage effluent 2.1 mg/l related to test substance 28 days</p>
<p>Test inoculum preparation</p>	<p>A sample of secondary effluent was collected on the day of the test from, a trickling-filter plant, which treats predominantly domestic waste. It was maintained under aerobic conditions in the laboratory, then, immediately before use, filtered through glass wool and the filtrate used as the inoculum for the test (1 ml filtrate/litre test medium).</p>
<p>Study design</p>	<p>Eighteen bottles were filled with a mineral salts medium, inoculated with unacclimated sewage effluent at a loading of 1ml/l, and the test substance at a nominal loading of 2.1 mg/l. The dissolved oxygen (DO) concentration in replicate bottles was measured on Days 0, 5, 7, 11, 14, 18, 21, 25 and 28. Four bottles were established for a concurrent five-day microbial inhibition assay, in which the biodegradation of the readily biodegradable reference substance, sodium benzoate, was examined in the presence of the test substance. DO concentration was measured in replicate bottles on Days 0 and 5.</p> <p>A further eighteen bottles were filled with mineral salts medium, inoculated with unacclimated sewage effluent at a loading of 1 ml/l, and the reference substance, sodium benzoate at a nominal loading of 5 mg/l. DO concentrations in replicate bottles was measured on Days 0, 5, 7, 11, 14, 18, 21, 25 and 28.</p> <p>All test systems were incubated at <math>22 \pm 2^\circ\text{C}</math> in darkness. Theoretical oxygen demands for the test and reference substances were based on their empirical formulae and molecular weights. The study was initiated on 8 October 2001.</p>





<p><b><u>Results</u></b></p> <p><b><u>Conclusions</u></b></p> <p><b><u>Data Quality</u></b></p> <p><b><u>Reference:</u></b></p> <p><b><u>Other</u></b> Last changed</p>	<p>After 96 hours, the highest measured concentration at which no mortality had occurred was 2.93 mg/l and the lowest at which there was 100% mortality was 8.51 mg/l. Treatment-related effects were exhibited at 5.33 mg/l and higher concentrations.</p> <p>Based on these findings the following values have been estimated: 96-hour LC<sub>50</sub> value = 4.99 mg/l (95% confidence limits of 2.93 and 8.51 mg/l)</p> <p>NOEC = 2.93 mg/l (measured concentration) LC<sub>50</sub> = 4.99 mg/l (measured concentration)</p> <p>Valid without restrictions</p> <p>Huntingdon Life Sciences Ltd. 2002. Acute Toxicity to Rainbow Trout (Semi-static exposure conditions). Project ID CSS 032. Huntingdon Life Sciences Ltd., Cambridgeshire, England</p> <p>21 January 2004 Robust summary prepared by contractor to Olefins Panel</p>
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## ROBUST SUMMARIES

### Repeated Dose Toxicity

<p><u><b>Test Substance</b></u> Remarks</p> <p><u><b>Method</b></u> Method/guideline followed Test type</p> <p>GLP Year Species Strain Route of administration Duration of test Doses/concentration levels Sex Exposure period Frequency of treatment Control group and treatment Post exposure observation period Statistical methods</p>	<p>2-methyl-2-butene (CAS number: 513-35-9) The test substance was stable for the duration of all studies performed at the test house.</p> <p>OECD 422 4 week general toxicity and reproduction/development toxicity screening test by inhalation exposure to rats (Toxicity phase) Yes. 2001/2002 Rat CrI:CD® (Sprague-Dawley) IGS BR Inhalation (gas). 28 days 0, 580, 2000, or 7000 ppm 12 males, 12 females per dose group for main study group 6 hours/day. 7 days/week 12 males, 12 females, air-only exposed. Not applicable. All statistical analyses were carried out separately for males and females. Data relating to food consumption was analysed on a cage basis. For all other parameters, the analyses were carried out using the individual animal as the basic experimental unit. The following data types were analysed at each timepoint separately:- Rearing and activity counts Bodyweight (FOB) and body temperature Grip strength, landing footsplay and motor activity. Bodyweight, using gains over appropriate study periods. Food consumption, over appropriate study periods, using cumulative cage totals. Blood chemistry and haematology Organ weights, absolute and/or adjusted for terminal bodyweight Pathological findings, for the number of animals with and without each finding. For categorical data, including rearing and activity counts and pathological findings, the proportion of animals was analysed using Fisher's Exact test (Fisher 1973) for each treated group versus the control.</p>
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<p><b><u>Conclusions</u></b></p> <p><b><u>Data Quality</u></b> Reliabilities</p> <p><b><u>References</u></b></p> <p><b><u>Other</u></b> Last changed</p>	<p>Slight effects on general systemic toxicity due to the test substance were apparent amongst animals receiving 7000 ppm, and to a lesser extent at 2000 ppm. The no effect level of the test substance for the general systemic toxicity to rats for 28 days inhalation administration was 580 ppm.</p> <p>Klimisch value = 1 (Reliable without restrictions). Huntingdon Life Sciences Ltd., 2004 4-week general toxicity and reproduction/development toxicity screening test by inhalation exposure to rats Project ID CSS 002. Huntingdon Life Sciences Ltd., Cambridgeshire, England.</p> <p>11 September 2003 Robust summary prepared by contract to Olefins Panel</p>
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### Toxicity to Reproduction

<p><b><u>Test Substance</u></b> Remarks</p> <p><b><u>Method</u></b> Method/guideline followed Test type</p> <p>GLP Year Species Strain Route of administration Duration of test</p> <p>Doses/concentration levels Sex Exposure period Frequency of treatment Control group and treatment Post exposure observation period Statistical methods</p>	<p>2-methyl-2-butene (CAS number: 513-35-9) The test substance was stable for the duration of all studies performed at the test house.</p> <p>OECD 422 4 week general toxicity and reproduction/development toxicity screening test by inhalation exposure to rats (Reproductive phase) Yes. 2001/2002 Rat CrI:CD<sup>®</sup> (Sprague-Dawley) IGS BR Inhalation (gas). Two weeks prior to breeding, during breeding, and continuing through day 19 of gestation. The dams were then allowed to deliver their litters, which were retained until lactation day 4. 0, 580, 2000, or 7000 ppm 12 females per dose group for this satellite study. 6 hours/day. 7 days/week 12 females, air-only exposed. Not applicable. All statistical analyses were carried out separately for males and females. Data relating to food consumption was analysed on a cage basis. For all other parameters, the analyses were carried out using the individual animal as the basic experimental unit. The following data types were analysed at each timepoint separately:- Rearing and activity counts Bodyweight (FOB) and body temperature Grip strength, landing footsplay and motor activity. Bodyweight, using gains over appropriate study periods. Food consumption, over appropriate study periods, using cumulative cage totals. Blood chemistry and haematology Organ weights, absolute and/or adjusted for terminal bodyweight Pathological findings, for the number of animals with and without each finding. For categorical data, including rearing and activity counts and pathological findings, the proportion of animals was analysed using Fisher's Exact test (Fisher 1973) for each treated group versus the control.</p>
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For continuous data, Bartlett's test (Bartlett 1937) was first applied to test the homogeneity of variance between the groups. Using tests dependent on the outcome of Bartlett's test, treated groups were then compared with the Control group, incorporating adjustment for multiple comparisons where necessary.

The following sequence of statistical tests was used for bodyweight (FOB), body temperature, grip strength, landing foot splay and motor activity, bodyweight, food consumption, organ weight and clinical pathology data.

If 75% of the data (across all groups) were the same value, for example c, then a frequency analysis was applied. Treatment groups were compared using a Mantel test for a trend in proportions (Mantel 1963) and also pairwise Fisher's Exact tests (Fisher 1973) for each dose group against the control both for i) values <c versus values >=c, and for ii) values <=c versus values >c, as applicable.

If Bartlett's test for variance homogeneity (Bartlett 1937) was not significant at the 1% level, then parametric analysis was applied. If the F1 test for monotonicity of dose-response (Healey 1999) was not significant at the 1% level, Williams' test for a monotonic trend (Williams 1971, 1972) was applied. If the F1 test was significant, suggesting that the dose-response was not monotone, Dunnett's test (Dunnett 1955, 1964) was performed instead.

If Bartlett's test was significant at the 1% level, then logarithmic and square-root transformations were tried. If Bartlett's test was still significant, then non-parametric tests were applied. If the H1 test for monotonicity of dose-response (Healey 1999) was not significant at the 1% level, Shirley's test for a monotonic trend (Shirley 1977) was applied. If the H1 test was significant, suggesting that the dose-response was not monotone, Steel's test (Steel 1959) was performed instead.

For organ weight data, analysis of variance was initially performed using terminal bodyweight as covariate. If the within group relationship between organ weight and bodyweight was significant at the 10% level (Angervall and Carlstrom, 1963), then the treatment comparisons were made on adjusted group means in order to allow for differences in bodyweight which might influence the organ weights.

Significant differences between Control and treated groups were expressed at the 5% ( $p < 0.05$ ) or 1% ( $p < 0.01$ ) level. Williams test is denoted by '\*'; t tests are denoted by '+', Dunnett's test is denoted by '\*+' and Shirley's test by '+±'.



**CHF 4227.01 AND RALOXIFENE  
TOXICITY STUDY BY ORAL GAVAGE ADMINISTRATION  
TO FEMALE CD RATS FOR 4 WEEKS**

**Sponsor**

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ENGLAND.**

**Report issued: 29 April 2004**

## SUMMARY

The systemic toxic potential of the test substance, CHF 4227.01 under development for the treatment of osteoporosis and Raloxifene (a SERM [Selective Estrogen Receptor Modulator] also for use in the treatment of osteoporosis), to female CrI:CD<sup>®</sup> (SD)IGS BR rats by oral administration was assessed over a period of 4 weeks. One group of ten female rats received CHF 4227.01 and a further group of ten female rats received Raloxifene by oral gavage both at a dosage of 30 mg/kg/day for 4 weeks. A similarly constituted Control group received the vehicle (0.5% Methylcellulose and 0.25% Tween 80) at the same volume-dosage.

During the study, clinical condition, bodyweight, organ weight, macroscopic and microscopic pathology investigations were undertaken.

Principal findings are summarised below:

### Results

The following treatment-related changes were observed following oral gavage administration of either 30 mg/kg/day CHF 4227.01 or 30 mg/kg/day Raloxifene for 4 weeks.

No clinical signs were observed which would indicate a reaction to treatment.

Bodyweight gain over the four weeks of treatment was similar to controls in the animals receiving CHF 4227.01. A lower, although not statistically significantly different, bodyweight gain was observed in animals treated with Raloxifene.

Group mean adjusted and unadjusted uterus weights were significantly lower in animals receiving CHF 4227.01 or Raloxifene in comparison with control animals. Animals receiving CHF 4227.01 had a slightly lower group mean uterus weight than that of the animals treated with Raloxifene. Ovary weights in both treated groups were noted to be significantly increased, again a slightly more pronounced reaction being evident in animals receiving CHF4227.01, these animals showing a higher terminal ovarian weight than those receiving Raloxifene. Additionally, adrenal glands in animals treated with CHF 4227.01, or, to a lower degree, with Raloxifene were noted to be smaller than those seen in control animals.

In addition to the enlargement seen in treated group ovaries it was also noted that 10/10 animals receiving CHF 4227.01 and 7/10 animals treated with Raloxifene had developed cysts upon the ovaries. Dark follicles were also noted in 1/10 CHF 4227.01 treated animals and 3/10 animals receiving Raloxifene. Adrenal glands in 1/10 animals receiving CHF 4227.01 were noted to be darkened. Similar changes were not observed in the control animals.

In the ovaries of treated females, follicular cysts were found in all animals receiving 30 mg/kg/day CHF 4227.01, and in several animals receiving 30 mg/kg/day Raloxifene, with a slightly higher degree in animals treated with CHF 4227.01. Luteal cysts were noted in both of the treatment groups, with a higher incidence and degree in the animals treated with 30 mg/kg/day Raloxifene. These findings are in agreement with both the significantly increased ovary weights in both treatment groups, and that the CHF 4227.01 group showed a higher group mean terminal ovarian weight compared with the Raloxifene treatment group.

In the uterine cervix and in the vagina epithelial mucification was observed in all animals receiving either 30 mg/kg/day CHF 4227.01 or 30 mg/kg/day Raloxifene, with a slightly greater degree in animals receiving CHF 4227.01.

In the mammary area, minimal or slight ductal/acinar hypertrophy/vacuolation was observed only in a few animals of the 30 mg/kg/day CHF 4227.01 treatment group.

These changes, with the exception of luteal cysts, were slightly more pronounced in animals receiving CHF 4227.01 than in those receiving Raloxifene at the same dose level.